Micronutrient status and disease state in patients with inflammatory bowel disease

by

Kacie Michelle Mallon Stull

B.A., Kansas State University, 2016
M.S., University of Kansas, 2020

AN ABSTRACT OF A DISSERTATION

submitted in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

Department of Food, Nutrition, Dietetics, and Health
College of Health and Human Sciences

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Abstract

Inflammatory Bowel Disease (IBD) is a collective term for chronic conditions that cause gastrointestinal inflammation. Micronutrient deficiencies are common in individuals with IBD and are thought to play a significant role in both the pathogenesis and progression of the disease. Despite the high prevalence of micronutrient deficiencies, nutritional screening is not a standard component of IBD care, limiting effective disease management and patient outcomes. This study aimed to describe individual patterns in dietary intake, micronutrient status, and disease burden among adults with IBD.

This case series examined the micronutrient levels of adults (n=7) with IBD through laboratory blood tests. Micronutrient intake was evaluated using the Food Frequency Questionnaire (FFQ) developed by the Nutrition Assessment Shared Resource (NASR) at Fred Hutchinson Cancer Center. Disease-related disability was measured using a modified Inflammatory Bowel Disease Disability Index (IBD-DI), and inflammation was assessed via C-reactive protein (CRP) levels.

Vitamin D deficiency was the most common concern observed in three cases. Two of the three participants had elevated CRP levels, indicating a relationship between inflammation and low vitamin D. Elevated B_{12} levels were noted in two cases, and one participant had low folate intake and deficiency. Iron and magnesium intake were associated with lower laboratory values, though no participants were iron deficient. IBD-DI scores indicated minimal disability despite micronutrient deficiencies and elevated CRP. Trends suggested a link between inflammation and lower nutrient levels.

This study emphasizes the need for monitoring micronutrient status in IBD patients and calls for further research with larger sample populations to better understand the complex

relationships between micronutrient levels, dietary intake, inflammation, and disease-related disability.

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Preface

This manuscript has been prepared in accordance with the publication requirements for the *Journal of Gastroenterology*. We intend to submit this research for publication at a future date.

Chapter 1 - Introduction

Inflammatory Bowel Disease (IBD) is a collective term for chronic conditions characterized by inflammation in the gastrointestinal tract, leading to symptoms such as diarrhea, weight loss, and abdominal pain.[1] The two primary forms of IBD are Crohn's disease (CD) and ulcerative colitis (UC). The pathogenesis of IBD is linked to complex interactions between genetic susceptibility, immune dysregulation, gut dysbiosis, and various environmental factors.[2] Since the mid-20th century, the global prevalence of IBD has increased significantly, with a rising incidence in developing regions, likely due to highly processed diets and increased antibiotic use.[1,3] The growing burden on patients and healthcare systems highlights the need for continued advancements in diagnosis and management strategies.[2]

The approach to treating IBD has shifted from focusing on symptom management to a treat-to-target strategy.[2] Modern treatments prioritize pharmacologic therapy to address underlying gastrointestinal inflammation, promote mucosal healing, provide symptomatic relief, and achieve clinical remission.[4,5] The development of biologic therapies that target key inflammatory mediators, along with advancements in minimally invasive surgical techniques, has significantly improved IBD disease management and patient outcomes. Effective IBD management now requires a holistic, personalized approach that incorporates pharmacological treatments, nutritional interventions, and lifestyle modifications to enhance overall health and reduce disease-related complications.[2] Despite its potential to significantly improve patient outcomes, nutritional care is not routinely integrated into IBD management, leaving critical gaps in care that may contribute to the high prevalence of nutrient deficiencies and exacerbate disease activity.

Problem statement

Patients with IBD are at an increased risk of malnutrition, which can lead to worsened clinical outcomes, increased hospitalizations, complications, and higher mortality rates. The causes of malnutrition in IBD are multifactorial, including reduced food intake, malabsorption, medication side effects, diarrhea, nutrient loss, and increased energy demands. [6,7] The chronic nature of IBD, combined with these challenges, heightens the risk of nutrient deficiencies, which can adversely affect health, disease progression, and the effectiveness of disease management.

Micronutrient deficiencies, including vitamin D, B_{12}, folate, iron, magnesium, and zinc, are common in more than half of IBD patients, with higher rates observed in those with CD compared to UC.[8–10] Malabsorption, caused by disrupted intestinal mucosa, bacterial overgrowth, and surgical interventions, is a key factor in the development of these deficiencies.[6] Micronutrient deficiencies can worsen disease activity and lead to complications such as anemia, osteoporosis, and cardiovascular disease, making effective IBD management even more complex.

Despite the high prevalence of nutrient deficiencies in IBD patients, nutritional screening is not routinely incorporated into standard care, resulting in critical gaps in disease management and underutilization of nutrition interventions to improve clinical outcomes.[11] A key barrier to addressing these nutritional needs is the insufficient knowledge among healthcare providers regarding the role of nutrition in the prevention and management of chronic diseases. Despite calls for comprehensive nutrition education in medical curricula, such training remains largely absent from medical schools in both the U.S. and Europe.[12] This educational gap limits the understanding of nutrition's essential role in managing IBD, weakening the effectiveness of standard interventions and reducing the potential for achieving clinical remission.

Justification of research

As recognition of nutrition's role in preventing and managing chronic diseases continues to develop, there is an urgent need to further investigate micronutrient deficiencies and their impact on comprehensive IBD care. Despite advancements in pharmacological therapies, the true prevalence of these deficiencies remains largely unknown. The lack of routine nutritional testing likely leads to undiagnosed deficiencies, exposing significant gaps in current management strategies and highlighting the need for structured screening practices. A more patient-centered approach that integrates regular nutritional assessments and targeted nutrition therapies into standard care could improve disease management, reduce complications, and enhance the overall quality of life for individuals with IBD.

This study aims to address these critical gaps by evaluating the prevalence of micronutrient deficiencies in IBD patients, offering valuable insights for a more comprehensive, multidisciplinary approach to IBD care. By integrating nutritional interventions alongside pharmacotherapy and surgical treatments, this research could enhance disease management, address deficiencies that may exacerbate disease activity, and ultimately improve long-term patient outcomes.

Purpose of research

This study was guided by the Protection Motivation Theory (PMT), which suggests that individuals assess and respond to health threats based on perceived severity, vulnerability, response efficacy, and self-efficacy. By investigating micronutrient status in IBD patients, we aimed to emphasize the prevalence and significance of nutrient deficiencies, which are often overlooked in standard care. Applying PMT to this research highlights the importance of understanding the role of nutrition in managing IBD while emphasizing the need to equip

healthcare providers and patients with the necessary tools for effective screening and intervention. Raising awareness and integrating nutritional assessments into routine care can empower patients to take an active role in managing their health, while supporting providers in delivering more comprehensive, patient-centered care.

This study sought to investigate the status of key micronutrients—such as folate, vitamin B_{12}, vitamin D, iron, magnesium, and zinc—in IBD patients. By identifying specific deficiencies and evaluating their impact on IBD progression, this research seeks to address critical gaps in knowledge and guide future clinical practices. Monitoring and appropriately supplementing these micronutrients could help improve disease management, reduce complications, and better address the nutritional needs of IBD patients, ultimately improving patient outcomes.

This project will apply the PMT framework to address the following research questions: (1) What is the correlation between dietary intake and micronutrient levels in patients with IBD? (2) What is the prevalence of specific micronutrient deficiencies (e.g., vitamin D, B_{12}, folate, iron, magnesium, zinc) in IBD patients? (3) How is disease-related disability associated with micronutrient status in patients with IBD?

Chapter 2 - Literature review

What is inflammatory bowel disease?

Inflammatory Bowel Disease (IBD) is an umbrella term for a series of chronic, inflammatory gastrointestinal diseases. IBD is characterized by the increase of cytokines, proteolytic enzymes, and free radicals, resulting in symptoms such as weight loss, diarrhea, abdominal pain, gastrointestinal bleeding, ulceration, and inflammation.[1] Although the symptoms can be similar, the two main classifications of IBD are Crohn's disease (CD) and ulcerative colitis (UC). The primary difference between the two conditions is their phenotypic presentation.[3]

No single assessment can differentiate between the types of IBD. Diagnosis is dependent on histological examination of tissue samples, endoscopic evaluation, and overall clinical presentation.[3] CD is transmural in nature and most often affects the terminal ileum or perianal area. However, it can affect any region of the gastrointestinal tract, from mouth to anus, in a discontinuous manner.[13] Complications of CD often include thickened submucosa, fissures, granulomas, abscesses, and strictures. Unlike CD, UC is limited to the colon and primarily affects the epithelium, lamina propria, and muscularis mucosa of the mucosal layer, as well as the superficial submucosa.[3,13] Abscesses and inflammation of the crypt are often observed in UC.[1] Of the two main types of IBD, UC has the highest rate of occurrence.[3]

Since the second half of the 20th century, the incidence of IBD has increased significantly.[1] Although IBD is most prevalent in Europe and North America, its incidence has also increased in the developing regions of Asia, Africa, and South America.[1,3] This increase mirrors industrialization and is likely influenced by changes in dietary patterns, such as increased consumption of processed foods, sugars, and fats, as well as overuse of antibiotics.[1]

Pathogenesis

Despite extensive research, the etiology of IBD remains unclear. Evidence suggests that its development results from a complex interplay of genetic susceptibility, environmental factors, intestinal microbiota, and immunologic abnormalities.[3,13]

Genetic factors

Over the past several decades, advancements in analytical technology and genetic testing have facilitated the study of genetics as a contributing factor in the development of IBD. Genome-wide association studies (GWAS) have played a key role in this progress, enabling the identification of single nucleotide polymorphisms (SNPs).[13] SNPs are variations in a nucleotide within a DNA sequence that occur at specific loci on a chromosome. These variations can significantly influence genetic characteristics, including population diversity, physical and familial traits, genome evolution, responses to medications, and various health conditions.[14] Additionally, SNPs can affect disease phenotypes and modulate inflammatory cytokine responses. To date, GWAS has identified more than 240 non-overlapping IBD-related gene loci, 30 of which are shared between Crohn's disease (CD) and ulcerative colitis (UC)[1].

In 2001, Nucleotide-binding oligomerization domain 2 (*NOD2*) gene was identified as the first susceptibility gene for CD.[13] Variants of the *NOD2* gene appear in approximately one-third of CD patients and are believed to contribute to various immune functions.[1] *NOD2* is essential for pathogen detection and encodes a protein that serves as a receptor for muramyl dipeptide (MDP).[1,13] Activation of MDP stimulates autophagy, a critical process in maintaining intestinal homeostasis.[13] Autophagy regulates both innate and adaptive immune responses in IBD by recycling cytosolic contents and organelles, removing intracellular pathogens, limiting the replication of bacteria, and reducing susceptibility to infection.[1,13]

Polymorphisms of two autophagy-related genes, *ATG16L1* and *IRGM*, have been linked to CD.[13] *ATG16L1* is essential for all forms of autophagy. In animal studies, selective deletion of *ATG16L1* in T cells was associated with intestinal inflammation, which reflects disruption of the mucosal barrier secondary to T cell dysregulation.[1] Polymorphisms in *IRGM* decrease protein production, which can contribute to inflammation and impair other biological processes.[13] Additionally, various SNPs in *IL-23R* are strongly associated with both CD and UC.[1]

While some IBD-related loci are found across multiple populations and geographic regions, others are population-specific. For example, variants of *NOD2* and *IL23R* are exclusive to individuals of European ancestry and are absent in populations of Asian descent. Although many people carry risk-related loci, the proportion of individuals who develop IBD remains relatively small.[1] Researchers estimate that only 20–25% of risk-related loci have been identified to date.[13] While genetics are a key factor in the pathogenesis of IBD, other environmental, microbial, and immune factors contribute to its development.[1,13]

Environmental factors

Over the past 50 years, the rising incidence of IBD has paralleled an increase in industrialization in more developed countries.[1] This trend is likely driven by lifestyle changes and environmental exposures associated with modernization. Factors such as smoking, dietary habits, medication use, geography, and psychological stress are all risk factors for IBD.[13]

Diet is a particularly important IBD risk factor, as food quality has arguably decreased over the last century. Western diets prioritize convenience and affordability, consequently decreasing the intake of fresh, whole foods. Research has demonstrated an inverse relationship between fruit and vegetable consumption and the risk for developing CD, with higher intake associated with lower risk.[1] Conversely, frequent consumption of fast food and foods high in fat

or sugar appears to accelerate the development of CD. Medium-chain triglycerides and food additives further contribute to intestinal inflammation and impair gut function.[1] As a result, many modern dietary components may serve as risk factors for IBD.

Given the impact of diet on IBD risk, specific nutrients, such as Vitamin D, have been linked to the progression and development of various diseases. Research suggests that lower levels of Vitamin D increase IBD risk, and deficiency is frequently observed in IBD patients.[13] The genomic actions of vitamin D on the vitamin D receptor (VDR) influence genes associated with innate and adaptive immune functions.[15,16] Vitamin D modulates the activity of immunoregulatory cells, including B and T lymphocytes, macrophages, and monocytes.[16] Notably, supplementation of vitamin D_3 has been shown to relieve intestinal inflammation.[13] The Nurses' Health Study, an ongoing prospective cohort study established in 1976, found that women in the highest quartile of vitamin D levels were 40% less likely to develop CD. However, no such correlation was observed for UC risk.[15] These findings highlight the need for further investigation into vitamin D as a potential indicator of clinical outcomes and modulator of disease progression in IBD patients.[17]

To date, smoking remains the most extensively researched environmental risk factor for IBD, and its relationship to disease development is compelling.[13] Since the discovery of an inverse relationship between UC and smoking in 1982, research has confirmed that chronic smoking is protective against UC and reduces the incidence of symptom relapse.[13] However, smoking increases the risk of CD and exacerbates disease progression.[1,13] Although the exact mechanism remains unclear, smoking may influence immune responses and stimulate colonic mucus production.[1,15] According to Abegunde et al[15] the mechanism by which smoking affects UC "…may involve the reduction in tumor necrosis factor (TNF alpha) production via the action

of nicotine on the nicotinic acetylcholine receptor a7 subunit, increased production IL-10 in response to carbon monoxide in cigarette smoke, increased mucin synthesis, decrease in IL-8 expression, hypoperfusion of the rectum and acutely damaged colonic tissue."[15(p6298)] In CD, carbon monoxide inhibits vasodilation in chronically inflamed vasculature and may contribute to ulceration and fibrosis.[15] Additionally, smoking interferes with autophagy and disrupts intestinal homeostasis.[1]

The use of certain medications, stress, and exposure to pollution are also known contributors to IBD development. Nonsteroidal anti-inflammatory drugs (NSAIDS) and antibiotics has been linked to both UC and CD.[13] While antibiotics may be necessary to combat certain infections, they can disrupt the microbiome and eliminate healthy or protective bacteria from the gut.

Stress is another important factor, with lower stress levels associated with a reduced risk of IBD. In individuals already diagnosed with the disease, depression and anxiety appear to accelerate disease progression. Unlike NSAIDs and antibiotics, antidepressants may help regulate IBD symptoms by mitigating perceived stress.[13]

Unsurprisingly, air pollution also contributes to IBD risk and has been associated with both CD and UC[13]. According to Zhang and Li[13], "Elevated air pollution is associated with an augment in circulating polymorphonuclear leukocytes and plasma cytokines."[13p93] The gut microbiome may play a key role in determining the extent to which air pollution and particulate matter influence IBD.[15] Additionally, rates of IBD-related hospitalizations appear to correspond with high levels of air pollution.[13] Ultimately, many environmental factors contribute to IBD risk, and understanding these influences is crucial for mitigating disease development.

Intestinal microbiota

The gut microbiome is a key component of immune regulation, influencing metabolism and the development of the gastrointestinal system.[1] It consists of more than 1000 species of microorganisms, the majority of which come from the phyla Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria.[1,15] Colonization of the gut microbiome begins immediately after birth, with microbial diversity rapidly establishing within the first few years of life.[15] The composition of the gut microbiome is shaped by an infant's mode of delivery, feeding practices, and various other factors, including antibiotic use, prebiotics and probiotics, genetics, and environmental exposures.[1,15]

The relationship between the host and its microbiome is symbiotic and plays a crucial role in maintaining intestinal homeostasis.[1] According to Abegunde et al[15], "the microbiota provide physiological benefits such as fermentation of indigestible carbohydrates; synthesis of short-chain fatty acids (SCFA) and certain vitamins; biotransformation of conjugated bile acids."[15(p6300)] These microorganisms also play a key role in immune system development, aiding in the recognition of nonimmune components and providing protection against pathogens.[1,15]

The pathophysiology of IBD is largely influenced by microbial factors, and studies have demonstrated compositional shifts in the microbiomes of IBD patients.[1,13] Although the exact mechanisms underlying microflora disruption remain unclear, this bacterial imbalance—combined with genetic susceptibility—promotes immune dysregulation and contributes to the development of IBD.[6,15]

Comparative studies analyzing the gut microbiomes of IBD patients and healthy controls have identified significant differences in microbial diversity and stability.[15] In patients with IBD, particularly those with CD, an increased presence of *Escherichia coli* (*E. coli*) has been observed

within the thin mucus layer that covers the inner colonic lining.[13] Under normal conditions, this inner mucus layer is free of bacteria, and small pores defend against pathogens.[18] However, the same strains of *E. coli* that have been found inside the adherent mucus layer have also been identified within granulomas of CD patients, suggesting a potential pathogenic role of *E. Coli*.[13] These findings support the widely accepted belief that dysbiosis contributes to IBD development.[15]

Immune function

Dysregulation of the immune system is believed to contribute to both the pathogenesis and progression of IBD. Intestinal inflammation is primarily driven by dysfunction in the innate and adaptive intestinal immune pathways and is characterized by damaged epithelial tissue.[1,13] The composition of gut microbiota as well as microbial invasion of the lamina propria determine the extent of inflammation and stimulate the production of proinflammatory cytokines.[1]

Within the gut, the innate immune pathway serves as the primary protective barrier against pathogens, acting rapidly in response to threats within minutes to hours of infiltration.[13] The pathway involves a variety of cells, including epithelial cells, neutrophils, dendritic cells (DCs), monocytes, macrophages, and natural killer cells.[13] Pattern recognition receptors (PRRs), such as toll-like receptors (TLRs) and NOD-like receptors (NLRs), trigger the innate immune response. Studies suggest that the activity of these cells facilitates innate immunity, and disruption of this process is common in patients with IBD.[13] Biopsies from the intestines of IBD patients have also revealed alterations in microbial peptides and junctional proteins, suggesting that barrier dysfunction plays a role in IBD development.[19]

Macrophages, DCs, epithelial cells, and myofibroblasts maintain intestinal homeostasis by detecting pathogens, which typically trigger the onset of autophagy. In patients with risk-

related polymorphisms, such as variations in *NOD2* and *ATG16L*, these functions are compromised.[13,19] Polymorphisms in *NOD2*, which have been linked to CD, encode TLRs and NLRs and contribute to immune strength.[13,19] These mutations often increase susceptibility to IBD by impairing the body's ability to respond to lipopolysaccharides (LPSs), resulting in the infiltration of microbial pathogens and the stimulation of inflammation.[20] Innate lymphoid cells (ILCs), which are concentrated in mucosal tissue, are also essential for intestinal homeostasis. ILCs induce immune responses that promote tissue strength and protect against infection. The improper function of ILCs has been linked to inflammation, thereby contributing to the pathogenesis of IBD.[19]

Whereas innate immunity is non-specific, the adaptive immune pathway is highly specialized.[1] Activation of the adaptive immune response may take several days and is heavily dependent on the quantity and variety of available T and B cells.[20] The adaptive immune pathway responds to specific pathogens and is typically activated when the innate immune system fails to eliminate harmful bacteria.[20] Disruptions in adaptive immunity, especially imbalances between Th1 and Th2 responses, can trigger the onset of IBD.[1,19] Studies suggest that the Th1 immune response is more common in CD, while Th2 is more prevalent in UC.[13] Th17, a pro-inflammatory cytokine, appears at higher frequencies in the mucosa and serum of both UC and CD patients. Its role is critical in the communication between the innate and adaptive immune pathways. The pro-inflammatory cytokine IFN-γ also plays a significant role in the progression of IBD at the mucosal level.[19]

T-cell function and the intestinal mucosa are believed to be closely associated with IBD. IL-5 and IL-3, which are released by mucosal T-cells, decrease the effectiveness of the intestinal epithelial barrier and are produced in higher quantities in UC patients.[19] Similarly, IL-9, which is

produced by the Th9 subset of T-cells, may interfere with the function of the intestinal barrier. These cells have been observed in the intestinal mucosa of UC patients. Permeation of the mucosal plasma cells in the intestines has been reported in CD patients. Anti-drug antibodies (ADAs), which can be produced by these plasma cells, may interfere with pharmacokinetics by forming immune complexes that alter efficacy, sensitivity, and reactivity. These interactions may explain decreased responsiveness or total failure of pharmacological interventions.[19]

Pharmacological therapies for IBD

Conventional IBD treatment has historically focused on symptom management; however, the severity of symptoms does not always accurately reflect disease activity. Diagnostic imaging and endoscopic examinations indicate that gastrointestinal inflammation may be present despite the absence of symptoms.[4] If left untreated, gastrointestinal inflammation can lead to complications such as intra-abdominal abscesses, fistulas, and bowel damage.[21]

Modern IBD treatment aims to address gastrointestinal inflammation, focusing on mucosal healing and improved long-term prognosis.[4] This approach primarily relies on pharmacologic therapy to provide symptomatic relief, prevent disease flare-ups, normalize CRP levels, improve quality of life, and achieve clinical remission, defined as the absence of disease activity.[5] Pharmacological therapies for IBD include aminosalicylates, glucocorticosteroids, immunomodulators, biological therapies, Janus kinase (JAK) inhibitors, sphingosine-1-phosphate (S1P) receptor modulators, and antibiotics.

Figure 2.1 Mechanisms of action of IBD pharmacotherapies

Treatment Type	Mechanism of Action
Aminosalicylates	Suppression of IL-1, TNF-α, and PAF activity, reduced antibody production[22]
Glucocorticoids	Inhibition of phospholipase A2, suppression of cytokine transcription, induction of lymphocyte apoptosis[22]
Immunomodulators	Inhibition of purine synthesis via the *de novo* pathway[22]
Biological Therapies	
Anti-Integrin	Inhibition of leukocyte adhesion and migration[22]
Anti-Interleukin	Induction of apoptosis in proinflammatory cells by binding to TNF-α and blocking receptor interaction[22]
JAK Inhibitors	Inhibition of cytokine signaling[23]
S1P Modulators	Suppression of lymphocyte infiltration by binding to S1P receptors[23]

Aminosalicylates

Aminosalicylates have been used clinically as the primary therapeutic option for treating mild-to-moderate ulcerative colitis for more than 50 years.[5,24,25] These medications can be administered orally or rectally and possess a broad spectrum of anti-inflammatory and immunoregulatory actions. These include antioxidant properties, inhibition of proinflammatory activities of cyclooxygenase and 5-lipoxygenase, and reduced production of antigen presentation T-cells.[5,26]

Aminosalicylates help to maintain remission in patients with UC by reducing intestinal inflammation and inhibiting the recruitment of leukocytes in the intestinal lining.[5] Additionally, several studies indicate that 5-aminosalicylates (5-ASA), the most prescribed member of the aminosalicylate family, may be protective against colorectal cancer.[24,25] Although most patients with mild-to-moderate UC respond well to treatment with aminosalicylates, the same level of effectiveness has not been demonstrated in Crohn's disease.[25]

Glucocorticoids

Glucocorticoids (GCs) are widely used non-selective, anti-inflammatory medications that can be administered intravenously, intramuscularly, orally, or rectally.[5] This class of steroid hormones is highly effective for the temporary or initial treatment of clinical flares in patients with UC or CD; however, long-term use has been associated with serious adverse effects.[5,23] Some risks associated with GCs include osteoporosis, increased appetite or weight gain, elevated blood glucose levels, and psychiatric conditions such as insomnia and depression, as well as disrupted growth patterns in young children.[5] Due to these risks, GCs are primarily used for rapid management of symptoms associated with acute disease activity.[23]

While glucocorticoids may be beneficial as an initial therapeutic intervention for moderate-to-severe IBD, they are not effective in achieving endoscopic remission or promoting mucosal healing.[5,23] Through both genomic and non-genomic mechanisms, GCs disrupt various inflammatory processes within the innate and adaptive immune pathways.[23] The immunosuppressive actions of GCs are largely achieved by decreasing abnormal cytokine production, a process closely linked to inflammation.[5] At the genomic level, GCs modify the expression of mRNA involved in producing pro-inflammatory mediators.[23,27] Non-genomic actions that mediate inflammation include "secondary intracellular transmissions and signal transduction cascades."[23] Although glucocorticoids are useful for the rapid induction of remission in patients with IBD, additional therapies are necessary for long-term maintenance.[5,23]

Immunomodulators

Immunomodulators, such as thiopurines and methotrexate, are immunosuppressive drugs that are frequently used in the treatment of IBD.[23] These medications can be administered orally or intravenously and reduce inflammation by inhibiting the inflammatory actions of T

lymphocytes.[5,28] Due to their ability to increase the effectiveness of anti-TNF treatments and prevent the formation of antibodies, immunomodulators are often prescribed as adjunct therapies.[5] They may also be prescribed to patients who do not respond well to aminosalicylates or corticosteroids.[5]

Although effective as a single-agent therapy for maintaining remission, immunomodulators have a delayed therapeutic effect. Therefore, they must be combined with another treatment modality to successfully induce remission.[5] Immunomodulators inhibit the *de novo* pathway of purine synthesis, reducing the excessive activity of immune cells in patients with IBD.[22] While generally considered safe, these medications are associated with an increased risk of lymphoma and are contraindicated in pregnant females, as they have been linked to congenital malformations.[23]

Biological therapies

Biologic therapies are a type of IBD treatment that reduce inflammation by targeting specific molecules or proteins involved in the inflammatory process. These medications, which are derived from bioengineered organisms, are generally prescribed to patients with moderate-to-severe IBD who have not responded well to other therapies.[5] Compared to traditional medications, biologics are more effective at reducing hospitalization rates and achieving higher rates of remission. The three main classes of biologic therapies include anti-TNF agents, anti-integrins (or CAM inhibitors), and anti-interleukins.[23]

Anti-TNF agents

Research suggests that tumor necrosis factor (TNF) plays a significant role in the development of IBD.[5] TNF can bind to both TNFR1 and TNFR2. In its soluble form, it primarily binds to the TNFR1 receptor, triggering apoptosis, cell proliferation, and cytokine secretion.

Elevated serum TNF levels in patients with UC and CD highlight its role as a key pro-inflammatory cytokine in IBD.[29] TNF inhibitors, such as adalimumab, infliximab, certolizumab, and golimumab, are pharmacologic treatments that have been developed to reduce gastrointestinal inflammation and alleviate symptoms in IBD. These medications have been shown to promote transmural healing, leading to the induction and maintenance of remission. Unfortunately, anti-TNF medications are ineffective or gradually lose effectiveness over time in 30–50% of IBD patients.[5]

Anti-integrin therapies (CAM inhibitors)

Integrins are transmembrane glycoproteins essential for immune cell proliferation, signaling, and movement. They consist of α and β subunits that bind to cell adhesion molecules (CAMs) on other cells, including immune cells, facilitating their movement to the gastrointestinal tract and other peripheral tissues. Increased levels of gut-tropic integrins and CAMs have been observed in the inflamed gastrointestinal tissue of patients with IBD.[30] Anti-integrin therapies (CAM inhibitors) have been developed to reduce intestinal inflammation in patients with IBD. In moderate-to-severe Crohn's disease, natalizumab has shown considerable clinical effectiveness. It prevents lymphocytes from permeating the gut by binding to α4-integrins, molecules known to draw T-cells to intestinal tissues and promote intestinal inflammation. Additional therapies, such as etrolizumab and ontamalimab, control inflammation and IBD symptoms by targeting T-cell migration.[5] Addressing integrins and their role in immune cell migration presents a promising strategy for treating IBD, offering potential for reducing intestinal inflammation and improving patient outcomes.

Anti-interleukin inhibitors

Interleukins are a type of cytokine that act as signaling molecules between cells and tissues, including innate and adaptive immune cells. Due to their role in the pathogenesis and progression of IBD, pharmacotherapies have been developed to inhibit their action.[31] In IBD, interleukins 12 and 23 (IL-12 and IL-23, respectively) play a role in lymphoid hematopoiesis.[23] IL-23 regulates T-helper 17 cells, promoting the release of pro-inflammatory cytokines.[5] Ustekinumab, a newer biologic therapy, targets the p40 subunit of IL-12 and IL-23, helping to induce and maintain remission in patients with active IBD.[5] Risankizumab, a humanized monoclonal IgG1 antibody, targets the p19 subunit of IL-23 to mediate inflammation. It is generally well-tolerated and has been effective for achieving endoscopic remission in patients with active CD.[5] Targeting interleukins and their pathways offers promising therapeutic strategies for managing IBD.

JAK inhibitors

The Janus kinase (JAK) family consists of four enzymes —JAK1, JAK2, JAK3, and TYK2—that activate cytokine receptors, leading to phosphorylation and interaction with signal transducer and activator of transcription (STAT) proteins within the JAK-STAT pathway.[23,32] Once activated, STATs translocate to the nucleus and regulate gene expression.[23] Combinations of JAK signaling, which occurs in pairs, trigger and direct various physiological functions, including apoptosis and cell proliferation.[23] Dysfunction of the JAK-STAT pathway can lead to various autoimmune diseases, including IBD. Therefore, JAKs present promising targets for drug development.[32]

The first JAK inhibitor, ruxolitinib, was approved in 2011. Since then, multiple JAK inhibitors have been developed to target one or more kinases, disrupting cytokine-activated

signaling pathways and preventing abnormal JAK-STAT signaling.[32] These pharmacotherapies regulate proinflammatory cytokines by suppressing T-cells and natural killer cells.[5] Tofacitinib, a JAK inhibitor approved for UC, mediates gastrointestinal inflammation by inhibiting JAK1, JAK2, and JAK3, thereby blocking the signaling pathways of gamma chain-containing cytokines.[5] Filgotinib, however, is often the preferred therapy for UC because research suggests it has five times five times the blocking potency than other JAK inhibitors.[23]

JAK inhibitors offer several benefits over other approved IBD therapies, including high potency, rapid therapeutic response, non-immunogenicity, and the convenience of oral administration.[33] Despite their efficacy, JAK inhibitors have been linked to several life-threatening adverse effects, including serious infections, major cardiovascular events, venous thromboembolisms, and cancer. Additionally, JAK inhibitors have limited selectivity and can become ineffective due to the development of drug resistance.[33] While JAK inhibitors provide significant advantages in treating IBD, their risk of serious side effects requires thorough evaluation and close monitoring in clinical settings.

S1P modulators

Sphingosine-1-Phosphate (S1P) is a phospholipid that binds to 5 G protein-coupled receptors (SRPR1-5), influencing intracellular pathways that regulate gene expression.[34] S1P activates pro-inflammatory NF-κB and inhibits histone deacetylases (HDACs), which are both regulators of epigenetic expression. Research has identified alterations in sphingolipid metabolism that contribute to inflammation and affect the integrity of gastrointestinal mucosa. Therefore, targeting S1P or its receptors may inhibit disease progression and alleviate symptoms in patients with IBD.[34]

S1P modulators are pharmacotherapies for IBD that prevent lymphocytes from infiltrating inflamed tissue.[34] They inhibit specific lymphocytes, such as SP1PR1, from entering the bloodstream by binding to their respective receptors. A reduced level of circulating lymphocytes ultimately results in decreased inflammation and helps control the immune response.[23] Ozanimod and Etrasimod, two potent S1P modulators, are administered orally and act as targeted S1P receptor agonists. Ozanimod specifically targets S1P1 and S1P5 receptors, reducing the number of activated lymphocytes from circulating to the GI tract by promoting their retention in peripheral lymph nodes.[5,23] While S1P modulators show promise for the management of IBD, it is important to consider their potential advantages and drawbacks.

Research has demonstrated the positive effects of S1P modulators on IBD disease progression, particularly in UC. Additional benefits of S1P modulators include a quick therapeutic effect, cost-effective production, oral administration, and a reduced potential for triggering an undesirable immune response.[34] Unfortunately, adverse effects have been reported, some of which may be serious. Reactions such as bradycardia, atrioventricular (AV) blocks, and basal cell carcinoma have been observed with the use of fingolimod.[35] More common side effects include anemia, headaches, and exacerbation of some GI symptoms.[5] Like other treatment modalities, the administration of S1P modulators can be beneficial for IBD patients but requires careful monitoring due to the risk of adverse effects.

Antibiotics

Dysbiosis of the gut microbiome and intra-abdominal infections are common in patients with IBD and are often linked to chronic gastrointestinal inflammation.[5] In CD, bacterial infections frequently lead to complications such as abscesses or fistulae. Antibiotics, along with

other therapies, are often prescribed with the goal of modulating the gut microbiome and resolving infections within the intestines.[5]

Although typically intended for short-term use, antibiotics have various applications in IBD.[5] In UC patients, they are prescribed in the event of acute infections and are a routine component of pre-operative care. Antibiotics are also frequently prescribed to prevent or treat post-surgical complications, such as pouchitis, and to manage complications associated with sepsis. At times, they are even useful for maintaining remission.[5] While antibiotics play a crucial role in managing infections and complications in IBD patients, their impact on the gut microbiome requires careful monitoring, and in some cases, the use of supplements may be necessary to promote healthy intestinal microflora.

Complementary or alternative approaches for symptom management

Complementary and alternative medical therapies may have positive effects on disease activity in patients with IBD. Several suggested therapies include probiotics, herbal and dietary supplementation, and fecal microbiota transplantation.

Probiotics

The use of probiotics as a treatment for IBD is one of the most popular alternative therapies.[36] When consumed or applied to the body, probiotics have perceived health benefits. Fermented foods and dairy products, such as kimchi or yogurt, contain lactic acid producing bacteria which appear to be safe and well-tolerated for human consumption. Probiotics possess the potential to decrease epithelial cell death and reduce inflammation of the intestinal mucosa. Research has demonstrated their benefit for modulating disease activity, especially in patients with UC.[37]

Probiotics may contain one or multiple strains of bacteria or yeast. The most studied probiotic is VSL#3, which contains *Streptococcus thermophilus*, 4 strains of *Lactobacilli* and 3 strains of *Bifidobacteria*. VSL#3 decreases tumor necrosis factor-α, interferon-γ, and matrix metalloproteinases 2 and 9, actions which are responsible for its anti-inflammatory nature.[36]

Research best supports the use of probiotic therapy for preventing the reoccurrence of pouchitis, a post-surgical condition characterized by inflammation of the ileal pouch-anal anastomosis in patients who have undergone a proctocolectomy or total colectomy. Gut dysbiosis and abnormal immune responses are suspected causes of pouchitis; therefore, probiotics may be beneficial in this patient demographic.[36] A double-blind, placebo-controlled trial that sought to assess the effectiveness of probiotic therapy for the prevention of acute pouchitis within the first year of pouch-anal anastomosis determined that treatment with VSL#3 reduces the risks of acute pouchitis and improves overall patient quality of life.[38] A separate randomized, placebo-controlled trial investigated the effect of daily VSL#3 administration on maintaining antibiotic-induced remission in patients who had experienced pouchitis twice or more in the previous year. Results demonstrated that remission was maintained at higher rates when patients were administered VSL#3 rather than the placebo. Of the patients who received VSL#3, 85% maintained remission for greater than 12 months in comparison to 6% of patients from the placebo group.[39] Additional research suggests that, especially in patients with mild-to-moderate UC, the use of certain probiotics may help achieve remission and reduce rates of relapse.[36]

Herbal and dietary supplements

Herbal and dietary supplements that have been investigated in the context of IBD include curcumin, cannabis, and fish oil.[36] Curcumin is the primary bioactive phytochemical of turmeric,

which belongs to the ginger family. Research suggests that it may be useful in inducing IBD remission because it possesses anti-inflammatory and antioxidative properties that act on lymphocytes and epithelial cells of the gastrointestinal tract. In a randomized clinical trial comparing the effects of curcumin to a placebo, clinical remission was achieved at week 4 in 53.8% of patients who received curcumin and 0% of patients who received placebo.[36] Additional studies have demonstrated a reduced incidence of symptom relapse in patients receiving curcumin supplementation. According to current research findings, consideration of curcumin as a complementary therapy may be especially beneficial for patients with UC.[36]

Cannabis, which is still widely controversial and federally illegal, possesses two main active cannabinoid compounds: cannabinol and tetrahydrocannabinol (THC).[36] Synthetic or plant-derived cannabinoids can activate cannabinoid receptors 1 and 2 (CB1, CB2) of the endocannabinoid system. These receptors are located within the gastrointestinal wall.[40] In animal models, CB1 decreases colitis while CB2 decreases the production of nitric oxide and reactive oxygen species in the gut. Pilot studies indicate that cannabis use in patients with IBD may positively impact quality of life, social function, and the ability to perform job-related duties. Additionally, cannabis use appears to decrease dependency on corticosteroids, a common pharmacotherapy that has been associated with adverse health outcomes. Unfortunately, there is still a lack of objective data regarding cannabis use as a complementary or alternative therapy for IBD, and its use outside of clinical trials is not advised until safety regulations have been established.[36]

Fish oil is derived from oily fish and is composed of omega-3 polyunsaturated fatty acids (n-3 PUFA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA).[36] Research has demonstrated decreased *Faecalibacterium* and increased *Bacteroidetes* in association with n-3

PUFA supplementation, which are microbial alterations that indicate positive changes within the gut microbiome. The overall benefits of n-3 PUFA in the management of IBD remain unclear; however, research is promising.[36] A randomized controlled trial that investigated the ability of EPA to decrease intestinal inflammation in UC patients at risk of relapse determined that twice-daily administration of EPA for a duration of 6 months may help induce and sustain remission in patients with UC. At 6 months, 76.7% of patients receiving EPA supplements maintained clinical remission and 63.3% experienced a 100-point reduction in fecal calprotectin, a biomarker of gastrointestinal inflammation.[41] A reduction in fecal calprotectin is, therefore, suggestive of reduced inflammation. Despite mixed evidence regarding the role of fish oil in maintaining IBD remission, it is considered safe and is widely recognized for its positive effects on risk factors of cardiovascular disease.[36]

Fecal microbiota transplantation (FMT)

FMT is a relatively new therapy in which the feces of healthy donors are transplanted into the gastrointestinal tract of patients with IBD.[37] Historically, this procedure has been used to treat *Clostridioides difficile* (*C. diff*). FMT is an advantageous therapy because the dysbiosis and dysfunction of gut microbiota in patients with IBD may be resolved by introducing a complete ecosystem of microorganisms obtained from healthy donors. Studies have shown that the composition of gut microbiota in transplant recipients largely reflects the microbiota of the donor. Therefore, the selection of a donor is important. Ultimately, higher microbial diversity of the donor is associated with higher transplant success.[37]

The ideal route of FMT administration has yet to be determined. In patients with UC, FMT administration in the lower gastrointestinal tract appears to be more effective. Alternative methods to traditional colonoscopic FMT are currently being explored. Proposed methods

include liquefaction, freezing, freeze-drying, and ingestion of oral capsules; however, these treatment approaches have not yet been validated.[37]

A meta-analysis of FMT in patients with UC determined that remission was more often achieved in patients that were treated with antibiotics prior to receiving the transplant. Clinical remission was observed in 54% of patients that received antibiotics as compared to 25% of patients that did not. Primary administration of antibiotics may help to eradicate potentially harmful microbes from the GI tract and allow beneficial bacteria to flourish. While the future of FMT as a potential therapy for IBD is promising, the long-term efficacy and safety are unknown. Future research will require additional investigation of donor selection methods, administration routes, and treatment strength.[37]

Nutritional concerns and recommendations

Patients with inflammatory bowel disease (IBD) are highly susceptible to malnutrition, which has been linked to poor clinical outcomes, increased risk of hospital admission, longer hospitalization duration, higher rates of complications, and increased mortality.[6,7] Protein-energy malnutrition (PEM), changes in body composition, and decreased micronutrient levels are hallmark signs of malnutrition.[6] Unfortunately, there is no standard definition of malnutrition, and as a result, its prevalence among IBD patients remains unclear.[7] Researchers estimate that between 20% and 85% of patients with IBD experience malnutrition, with higher rates of PEM and nutrient deficiencies occurring in Crohn's disease (CD) than in ulcerative colitis (UC).[6]

The causes of malnutrition in patients with IBD are multifaceted.[7] Contributing factors may include reduced food intake or anorexia, malabsorption, medication side effects, diarrhea, enteric nutrient loss, and increased energy requirements. [6,7] Additionally, dietary intake may be

limited due to intentional avoidance of certain foods that cause adverse reactions. In a prospective cohort study, 68% of 183 patients diagnosed with UC intentionally avoided certain foods because they felt that these items directly influenced the prevalence and severity of their symptoms.[7] Patients may also experience reduced appetite due to nausea, vomiting, diarrhea, and the side effects of certain medications.[6]

Disruptions in the intestinal mucosa of IBD patients, such as structural or functional modifications of the epithelium, lead to malabsorption of nutrients during digestion.[6,11] Due to the frequent involvement of the ileum, malabsorption occurs more often in patients with CD.[11] Chronic inflammation and some IBD-related surgeries can decrease gastrointestinal transit time, limiting the duration of contact between luminal contents and the mucosal surface. Rapid transit times ultimately lead to malabsorption, increasing the volume of stool and incidence of diarrhea. As a result, dehydration may become another significant concern, especially for patients with an ostomy. Diarrhea or ostomy output >1000–2000 mL of liquid waste per day can lead to dehydration, electrolyte imbalance, and micronutrient deficiencies.[7] Patients who have had bowel resections, postoperative complications, chronic or frequent diarrhea, or who have clinically active CD are more likely to experience malnourishment and dehydration.[9,11]

Overgrowth of bacteria within the small intestine is common in IBD patients and can negatively impact the function of the intestinal barrier. Bacterial overgrowth may trigger gastrointestinal inflammation and result in resection of the ileocecal valve.[6] It may also impair proper nutrient metabolism and stimulate the production of small metabolites that can alter osmotic homeostasis, contributing to abdominal discomfort and diarrhea.[6,11] The consequence is, once again, decreased transit time of gastrointestinal contents, which may result in malabsorption of key nutrients and lead to dehydration.[6]

Malabsorption is the primary cause of malnutrition in patients with IBD, and research indicates a higher risk of micronutrient deficiencies in this demographic than in healthy controls.[11] In a cohort of newly diagnosed IBD patients whose micronutrient levels were assessed at initial contact, at least one deficiency was observed in 78% of the population.[9] This highlights the need for nutritional screening at the time of diagnosis, as well as routine monitoring throughout the duration of care.[42] Evidence from observational studies suggests that as many as 50% of patients with IBD may be deficient in iron, vitamin D, vitamins B6 and B_{12}, folic acid, selenium, and zinc.[9]

Anemia is the nutritional complication that is most often observed in patients with IBD, and it is more common in hospitalized patients than in outpatients.[11] The prevalence of iron deficiency anemia in the IBD population is estimated to range from 36% to 90%. Factors that increase the risk for iron deficiency anemia include inadequate dietary intake, gastrointestinal bleeding, impaired iron metabolism, and reduced iron uptake via the duodeno-jejunal mucosa.[6] Routine monitoring of iron levels should be conducted to identify and address insufficiencies; however, inflammatory status should also be considered, as iron levels are known to fluctuate with inflammation.[11]

Vitamin D deficiency is also common, affecting up to 40% of patients with UC and 70% of patients with CD.[6] Corticosteroids are known to contribute to the depletion of micronutrients, especially vitamin D.[11] They may also impair the absorption of phosphorus, zinc, and calcium, which contributes to the risk of osteoporosis. Routine nutritional screening and supplementation with both vitamin D and calcium are recommended, as reduced absorptive surfaces in the intestine, malabsorption of fatty acids in the lumen, and inadequate dietary intake can lead to deficiencies. Maintaining adequate levels of vitamin D and calcium is essential for preserving

bone mineral density and supporting the optimal function of the innate and adaptive immune pathways.[6]

Deficiencies of vitamin B_{12}, folate, magnesium, and zinc have been observed in IBD patients. Research suggests that deficiencies of each are more strongly associated with CD than UC.[6,11] Both vitamin B_{12} and magnesium are absorbed in the small intestine. Therefore, ileal involvement during active disease or extensive bowel resection may impair the absorption and metabolism of vitamin B_{12} and magnesium. Folate deficiency may occur due to inadequate intake or malabsorption, but it can also be caused by certain medications.[6] Sulfasalazine and methotrexate, medications frequently used to treat mild-to-moderate IBD, have been shown to restrict folate metabolism, increasing the risk of anemia, cardiovascular disease, and colorectal cancer.[6] During the acute phase, serum zinc concentrations are reduced due to a decrease in albumin, a carrier protein. Additionally, chronic diarrhea may deplete zinc levels and lead to deficiency.[11] Monitoring and supplementation of each micronutrient are recommended to prevent the development of additional health complications.

In addition to micronutrient deficiencies, changes in the ratio of fat mass versus fat-free mass can influence disease progression, the effectiveness of pharmacological treatment, surgical outcomes, and the overall quality of life for patients with IBD.[6] A gradual reduction of lean mass and an increase in obesity is often observed in this population.[42] These changes may be linked to the side effects of certain medications, increased rates of protein turnover during active disease states, malabsorption, and poor intake. Corticosteroids, especially, have been associated with an increased net loss of protein.[42]

A systematic review by Ryan et al[43] found that up to 60% of patients with IBD experience a decrease in muscle mass. This is often indicative of sarcopenia, a condition

characterized by the loss of lean muscle mass and physical strength.[6] Sarcopenia is closely linked to chronic inflammation and malnutrition. In IBD patients, its presence increases the likelihood of requiring surgery, negatively affects postoperative recovery, and increases the risk of mortality during or shortly after surgery.[43] Studies suggest that a significant percentage of IBD patients who have a normal body mass index (BMI) meet the criteria for sarcopenia. A normal BMI can mask malnutrition, leading to underdiagnosis. Nutritional screening is, therefore, important for all patients with IBD regardless of physical presentation.[6]

Current research suggests that the general energy requirements of IBD patients are comparable to those of healthy individuals.[11] During active disease flare-ups, which are characterized by acute inflammation and hypermetabolism, energy and protein requirements may increase. The recommended daily allowance (RDA) for protein is 0.8 g/kg per day; however, protein needs may increase to 1.2–1.5 g/kg per day during active IBD.[11] This is due to an increased rate of protein catabolism during inflammatory states.[7] In conclusion, while the general energy needs of IBD patients align with those of healthy individuals, the increased protein requirements during active disease flare-ups highlight the importance of adjusting nutritional intake to support heightened metabolic demands.

To date, there are no standardized dietary recommendations for patients with IBD.[44] Dietary guidance should be personalized and tailored to the patient's individual needs. Key considerations should include the diagnosis, severity of disease activity, affected regions of the gastrointestinal tract, patient preferences and experiences, and current nutritional status. When medical nutrition is indicated, oral nutritional supplements (ONS) are the preferred first-line intervention.[42] Appropriate dietary interventions can help reduce disease symptoms, minimize complications, and enhance overall quality of life for patients with IBD.[44]

Barriers to meeting nutritional recommendations

Maintaining adequate nutrition can be challenging for patients with inflammatory bowel disease (IBD). In addition to physiological factors that can influence nutritional status, such as malabsorption or decreased appetite, outside determinants can affect dietary health. Addressing these external barriers may help patients to meet nutritional recommendations and improve overall health.

The knowledge, attitudes, and beliefs of medical providers

A lack of sufficient provider knowledge is a notable barrier to meeting nutrition recommendations for patients with IBD.[45] Although the urgent need to incorporate nutritional training into medical school curricula was identified by the American Council on Foods and Nutrition in 1963, it remains essentially absent from both American and European medical education.[12] The National Academy of Sciences encourages a minimum of 25 hours of nutrition education; however, a survey conducted by the Nutrition in Medicine team found that less than one-fourth of U.S. medical schools meet this guideline.[12,46]

Researchers hypothesize that the perspective of medical providers regarding the importance of nutrition in healthcare is largely influenced by their school's approach to nutrition training.[12] A study conducted by Tinsley et al[45] found that only 48.9% of gastroenterologists felt that nutrition was "very important" in the management of IBD. Medications were held in higher regard than dietary modifications, and nutrition was given higher value as adjunct therapy than as a first-line intervention.[45] Some gastroenterologists admitted to having minimal foundational knowledge of nutrition relative to IBD, and many felt that the guidance they had been provided regarding nutritional concerns and counseling was insufficient. Similarly, fewer than 1 in 5 nurses and nurse practitioners self-reported good knowledge of IBD-related nutrition concepts.[45]

Unfortunately, this may be because nutrition remains largely unrecognized as a medical discipline.[12]

Tinsley et al[45] determined that routine malnutrition screening among patients with IBD was infrequent. Patients categorized as high-risk, such as those who had undergone a bowel resection, received nutritional screening.[45] Providers reported a lack of familiarity with nutrition screening and assessment methods, and addressing nutrition concerns was not a routine point of care.[45] Although these findings emphasize a fundamental need for the involvement of nutrition professionals in comprehensive patient care, referral rates remain low.[45,46]

Research suggests that nutrition plays a pivotal role in the long-term outcomes and overall health of patients.[12] While the definitive reasons for infrequent nutrition screening are unknown, underestimation of risk, associated costs, time limitations, and unfamiliarity with diagnostic criteria are all contributing factors. Additionally, providers require specialized nutrition training that is adapted to their certification level. Studies indicate that patients ultimately benefit from longer appointments, affordable nutrition services, and a multidisciplinary care team that includes a registered dietitian.[45]

Standardizing a process for identifying malnutrition

Although there is a discernible risk for malnutrition in patients with IBD, it is often overlooked due to a lack of formal diagnostic criteria. Therefore, the absence of standardized diagnostic procedures leads to inconsistencies in clinical practice, posing a barrier to meeting IBD nutrition guidelines.[47,48] Nutritional outcomes for IBD patients could be significantly improved by establishing routine assessment methods and incorporating these procedures into patient care.[47]

Over the last decade, multiple organizations, including the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society of Clinical Nutrition and Metabolism (ESPEN), have released consensus statements advocating for the use of a standardized set of diagnostic characteristics to identify and document adult malnutrition.[49] In 2016, the Global Leadership Initiative on Malnutrition (GLIM) assembled and formulated a consensus report founded on the same principle.[47]

GLIM determined that the first step in performing a nutritional evaluation should be an assessment of malnutrition risk using any validated screening tool, such as the Malnutrition Universal Screening Tool (MUST) or the Mini Nutritional Assessment-Short Form (MNA-SF).[47] Following screening, patients should be evaluated for phenotypic and etiological criteria, such as reduced muscle mass or disease burden. The committee advised that a malnutrition diagnosis should require the patient to meet at least one criterion from each category. If the patient meets these qualifications, the severity of the final diagnosis should ultimately be determined based on the phenotypic criteria.[47]

The purpose of the proposed approach is to standardize malnutrition assessments, ensuring that all at-risk patients are consistently evaluated using the same guidelines.[47] Preliminary nutrition screening, based on the proposed practices, should be implemented in clinical settings upon the initial diagnosis of IBD and repeated annually or during periods of active disease. Patients diagnosed with malnutrition should then be referred to nutrition professionals to ensure they receive appropriate care. These evaluation methods could increase the opportunity for early malnutrition diagnosis and intervention.

Food quality and insecurity

Extensive healthcare costs are associated with inflammatory bowel disease (IBD), including emergency care, hospitalizations, and the prices of medications. These unanticipated expenses can exacerbate an already strenuous economic situation.[50] Since the COVID-19 pandemic, inflation has increased, and the price of food has skyrocketed significantly, escalating the risk of food insecurity.[51] Food insecurity is defined as "limited or uncertain access to nutritionally adequate, safe, and acceptable foods."[50] While research is limited in the IBD population, studies from a generalized demographic suggest that higher food prices result in reduced consumption of high-quality, nutrient-dense foods because processed foods with low nutritional value are more affordable.[51]

According to Nguyen et al,[50] patients with IBD are 69% more susceptible to food insecurity than patients without IBD. In 2015, the National Health Interview Survey determined that 1 in every 7 IBD patients were actively experiencing food insecurity. Financial hardships related to personal or medical expenses were reported by 88% of these individuals.[50] Unfortunately, the 2015 data do not reflect the effect of the COVID-19 pandemic on the economy and may not adequately represent the current percentage of IBD patients impacted by food insecurity.[51]

In the presence of food insecurity, nutritional habits and patterns often change.[51] Studies have found that the greatest volume of ultra-processed foods, which contain large quantities of sweeteners and additives, is consumed by IBD patients who have the highest risk for food insecurity. The consumption of ultra-processed foods raises rates of all-cause mortality and has been linked to the development of gastrointestinal disease, including IBD. This may be due to the ingestion of food additives, such as thickening agents and artificial food dyes, which disrupt

the homeostasis of the gut microbiome, alter the integrity of the intestinal mucosa, and suppress synthesis of short-chain fatty acids.[51] Poor-quality foods can exacerbate intestinal inflammation, worsening health disparities.

For patients with IBD, the presence of food insecurity increases the risk for developing malnutrition; however, federal food assistance programs were only utilized by a fraction of patients who had been classified as high-risk.[51] The implementation of routine screening in clinical practice could help identify the risk of food insecurity in this population. Once identified, federal and community resources should be made available for IBD patients in need of assistance. Additionally, patients should be educated about healthy and affordable substitutions for traditional nutrient-rich foods, such as frozen fruits and vegetables, oats, and canned fish.[51] Incorporating these strategies into clinical care could positively affect the nutritional status of IBD patients and help reduce the risk of malnutrition associated with food insecurity.

Dietary interventions for IBD

Dietary intake plays a crucial role in both the development and management of intestinal inflammation, making it a key consideration for individuals with Inflammatory Bowel Disease (IBD).[5] Although the therapeutic benefits of dietary interventions have been explored, no single ideal diet has been identified for all IBD patients.[5] Given the complexity and variability of IBD, a personalized approach to nutrition therapy is essential to address dietary triggers, nutritional deficiencies, and overall disease management.

Enteral nutrition

Enteral nutrition (EN) is a formula-based diet that can impact intestinal barrier function, elicit an immune response, and positively influence the gut microbiome.[5] Formula can be administered exclusively or partially; however, in the context of IBD, exclusive enteral nutrition

(EEN) is the most widely researched and replicated diet therapy.[5,52] EEN requires the complete avoidance of solid foods for a duration of 6–8 weeks, relying solely on the intake of liquid formulas to meet 100% of essential nutritional requirements. It is a low-risk, non-invasive therapy that is preferred over total parental nutrition (TPN), as its route of administration helps to maintain the integrity of the gastrointestinal tract.[53] The primary objectives of EEN are to induce and sustain remission in patients with active IBD.[52]

EEN is recommended as the primary treatment option to induce remission in adolescents with active Crohn's disease (CD). A meta-analysis comparing the efficacy of corticosteroids and EEN in pediatric CD patients determined that both interventions are effective in inducing clinical remission.[52] While EEN is associated with positive outcomes in adolescents, a 2018 Cochrane review concluded that corticosteroids are more effective than EEN in adult populations.[53] This discrepancy may be attributed to decreased adherence often due to poor palatability, lack of guidance or support, and social pressures.[52,53]

In addition to EEN, EN may be administered as partial enteral nutrition (PEN).[53] While EEN relies solely on formula to meet nutrition needs, only 35–50% of daily food intake is substituted with formula in PEN. The formulas used in both EEN and PEN are classified based on their nitrogen source and include three types: elemental (amino acid-based), semi-elemental (oligopeptide-based), and polymeric (whole protein-based). No significant differences in efficacy have been observed between the different types of formulas. Beyond its therapeutic benefits, EN can provide essential nutritional support to IBD patients who may be at risk of malnutrition, especially sarcopenia and micronutrient deficiencies.[53] Despite its potential benefits, EN remains a controversial diet due to its formula component.[5] Further research is needed to optimize its use in clinical practice.

Crohn's disease exclusion diet

The Crohn's disease exclusion diet (CDED) is a dietary therapy that prioritizes whole foods, including fruits, vegetables, meats, and both simple and complex carbohydrates. It eliminates foods that interfere with the intestinal mucosa or disrupt the gut microbiome, such as certain animal fats and food additives.[52] The CDED was created to be used in combination with PEN, limiting or excluding dietary components that have been linked to inflammation, such as gluten, dairy, processed meats, and some canned or packaged foods.[53] Research has shown that, regardless of its use in conjunction with PEN, CDED effectively improves biomarkers of inflammation and induces remission in both pediatric and adult patients with CD. When combined with PEN, CDED was better tolerated than EEN and was more successful at sustaining remission.[54] Overall, CDED offers a well-tolerated therapeutic approach that, when used with or without PEN, supports remission and reduces inflammation in patients with Crohn's disease.

Specific carbohydrate diet

Originally developed for pediatric patients with celiac disease, the specific carbohydrate diet (SCD) has been in use since the 1920's.[53] This therapeutic elimination diet has become a popular choice for patients with IBD.[44] The SCD focuses on eliminating complex carbohydrates and disaccharides from the diet, as these components are not easily digestible and may contribute to inflammation.[44] The diet excludes dairy products, except aged cheeses and lacto-fermented foods, as well as complex carbohydrates such as wheat, quinoa, and rice, and all sugars, except honey.[44,53] The SCD, however, permits the consumption of monosaccharides, commonly found in fruits and vegetables, as well as solid proteins like poultry or beef, and fats such as butter or coconut oil.[52]

Disaccharides and polysaccharides are difficult to digest, leading to the overgrowth of certain bacteria within the gut microbiome.[52] This dysbiosis, in turn, weakens the integrity of the intestinal barrier, contributing to inflammation[44]. Unlike disaccharides and polysaccharides, monosaccharides are easily absorbed in the small intestine and do not leave behind undigested particles that could lead to bacterial overgrowth.[52] By restricting or eliminating complex carbohydrates, the SCD helps control dysbiosis, ultimately reducing the inflammatory response and improving the symptoms of IBD.[44]

Studies suggest that adhering to the SCD may be beneficial for children with CD.[44] In pediatric patients who followed the SCD for at least 12 weeks, capsule endoscopy revealed improvements in intestinal mucosa and a reduction in pro-inflammatory microbiota, such as *Bacteroides* and *Parabacteroides*. Additionally, improvements in inflammatory biomarkers—including CRP, albumin, hematocrit, and fecal calprotectin—were observed.[44] However, despite its anti-inflammatory potential, concerns have been raised regarding the nutritional adequacy of the SCD. A prospective pediatric study found that 100% of the study population had inadequate vitamin D intake, while 75% had insufficient calcium intake.[52] Given the potential risk of deficiencies, supplementation of vitamin D and calcium should be considered to prevent the development of malnutrition. Additionally, routine monitoring of nutritional status is essential to ensure adequate intake of key nutrients and prevent deficiencies while following the SCD.

IBD anti-inflammatory diet

The IBD anti-inflammatory diet (IBD-AID) is derived from the specific carbohydrate diet (SCD) and designed to reduce intestinal inflammation and regulate the gut microbiome.[52,53] Certain carbohydrates, including specific sugars, starches, and grains, facilitate the growth of harmful bacteria in the gut.[52] Like the SCD, the IBD-AID restricts pro-inflammatory

carbohydrates while encouraging regular consumption of anti-inflammatory prebiotics and probiotics.[44] The IBD-AID is based on five fundamental guidelines: (1) restricting consumption of difficult-to-digest carbohydrates (2) introducing prebiotic and probiotic foods (3) decreasing overall intake of saturated fats (4) identifying food intolerances or nutrient deficiencies; and (5) modifying food texture when indicated.[53]

In the IBD-AID, food textures are modified based on the severity of IBD symptoms. Patients experiencing active flares often require softened or pureed foods, as fibrous foods can create friction while passing through an already inflamed gastrointestinal tract, potentially worsening symptoms and increasing swelling.[53] The use of probiotics can help reduce inflammation by positively affecting the diversity of the gut microbiome, inhibiting the growth of harmful bacteria, and enhancing the function of the epithelial and mucosal barriers. Despite these benefits, the American Gastroenterological Association has not established formal guidelines recommending probiotic use for all IBD patients. Nevertheless, prebiotics and probiotics are prevalent components of the IBD-AID, and studies have demonstrated the positive effects of this diet therapy on managing IBD symptoms.[44]

In patients with IBD, bacteria that produce short-chain fatty acids are often depleted. A study conducted by Olednzki et al[55] found that the IBD-AID stimulates growth of beneficial bacteria. Increased levels of anti-inflammatory microbes, such as *Faecalibacterium prausnitzii*, *Eubacterium eligens*, and *Roseburia hominis*, have been observed.[44] Additionally, a retrospective case study showed that 100% of patients who followed the IBD-AID for a minimum of 4 weeks experienced a notable decrease in disease symptoms and were able to reduce the dosage of their current pharmacotherapy.[52] Although the benefits are tangible, a notable concern of the IBD-AID is the potential for nutrient deficiencies. Like the SCD, the IBD-AID eliminates some food

groups that are rich in iron, vitamin D, calcium, and B vitamins, which increases the potential for inadequate intake.[44] Despite this challenge, the positive effects of the IBD-AID on managing IBD symptoms highlight its potential as an effective diet therapy.

Mediterranean diet

The Mediterranean diet (MD) is a preventative model that reduces the risk for a variety of health conditions, including cardiovascular disease, neurodegenerative diseases, cancer, hypertension, and type 2 diabetes. It is associated with reduced rates of all-cause mortality.[44] The MD promotes high intake of vegetables, fruits, unsaturated fatty acids —especially from olive oil and nuts—legumes, dairy products, and fish. It also recommends limiting the consumption of red meat, poultry, and sweets.[44]

The MD is rich in vitamins A and C, β-carotene, various minerals, flavonoids, and fiber, all of which are known for their antioxidant and anti-inflammatory properties.[44] Fiber promotes a diverse gut microbiome and the production of short-chain fatty acids, supporting healthy gastrointestinal function by encouraging fermentation in the large intestine and shortening the transit time of digestive contents. This not only helps improve IBD symptoms, such as diarrhea and constipation, but also suppresses the inflammatory response and promotes mucosal healing. Adherence to the MD can, therefore, restore the balance of gut microbiota and reduce intestinal inflammation.[44]

Many studies have demonstrated the positive effects of the MD on patients with IBD, including a reduction in inflammatory biomarkers and the restoration of a healthy gut microbiome.[44] [53]Greater adherence to the MD is linked to higher rates of remission, improved health and well-being, and the resolution of IBD symptoms.[53] Chicco et al[56] observed significant improvements in various health parameters, such as body mass index (BMI), disease activity,

CRP levels, and overall quality of life in 142 patients with CD and ulcerative colitis (UC). Therefore, when combined with an active and health-conscious lifestyle, the MD offers a comprehensive approach to enhancing overall wellness.[44]

Low FODMAP diet

The low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet restricts the intake of mono-, di-, and oligosaccharides, as well as polyols.[44] Many foods that belong to these categories are difficult to digest and are highly fermentable.[53] Due to their poor digestibility, these products pass into the intestine largely intact. The osmotic nature of these foods draws water into the small intestines, resulting in abdominal distension and hypersensitivity.[44,53] FODMAPs may also be fermented by bacteria in the large intestine, which can cause gas, bloating, and discomfort.[44]

Many IBD patients self-eliminate foods rich in FODMAPS, particularly during periods of high disease activity.[44] During active disease, a low FODMAP diet can help improve symptoms such as abdominal pain, bloating, and diarrhea, which ultimately enhances overall quality of life. This diet therapy may also be beneficial in treating small intestinal bacterial overgrowth (SIBO), a common condition in IBD, characterized by an excessive bacterial presence in the small intestine that leads to dysbiosis of the gut microbiome. While a low FODMAP diet can provide symptom relief, it is important to recognize the potential risks of nutrient deficiencies that can arise due to its restrictive nature.[44]

Many of the foods eliminated while following the low FODMAP diet are key sources of calcium, iron, zinc, folic acid, vitamin D, and antioxidant-rich compounds.[44] Additionally, adhering to a low FODMAP diet reduces the intake of natural prebiotics, such as fructo-oligosaccharides and fiber. These dietary restrictions not only increase the risk of nutrient

deficiencies but also negatively impact the gut microbiome as well as the production of short-chain fatty acids.[44] At present, there is a lack of research on the long-term effects of the low FODMAP diet in IBD patients, which is a notable concern given that the diet is designed for short-term use.[44] Therefore, further research is essential to fully understand the potential long-term consequences of this dietary intervention.

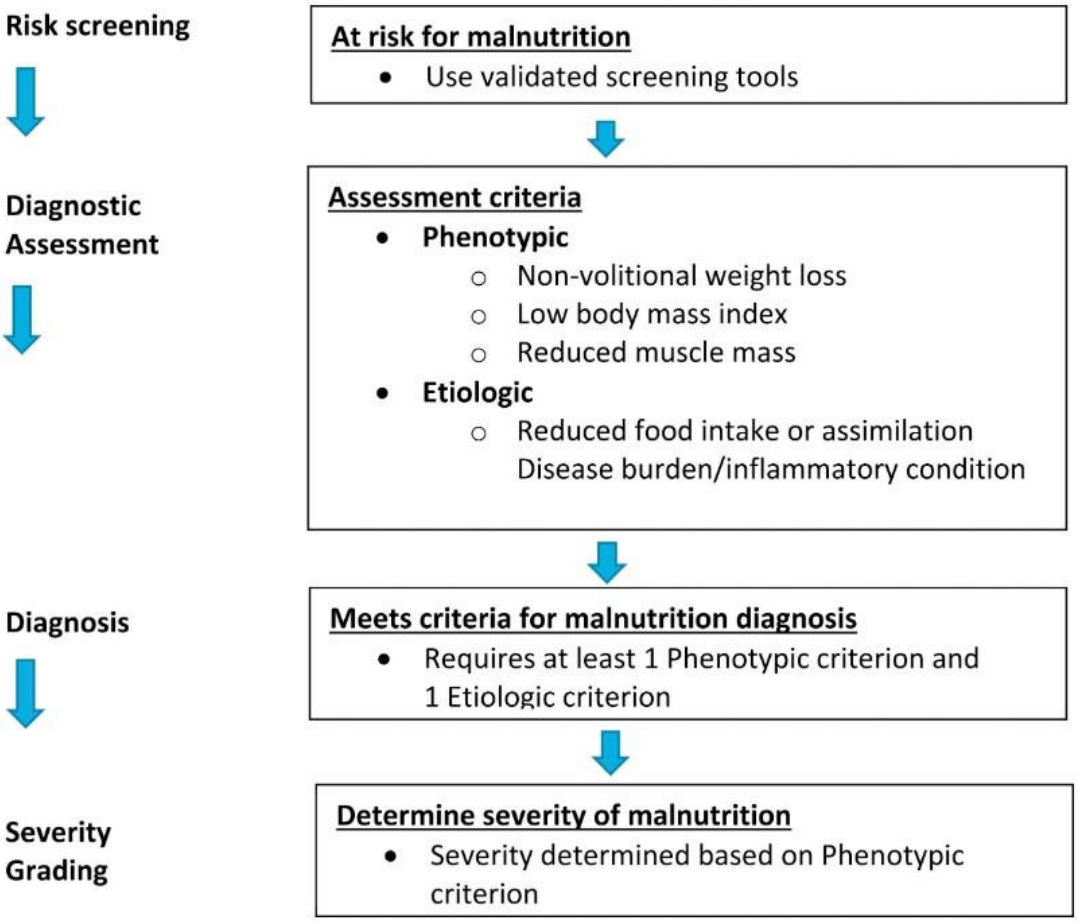
Identifying malnutrition

According to the Global Leadership Initiative on Malnutrition (GLIM), malnutrition is defined as "a subacute or chronic state of nutrition, in which a combination of varying degrees of undernutrition or overnutrition and inflammatory activity have led to changes in body composition and diminished function."[57(p993)] While this definition encompasses both undernutrition and overnutrition due to excess calorie intake, malnutrition is more commonly associated with undernutrition.[49] It can arise from both primary and secondary factors. Primary causes of malnutrition include poverty and food scarcity, whereas secondary causes involve conditions such as disease-related anorexia, metabolic stress, increased protein catabolism, and impaired immune or organ function.[49,58] Understanding the causes of malnutrition is essential for developing effective prevention and intervention strategies.

Research suggests that inflammation and body composition influence outcomes related to malnutrition. Consequently, the definition and diagnostic criteria have evolved over time and continue to change.[57] These criteria primarily aim to identify protein energy-malnutrition, specifically undernutrition, and generally do not account for micronutrient deficiencies.[57] Currently, there is no universal method for diagnosing malnutrition; however, GLIM has established a set of criteria for diagnosing adult malnutrition based on global variations in nutrition screening and assessment methods. These criteria are not meant to replace a

comprehensive nutritional assessment but rather to help identify the prevalence of protein-energy malnutrition.[49,57] **Figure 2.2** outlines the GLIM process for identifying malnutrition.

Figure 2.2 GLIM diagnostic scheme for screening, assessment, diagnosing, and grading



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Risk assessment

Evaluation of nutritional status should begin with a validated risk screening tool, such as the Mini Nutritional Assessment-Short Form (MNA-SF), the Malnutrition Universal Screening Tool (MUST), or the Subjective Global Assessment (SGA).[47] The American Society for

Parenteral and Enteral Nutrition (ASPEN) recommends nutrition screening for all at-risk adult and pediatric populations.[59] At-risk adults are defined as those with involuntary weight loss of ≥10% within six months or ≥5% within one-month, involuntary weight loss or weight gain within six months, a BMI <18.5 kg/m² or >25 kg/m², chronic disease, increased metabolic demand, altered diets or diet schedules, or inadequate nutritional intake. Criteria for at-risk neonates include preterm birth, low birth weight, intrauterine growth restrictions, and illnesses or congenital conditions that may affect feeding. Children may be considered at risk for malnutrition if they fall below the 10th percentile or above the 95th percentile on growth charts, have a BMI <5th percentile or >85th percentile, experience increased metabolic demands, are unable to tolerate oral feedings, have documented nutrient inadequacies or intolerances, show inadequate weight gain, or experience a substantial decrease in growth percentile.[59] Despite generalized guidelines for assessment and diagnosis, provider judgment and proactive evaluation may still be required for an accurate and timely diagnosis of malnutrition.

Assessment criteria

Once a patient is identified as at risk, they should be evaluated using five key assessment criteria: non-volitional weight loss, low body mass index (BMI), reduced muscle mass, reduced food intake or assimilation, and disease burden or inflammation.[47] These criteria are categorized as either phenotypic or etiologic.

Table 2.1 Phenotypic and etiologic criteria for the diagnosis of malnutrition

Phenotypic Criteria[g]			Etiologic Criteria[g]	
Weight loss (%)	Low body mass index (kg/m^2)	Reduced muscle mass[a]	Reduced food intake or assimilation[b,c]	Inflammation[d–f]
>5% within past 6 months, or >10% beyond 6 months	<20 if < 70 years, or <22 if >70 years Asia: <18.5 if < 70 years, or <20 if >70 years	Reduced by validated body composition measuring techniques[a]	≤50% of ER > 1 week, or any reduction for >2 weeks, or any chronic GI condition that adversely impacts food assimilation or absorption[b,c]	Acute disease/injury[d,f] or chronic disease-related[e,f]

GI = gastro-intestinal, ER = energy requirements.

a For example fat free mass index (FFMI, kg/m^2)) by dual-energy absorptiometry (DXA) or corresponding standards using other body composition methods like bioelectrical impedance analysis (BIA), CT or MRI. When not available or by regional preference, physical examination or standard anthropometric measures like mid-arm muscle or calf circumferences may be used. Thresholds for reduced muscle mass need to be adapted to race (Asia). Functional assessments like hand-grip strength may be considered as a supportive measure.

b Consider gastrointestinal symptoms as supportive indicators that can impair food intake or absorption e.g. dysphagia, nausea, vomiting, diarrhea, constipation or abdominal pain. Use clinical judgment to discern severity based upon the degree to which intake or absorption are impaired. Symptom intensity, frequency, and duration should be noted.

c Reduced assimilation of food/nutrients is associated with malabsorptive disorders like short bowel syndrome, pancreatic insufficiency and after bariatric surgery. It is also associated with disorders like esophageal strictures, gastroparesis, and intestinal pseudo-obstruction. Malabsorption is a clinical diagnosis manifest as chronic diarrhea or steatorrhea. Malabsorption in those with ostomies is evidenced by elevated volumes of output. Use clinical judgment or additional evaluation to discern severity based upon frequency, duration, and quantitation of fecal fat and/or volume of losses.

d Acute disease/injury-related. Severe inflammation is likely to be associated with major infection, burns, trauma or closed head injury. Other acute disease/injury-related conditions are likely to be associated with mild to moderate inflammation.

e Chronic disease-related. Severe inflammation is not generally associated with chronic disease conditions. Chronic or recurrent mild to moderate inflammation is likely to be associated with malignant disease, chronic obstructive pulmonary disease, congestive heart failure, chronic renal disease or any disease with chronic or recurrent Inflammation. Note that transient inflammation of a mild degree does not meet the threshold for this etiologic criterion.

f C-reactive protein may be used as a supportive laboratory measure.

g Requires at least 1 phenotypic criterion and 1 etiologic criterion for diagnosis of malnutrition.

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Phenotypic criteria

Phenotypic criteria include non-volitional weight loss, low BMI, and reduced muscle mass.[47] Diagnosis of non-volitional weight loss requires repeated weight measurements over time to track changes. Low BMI is another commonly used diagnostic criterion, particularly in many regions worldwide. However, in North America, where overweight and obesity are more prevalent, low BMI is less applicable. In such cases, substantial weight loss must occur before

BMI is considered a relevant diagnostic marker. Reduced muscle mass, the final phenotypic criterion, has no universal standard for measurement. Recommended assessment methods include dual-energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). Additionally, grip strength and muscle function assessments can serve as supportive measures.[47]

Etiologic criteria

Etiologic criteria include reduced food intake and disease burden or inflammation.[47] Reduced food intake can have many causes, including medication side effects, depression, malabsorptive disorders, GI symptoms, etc. Reduced food intake can have various causes, including medication side effects, depression, malabsorptive disorders, and gastrointestinal (GI) symptoms. Disease burden or inflammation is associated with conditions such as infection, trauma, head injury, cancer, and chronic disease. When assessing etiologic criteria, clinical judgment may be required to recognize less obvious systemic inflammation. Biomarkers of inflammation, such as C-reactive protein (CRP), albumin, and prealbumin, may be necessary to confirm inflammatory status.[47]

Diagnosing malnutrition and determining the severity of the diagnosis

A combination of one phenotypic criterion and one etiologic criterion is required for the diagnosis of malnutrition.[47] The phenotypic criterion allows for the assessment of severity, while the etiologic criterion guides intervention. The severity of malnutrition is classified as Stage 1 (moderate) and Stage 2 (severe). Stage 1 requires the presence of at least one phenotypic criterion that meets this grade. Possible criteria include weight loss of 5–10% within the past six months or 10–20% beyond six months, a BMI of <20 for individuals under 70 years old or <22 for those over 70, or mild to moderate reductions in muscle mass. Phenotypic criteria for Stage 2

include greater than 10% weight loss within the past six months or more than 20% beyond six months, a BMI of <18.5 for individuals under 70 years old or <20 for those over 70, or severe reductions in muscle mass. In terms of etiology, diagnosis classifications include malnutrition related to chronic disease with inflammation, malnutrition related to chronic disease with minimal or no perceived inflammation, malnutrition related to acute disease or injury with severe inflammation, and malnutrition of unspecified etiology.[47]

Assessing and diagnosing malnutrition can be challenging, as the characteristics used for diagnosis may also appear in populations for whom malnutrition is not applicable.[49] For instance, patients with spinal cord injuries may experience weight loss due to physical impairment, despite adequate nutrient and energy intake. Furthermore, patients may be unable to provide accurate responses to nutrition-screening questions, or relevant medical histories may be unavailable.[49] A similar challenge arises in patients with inflammatory bowel disease, where malnutrition symptoms, such as weight loss and reduced nutrient absorption, may overlap with disease-related factors, complicating the accurate diagnosis and treatment of malnutrition.

Dysbiosis and IBD

Although generally stable throughout life, the composition of gut microbiota can be influenced by environmental changes, medications, diet, lifestyle, and pathogens.[60] While it is unclear whether gut dysbiosis is a cause or consequence of inflammatory bowel disease (IBD), shifts in microbiota suggest that composition of bacteria within the gut microbiome may play a key role in disease development.[60,61] Commensal organisms, known as pathobionts, contribute to various gastrointestinal functions, including homeostasis, immune regulation, mucosal integrity, and nutrient metabolism. Under certain conditions, pathobionts can transition from a beneficial

to a harmful state, exhibiting pathogenic properties. Consequently, the suppression of key commensal bacteria may disrupt microbial balance, reduce metabolic activity, and contribute to the development of IBD.[62]

In patients with IBD, gastrointestinal inflammation leads to increased levels of free radicals and oxygen.[62] As a result, the gut microbiota may become more selective for oxygen-tolerant bacteria that thrive in proinflammatory environments. These microorganisms can further contribute to inflammation, preventing the recolonization of commensal bacteria and perpetuating the inflammatory cycle.[62] Studies indicate that IBD activity is the most prevalent in regions of the bowel where bacterial populations are typically the densest and most diverse. Microbial samples from IBD patients consistently show reduced diversity and lower levels of anti-inflammatory bacteria compared to those from healthy individuals.[63] One such bacterium, *Faecalibacterium prausnitzii*, plays a crucial role in gut health by producing short-chain fatty acids that protect the epithelium from inflammation. However, its levels are significantly reduced in patients with active IBD, leading to disrupted intestinal homeostasis and impaired metabolic function.[62] This imbalance in gut microbiota composition further exacerbates inflammation and disrupts key protective mechanisms.

Colonization by pathobionts does not typically cause disease in healthy hosts, making them difficult to detect.[62] One such pathobiont is *Bilophila wadsworthia*, a type of Proteobacteria. While *B. wadsworthia* is commensal in humans without IBD, higher levels of this bacterium have been associated with increased IBD disease activity. Studies have shown that in genetically susceptible mice fed a high-saturated-fat diet, *B. wadsworthia* proliferates and causes colitis.[62] Similarly, *Escherichia coli*, another type of Proteobacteria, has been found in higher quantities in patients with IBD. Translocation of five *E. coli* subtypes has been linked to

various illnesses, including pneumonia, meningitis, and gastrointestinal disorders.[63] This suggests that specific pathobionts, such as *B. wadsworthia* and *E. coli*, may influence the progression and severity of IBD.

Research suggests that the functional activity of microorganisms does not always directly correlate with their potential.[64] Under normal conditions, *Bacteroides fragilis* synthesizes sphingolipids that help reduce natural killer T (iNKT) cell activation, and reduced iNKT activity is typically protective against colitis. However, a longitudinal study of UC pouch patients revealed that certain strains of *B. fragilis* may trigger disease onset. These strains, usually a low-quantity commensal microbiota, proliferated prior to and during episodes of pouchitis and have been identified in more than 60% of microbial samples from patients with IBD.[60,62] While the quantity of *B. fragilis* is typically low in healthy individuals, its increased prevalence in IBD patients suggests that it may function as a pathobiont. *B. fragilis* can adapt and thrive in inflammatory environments, raising the question of whether its impact stems primarily from its role in IBD pathogenesis or from its effects on the commensal microbiota.[62]

In conclusion, the composition of the gut microbiota may influence the development and progression of inflammatory bowel disease (IBD). Shifts in microbial balance, particularly the overgrowth of certain pathobionts, can exacerbate inflammation and contribute to disease activity. While commensal organisms like *B. fragilis* and *B. wadsworthia* are typically benign, their increased prevalence in IBD patients suggests that they may act as pathobionts under certain conditions. Ultimately, understanding the complex interactions between the gut microbiota and IBD is essential for developing more targeted therapeutic strategies aimed at restoring microbial balance and improving patient outcomes.

The gut microbiome and nutrient metabolism

The relationship between micronutrients and the microbiome is reciprocal. While bacteria in the gut influence the bioavailability, absorption, and synthesis of certain micronutrients, the intake and supplementation of these micronutrients also affect the composition and function of the microbiome. Intestinal microbes play a critical role in the metabolism and production of essential nutrients, such as iron and vitamin D, which can affect the overall health of the host.[65] Understanding the relationship between microbes and nutrient metabolism could enhance nutritional interventions and pave the way for developing new strategies to correct deficiencies.

At the gastrointestinal level, the biodiversity of the microbiome influences the rate of mineral absorption. Microbes produce a variety of enzymes that help cleave minerals from digestive products.[66] For example, phytases, bacterial enzymes that catalyze the hydrolysis of phytic acid in plant-based foods, aid in the release of bioavailable minerals such as calcium and iron.[65,66] Iron uptake is also influenced by short-chain fatty acid (SCFA) microbial metabolites and can be inhibited by products from *Lactobacillus reuteri*.[66] Furthermore, studies have found that siderophore enterobactin, molecules secreted by bacteria like *Escherichia coli*, promote mitochondrial uptake of iron, thereby increasing overall host absorption. This discovery highlights a previously unknown benefit of commensal bacteria in regulating iron levels.[65]

Zinc is another nutrient influenced by the micronutrient–microbiome axis.[65] The in vitro digestion model suggests that zinc may become less bioavailable once it dissolves in the colon. Clinical trials examining the treatment of zinc deficiency through probiotic supplementation have produced conflicting results.[66] In one pediatric trial, the supplementation of *Lactobacillus casei* and *Limosilactobacillus reuteri* did not affect the bioavailability of zinc. However, in a second trial, simultaneous administration of probiotics and zinc supplements effectively

increased blood zinc concentrations. The results from a third clinical trial indicate that combining prebiotic fructooligosaccharide with a supplement containing *Lactiplantibacillus plantarum, Lactobacillus acidophilus, Bifidobacterium infantis*, and *Bifidobacterium lactis* increased levels of zinc.[66] Ultimately, these findings emphasize the complexity of the relationship between zinc and the gut microbiome and support the need for further research.

The relationship between vitamin D, calcium absorption, and intestinal microbes is complex, with various bacteria playing a key role in calcium bioavailability. While increasing vitamin D intake can improve absorption, the bioavailability of calcium is primarily influenced by the diversity of the gut microbiota. Administration of prebiotics can increase the levels of beneficial bacteria, such as *Bifidobacteria*, *Lactobacilli*, and *Eubacterium*, which enhance short-chain fatty acid (SCFA) production and promote increased calcium absorption.[65] Although commensal bacteria do not typically produce fat-soluble vitamins, studies have found a correlation between the phylum *Firmicutes* and serum vitamin D levels.[66] Additionally, bacteria that produce butyrate, a type of SCFA, have been linked to the increased expression of vitamin D receptor protein, which facilitates the regulation genes involved in calcium and phosphate homeostasis and several other physiological processes.[65] The complex relationship between microbiota, calcium absorption, and vitamin D highlights the role of gut health in optimizing micronutrient bioavailability.

Group B vitamins, particularly the water-soluble forms, are synthesized by *Bifidobacterium*, *Bacteroides*, and *Enterococcus*.[66] Numerous studies have explored the biosynthetic capabilities of commensal bacteria.[65,66] A systematic review investigating the production of biotin, cobalamin (B_{12}), folate, niacin, pantothenate, pyridoxine, riboflavin, and thiamine by 256 common bacterial species found that 40–65% of these vitamins are synthesized

by bacteria in the digestive tract.[66] Although some bacteria found in the large intestine can produce cobalamin, these bacteria do not likely contribute to vitamin B_{12} bioavailability, as B_{12} can only be absorbed in the ileum. Therefore, vitamin biosynthesis must occur in a part of the digestive tract situated before its respective absorptive site.[66] Understanding the specific locations of vitamin biosynthesis and absorption is crucial for optimizing nutrient bioavailability and ensuring efficient utilization.

In conclusion, the relationship between the gut microbiome and nutrient status is complex. Many intestinal microbes are essential for the synthesis and absorption of micronutrients, and nutrient intake can influence the diversity of the gut microbiome. As a result, dysbiosis can impact the bioavailability of vitamins and minerals, impair their absorptive capacity, and lead to both short- and long-term health consequences.[65,66] Micronutrient deficiencies are associated with serious health problems, including impaired physical and mental development in children, increased susceptibility to infections, allergies, and inflammatory conditions. Targeted therapies aimed at improving the composition of the gut microbiota could enhance micronutrient status and help reduce the incidence of severe health complications.[65]

Assessment of micronutrient status in biological samples

Biological samples such as plasma, serum, whole blood, and red blood cells (RBCs) are the gold standard for assessing micronutrient (MN) status.[67] However, the acute phase response (APR)—a rapid systemic reaction to trauma, infection, or inflammation—can significantly alter plasma and serum MN concentrations. Increased MN requirements due to elevated reactive oxygen species can lead to reduced circulating levels in plasma.[68] As a result, plasma or serum analyses may not accurately reflect long-term MN status.[67,69]

Monitoring C-reactive protein (CRP) levels can help assess the impact of inflammation on circulating MN concentrations.[67] Research suggests that the APR can decrease levels of vitamins A and C, iron, and selenium by more than 40%, while CRP levels above 10 mg/L can compromise the reliability of plasma copper, iron, selenium, and vitamin C measurements. When CRP exceeds 20 mg/L, the reliability of plasma zinc, vitamin A, and vitamin D is also reduced. While most plasma MN concentrations decrease in response to the APR, some micronutrient levels, such as copper, may rise. These findings highlight the importance of considering inflammatory markers when interpreting plasma micronutrient concentrations to ensure accurate assessments of nutritional status.[67]

Intracellular and functional methods for assessing MN status are more reliable than plasma measurements because functional tests, such as glutathione peroxidases 1 and 2 and the transketolase test, are unaffected by the APR.[67] Additionally, intracellular measurements of blood cells are more accurate, as they reflect MN status in tissues rather than in circulation. In the presence of inflammation, functional and intracellular tests reduce the likelihood of misinterpreted data. A true micronutrient deficiency is confirmed by either measurable loss in body fluids or inadequate intake, along with clinical symptoms or low blood/plasma levels accompanied by metabolic dysfunction.[67]

Plasma mass spectrometry is the most reliable method for measuring trace elements in blood due to its high validity.[67] Standardized measurements are possible because certified reference materials are available. High-Performance Liquid Chromatography (HPLC) is the preferred method for quantification of vitamins because the procedure is both highly specific and highly sensitive. However, the absence of certified reference materials may lead to variability in results between laboratories. Immunoassays can be used to assess vitamin D, folate, and Vitamin

B_{12}, but they are susceptible to cross reactivity and are used infrequently. Spectrophotometry may be used for certain MNs, but it is less specific and less preferable than chromatographic techniques. Regardless of the selected method, repeated testing is recommended to effectively assess and monitor MN status.[67]

Evaluating micronutrient status in patients with IBD

Micronutrient deficiencies are common in more than half of patients with inflammatory bowel disease (IBD), with higher rates observed in those with Crohn's disease (CD) compared to ulcerative colitis (UC). While disruptions in the gut microbiome and the integrity of the gastrointestinal tract are known contributors to malabsorption, the extent to which nutritional deficiencies influence the pathogenesis or progression of IBD remains unclear.[8] Numerous combinations of micronutrient deficiencies have been reported in the literature, but there is ongoing debate regarding which deficiencies are most prevalent in patients with IBD.[10] Brownson et al[10] identified vitamin C, folate, zinc, selenium, and ferritin as the most commonly deficient micronutrients. Valvano et al[70] also observed deficiencies in these nutrients, while additionally highlighted deficiencies in copper, manganese, and vitamins A, E, K, B_1, B_6, and B_{12}. This study aims to investigate the status of Vitamin B_9 (folate), Vitamin B_{12}, Vitamin D, iron, magnesium, and zinc in patients with IBD. A variety of techniques can be used to assess these micronutrients, though the reliability of some methods may be influenced by factors such as the acute phase response (APR), age, or hormonal variations, warranting further investigation to validate their accuracy.

Vitamin B_9 (folate)

Vitamins B_9 (folate) and B_{12} are closely linked and are often measured together because a deficiency in one can influence the biomarker levels of the other.[71] Most analytical methods focus on measuring the monoglutamate form of folate. Both serum and RBC folate provide valuable clinical and nutritional insights. Serum or plasma folate is considered a reliable indicator of short-term folate status and is commonly used to diagnose folate deficiency. In contrast, RBC folate reflects longer-term tissue folate status and has been widely used in both nutritional and clinical studies. Various techniques, including High-Performance Liquid Chromatography coupled with Tandem Mass Spectrometry (HPLC-MS/MS), electrochemical methods, fluorescence-based assays, and traditional approaches such as the *Lactobacillus casei* growth assay, can be used to assess folate levels.[71] Ultimately, the use of reference standards and proficiency-testing programs is crucial for improving the comparison of folate status across different populations.

Vitamin B_{12}

Vitamin B_{12}, a group of corrinoids known as cobalamins, is transported in the blood by transcobalamin (TC) and haptocorrin (HC).[71] While only 20% of cobalamin is bound to TC, it more accurately reflects B_{12} status because this form is transported to the tissues. Although vitamin B_{12} levels have historically been assessed using microbiological assays such as the *Lactobacillus delbrueckii* method, serum levels are now primarily used to diagnose vitamin B_{12} deficiency. Alternatively, metabolite markers like methylmalonic acid (MMA) and homocysteine (Hcy) may also be measured. Elevated levels of MMA and Hcy can indicate vitamin B_{12} deficiency; however, increased levels of Hcy may also suggest folate or vitamin B6 deficiencies.

Currently, holotranscobalamin (HoloTC) is considered the most reliable marker of vitamin B_{12} status, but further research is needed to standardize testing methods.[71]

Vitamin D

The best clinical marker of vitamin D status is 25-OH-vitamin D, as its concentration in the body is well-represented in plasma or serum.[71] Using total 25-OH-vitamin D_3, vitamin D binding protein, and human serum albumin (HSA) levels, vitamin D levels can also be determined from free 25-OH-vitamin D_3. Clinical methods for measuring vitamin D include chemiluminescence immunoassays and HPLC-MS/MS analysis, with the latter considered the gold standard due to its accuracy in separating and quantifying 25-OH-vitamin D_2 and 25-OH-vitamin D_3. Although it requires an additional procedure, sensitivity can be further enhanced by derivatization prior to performing LC-MS/MS analysis. Additionally, non-invasive methods, such as saliva testing and miniaturized immunoassays for point-of-care testing, are being explored, though further validation is required. The development of standardization and qualification procedures is essential for accurate vitamin D analysis.[71]

Iron

Iron, an essential constituent of heme, can be assessed using various matrices, including serum, plasma, and bone marrow.[71] Serum ferritin is the preferred marker for diagnosing iron deficiency, as its concentration reflects total iron stores. However, ferritin is subject to the acute-phase response (APR), which affects its reliability as a marker of nutrient status. A more stable alternative is the measurement of soluble transferrin receptor (sTfR), which remains unaffected by inflammation. Combining ferritin with sTfR to form the sTfR Index may more accurately reflect iron status. Additionally, hepcidin-25, a peptide implicated in iron homeostasis, may reliably represent iron status, though further clinical validation is required.[71]

Magnesium

Magnesium status is difficult to assess due to various factors influencing its distribution and excretion.[72] Urinary magnesium is an unreliable marker for evaluating magnesium status, as its levels are influenced by fluctuations in hormones, medications, physiological homeostasis, and factors such as age and gender.[72] Blood tests, including serum and plasma, may also provide limited insight into total body magnesium because serum magnesium accounts for just 0.3–1% of total body magnesium. Although approximately 99% of magnesium is found in bone, muscle, and soft tissue, the assessment of tissue samples requires invasive methods.[72]

In the clinical setting, assessment of serum magnesium concentration remains the most used method, though it is most accurate when sampled from interstitial fluid and bone. RBC magnesium levels are typically higher than those in serum and, therefore, are also often used in clinical practice.[73] While various methods are used to assess magnesium status, standard methods may not provide a comprehensive reflection of total body magnesium, highlighting the need for more accurate and less invasive diagnostic approaches.

Zinc

Zinc, which acts as both a structural element and an enzyme catalyst in many biological processes, is primarily stored in skeletal muscle, bone, liver, and skin cells.[71] While deficiency is prevalent and commonly recognized, there is still no universally accepted biomarker for assessing zinc status. Total zinc concentrations in plasma and serum are frequently used as biomarkers, as their levels fluctuate in response to both supplementation and depletion. Due to the linear relationship between intake and excretion, urinary zinc serves as a useful indicator of status. Additional techniques, such as atomic absorption spectrometry (AAS), inductively coupled plasma optical emission spectroscopy (ICP-OES), and ICP-mass spectrometry (ICP-

MS), can also be used to quantify zinc.[71] While various methods may be utilized to evaluate zinc status, further research is required to establish validity and identify a universally accepted biomarker for accurate diagnosis and monitoring.

Dietary assessment: Methods and tools

Biomarkers obtained from biological samples such as plasma, serum, red blood cells, and urine are the gold standard for assessing micronutrient status due to their accuracy and reliability. Non-invasive dietary assessment methods, such as food records and 24-hour recalls, are valuable for estimating average nutrient intake but are often less precise.[74] This limitation stems from challenges related to data collection, as well as reporting and selection biases. Consequently, these methods are more suitable for evaluating consumption patterns rather than quantifying specific nutrient concentrations.[74,75] To ensure valid and reliable data, the choice of assessment method should align with the study's design, objectives, and sample size. Given these factors, it is important to consider the strengths and limitations of each dietary assessment method.

Duplicate diet approach

The duplicate diet approach is an objective measure of dietary intake that involves collecting duplicate portions of foods and beverages consumed by participants throughout a given study period.[76] Participants must retain an identical portion of all foods and beverages consumed over a 24-hour period, except when a meal is prepared or purchased from a third party. In such cases, meal details, including any modifications, must be documented.[76] The first portion is consumed by the participant, while the second portion is collected and analyzed.[77,78] Participants may also be asked to maintain a weighed food record to ensure portion size accuracy, but researchers are ultimately responsible for monitoring compliance. After collection,

the duplicate samples undergo calorimetric or biochemical analysis to assess the dietary intake of the study population.[76]

This dietary assessment method has primarily been used in epidemiological research to evaluate exposure to environmental contaminants in foods and beverages, such as phytochemicals and phthalates.[78] It can also assess total dietary nutrient and energy intake, specific nutrient or food consumption, infrequently consumed foods, dietary patterns, meal frequency, and meal environments. Additionally, duplicate diets can validate laboratory biomarkers and are particularly useful in studies where participants consume meals provided by the researchers. This method is ideal for measuring minerals, as they are stable and do not require immediate sample analysis. For this reason, the duplicate diet approach is the preferred method for assessing individual nutrients and minerals.[76]

One notable strength of the duplicate diet approach is its ability to reliably measure dietary exposures.[78] Additionally, it does not require composition data from external sources and is not subject to inherent data processing errors.[76] However, this method also has several limitations. One major drawback is the complexity of collecting duplicate portions.[77] Weighing and replicating meals places a high burden on participants, demanding significant motivation and adherence. To reduce this burden, participants may be motivated to alter their food intake, which could compromise the accuracy of the collected data. This approach may also be unsuitable for certain demographics, such as children or older adults, who require a proxy or struggle with cognitive impairments. Another challenge is capturing habitual dietary patterns, which requires measurements to repeated over a period of multiple days.[76] Although the duplicate diet method is objective and statistically more reliable than subjective dietary assessment measures, it is also

labor-intensive, costly, and dependent on specialized laboratory equipment and personnel, making it impractical for large-scale studies.[76,79]

Food consumption record

A food consumption record is used to directly monitor the preparation and consumption of food, providing an objective measure of a study population's dietary intake.[80] Traditionally, trained field staff observe and document the required information within the participant's home environment.[78] This dietary assessment method can also be applied in settings such as nursing homes, community centers, and schools. If researchers are unable to complete the consumption records themselves, participants or proxies may use provided catalogs to document the types and quantities of foods consumed. The nutrient content of these foods is then calculated using standard recipes and analytical software.[81]

Food consumption records are most suitable for individuals who primarily eat meals at home. However, this has become more challenging with the increasing prevalence of dining out.[78] This method is often preferred for populations with low literacy levels, as it can be administered by a third party, eliminating the need to train participants themselves.[78,82] Food consumption records can assess total energy and nutrient intake, specific nutrients and foods, infrequently consumed foods, dietary patterns, habitual diets, meal composition, and meal frequency or eating environments. This approach is particularly valuable for evaluating the effectiveness of nutrition education interventions.[80]

As an objective assessment tool, food consumption records are advantageous because they reduce errors related to social desirability and recall bias.[80] They can also be used for populations with cognitive or physical impairments that affect the ability to self-report food intake. Additionally, consumption records provide insight into the social and physical aspects of

a participant's diet. However, due to the short duration of observation periods, assessing habitual dietary patterns may be challenging without separate, repeated assessments. Although the participant burden is low, accurately capturing dietary intake through food consumption records requires extensively trained researchers, significant time investment, and specialized analytical tools.[80]

Table 2.2 Objective methods of dietary assessment

Objective Assessment Method	Strengths	Limitations
Duplicate Diet Approach[76]	• Provides accurate nutrient intake data without data processing errors. • Independent of external food composition data.	• Costly and complex • High individual burden • Requires high participant motivation • Unsuitable for large studies • May not reflect habitual diet without repeated assessments • Foods may be underreported or exclude to present more favorable diet • Risk of altered intake for convenience • Requires complete duplication of foods • May not account for leftovers • Requires specialty lab analysis
Food Consumption Record[80]	• Offers objective assessment of dietary intake • Reduces recall and social desirability biases • Provides context on social and physical aspects of eating • Useful for populations unable to record their own intake	• Observer inattention and imprecise recording can cause errors • Extensive training needed for observers • Labor-intensive and costly for researchers • Limited to specific settings and observation times (e.g., nursing homes, schools) • Observation may influence an individual to alter eating patterns • Home observations may lead to behavior changes or feel invasive • Difficult to generalize habitual intake without multiple assessments over time

24-hour dietary recall (24HR)

A 24-hour recall (24HR) is a retrospective dietary assessment method in which participants recall and describe all foods and beverages consumed the previous day.[83] The assessment can be conducted by an interviewer or self-administered, with the latter becoming increasingly common.[77,83] Interviews are typically structured and follow a chronological,

multiple-pass approach that is designed to mirror cognitive processing. Various outcomes can be derived from the collected data, which is analyzed using processing software for accessibility and efficiency.[20,83]

The 24HR method can be used in various settings to evaluate dietary habits, meal frequency and composition, eating environments, and the intake of specific nutrients, foods, or overall energy and nutrient consumption.[20] A single 24HR can estimate the average intake of a population, but multiple administrations are necessary to assess population-level dietary distributions and assess individual intake.[20,83] Depending on the objective of a study, repeated administration may provide limitations.[83]

As a subjective dietary assessment method, 24HRs are susceptible to recall bias.[77] Participants may selectively report food consumption, leading to underreporting and negatively impacting the reliability of the data.[77,83] The costs associated with 24HRs vary depending on the method of administration. For example, interviewer-administered recalls require extensive personnel training, and manually entering data from paper-based interviews can be both time-consuming and labor-intensive. Additionally, the frequency of administration—single versus multiple—affects both participant and researcher burden.[20] One notable benefit of the 24HR design is that immediate collection of information minimizes the likelihood of reactivity, enhancing the accuracy of the data. Single-administration 24HRs are especially beneficial due to their low participant burden and wide applicability across various populations and settings.[83] (Thompson & Subar, 2017). Overall, while the 24HR method has some limitations, such as recall bias and varying costs, its advantages—such as minimizing reactivity, reducing participant burden, and being applicable to diverse populations—make it a valuable tool for dietary assessment in many research settings.

Dietary record

Dietary records are prospective assessment methods in which participants document the amounts of all foods and beverages consumed over a defined observation period.[83,84] Ideally, recordings should be completed in real time to minimize recall bias.[83] Portions should be measured using a food scale or standard measuring devices (e.g., cups, tablespoons), and participants or proxies should receive proper training on how to accurately measure and record intake.[83,84] Collecting records from non-consecutive days can help capture variation in dietary patterns, but periods of observation spanning greater than seven days are not recommended. Research suggests that data collected over four or more consecutive days becomes less accurate due to decreased compliance and study fatigue.[83,84] Once collected, the data can be analyzed to estimate dietary intake variables.[84]

This method is useful for evaluating meal frequency, eating environments, meal composition, dietary patterns, and energy or nutrient intake from specific foods or the overall diet. Additionally, dietary records can contribute to the development of other assessment tools, such as diet history and food frequency questionnaires. The collected data also helps identify dietary behavior patterns and explore correlations between diet and disease.[84]

Dietary records require participants to be motivated, literate, and compliant, which can limit their applicability in certain populations and increase participant burden.[83,84] Accurately weighing food can also be challenging when meals are consumed outside the home. Additionally, dietary records are susceptible to reactivity bias, as participants may modify their diet to ease recording or mask unhealthy eating habits. Several studies have shown that reported food consumption may be underestimated by 4–37%.[83] Despite these challenges, dietary records offer several advantages. Development is cost-effective, which allows the assessment to be easily

administered to large study populations. Real-time documentation reduces reliance on memory, and recording measurements of foods and beverages enhances the accuracy of dietary analysis.[84] Overall, while dietary records pose certain challenges, their ability to provide detailed, real-time data makes them a valuable tool for evaluating dietary intake patterns in nutritional research and public health studies.

Diet history

Diet history is a retrospective assessment tool designed to evaluate a participant's overall food intake.[85] This method typically involves a structured interview with questions about food type, frequency, portion sizes, and preparation methods.[83] The questions may be open-ended and include a cross-check feature to clarify past intake.[83,85] Portion sizes are estimated using standard household measures or reference photos. Interview questions can be tailored to focus on specific behaviors or food items. Estimations of energy or nutrient intake can be calculated based on the responses.[85] This approach provides valuable insights into a participant's dietary habits.

Diet history can provide detailed information about eating habits during a previous life stage, such as vegetable consumption during childhood.[85] This method tends to reflect dietary patterns more accurately than specific nutrient intake, as the data is often based on estimates and may not provide precise values. It can also be used to assess dietary patterns, habitual intake, and infrequently consumed foods.[85] In the 1990s, cohort studies primarily relied on diet history for nutritional evaluation; however, more refined techniques have since been developed, and its use has become less common.[83]

Although diet histories are useful for establishing historical intake patterns, the accuracy of the data is susceptible to observer bias.[83,85] Participants may also struggle to recall accurate portion sizes, meal components, or food quantities.[85] Diet histories are less effective for

individuals who “graze” or lack a consistent eating pattern, but they can be useful for assessing large sample populations.[85] Additionally, while diet histories can be developed at a relatively low cost, they place a high burden on researchers in terms of data collection and analysis.[85] In conclusion, diet histories provide valuable insights into historical intake patterns, but they may inaccurately reflect certain eating behaviors and may not be suitable for certain populations.

Food frequency questionnaire

Food frequency questionnaires (FFQs) are retrospective dietary assessment tools that record the frequency of food and beverage consumption by participants over an extended period.[77] The key component of this method is a questionnaire, which can be completed by the participant independently or administered by an interviewer. The length of the questionnaire varies depending on the study, but research suggests that shorter FFQs may lead to an underestimation of consumption, while longer FFQs may increase participant burden and reduce the reliability of the data. The questions can be semi-quantitative, quantitative, or non-quantitative and may list foods or beverages individually or by category.[77] FFQs typically provide limited information about preparation methods, and questions about portion size may be asked separately or included within each question. Once completed, the results are summarized, and the data are analyzed to estimate overall nutrient intake over the given period.[83]

FFQs have become the most widely used retrospective dietary assessment tool due to their low cost, minimal participant burden, and ease of administration.[86,87] They are commonly used in epidemiological research to explore associations between diet and disease risk.[87] FFQs are also particularly valuable for assessing the intake of specific food groups, tracking consumption of less common foods, evaluating dietary behaviors, and measuring selected micronutrients.[86] While frequently used in large-scale prospective cohort studies, there is

ongoing debate about whether FFQs are sensitive enough to detect meaningful relationships between diet and disease.[86] One challenge is the potential bias introduced by over- or underestimating dietary intake, as participants often struggle with accurately estimating portion sizes.[83,87] Despite these limitations, FFQs offer unique flexibility because existing questionnaires can be adapted for new populations, and standardized responses allow for efficient data analysis.[86] Ultimately, FFQs are a practical and efficient tool for dietary assessment in epidemiological studies, but their effectiveness requires careful adaptation to the study population and addressing potential biases.

Table 2.3 Subjective methods of dietary assessment

Subjective Assessment Method	Strengths	Limitations
24-Hour Dietary Recall[20]	• Allows highly detailed food reporting • Low respondent burden • Does not alter eating habits • No literacy required • Brief interviews • Captures ethnic dietary differences (NIHR| Cambridge Biomedical Research Centre, n.d.)	• Relies on accurate recall, prone to recall bias • High administration cost due to high interviewer burden • Costly and labor-intensive, especially with paper-based recalls, due to data entry • Repeat recalls increase time and costs • Coding and nutrient conversion require skilled coders, a nutrient database, and analysis tools (NIHR| Cambridge Biomedical Research Centre, n.d.)
Dietary Record[84]	• Records food/drink at consumption, avoiding memory reliance • Uses weighed portions, eliminating estimation errors • Provides detailed food descriptions and eating occasions	• High respondent burden; requires motivation and compliance • Needs numeracy and literacy skills • Difficult to weigh/record food eaten away from home • Infrequently eaten foods may be missed • Risk of diet alteration due to tracking • Time-consuming, labor-intensive, and costly for researchers • Complex data entry and nutrient translation • Accuracy may vary based on meal preparation involvement
Diet History[85]	• No literacy required • Provides overview of usual diet in a single interview • Provides details of individual foods consumed • Captures information about consumed infrequently foods • Estimates energy intake and most nutrients with reasonable accuracy	• Data quality depends on interviewer skill • Observer bias may occur in interview-based methods • Recall bias can affect accuracy due to memory limitations • Difficult to assess portion sizes of past meals • Difficult for individuals with irregular eating patterns (e.g., shift workers) • Requires time-consuming and costly individual food coding by trained staff
Food Frequency Questionnaire[86]	• Low respondent burden • Easy and flexible to administer • Lower cost compared to other methods • Suitable for long-term, repeated assessments • More complete data with interviewer-administered FFQs, but less respondent bias if self-administered • Standardized responses allow for quick, sometimes automated, analysis • Existing FFQs can be modified for new studies with the right analysis tools • Designed to capture habitual and irregular foods	• Limited to foods included in the food list • Accurate reporting depends on respondent memory • Bias may occur, with over-reporting of "good" foods and under-reporting of "bad" foods • Over-estimation may increase with longer food lists • Requires moderate literacy and numeracy skills when self-administered • Portion size may be difficult to assess • Population-specific; may not be suitable for diverse groups without confirming similar dietary habits • Food list may not reflect all dietary patterns, especially ethnic or regional differences • Pre-prepared or fast-food meals may be hard to classify within basic food categories

Improving health outcomes for IBD patients: Theoretical models for preventative healthcare

Theoretical models can be valuable in preventive healthcare, as they provide guidance for understanding and influencing health behaviors. By applying these models, healthcare professionals can identify key factors that affect health decisions, such as social influences, individual motivations, and environmental conditions. This approach helps in designing effective interventions that promote healthy lifestyles, prevent disease, and improve overall public health outcomes. The application of these models enables a more systematic and evidence-driven approach to proactively preventing healthcare issues.

Health Belief Model

In the 1950's, psychologists developed the Health Belief Model (HBM) to help explain the selective use of healthcare services.[88] This model explores how individuals perceive health risks and make decisions. HBM is based on two key factors: the significance individuals place on specific goals and their expectations of how effective their actions will be in achieving them.[89] The six constructs of HBM include perceived susceptibility to disease, perceived severity of the disease, perceived benefits of adopting a recommended action, perceived barriers or disadvantages associated with the action, self-efficacy, and cues to action.[88,89] In practice, individuals assess the benefits of modifying their behavior to reduce health risks and make decisions based on these assessments.[89]

Health belief models have been extensively used to understand social judgment in health behaviors, including screening, vaccination, and the cessation of harmful habits. While highly applicable, the model is not without limitations. It fails to account for the role of emotions in decision making and overlooks cultural and social influences, assuming decisions are purely

rationale.[89] Studies show that individuals are more likely to adopt recommended health behaviors when they perceive fewer barriers as well as greater susceptibility, severity, and benefit.[88] While HBM provides valuable insights into understanding health-related decision-making, its limitations highlight the need for a more comprehensive approach to health behavior change.

Social Learning Theory

The Social Learning Theory (SLT), developed by psychologists in 1952, examines how intellectual growth and development take place within social environments through observation, imitation, and modeling. It investigates the relationships between the learning environment, cognition, and behavior in shaping an individual's learning patterns. SLT emphasizes the significance of both environmental influences and personal determinants of behavior.[90]

In the context of health, SLT offers insight into how illness behaviors are developed and maintained.[91] Behaviors often reflect an individual's learning history, meaning coping strategies and difficulties coping with pain are two illness behaviors that may have evolved over time. These behaviors are sustained because they are perceived to bring social rewards and persist because they have been associated with positive outcomes or a reduction in negative experiences.[91] This perspective highlights the role of learned behaviors in shaping individuals' responses to illness, which offers valuable insights into how health-related behaviors can be modified.

Historically, SLT has been predominantly applied in fields such as behaviorism, criminology, and psychology.[90] In the context of public health education, social learning theories are valuable for addressing the spread of inaccurate medical information, global health concerns, and barriers to accessing health education resources. Applying SLT in public health settings can help foster motivational learning and support the development of individual learning behaviors.[90]

In conclusion, SLT can be used to help address key challenges and promote effective learning behaviors in the public health environment.

Theory of Planned Behavior

The Theory of Planned Behavior (TPB) is derived from the Theory of Reasoned Action (TRA).[92] This theory is based on the principle that behavior is influenced by behavioral beliefs, normative beliefs, and control beliefs.[93] These beliefs are connected through attitudes, social expectations, and perceived control over the behavior. Ultimately, intention mediates a particular behavior. TPB is rooted in the idea that many beliefs and attitudes are modifiable, making them a key focus for interventions.[92]

This theory is commonly used to design and evaluate behavior modification strategies and their associated outcomes. TPB is particularly useful for measuring various types of adherence behaviors in the context of chronic illness.[92] According to Bosnjak et al[93], "behavioral beliefs produce a favorable or unfavorable attitude toward the behavior; normative beliefs result in perceived social pressure or subjective norms; and control beliefs give rise to perceived behavioral control or self-efficacy."[93(p323)] In healthcare settings, TPB can offer positive reinforcement and support for patients who take proactive steps to monitor and improve their health, motivating them to adopt positive health behaviors. Overall, TPB provides a valuable framework for understanding and influencing health-related behaviors, offering effective strategies to promote adherence and encourage proactive health management.

Self-Determination Theory

The Self-Determination Theory (SDT) focuses on both intrinsic and extrinsic motivation, emphasizing the roles of autonomy, competence, and relatedness in influencing behavior.[94,95] Autonomy is driven by personal choice and self-validation, while competence reflects the need

to feel capable of achieving goals, and relatedness involves a sense of connection and understanding with others. SDT suggests that satisfying these three basic psychological needs fosters intrinsic motivation. Additionally, when the social environment supports these needs, individuals are more likely to make voluntary changes, instead of being led by external pressures.[95]

In healthcare, autonomy is a fundamental ethical concept. Within the framework of SDT, autonomy refers to an individual's ability to make informed decisions about their medical care.[94] SDT is the only theory that has extensively explored autonomy within the research setting, providing valuable insights into the support required to help individuals make independent and educated healthcare decisions. Application of SDT can encourage patients to ask questions and actively engage in healthcare discussions, focusing on topics such as treatment options and personal beliefs. The quality of these conversations has significant implications for behavioral changes and patient outcomes.[94] In conclusion, applying SDT in healthcare can improve patient autonomy, leading to more informed decision-making and improved health outcomes.

Protection Motivation Theory

The Protection Motivation Theory (PMT) is a well-established framework used to explain and predict human behaviors, specifically focusing on the motivation to protect oneself from adverse health consequences. It was developed to understand how individuals respond to perceived threats or negative outcomes.[88,96] The four key concepts of this theory are vulnerability, severity, belief in the positive outcomes of the recommended action, and perceived self-efficacy.[88] According to PMT, protective motivation is influenced by both threat appraisal, which involves an individual’s perception of a health threat, and coping appraisal, which includes self-efficacy, response efficacy, and response cost. Together, these factors shape

behavior.[96] A person is more likely to adopt a recommended action if they believe it will improve the outcome, they can perform the action, or they perceive inaction will result in a negative consequence.[88]

By applying threat and coping appraisals to explain behavioral changes, PMT is highly relevant in various healthcare settings for promoting healthy behaviors.[97] Research on PMT interventions has shifted towards promoting health improvements, addressing public health issues such as oral health and diabetes prevention, and enhancing hygiene practices in healthcare settings. Clinical studies on COVID-19 have demonstrated that threat and coping appraisals are key predictors of protective motivation. Using PMT to design targeted nursing interventions that increase awareness of perceived threats and improve self-efficacy in preventing the spread of COVID-19 enhances protective motivation and improves overall outcomes.[97] Ultimately, PMT provides a valuable framework for healthcare interventions, helping to promote healthy behaviors and addressing determinants of health-related behaviors, such as threat perception and self-efficacy.

Applying the Protection Motivation Theory to improve micronutrient status in patients with IBD

Although the Health Belief Model, Social Learning Theory, Theory of Planned Behavior, and Self-Determination Theory can all be adapted to encourage proactive and preventative health behaviors among both healthcare professionals and patients, the Protection Motivation Theory (PMT) has been selected as the framework for our research study. PMT is highly relevant to both patients and healthcare providers, as it emphasizes the motivation to respond proactively to perceived health threats. In our study, PMT principles encourage patients with inflammatory bowel disease (IBD) and healthcare providers to adopt preventative health measures.[88] A key

objective of our research is to identify patterns of micronutrient deficiencies in IBD patients, aligning with PMT's concept of threat appraisal, in which individuals assess the severity of their health condition.[97] By highlighting the risks associated with micronutrient deficiencies, we aim to increase patient awareness and encourage proactive efforts to protect their health.

Secondly, our goal is to encourage healthcare providers to conduct routine medical testing and implement tailored interventions, including dietary modifications and supplementation for nutrient deficiencies. This objective aligns with PMT's coping appraisal, as it encourages providers to view their role in addressing nutritional problems as both effective and feasible, ultimately strengthening their confidence in their ability to deliver quality patient care.[96] Lastly, our research aims to empower patients to advocate for themselves and seek nutritional guidance, aligning with the self-efficacy component of PMT.[96] By fostering confidence in their ability to make informed nutritional decisions, patients will be more motivated to actively participate in their care and will experience improved health outcomes. Through these objectives, PMT provides a comprehensive framework for influencing both provider actions and patient behaviors, enhancing the management of micronutrient deficiencies in IBD.

Chapter 3 - Methods

Study Design

This case series presents detailed clinical and nutritional profiles of adult patients diagnosed with inflammatory bowel disease (IBD), including both ulcerative colitis (UC) and Crohn's disease (CD). Each case includes self-reported dietary intake data, subjective measures of disease-related disability, and objective laboratory markers of micronutrient status and systemic inflammation. Dietary intake data were collected using a food frequency questionnaire (FFQ) developed by the Nutrition Assessment Shared Resource (NASR) of Fred Hutchinson Cancer Center, Seattle, Washington. A modified, self-administered version of the Inflammatory Bowel Disease-Disability Index (IBD-DI),[98] a validated tool for assessing disease-related disability, was used to evaluate participants' perceived disease activity.[99] Blood samples were analyzed for vitamin D, vitamin B_{12}, folate, magnesium, iron, and zinc, as well as C-reactive protein (CRP), an established biomarker of systemic inflammation. The objective of this case series was to assess individual patterns in dietary intake, micronutrient status, and disease burden among patients with IBD, and to highlight the clinical value of routine nutritional assessment in this population.

Participant Recruitment and Eligibility

Participants were recruited through various outreach efforts, including community postings and personal referrals. Recruitment materials were distributed at local healthcare clinics, emergency departments, private businesses, and gyms; however, most participants were recruited through word-of-mouth and social media. All participants were required to meet the established inclusion criteria prior to enrollment, and those who met exclusion criteria were not ineligible. Written informed consent was obtained prior to data collection.

Table 3.1 Inclusion and exclusion criteria

Inclusion Criteria	Exclusion criteria
• Age 18–65 • Existing IBD diagnosis, including Crohn's disease or ulcerative colitis • No additional active gastrointestinal illnesses (including, but not limited to, diverticulitis, Celiac disease, colorectal cancer, gastritis, liver disease, etc.) • Actively receiving care under a licensed gastroenterologist • Omnivorous diet • English-speaking • Access to a computer, mobile phone, or tablet for completion of surveys/informed consent	• Age <18 or >65 • No confirmed IBD diagnosis • Additional active gastrointestinal illnesses (including, but not limited to, diverticulitis, Celiac disease, colorectal cancer, gastritis, liver disease, etc.) • Not actively receiving care under a licensed gastroenterologist • Vegan or vegetarian diet • Non-English speaking • No access to a computer, mobile phone, or tablet for completion of surveys/informed consent

Surveys

After providing informed consent, participants received a confirmation email with instructions to contact a specific clinic in a Midwest city to schedule a blood draw. The email also included secure links to the dietary and disability assessment surveys. The FFQ assessed general dietary intake patterns over the previous 12 months, while the IBD-DI evaluated disease-related disability based on subjective factors such as weight loss, body image, and the type and frequency of bowel movements. The scoring guide for the IBD-DI is outlined in Table 3.2. Participants were asked to complete the surveys within one week of their blood draw.

Table 3.2 Inflammatory Bowel Disease-Disability Index (IBD-DI) scoring guide.[98]

TOTAL SCORE	
Degree of Disability	**Total Score**
No Disability	22
Point of Neutrality	0
Minimal Disability	0 to -10
Mild Disability	-10 to -19
Moderate Disability	-20 to -35
Severe Disability	≤-35
Maximum Disability	-80

Blood Sample Collection and Analysis

Participants presented to the designated clinic for their scheduled appointment, where blood samples were drawn by certified phlebotomy personnel via venipuncture. A total of 27 mL of blood was drawn and distributed into two 9 mL serum separator tubes (SSTs) and one 9 mL heparin tube. The samples were stored frozen at temperatures below -20°F until analysis, which was conducted within 7–10 business days of collection. Blood samples were processed by a certified laboratory at the clinic and analyzed for vitamin B_{12}, vitamin D, folate, iron, magnesium and zinc. High-sensitivity CRP levels were also assessed. CRP levels were compared to micronutrient lab results to help identify correlations between inflammation and micronutrient levels. CRP levels between 1.9 and 10 mg/L were considered indicative of mild to moderate inflammation, while levels greater than 10 mg/L suggest more serious inflammation. Reference ranges were provided by the clinical laboratory responsible for sample analysis and reflect standard values used at the time of testing.

Table 3.3 Micronutrient biomarker matrices and reference ranges

Micronutrient	Matrix	Reference Range
Vitamin B_{12}	Serum	165–1100 pg/mL
Vitamin D	Serum	40–80 ng/mL
Folic acid (folate)	Serum	7.2–17.2 ng/mL
Magnesium	RBC	4.0–6.4 mg/dL
Zinc	RBC	8.6–15.8 ug/mL
Iron	Serum	
Males		50–195 mcg/dL
Females		40–190 mcg/dL

[a]Red blood cell (RBC)
[b] Reference ranges were provided by the clinical laboratory responsible for sample analysis and reflect standard values used at the time of testing

Data Analysis

Data were de-identified prior to analysis. Nutrient calculations were performed using the Nutrient Data System for Research (NDSR) software version 2024, developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN. Descriptive statistics were generated using R statistical software to summarize demographic and clinical characteristics. Prevalence of micronutrient deficiencies was determined by using counts and proportions.

Ethical Considerations

Ethical approval was obtained from the relevant Institutional Review Board before the study began. To ensure confidentiality, all data were de-identified, and electronic records were securely stored. Participants were provided with access to their individual micronutrient results, which were de-identified upon delivery to protect privacy. A participation incentive was

provided to each participant upon completion of the study. All components of the study, including the incentive, were funded through internal resources.

Chapter 4 - Results

A total of 11 individuals enrolled in the study; however, one withdrew from the study and laboratory data for three was not received in time for analysis. Therefore, data from only seven cases were included in the analysis. The final sample consisted of three females (42.9%) and four males (57.1%). Among the final sample, two participants (28.6%) were diagnosed with Crohn's disease, while five (71.4%) had ulcerative colitis. The mean age was 33.57 years (SD = 10.91), and the mean BMI was 26.14 (SD = 4.37), indicating that participants were overweight on average. The Shapiro-Wilk test confirmed that both age ($p = 0.4693$) and BMI ($p = 0.7262$) followed a normal distribution. The demographic and clinical characteristics of the cases are outlined in table 4.1.

Table 4.1 Demographic and clinical characteristics of cases

Case	Age (years)	Sex	IBD diagnosis	Decreased MN levels	Elevated MN levels	IBD-DI score	CRP level (mg/L)	BMI
1	24	M	UC	Vitamin D, folate	Iron	-9	5.70	29.3
2	21	M	CD	None	Vitamin D	3	1.19	25.8
3	40	F	CD	Vitamin B_{12}	None	-8	11.79	21
4	49	F	UC	None	None	-17	2.17	23.9
5	44	M	UC	Vitamin B_{12}	None	-16	0.80	28.6
6	32	M	UC	Vitamin D	None	-7	6.15	32.9
7	25	F	CD	Vitamin D	None	-4	1.80	21.5

[a]Sex: male (M) or female (F)
[b]Inflammatory bowel disease (IBD) diagnosis: Crohn's disease (CD) or ulcerative colitis (UC)
[c]Micronutrient (MN)
[d]Inflammatory Bowel Disease Disability Index (IBD-DI) Score: Range -80–22; lower scores are associated with higher degree of disability
[e]C-reactive protein (CRP) reference range: 0.00–1.90 mg/L

The objective of this case series was to assess individual patterns in dietary intake, micronutrient status, and disease burden among patients with IBD. Additional analyses aimed to examine variations in dietary intake and micronutrient levels across cases and assess the prevalence of specific micronutrient deficiencies (e.g., vitamin D, B_{12}, folate, iron, magnesium, zinc) within the population.

Case 1

Case 1 was a 24-year-old male with a BMI of 29.3, diagnosed with ulcerative colitis (UC). He reported no history of gastrointestinal (GI) surgery or additional chronic health

conditions, and no symptoms of arthritis or arthralgia. Case 1 was prescribed mesalamine for management of his UC. Laboratory analysis revealed deficiencies in vitamin D (7 ng/mL) and folate (5.9 ng/mL). His C-reactive protein (CRP) level was elevated at 5.7 mg/L, indicating mild to moderate systemic inflammation. The patient's Inflammatory Bowel Disease-Disability Index (IBD-DI) score was -9, indicating minimal disease-related disability.

Case 2

Case 2 was a 21-year-old male with a BMI of 25.8, diagnosed with Crohn's disease (CD). He reported no history of GI surgeries or additional chronic health conditions, and no symptoms of arthritis or arthralgia. Case 2 was prescribed azathioprine for management of his CD. Laboratory analysis showed elevated vitamin D levels (98 ng/mL) with no micronutrient deficiencies identified. His CRP was within normal range, and his IBD-DI score was 3, which is close to the point of neutrality but indicates some disease-related disability.

Case 3

Case 3 was a 40-year-old female with a BMI of 21, diagnosed with Crohn's disease. She reported a history of autoimmune hepatitis and has undergone a total colectomy with a subsequent pull-through and J-pouch reconstruction. The participant was prescribed prednisone and Skyrizi, and also reported taking probiotics, prebiotics, and N-acetyl L-cysteine as part of her CD management regimen. Laboratory analysis revealed elevated vitamin B_{12} levels (1379 pg/mL) but did not identify micronutrient deficiencies. Her CRP level was elevated at 11.79 mg/L, indicating moderate to severe systemic inflammation. Case 2 has an IBD-DI score of -8, indicating minimal disease-related disability. She denied symptoms of arthritis or arthralgia.

Case 4:

Case 4 was a 49-year-old female with a BMI of 23.9, diagnosed with UC. She reported no history of GI surgery or additional chronic medical conditions, but she did report symptoms of arthritis or arthralgia. Case 4 was prescribed balsalazide for management of her UC. Laboratory analysis revealed no micronutrient deficiencies, but her CRP level was elevated at 2.17 mg/L, indicating mild systemic inflammation. Her IBD-DI score was -17, indicating mild disease-related disability.

Case 5:

Case 5 was a 44-year-old female with a BMI of 28.6, diagnosed with UC. She reported a history of gastric bypass surgery and symptoms of arthritis or arthralgia but denied any other chronic medical conditions. Case 5 was prescribed mesalamine for management of her UC. Laboratory analysis showed an elevated serum vitamin B_{12} level at 1469 pg/mL but no micronutrient deficiencies. Her CRP level was within the normal range at 0.80 mg/L. The participant's IBD-DI score was -16, indicating mild disease-related disability.

Case 6:

Case 6 was a 32-year-old male with a BMI of 32.9, diagnosed with UC. He reported a surgical history of proctocolectomy with ileoanal J-pouch formation and subsequent ileostomy takedown. Case 6 reported symptoms of arthritis or arthralgia but no other chronic medical conditions. He was taking loperamide and protonix for symptom management. Laboratory analysis revealed vitamin D deficiency with a serum level of 25 ng/mL and an elevated CRP level of 6.15 mg/L, indicating mild to moderate systemic inflammation. His IBD-DI score was -7, indicating minimal disease-related disability.

Case 7:

Case 7 was a 25-year-old male with a BMI of 21.5, diagnosed with UC. He reported no history of gastrointestinal surgery, arthritis, arthralgia, or other chronic medical conditions. Case 5 was prescribed mesalamine and nortriptyline. Laboratory analysis revealed a vitamin D deficiency (20 ng/mL), but his CRP level was within normal limits. His IBD-DI score was –4, indicating minimal disease-related disability.

Table 4.2 Average daily micronutrient intake vs. micronutrient lab values

Case		Vitamin B_{12}	Vitamin D	Dietary Folate	Magnesium	Zinc	Iron
1	**Average daily intake**	2.47 mcg	3.44 mcg	184.74 mcg	131.81 mg	5.25 mg	6.73 mg
	Lab value	406 pg/mL	7 ng/mL	5.9 ng/mL	4.9 mg/dL	10.6 ug/mL	211 mcg/dL
2	**Average daily intake**	5.13 mcg	7.69 mcg	286.04 mcg	223.61 mg	9.28 mg	10.35 mg
	Lab value	908 pg/mL	98 ng/mL	8.9 ng/mL	4.7 mg/dL	11 ug/mL	104 mcg/dL
3	**Average daily intake**	13.67 mcg	12.09 mcg	379.79 mcg	427.38 mg	31.54 mg	21.01 mg
	Lab value	1379 pg/mL	47 ng/mL	11.8 ng/mL	4.6 mg/dL	13.2 ug/mL	109 mcg/dL
4	**Average daily intake**	7.816 mcg	7.01 mcg	138.63 mcg	111.06 mg	13.86 mg	7.82mg
	Lab value	735 pg/mL	75 ng/mL	10.1 ng/mL	5.3 mg/dL	12.9 ug/mL	89 mcg/dL
5	**Average daily intake**	4.62 mcg	3.65 mcg	312.68 mcg	238.60 mg	10.99 mg	10.50 mg
	Lab value	1469 pg/mL	52 ng/mL	16.5 ng/mL	4.9 mg/dL	11.6 ug/mL	146 mcg/dL
6	**Average daily intake**	6.70 mcg	6.78 mcg	401.90 mcg	345.46 mg	15.37 mg	13.89 mg
	Lab value	640 pg/mL	25 ng/mL	14.3 ng/mL	4.1 mg/dL	9.3 ug/mL	81 mcg/dL
7	**Average daily intake**	7.47 mcg	15.22 mcg	464.91 mcg	408.76 mg	16.26 mg	17.10 mg
	Lab value	523 pg/mL	20 ng/mL	15.4 ng/mL	5.1 mg/dL	12 ug/mL	77 mcg/dL

Prevalence of micronutrient deficiencies

Vitamin D deficiency was the most prevalent, affecting 43% of participants. Folate and magnesium deficiencies were each observed in 14% of the sample, while no deficiencies were

detected for vitamin B_{12}, zinc, or iron. Additionally, 29% of participants had elevated vitamin B_{12} levels, and 14% had high iron levels. The small sample size (n=7) limited further statistical analysis.

Chapter 5 - Micronutrient status and disease state in patients with inflammatory bowel disease: A case series

Abstract

Background

Inflammatory Bowel Disease (IBD) refers to chronic conditions that cause gastrointestinal inflammation. Micronutrient deficiencies are common in IBD and may contribute to disease progression. Despite this, nutritional screening is not standard practice in IBD care, potentially limiting effective disease management. This study aimed to describe individual patterns in dietary intake, micronutrient status, and disease burden among adults with IBD.

Methods

This case series examined the micronutrient levels of adults (n=7) with IBD through laboratory blood tests. Micronutrient intake was assessed using the Food Frequency Questionnaire (FFQ) from Fred Hutchinson Cancer Center. Disease-related disability was measured using the modified Inflammatory Bowel Disease Disability Index (IBD-DI), and inflammation was evaluated through C-reactive protein (CRP) levels.

Results

Vitamin D deficiency was the most common concern, observed in three cases. Two of the three participants had elevated CRP levels, indicating a relationship between inflammation and low vitamin D. Elevated B_{12} levels were noted in two cases, and one participant had low folate intake and deficiency. Iron and magnesium intake were associated with lower laboratory values, though no participants were iron deficient. IBD-DI scores indicated minimal disability despite

micronutrient deficiencies and elevated CRP. Trends suggested a link between inflammation and lower nutrient levels.

Conclusions

This study emphasizes the need for monitoring micronutrient status in IBD patients and calls for further research with larger sample populations to better understand the complex relationships between micronutrient levels, dietary intake, inflammation, and disease-related disability.

Background

Inflammatory Bowel Disease (IBD) refers to a group of chronic, inflammatory disorders of the gastrointestinal tract. The two most prevalent types of IBD are Crohn's disease (CD) and ulcerative colitis (UC), both of which often lead to debilitating symptoms such as diarrhea, abdominal pain, weight loss, and fatigue.[1] The pathogenesis of IBD is multifactorial, involving genetic susceptibility, immune dysregulation, disruptions of gut microbiota, and various environmental factors.[100] Over the past few decades, the global prevalence of IBD has risen significantly, especially in newly industrialized regions, reflecting increased reliance on convenience foods and higher antibiotic use.[1,3] The increasing incidence of IBD presents substantial challenges for healthcare systems, highlighting the need for continued innovations in both diagnostic and therapeutic strategies.

Management of IBD has historically focused on controlling symptoms and preventing complications. However, current treatment paradigms now emphasize a treat-to-target approach, prioritizing mucosal healing, clinical remission, and the reduction of long-term disease-related complications.[4,101] The recent development of biologic therapies targeting key inflammatory mediators, along with advancements in minimally invasive surgical techniques, has significantly

improved patient outcomes. Despite these advances, a comprehensive approach that combines pharmacological treatments with nutritional care and lifestyle modifications is essential for improving disease management and optimizing overall health.[100] Unfortunately, nutritional interventions are often underutilized in IBD care, further contributing to the high prevalence of micronutrient deficiencies in this population.

Patients with IBD are at an increased risk of malnutrition, which exacerbates disease symptoms, leads to complications, and negatively affects long-term outcomes.[6,7] The causes of malnutrition in IBD are complex, involving factors such as reduced nutrient absorption, surgical complications, dysbiosis, medication side effects, and increased nutritional demands during periods of active disease.[6,7] Micronutrient deficiencies, particularly vitamin D, B_{12}, folate, iron, magnesium, and zinc, are common in more than half of IBD patients, with higher rates observed in those with CD.[8–10] These deficiencies can further complicate disease management, increasing the risk of anemia, osteoporosis, and cardiovascular disease.

Despite the high prevalence of micronutrient deficiencies in IBD patients, routine nutritional screening is not a standard component of IBD care.[11] This results in significant gaps in disease management and underutilization of potential nutritional interventions that could improve clinical outcomes. A significant challenge in addressing these deficiencies is the limited knowledge among healthcare providers about the role of nutrition in managing chronic diseases.[12] Medical curricula in both the U.S. and Europe often lack thorough nutrition education, resulting in providers being less equipped to effectively integrate nutrition into IBD care.[12] This educational gap limits the application of nutrition-based interventions, potentially diminishing the overall effectiveness of treatment strategies.

While advancements in pharmacological therapies have significantly improved IBD management, the issue of micronutrient deficiencies remains largely unaddressed. This case series aimed to describe individual patterns in dietary intake, micronutrient status, and disease burden among adults with IBD. The findings highlight differences between cases and emphasize the importance of incorporating routine nutritional assessments into standard IBD care. Such assessments may aid in the early identification and management of micronutrient deficiencies, helping to prevent complications and promote overall health. Through detailed clinical and nutritional profiles, this case series contributes to the growing body of evidence that investigates relationships between nutrition, inflammation, and disease-related disability in the context of IBD.

Methods

Study Design

This case series presents detailed clinical and nutritional profiles of adult patients diagnosed with inflammatory bowel disease (IBD), including both ulcerative colitis (UC) and Crohn's disease (CD). Each case includes self-reported dietary intake data, subjective measures of disease-related disability, and objective laboratory markers of micronutrient status and systemic inflammation. Dietary intake data were collected using a food frequency questionnaire (FFQ) developed by the Nutrition Assessment Shared Resource (NASR) of Fred Hutchinson Cancer Center, Seattle, Washington. A modified, self-administered version of the Inflammatory Bowel Disease-Disability Index (IBD-DI),[98] a validated tool for assessing disease-related disability, was used to evaluate participants' perceived disease activity.[99] Blood samples were analyzed for vitamin D, vitamin B_{12}, folate, magnesium, iron, and zinc, as well as C-reactive protein (CRP), an established biomarker of systemic inflammation. The objective of this case

series was to assess individual patterns in dietary intake, micronutrient status, and disease burden among patients with IBD, and to highlight the clinical value of routine nutritional assessment in this population.

Participant Recruitment and Eligibility

Participants were recruited through various outreach efforts, including community postings and personal referrals. Recruitment materials were distributed at local healthcare clinics, emergency departments, private businesses, and gyms; however, most participants were recruited through word-of-mouth and social media. All participants were required to meet the established inclusion criteria prior to enrollment, and those who met exclusion criteria were not ineligible. Written informed consent was obtained prior to data collection.

Table 5.1 Inclusion and exclusion criteria

Inclusion Criteria	Exclusion criteria
• Age 18–65 • Existing IBD diagnosis, including Crohn's disease or ulcerative colitis • No additional active gastrointestinal illnesses (including, but not limited to, diverticulitis, Celiac disease, colorectal cancer, gastritis, liver disease, etc.) • Actively receiving care under a licensed gastroenterologist • Omnivorous diet • English-speaking • Access to a computer, mobile phone, or tablet for completion of surveys/informed consent	• Age <18 or >65 • No confirmed IBD diagnosis • Additional active gastrointestinal illnesses (including, but not limited to, diverticulitis, Celiac disease, colorectal cancer, gastritis, liver disease, etc.) • Not actively receiving care under a licensed gastroenterologist • Vegan or vegetarian diet • Non-English speaking • No access to a computer, mobile phone, or tablet for completion of surveys/informed consent

Surveys

After providing informed consent, participants received a confirmation email with instructions to contact a specific clinic in a Midwest city to schedule a blood draw. The email

also included secure links to the dietary and disability assessment surveys. The FFQ assessed general dietary intake patterns over the previous 12 months, while the IBD-DI evaluated disease-related disability based on subjective factors such as weight loss, body image, and the type and frequency of bowel movements. The scoring guide for the IBD-DI is outlined in Table 5.2. Participants were asked to complete the surveys within one week of their blood draw.

Table 5.2 Inflammatory Bowel Disease-Disability Index (IBD-DI) scoring guide.[98]

TOTAL SCORE	
Degree of Disability	**Total Score**
No Disability	22
Point of Neutrality	0
Minimal Disability	0 to -10
Mild Disability	-10 to -19
Moderate Disability	-20 to -35
Severe Disability	≤-35
Maximum Disability	-80

Blood Sample Collection and Analysis

Participants presented to the designated clinic for their scheduled appointment, where blood samples were drawn by certified phlebotomy personnel via venipuncture. A total of 27 mL of blood was drawn and distributed into two 9 mL serum separator tubes (SSTs) and one 9 mL heparin tube. The samples were stored frozen at temperatures below -20°F until analysis, which was conducted within 7–10 business days of collection. Blood samples were processed by a certified laboratory at the clinic and analyzed for vitamin B_{12}, vitamin D, folate, iron, magnesium and zinc. High-sensitivity CRP levels were also assessed. CRP levels were compared to micronutrient lab results to help identify correlations between inflammation and micronutrient levels. CRP levels between 1.9 and 10 mg/L were considered indicative of mild to moderate

inflammation, while levels greater than 10 mg/L suggest more serious inflammation. Reference ranges were provided by the clinical laboratory responsible for sample analysis and reflect standard values used at the time of testing

Table 5.3 Micronutrient biomarker matrices and reference ranges

Micronutrient	Matrix	Reference Range
Vitamin B_{12}	Serum	165–1100 pg/mL
Vitamin D	Serum	40–80 ng/mL
Folic acid (folate)	Serum	7.2–17.2 ng/mL
Magnesium	RBC	4.0–6.4 mg/dL
Zinc	RBC	8.6–15.8 ug/mL
Iron	Serum	
Males		50–195 mcg/dL
Females		40–190 mcg/dL

[a]Red blood cell (RBC)
[b] Reference ranges were provided by the clinical laboratory responsible for sample analysis and reflect standard values used at the time of testing

Data Analysis

Data were de-identified prior to analysis. Nutrient calculations were performed using the Nutrient Data System for Research (NDSR) software version 2024, developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN. Descriptive statistics were generated using R statistical software to summarize demographic and clinical characteristics. Prevalence of micronutrient deficiencies was determined by using counts and proportions.

Ethical Considerations

Ethical approval was obtained from the relevant Institutional Review Board before the study began. To ensure confidentiality, all data were de-identified, and electronic records were securely stored. Participants were provided with access to their individual micronutrient results, which were de-identified upon delivery to protect privacy. A participation incentive was provided to each participant upon completion of the study. All components of the study, including the incentive, were funded through internal resources.

Results

A total of 11 individuals enrolled in the study; however, one withdrew from the study and laboratory data for three was not received in time for analysis. Therefore, data from only seven cases were included in the analysis. The final sample consisted of three females (42.9%) and four males (57.1%). Among the final sample, two participants (28.6%) were diagnosed with Crohn's disease, while five (71.4%) had ulcerative colitis. The mean age was 33.57 years (SD = 10.91), and the mean BMI was 26.14 (SD = 4.37), indicating that participants were overweight on average. The Shapiro-Wilk test confirmed that both age ($p = 0.4693$) and BMI ($p = 0.7262$) followed a normal distribution. The demographic and clinical characteristics of the cases are outlined Table 5.4.

Table 5.4 Demographic and clinical characteristics of cases

Case	Age (years)	Sex	IBD diagnosis	Decreased MN levels	Elevated MN levels	IBD-DI score	CRP level (mg/L)	BMI
1	24	M	UC	Vitamin D, folate	Iron	-9	5.70	29.3
2	21	M	CD	None	Vitamin D	3	1.19	25.8
3	40	F	CD	None	Vitamin B_{12}	-8	11.79	21
4	49	F	UC	None	None	-17	2.17	23.9
5	44	F	UC	None	Vitamin B_{12}	-16	0.80	28.6
6	32	M	UC	Vitamin D	None	-7	6.15	32.9
7	25	M	UC	Vitamin D	None	-4	1.80	21.5

[a]Sex: male (M) or female (F)
[b]Inflammatory bowel disease (IBD) diagnosis: Crohn's disease (CD) or ulcerative colitis (UC)
[c]Micronutrient (MN)
[d]Inflammatory Bowel Disease Disability Index (IBD-DI) Score: Range -80–22; lower scores are associated with higher degree of disability
[e]C-reactive protein (CRP) reference range: 0.00–1.90 mg/L

The objective of this case series was to assess individual patterns in dietary intake, micronutrient status, and disease burden among patients with IBD. Additional analyses aimed to examine variations in dietary intake and micronutrient levels across cases and assess the prevalence of specific micronutrient deficiencies (e.g., vitamin D, B_{12}, folate, iron, magnesium, zinc) within the population.

Case 1

Case 1 was a 24-year-old male with a BMI of 29.3, diagnosed with ulcerative colitis (UC). He reported no history of gastrointestinal (GI) surgery or additional chronic health conditions, and no symptoms of arthritis or arthralgia. Case 1 was prescribed mesalamine for management of his UC. Laboratory analysis revealed deficiencies in vitamin D (7 ng/mL) and folate (5.9 ng/mL). His C-reactive protein (CRP) level was elevated at 5.7 mg/L, indicating mild

to moderate systemic inflammation. The patient's Inflammatory Bowel Disease-Disability Index (IBD-DI) score was -9, indicating minimal disease-related disability.

Case 2

Case 2 was a 21-year-old male with a BMI of 25.8, diagnosed with Crohn's disease (CD). He reported no history of GI surgeries or additional chronic health conditions, and no symptoms of arthritis or arthralgia. Case 2 was prescribed azathioprine for management of his CD. Laboratory analysis showed elevated vitamin D levels (98 ng/mL) with no micronutrient deficiencies identified. His CRP was within normal range, and his IBD-DI score was 3, which is close to the point of neutrality but indicates some disease-related disability.

Case 3

Case 3 was a 40-year-old female with a BMI of 21, diagnosed with Crohn's disease. She reported a history of autoimmune hepatitis and has undergone a total colectomy with a subsequent pull-through and J-pouch reconstruction. The participant was prescribed prednisone and Skyrizi, and also reported taking probiotics, prebiotics, and N-acetyl L-cysteine as part of her CD management regimen. Laboratory analysis revealed elevated vitamin B_{12} levels (1379 pg/mL) but did not identify micronutrient deficiencies. Her CRP level was elevated at 11.79 mg/L, indicating moderate to severe systemic inflammation. Case 3 has an IBD-DI score of -8, indicating minimal disease-related disability. She denied symptoms of arthritis or arthralgia.

Case 4:

Case 4 was a 49-year-old female with a BMI of 23.9, diagnosed with UC. She reported no history of GI surgery or additional chronic medical conditions, but she did report symptoms of arthritis or arthralgia. Case 4 was prescribed balsalazide for management of her UC. Laboratory analysis revealed no micronutrient deficiencies, but her CRP level was elevated at

2.17 mg/L, indicating mild systemic inflammation. Her IBD-DI score was -17, indicating mild disease-related disability.

Case 5:

Case 5 was a 44-year-old female with a BMI of 28.6, diagnosed with UC. She reported a history of gastric bypass surgery and symptoms of arthritis or arthralgia but denied any other chronic medical conditions. Case 5 was prescribed mesalamine for management of her UC. Laboratory analysis showed an elevated serum vitamin B_{12} level at 1469 pg/mL but no micronutrient deficiencies. Her CRP level was within the normal range at 0.80 mg/L. The participant's IBD-DI score was -16, indicating mild disease-related disability.

Case 6:

Case 6 was a 32-year-old male with a BMI of 32.9, diagnosed with UC. He reported a surgical history of proctocolectomy with ileoanal J-pouch formation and subsequent ileostomy takedown. Case 6 reported symptoms of arthritis or arthralgia but no other chronic medical conditions. He was taking loperamide and protonix for symptom management. Laboratory analysis revealed vitamin D deficiency with a serum level of 25 ng/mL and an elevated CRP level of 6.15 mg/L, indicating mild to moderate systemic inflammation. His IBD-DI score was -7, indicating minimal disease-related disability.

Case 7:

Case 7 was a 25-year-old male with a BMI of 21.5, diagnosed with UC. He reported no history of gastrointestinal surgery, arthritis, arthralgia, or other chronic medical conditions. Case 5 was prescribed mesalamine and nortriptyline. Laboratory analysis revealed a vitamin D deficiency (20 ng/mL), but his CRP level was within normal limits. His IBD-DI score was –4, indicating minimal disease-related disability.

Table 5.5 Average daily micronutrient intake vs. micronutrient lab values

Case		Vitamin B_{12}	Vitamin D	Dietary Folate	Magnesium	Zinc	Iron
1	**Average daily intake**	2.47 mcg	3.44 mcg	184.74 mcg	131.81 mg	5.25 mg	6.73 mg
	Lab value	406 pg/mL	7 ng/mL	5.9 ng/mL	4.9 mg/dL	10.6 ug/mL	211 mcg/dL
2	**Average daily intake**	5.13 mcg	7.69 mcg	286.04 mcg	223.61 mg	9.28 mg	10.35 mg
	Lab value	908 pg/mL	98 ng/mL	8.9 ng/mL	4.7 mg/dL	11 ug/mL	104 mcg/dL
3	**Average daily intake**	13.67 mcg	12.09 mcg	379.79 mcg	427.38 mg	31.54 mg	21.01 mg
	Lab value	1379 pg/mL	47 ng/mL	11.8 ng/mL	4.6 mg/dL	13.2 ug/mL	109 mcg/dL
4	**Average daily intake**	7.816 mcg	7.01 mcg	138.63 mcg	111.06 mg	13.86 mg	7.82mg
	Lab value	735 pg/mL	75 ng/mL	10.1 ng/mL	5.3 mg/dL	12.9 ug/mL	89 mcg/dL
5	**Average daily intake**	4.62 mcg	3.65 mcg	312.68 mcg	238.60 mg	10.99 mg	10.50 mg
	Lab value	1469 pg/mL	52 ng/mL	16.5 ng/mL	4.9 mg/dL	11.6 ug/mL	146 mcg/dL
6	**Average daily intake**	6.70 mcg	6.78 mcg	401.90 mcg	345.46 mg	15.37 mg	13.89 mg
	Lab value	640 pg/mL	25 ng/mL	14.3 ng/mL	4.1 mg/dL	9.3 ug/mL	81 mcg/dL
7	**Average daily intake**	7.47 mcg	15.22 mcg	464.91 mcg	408.76 mg	16.26 mg	17.10 mg
	Lab value	523 pg/mL	20 ng/mL	15.4 ng/mL	5.1 mg/dL	12 ug/mL	77 mcg/dL

Prevalence of micronutrient deficiencies

Vitamin D deficiency was the most prevalent, affecting 43% of participants. Folate and magnesium deficiencies were each observed in 14% of the sample, while no deficiencies were detected for vitamin B_{12}, zinc, or iron. Additionally, 29% of participants had elevated vitamin B_{12} levels, and 14% had high iron levels. The small sample size (n=7) limited further statistical analysis.

Conclusions

This case series aimed to explore individual patterns in dietary intake, micronutrient status, and disease burden in adults with IBD. By examining these variables, the study sought to identify trends that could inform clinical care and provide insight into the variability of nutritional needs. These findings reinforce the importance of personalized care strategies and point to areas where further research is needed.

Among the participants, vitamin D deficiency was the most common nutritional concern, affecting Cases 1, 6, and 7. Each of the participants had low serum vitamin D levels (ranging from 7–25 ng/mL), which aligns with existing literature that identifies vitamin D deficiency as a common issue in IBD populations.[6] Notably, two of these individuals (Cases 1 and 6) also had elevated CRP levels, suggesting a possible relationship between inflammation and low vitamin D status. In contrast, Case 7 exhibited a normal CRP level despite having a vitamin D deficiency, suggesting that deficiencies may develop even without apparent inflammation. Variability in serum vitamin D levels may also reflect differences in individual absorption and metabolism. Additionally, factors such as glucocorticoid use, chronic inflammation, small-bowel resection, and deficiencies in other nutrients may influence vitamin D status.[6]

Vitamin B_{12} intake appeared higher in some participants with elevated serum levels, which may reflect over-supplementation or altered metabolism. Cases 3 and 5 both exhibited elevated B_{12} levels without any reported deficiencies. Folate status also appeared to align with dietary patterns. Case 1, the only participant with a folate deficiency, also reported a low folate intake, suggesting inadequate intake may have contributed to the deficiency.

Unexpectedly, participants who reported higher intakes of iron and magnesium tended to have lower laboratory values, which may reflect inflammation-related malabsorption. Iron-

deficiency anemia is the most common nutritional complication of IBD, and circulating iron levels can be influenced by the acute-phase response.[11] While no participants in this case series were iron-deficient, the trend warrants further investigation in larger cohorts. Additionally, lower magnesium levels are reported more frequently in males, and since this case series included more male than female participants, this may partially explain the observed patterns.[11] Zinc levels appeared to align with dietary intake; however, individual variability suggests that serum levels may be affected by other physiological or clinical factors.

Elevated CRP levels were observed in four individuals (Cases 1, 3, 4, and 6), with Case 3 exhibiting the highest level (11.79 mg/L), which is indicative of moderate to severe inflammation. Notably, Case 3 also had a history of autoimmune hepatitis and extensive gastrointestinal surgery, factors that may contribute to systemic inflammation. These findings support the use of CRP as a valuable clinical marker for assessing disease activity, while also highlighting the importance of interpreting it in conjunction with other clinical and nutritional indicators.

Disease-related disability, as measured by the IBD-DI, ranged from –17 (mild disability) to 3, which is close to the point of neutrality. Interestingly, participants with both elevated CRP and micronutrient deficiencies (e.g., Cases 1 and 6) reported only minimal disability. This suggests that self-reported disability may not always align with objective clinical markers, highlighting the need for a multidimensional approach to IBD management. Observations from this case series also raise questions about the potential relationship between inflammation, nutrient status—particularly vitamin D—and perceived disability, warranting further exploration in larger studies.

The mean BMI across the cases was 26.1 (SD = 4.37), which falls within the overweight range. This reflects broader trends observed in the IBD population. Valvano et al[70] reported an increase in the incidence of overweight and obesity in IBD patients over the past several decades, with the mean BMI rising from 20.8 to 27.0. Obesity in IBD patients may contribute to increased inflammation, as visceral fat can promote the release of inflammatory cytokines.[70] These findings emphasize the importance of considering body composition and metabolic health in addition to nutritional and inflammatory biomarkers.

From a clinical perspective, routine vitamin D monitoring may be necessary, especially given its potential link to low bone mineral density.[11] The observed patterns between iron and magnesium intake and laboratory levels raise concerns about nutrient metabolism in IBD, as inflammation and malabsorption may affect nutrient bioavailability.[6] While zinc and magnesium deficiencies were not observed in this case series, the potential for managing these nutrients through diet or supplementation warrants further investigation. Larger studies are needed to confirm these trends and explore their clinical implications.

Another important consideration is the prevalence of elevated vitamin B_{12} levels, which were observed in 29% of the cases included in this study. Research suggests that factors such as advanced age, high blood pressure, decreased kidney function, and elevated liver enzyme concentrations are associated with higher plasma B_{12} levels.[102] These factors may reflect altered B_{12} metabolism and could indicate a potential link to over-supplementation. Elevated B_{12} levels have been associated with an increased risk of all-cause mortality.[102] Therefore, careful monitoring of B_{12} levels in IBD patients, particularly in those receiving supplementation, is crucial.

This case series focused on a limited range of micronutrients, but prior studies have identified frequent deficiencies in other nutrients, including vitamins A, C, E, K, B_1, and B_6, as well as ferritin, calcium, selenium, copper, and manganese.[10,70] To gain a more comprehensive understanding of the role micronutrients play in IBD, future studies should explore a broader spectrum of nutrients. Larger cohorts will be critical to enhancing the evidence base and refining clinical recommendations for micronutrient monitoring and targeted interventions in IBD care.

Although this case series offers insight into the micronutrient status of adults with IBD, several limitations should be considered. The focus on individual cases limits the ability to draw broader conclusions, and the lack of variation in disease severity and treatment approaches may have influenced the observed patterns in micronutrient status and disease-related disability. As a descriptive analysis of individual cases, this study offers valuable observations, but due to its small sample size (n = 7), the findings cannot be generalized to the broader IBD population.

An additional limitation of this study was the reliance on participant-reported dietary intake through the FFQ, which may have introduced recall bias and affected the accuracy of nutrient intake assessments. More objective measures, such as food diaries, could provide more reliable data by reducing reliance on memory and minimizing the risk of misreporting portion sizes. Additionally, several confounding factors, including inflammation, disease duration and severity, previous surgical interventions, pharmacotherapy, and malabsorption, may have influenced the micronutrient levels observed. Biological variability, such as differences in nutrient absorption and metabolic demands, could also have impacted the results. Given the small sample size and descriptive nature of this case series, future studies with larger and more diverse cohorts are needed to confirm these findings and help define the complex interactions between dietary intake, micronutrient status, inflammation, and disease-related factors in IBD.

In conclusion, this case series provides valuable insights into the potential relationships between micronutrient status and disease-related factors in adults with IBD. The observed vitamin D deficiencies highlight the importance of nutritional evaluations and targeted interventions. While other micronutrient levels appeared adequate, unexpected patterns—particularly in relation to inflammation and disease-related disability—warrant further investigation. Although trends indicate a possible link between inflammation and lower nutrient levels, these results emphasize the need for larger, more comprehensive studies. Differences observed within this small group demonstrate the importance of personalized care strategies in IBD management. Routine nutritional assessments, combined with clinical and biochemical evaluations, can provide a more complete understanding of a patient's health and can be used to help develop personalized interventions. Although the results of this case series are preliminary, they contribute to the growing body of knowledge on the complex interactions between diet, micronutrient status, inflammation, and disability in IBD, while establishing the foundation for future research to further investigate their role in disease progression and patient outcomes.

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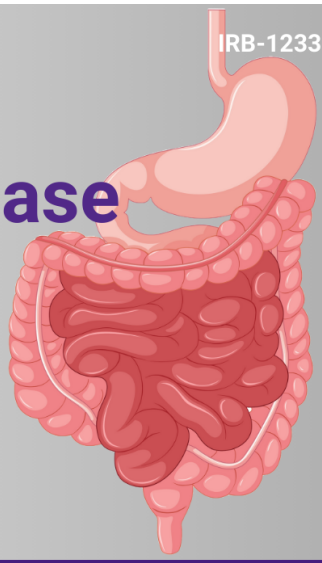
Appendix A - Recruitment flyer: Version A

IRB-12334

Micronutrients and Inflammatory Bowel Disease

If you are 18 or older and suffer from Crohn's disease or ulcerative colitis (UC), you may be eligible to participate in a research study designed to explore the relationship between micronutrients and the symptoms of your inflammatory bowel disease (IBD).



You may be eligible if...

- You are between the ages of 18 and 65
- You have been diagnosed with IBD
- You have not been diagnosed with other gastrointestinal issues, such as celiac disease or diverticulitis

Study Requirements

- Complete a food frequency questionnaire
- Complete a survey designed to assess the severity of your symptoms
- Allow us to draw a sample of your blood

Participant Benefits

- A **$100 award** for your participation
- A free micronutrient assessment
- The opportunity to learn more about your health

Riordan Clinic

3100 N Hillside St.
Wichita, KS 67219

Contact & Registration

Kacie Stull, M.S.
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(785) 313-1272
kmmallon@ksu.edu

KANSAS STATE UNIVERSITY

Appendix B - Recruitment flyer: Version B

IRB-12334

Micronutrients and Inflammatory Bowel Disease

If you are 18 or older and suffer from Crohn's disease or ulcerative colitis (UC), you may be eligible to participate in a research study designed to explore the relationship between micronutrients and the symptoms of your inflammatory bowel disease (IBD).

You may be eligible if...

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- Complete a food frequency questionnaire
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Participant Benefits

- A **$100 award** for your participation
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- The opportunity to learn more about your health

Contact & Registration

Kacie Stull, M.S.
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KANSAS STATE UNIVERSITY

Appendix C - Information flyer: Project overview

KANSAS STATE UNIVERSITY

MICRONUTRIENT STATUS AND DISEASE STATE IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

A Doctoral Research Project

RESEARCH PROTOCOL: IRB-12334

SYNOPSIS:

The proposed research study will investigate the relationship between micronutrient levels and disease activity in adult patients with inflammatory bowel disease (IBD). Study participants will complete a food frequency questionnaire designed to estimate nutrient status, and a survey designed to assess the frequency and severity of their disease symptoms. Participants will also consent to have a sample of their blood drawn. Blood samples will be analyzed to measure micronutrient levels. The results of the study will identify patterns between micronutrients levels and IBD symptoms that may help predict disease activity.

STUDY BENEFITS:

This study may identify micronutrient deficiencies within the study population that may have otherwise been overlooked. This information may be used to address nutritional deficiencies amongst the participants while also highlighting the importance of routine nutritional assessment in patients with inflammatory bowel disease. Correction of deficiencies could potentially improve disease symptoms and reduce the risk for other health concerns. The results of this study may identify micronutrient deficiencies that contribute to disease activity and may encourage researchers to further explore correlations between nutrient status and IBD disease activity.

STUDY DESCRIPTION:

The proposed research will explore correlations between disease activity and micronutrient status in adult patients diagnosed with inflammatory bowel disease (IBD), specifically ulcerative colitis and Crohn's disease. The sample population will be recruited locally via social media, flyers, and gastroenterology clinics and must meet all established inclusion/exclusion criteria prior to participation.

After providing informed consent, participants will receive a confirmation email. This email will ask the participants to call the Riordan Clinic in Wichita, KS and schedule an appointment to have a sample of their blood drawn by certified phlebotomy personnel. The email will also include links to two surveys: a web-based Food Frequency Questionnaire (FFQ) validated by the Fred Hutchinson Cancer Center and a modified, self-administered version of the Inflammatory Bowel Disease-Disability Index (IBD-DI). The FFQ will detect dietary intake patterns that may contribute to micronutrient deficiencies and the IBD-DI will classify the disease state of each participant as active or inactive. Participants will be required to complete the surveys independently within one week of having their blood drawn. Participants will receive a reminder to complete the surveys via their preferred method of communication.

Participants will present to the Riordan Clinic at the time of their scheduled appointment to have a sample of their blood drawn. The amount of blood required from each participant will equate to 27 mL in total: 2 x 9 mL serum (SST) tubes and 1 x 9mL heparin tube. After collection, blood samples will be processed by Bio-Center Lab at Riordan Clinic. Each sample will be analyzed to assess levels of B12, folate (B-9), vitamin D, magnesium, zinc, ferratin, iron, and c-reactive protein (CRP). CRP levels obtained from analysis of blood samples will be compared to the results of the IBD-DI to help validate the survey results. Statistical analysis of the results will be interpreted to identify relationships or patterns between micronutrient status and disease activity.

VARIABLES TO BE STUDIED:

- Micronutrients: B12, folate, vitamin D, magnesium (red blood cell), zinc (red blood cell), serum ferratin, iron (and total iron-binding capacity)
- Inflammatory Markers: high sensitivity c-reactive protein (CRP-hs), disease activity (active vs. inactive disease)
- Dietary Intake via FFQ: frequency/quantity of micronutrients consumed (B12, folate, vit. D, magnesium, zinc, iron)

INCLUSION CRITERIA:

To be eligible to participate in the research study, participants must meet the following criteria:

- Ages18–65
- Diagnosis of inflammatory bowel disease (IBD), to include Crohn's disease or ulcerative colitis
- No additional active gastrointestinal illnesses (including, but not limited to, diverticulitis, Celiac disease, colorectal cancer, gastritis, liver disease, etc.); irritable bowel syndrome does not exclude participants from eligibility
- Actively receiving care under a gastroenterologist
- Consumes an omnivorous diet
- Can read, write, and speak English
- Has access to computer/mobile phone/tablet for completion of surveys/informed consent

EXCLUSION CRITERIA:

Subjects will not be eligible to participate in the study if they meet any of the following criteria:

- Ages <18 or >65
- No confirmed inflammatory bowel disease diagnosis
- Additional active gastrointestinal illnesses (including, but not limited to, diverticulitis, Celiac disease, colorectal cancer, gastritis, liver disease, etc.); irritable bowel syndrome does not exclude participants from eligibility
- Not actively receiving care under a gastroenterologist
- Vegan or vegetarian diet
- Non-English speaking
- Does not have access to computer/mobile phone/tablet for completion of surveys/informed consent

INCENTIVE

Upon completion of the two surveys and the blood draw, Kansas State University will award each participant $100 in compensation for their participation. Payment will be distributed via the participant's preferred method (debit card, direct deposit, or physical check).

CONTACT INFORMATION

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Appendix D - Informed consent document

KANSAS STATE UNIVERSITY
University Research Compliance Office

Institutional Review Board (IRB)
Informed Consent
comply@k-state.edu | 785-532-3224

PROJECT TITLE:
Micronutrient Status and Disease State in Patients with Inflammatory Bowel Disease

PROJECT APPROVAL DATE:	10/01/2024	**PROJECT EXPIRATION DATE:**	9/30/2027	**LENGTH OF STUDY:**	3 years

PRINCIPAL INVESTIGATOR: Tandalayo Kidd

CO-INVESTIGATOR(S): Kacie (Mallon) Stull, Linda Yarrow, Jennifer Hanson

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PURPOSE OF THE RESEARCH:
During this research study, we will ask you to complete two surveys and to allow us to draw a sample of your blood. These tests will help us measure specific nutrients in your blood and the foods you eat and will help us evaluate your disease symptoms. By measuring and comparing these items, we believe we will discover patterns in micronutrient levels that will help us predict how often symptoms of inflammatory bowel disease will occur and how serious they may be.

PROCEDURES OR METHODS TO BE USED:
Once you have been enrolled in the study, you will receive a confirmation email containing instructions. You will be required to call the Riordan Clinic in Wichita, KS and schedule an appointment to have a sample of your blood drawn by a trained staff member. You will also be asked to independently complete two electronic surveys, the Fred Hutch Cancer Center Food Frequency Questionnaire (FFQ) and a modified version of the Inflammatory Bowel Disease-Disability Index (IBD-DI). These surveys must be completed within one week of having your blood drawn. After you have completed the two surveys and had your blood drawn, you will be awarded $100 for your participation. You may choose to receive this compensation via debit card, direct deposit, or physical check. Once we have received the results of your surveys and blood analysis, we will contact you to share any information with you that we believe may be beneficial for your health.

BIOLOGICAL SAMPLES COLLECTED (Describe procedure, storage, etc.):
A sample of your blood will be taken and stored frozen at Riordan Clinic for 7–10 business days before it is analyzed. After your blood sample has been analyzed, it will be stored frozen for one month. After one month, a company that specializes in destroying biohazardous material will destroy your blood sample.

Whole genome sequencing will not be included as part of the research
You will be informed of clinically relevant results that are discovered as part of the research.

RISKS OR DISCOMFORTS ANTICIPATED:

Some of the information that you will be asked to provide may be considered private or sensitive. When providing your blood sample, you may be at risk for pain, bleeding, fainting, bruising, infection, or hematoma, which is a small collection of blood under the skin/tissue that is typically caused by a broken blood vessel. These risks are not generally serious or life-threatening.

BENEFITS ANTICPATED:

We believe the results of this study will help us understand the relationship between micronutrients and the symptoms of inflammatory bowel disease (IBD). We expect to learn that some individuals who participate in this study will be low or deficient in specific micronutrients. We hope the results of this study will inspire future research and will encourage physicians to perform regular nutritional testing for patients with IBD.

EXTENT OF CONFIDENTIALITY:

All health information collected by Riordan Clinic will be stored according to the clinic's policies; HIPPA guidelines will be followed. Any information that could reveal your identity will be removed from the data after it has been collected. All private or sensitive data will be de-identified and stored on a password-protected OneDrive account that will only be accessed by the principal investigator. Co-investigators may only access data via private invitation. No information that could be used to reveal your identity will be included in published materials.

The information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

IS COMPENSATION OR MEDICAL TREATMENT AVAILABLE IF INJURY OCCURS? ☐ Yes ☒ No

Terms of participation: I understand this project is research, and that my participation is voluntary. I also understand that if I decide to participate in this study, I may withdraw my consent at any time, and stop participating at any time without explanation, penalty, or loss of benefits, or academic standing to which I may otherwise be entitled. Should I choose to withdraw from this study, I understand that I will no longer be eligible for the participation incentive, and I will not receive compensation for my participation.

I verify that my signature below indicates that I have read and understand this consent form, and willingly agree to participate in this study under the terms described, and that my signature acknowledges that I have received a signed and dated copy of this consent form.

(Remember that it is a requirement for the P.I. to maintain a signed and dated copy of the same consent form signed and kept by the participant).

PARTICIPANT NAME:			
PARTICIPANT SIGNATURE:		**DATE:**	
WITNESS TO SIGNATURE: (PROJECT STAFF)		**DATE:**	

Appendix E - Sample food frequency questionnaire developed by the Nutrition Assessment Shared Resource (NASR) at Fred Hutchinson Cancer Center

Food Questionnaire

This form asks about your usual food intake during _____ .

Please use **pencil**.

Answer by filling in the correct oval.

● Yes ○ No

Do not make any other marks on the form. Please use a separate piece of paper to make comments.

SEX
○ Male
○ Female

TODAY'S DATE
MO DAY YEAR

IDENTIFICATION NUMBER

GNA

SAMPLE

Contact nasr@fredhutch.org for a cost estimate.

For information about our services, visit fredhutch.org/nasr.

Part I: Usual Food Choices

These questions are about the types of foods you ate during _____.

1. Did you eat chicken or turkey?

- ○ Yes → **When you ate chicken or turkey, how often did you eat the skin?**
  - ○ Almost always
  - ○ Often
  - ○ Sometimes
  - ○ Rarely
  - ○ Never
- ○ No

2. Did you eat beef, pork, ham or lamb?

- ○ Yes → **When you ate beef, pork, ham or lamb, how often did you eat the fat?**
  - ○ Almost always
  - ○ Often
  - ○ Sometimes
  - ○ Rarely
  - ○ Never
- ○ No

3. Did you eat hamburger or other ground meat?

- ○ Yes → **When you ate hamburger or other ground meat, was it usually...** *Mark one or two.*
  - ○ Regular
  - ○ Lean
  - ○ Extra lean
  - ○ Ground chicken or turkey
  - ○ Don't know
- ○ No

4. Did you drink orange, grapefruit or other fruit juices?

- ○ Yes → **Were any of these vitamins or minerals added (specially fortified) to the juices you drank?** *Mark all that apply.*
  - ○ Extra Vitamin C
  - ○ Vitamin E
  - ○ Calcium
  - ○ None
  - ○ Don't know
- ○ No

5. Did you eat cold cereals?

- ○ Yes → **When you ate cold cereal, what type did you usually eat?** *Mark one or two.*
  - ○ Highly fortified cereals (100% of Daily Values) such as Total®, Smart Start® and Product 19®
  - ○ High fiber or bran cereals such as Raisin Bran® and All Bran®
  - ○ Sweetened cereals such as Frosted Flakes® and Froot Loops®
  - ○ All other cereals such as Cheerios®, Corn Flakes® and granola
- ○ No

6. Did you put milk (all types), cream or creamer on cereal?

- ○ Yes → **When you put milk, cream or creamer on cereal, what type did you usually use?** *Mark one or two.*
  - ○ Cream or half and half
  - ○ Whole milk
  - ○ 2% milk
  - ○ 1% milk or buttermilk
  - ○ Nonfat or skim milk
  - ○ Soy milk
  - ○ Non-dairy creamer
  - ○ Don't know
- ○ No

7. Did you put milk (all types), cream or creamer in coffee or tea?

- ○ Yes → **When you put milk, cream or creamer in coffee or tea, what type did you usually use?** *Mark one or two.*
  - ○ Cream or half and half
  - ○ Whole milk
  - ○ 2% milk
  - ○ 1% milk or buttermilk
  - ○ Nonfat or skim milk
  - ○ Soy milk
  - ○ Non-dairy creamer
  - ○ Don't know
- ○ No

8. Did you drink milk (all types)? *Also include beverages made with milk, such as lattes, cappuccinos, mochas or hot chocolate.*

- ○ Yes → **When you drank milk or beverages made with milk, was it usually...** *Mark one or two.*
  - ○ Whole milk
  - ○ 2% milk
  - ○ 1% milk or buttermilk
  - ○ Nonfat or skim milk
  - ○ Soy milk
  - ○ Don't know
- ○ No

9. Did you use salad dressing?

- ○ Yes → **When you used salad dressing, what type did you usually use?** *Mark one or two.*
  - ○ Regular, including oil and vinegar
  - ○ Low or reduced fat
  - ○ Fat free or nonfat
- ○ No

10. Did you use mayonnaise?

- ○ Yes → **When you used mayonnaise, what type did you usually use?** *Mark one or two.*
  - ○ Regular
  - ○ Low or reduced fat
  - ○ Fat free or nonfat
- ○ No

11. Did you eat cookies or cakes?

- ○ Yes → **When you ate cookies or cakes, how often were they fig bars, angel food cakes, or other types of low or nonfat cookies or cakes?**
  - ○ Almost always
  - ○ Often
  - ○ Sometimes
  - ○ Rarely
  - ○ Never
- ○ No

12. In your household, what kinds of fat were usually used when cooking, for example to flavor vegetables or fry meat? *Mark up to four.*

- ○ Butter
- ○ Butter blended with oil or margarine
- ○ Stick margarine
- ○ Regular tub margarine
- ○ Diet or light margarine (tub or liquid)
- ○ Olive oil
- ○ Canola oil
- ○ Other oils such as corn, soybean, peanut and safflower
- ○ Lard, bacon fat or meat drippings
- ○ Didn't use fat or used non-stick spray (Pam®)

13. What kinds of fat did you use at the table, for example on breads, vegetables or potatoes? *Mark up to four.*

- ○ Butter
- ○ Butter blended with oil or margarine
- ○ Stick margarine
- ○ Regular tub margarine
- ○ Diet or light margarine (tub or liquid)
- ○ Olive oil
- ○ Sour cream
- ○ Didn't use fat

PLEASE DO NOT WRITE IN THIS AREA

Part II: Usual Food Use

These questions are about foods you ate during _____.

14. Mark the column to show how often, on average, you ate the following foods. Mark your usual serving size as small, medium or large.

- A small serving is about one-half (½) the medium serving size or less.
- A large serving is about one-and-a-half (1½) times the medium serving size or more.

EXAMPLE: This person ate spaghetti with meat sauce every Saturday. They usually ate about 1½ cups.

	HOW OFTEN DID YOU EAT THESE FOODS?									→ AMOUNT?			
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Spaghetti, lasagna, and other pasta with tomato and meat sauce	○	○	○	●	○	○	○	○	○	1 cup	○	○	●

CEREALS, BREADS, SNACKS

	HOW OFTEN DID YOU EAT THESE FOODS?									→ AMOUNT?			
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Cold cereals	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Cooked cereals and grits	○	○	○	○	○	○	○	○	○	1cup	○	○	○
Milk on cereals	○	○	○	○	○	○	○	○	○	½ cup	○	○	○
Pancakes, French toast and waffles	○	○	○	○	○	○	○	○	○	2 pieces	○	○	○
Muffins, scones, croissants and biscuits	○	○	○	○	○	○	○	○	○	1 medium	○	○	○
White breads, including bagels, rolls and English muffins	○	○	○	○	○	○	○	○	○	2 slices or 1 medium	○	○	○
Whole grain breads and rolls	○	○	○	○	○	○	○	○	○	2 slices or 1 medium	○	○	○
Plain tortillas as a side dish (include flour and corn)	○	○	○	○	○	○	○	○	○	2 small or 1 medium	○	○	○
Cornbread and corn muffins	○	○	○	○	○	○	○	○	○	2 slices or 1 medium	○	○	○
Butter or margarine on breads, cereals, pancakes, etc.	○	○	○	○	○	○	○	○	○	2 pats or 2 teaspoons	○	○	○
Jam, jelly, honey, syrup and sugar (including in coffee, tea and cereal)	○	○	○	○	○	○	○	○	○	2 Tbsp.	○	○	○
Granola bars and cereal bars such as Nutri-Grain Bars®	○	○	○	○	○	○	○	○	○	1 bar	○	○	○
Sports or meal replacement bars such as Power Bars® and Clif Bars®	○	○	○	○	○	○	○	○	○	1 bar	○	○	○

CEREALS, BREADS, SNACKS (continued)

	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Low or nonfat potato chips, tortilla chips, corn chips and pretzels	○	○	○	○	○	○	○	○	○	2 handfuls or 1 sm. bag	○	○	○
Regular potato chips, tortilla chips, corn chips and puffs	○	○	○	○	○	○	○	○	○	2 handfuls or 1 sm. bag	○	○	○
Plain popcorn (no butter) or lowfat microwave popcorn	○	○	○	○	○	○	○	○	○	4 handfuls	○	○	○
Buttered or regular microwave popcorn	○	○	○	○	○	○	○	○	○	4 handfuls	○	○	○
Low or nonfat crackers such as saltines	○	○	○	○	○	○	○	○	○	6 medium	○	○	○
Whole grain crackers such as Triscuits® and rye crispbread	○	○	○	○	○	○	○	○	○	6 medium	○	○	○
Regular crackers such as Ritz® and club crackers	○	○	○	○	○	○	○	○	○	6 medium	○	○	○
Peanut butter, peanuts and other nuts and seeds	○	○	○	○	○	○	○	○	○	2 Tbsp. (spreads) or 1/4 cup (nuts)	○	○	○

MEAT, FISH, EGGS

	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Eggs (egg substitute, mark "NEVER")	○	○	○	○	○	○	○	○	○	2 eggs	○	○	○
Bacon and breakfast sausage	○	○	○	○	○	○	○	○	○	3 strips or 2 links	○	○	○
Low or reduced fat hot dogs and sausage	○	○	○	○	○	○	○	○	○	1 hot dog or 2 ounces	○	○	○
Regular hot dogs and sausage such as bratwurst and chorizo	○	○	○	○	○	○	○	○	○	1 hot dog or 2 ounces	○	○	○
Lunch meats such as ham, turkey and lowfat bologna	○	○	○	○	○	○	○	○	○	2 slices	○	○	○
All other lunch meat such as bologna, salami and Spam®	○	○	○	○	○	○	○	○	○	2 slices	○	○	○
Canned tuna, tuna salad and tuna casserole	○	○	○	○	○	○	○	○	○	1/2 can tuna or 1 cup casserole	○	○	○
Beef, pork, ham and lamb	○	○	○	○	○	○	○	○	○	4 ounces	○	○	○
Ground meat, including hamburgers and meatloaf	○	○	○	○	○	○	○	○	○	1 medium patty or 3 ounces	○	○	○
Liver, chicken liver and organ meats	○	○	○	○	○	○	○	○	○	4 ounces	○	○	○
Fried chicken, including nuggets and tenders	○	○	○	○	○	○	○	○	○	1 large piece or 6 nuggets	○	○	○

PLEASE DO NOT WRITE IN THIS AREA

MEAT, FISH, EGGS (continued)

	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Chicken and turkey (roasted, stewed, grilled or broiled)	○	○	○	○	○	○	○	○	○	1 large or 2 small pieces	○	○	○
Fried fish, fish sandwich and fried shellfish (shrimp and oysters)	○	○	○	○	○	○	○	○	○	3 ounces or 1 sandwich	○	○	○
Shellfish, not fried (shrimp, lobster, crab and oysters)	○	○	○	○	○	○	○	○	○	3 ounces or ½ cup	○	○	○
White fish (broiled or baked) such as sole, halibut, snapper and cod	○	○	○	○	○	○	○	○	○	4 ounces	○	○	○
Dark fish (broiled or baked) such as salmon, mackerel and bluefish	○	○	○	○	○	○	○	○	○	4 ounces	○	○	○

SPAGHETTI, MIXED DISHES, SOUPS

	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Stew, pot pie, curries and casseroles with meat or chicken	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Chili with meat and beans	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Spaghetti, lasagna and other pasta with tomato and meat sauce	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Spaghetti and other pasta with tomato sauce (no meat)	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Pasta with oil, cheese, or cream sauce, including macaroni and cheese	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Asian-style (stir-fried) noodles and rice such as chow mein, fried rice and Pad Thai	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Pizza	○	○	○	○	○	○	○	○	○	2 slices	○	○	○
Tofu, tempeh and products such as tofu hot dogs, soy burgers and tofu cheese	○	○	○	○	○	○	○	○	○	3 ounces, 1 hot dog or 1 burger	○	○	○
Burritos, tacos, tostadas and quesadillas	○	○	○	○	○	○	○	○	○	1 medium	○	○	○
Enchiladas and tamales	○	○	○	○	○	○	○	○	○	1 medium	○	○	○
Vegetable, minestrone and tomato soup	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Cream soups such as chowders, potato and cheese	○	○	○	○	○	○	○	○	○	1 cup	○	○	○

SPAGHETTI, MIXED DISHES, SOUPS (continued)

	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Bean soups such as pea, lentil and black bean	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Miso soup	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Ramen noodle soup	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Other soups such as chicken noodle	○	○	○	○	○	○	○	○	○	1 cup	○	○	○

DAIRY PRODUCTS

	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Cottage cheese and ricotta cheese	○	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Low or reduced fat cheese, including cheese used in cooking	○	○	○	○	○	○	○	○	○	1 slice or 1/4 cup shredded	○	○	○
All other cheese (American, cheddar or cream), including cheese used in cooking	○	○	○	○	○	○	○	○	○	1 slice, 1/4 cup shredded or 2 Tbsp. cream	○	○	○
Yogurt, all types except frozen	○	○	○	○	○	○	○	○	○	6 ounces	○	○	○

VEGETABLES and GRAINS

	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Mark all vegetables you ate, including in salads, mixed dishes, sandwiches and stir-fries.													
Green salad (lettuce or spinach)	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Salad dressing (all types)	○	○	○	○	○	○	○	○	○	2 Tbsp.	○	○	○
Fresh tomatoes	○	○	○	○	○	○	○	○	○	1 medium or 4 slices	○	○	○
Carrots	○	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Green peppers and green chilies	○	○	○	○	○	○	○	○	○	1/4 cup	○	○	○
Red peppers and red chilies	○	○	○	○	○	○	○	○	○	1/4 cup	○	○	○

VEGETABLES and GRAINS (continued)	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Mark all vegetables you ate, including in salads, mixed dishes, sandwiches and stir-fries.													
Broccoli	○	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Cauliflower, cabbage and Brussels sprouts	○	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Green or string beans	○	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Green peas	○	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Corn and hominy	○	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Summer squash and zucchini	○	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Winter squash such as acorn, butternut and pumpkin	○	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Yams and sweet potatoes	○	○	○	○	○	○	○	○	○	1 medium	○	○	○
Cooked greens such as spinach, mustard greens and collards	○	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Onions and leeks	○	○	○	○	○	○	○	○	○	1/4 cup	○	○	○
Fresh garlic, including in cooking	○	○	○	○	○	○	○	○	○	1 clove	○	○	○
Avocado and guacamole	○	○	○	○	○	○	○	○	○	1/4 medium or 1/4 cup	○	○	○
French fries, fried potatoes and hash browns	○	○	○	○	○	○	○	○	○	3/4 cup	○	○	○
Potatoes (boiled, baked or mashed)	○	○	○	○	○	○	○	○	○	1 medium or 3/4 cup	○	○	○
Refried beans	○	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
All other beans (baked, lima or chili without meat)	○	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Coleslaw	○	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Potato, macaroni and pasta salads made with mayonnaise or oil	○	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Brown rice, whole wheat pasta and other whole grains (as a side dish)	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
White rice, noodles and other grains (as a side dish)	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Butter, margarine, sour cream and other fat added to vegetables, potatoes and rice	○	○	○	○	○	○	○	○	○	1 pat or 1 teaspoon	○	○	○

PLEASE DO NOT WRITE IN THIS AREA

SAUCES and CONDIMENTS

	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Cheese sauce and cream sauce	○	○	○	○	○	○	○	○	○	1/4 cup	○	○	○
Meat gravies	○	○	○	○	○	○	○	○	○	1/4 cup	○	○	○
Ketchup	○	○	○	○	○	○	○	○	○	2 Tbsp.	○	○	○
Salsa (as dip or on foods)	○	○	○	○	○	○	○	○	○	1/4 cup	○	○	○
Mayonnaise and mayonnaise-type spreads	○	○	○	○	○	○	○	○	○	2 Tbsp.	○	○	○

FRUITS

	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Apples, applesauce and pears	○	○	○	○	○	○	○	○	○	1 medium or 1/2 cup	○	○	○
Bananas	○	○	○	○	○	○	○	○	○	1 medium	○	○	○
Peaches, nectarines and plums	○	○	○	○	○	○	○	○	○	1 medium or 1/2 cup	○	○	○
Apricots (fresh, canned or dried)	○	○	○	○	○	○	○	○	○	2 medium or 4 halves	○	○	○
Dried fruit (other than apricots) such as raisins and prunes	○	○	○	○	○	○	○	○	○	1/4 cup	○	○	○
Oranges, grapefruit and tangerines (not juice)	○	○	○	○	○	○	○	○	○	1 orange or 1/2 grapefruit	○	○	○
Berries such as strawberries and blueberries	○	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Cantaloupe, orange melon and mango	○	○	○	○	○	○	○	○	○	1/4 melon or 1/2 mango	○	○	○
Watermelon and red melon	○	○	○	○	○	○	○	○	○	1 medium slice	○	○	○
Any other fruit such as grapes, fruit cocktail, pineapple and cherries	○	○	○	○	○	○	○	○	○	1/2 cup	○	○	○

SWEETS

	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Low or nonfat frozen desserts such as lowfat ice cream, frozen yogurt and sherbet	○	○	○	○	○	○	○	○	○	1 scoop	○	○	○
Ice cream and milkshakes	○	○	○	○	○	○	○	○	○	1 scoop or 1 shake	○	○	○
Pudding, custard and flan	○	○	○	○	○	○	○	○	○	¾ cup	○	○	○
Doughnuts, pies and pastries	○	○	○	○	○	○	○	○	○	1 medium piece or slice	○	○	○
Cookies and cakes	○	○	○	○	○	○	○	○	○	2 med. cookies or 1 piece of cake	○	○	○
Chocolate, candy bars and toffee	○	○	○	○	○	○	○	○	○	1 regular bar or 2 pieces	○	○	○
Other candy such as Lifesavers®, licorice and jelly beans	○	○	○	○	○	○	○	○	○	4 pieces or 12 jellybeans	○	○	○

PLEASE ANSWER THESE THREE IMPORTANT QUESTIONS!

	NEVER or less than once per week	1-2 per week	3-4 per week	5-6 per week	1 per day	2 per day	3 per day	4 per day	5+ per day
	Note that the frequency headings are different.								
How often did you eat foods that were cooked in fat (pan-fried, sautéed, or deep-fried)? *Count all fat such as margarine, butter, oil or lard.*	○	○	○	○	○	○	○	○	○
How often did you eat a serving of vegetables? *Do not count potatoes, salad or beans.*	○	○	○	○	○	○	○	○	○
How often did you eat a serving of fruit? *Do not count juices.*	○	○	○	○	○	○	○	○	○

PLEASE DO NOT WRITE IN THIS AREA

BEVERAGES and ALCOHOL

	HOW OFTEN DID YOU DRINK THESE BEVERAGES?									→	AMOUNT?		
	NEVER or less than once per month	1-3 per month	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day	Medium serving size	S	M	L
	Note that the frequency headings are different.												
Milk (all types) as a beverage	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Latte, cappuccino, mocha or hot chocolate	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Coffee (not lattes or mochas)	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Tea, unsweetened or diet	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Tea, presweetened, bottled or instant	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Milk, cream or creamer added to tea and coffee	○	○	○	○	○	○	○	○	○	1 Tbsp.	○	○	○
Tomato juice, V-8® and other vegetable juices	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Orange juice and grapefruit juice	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Other 100% fruit juice such as apple, grape and cranberry	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Fruit drinks fortified with Vitamin C such as Hi-C®, and Kool-Aid®	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Meal replacement drinks and shakes such as Slim-Fast® and Ensure®	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Diet soft drinks (include energy drinks)	○	○	○	○	○	○	○	○	○	12 ounces or 1 can	○	○	○
Regular soft drinks (include energy drinks)	○	○	○	○	○	○	○	○	○	12 ounces or 1 can	○	○	○
Water (tap, bottled or sparkling)	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Beer (all types)	○	○	○	○	○	○	○	○	○	12 ounce can or bottle	○	○	○
Red wine	○	○	○	○	○	○	○	○	○	1 medium glass (6 oz)	○	○	○
White or rosé wine	○	○	○	○	○	○	○	○	○	1 medium glass (6 oz)	○	○	○
Liquor and mixed drinks	○	○	○	○	○	○	○	○	○	1 shot (1½oz) or 1 mixed drink	○	○	○

THANK YOU!

Please take a moment to fill in any questions you may have skipped.

Appendix F - Modified Inflammatory Bowel Disease Disability Index

MODIFIED INFLAMMATORY BOWEL DISEASE-DISABILITY INDEX

The first question is about your overall health, this includes both physical and mental health. Use the following scale to answer the question.

Scale: 1=very good 2=good 3=moderate 4=bad 5=very bad

OVERALL HEALTH

1) In general, how would you rate your health today?

1☐ 2☐ 3☐ 4☐ 5☐

The following section will review different functions of your body and activities of daily life. When answering these questions, think about the past week. On average, how much difficulty did you experience while doing each activity in the way that you usually do it? Difficulty means that activity required more effort than usual, that you experienced discomfort or joint pain while doing the activity, that you had to perform the activity more slowly, or that you had to make changes to the way you do the activity. Use the following scale to answer the questions below.

Scale: 1=none 2=mild 3=moderate 4=severe 5=extreme

SLEEP AND ENERGY

2) Throughout the past week, how much of a problem have you had with sleep? (This includes falling asleep, waking up frequently during the night, or waking up too early in the morning.)

1☐ 2☐ 3☐ 4☐ 5☐

3) Throughout the past week, how much of a problem have you had with feeling tired or not feeling energized?

1☐ 2☐ 3☐ 4☐ 5☐

AFFECT

4) Throughout the past week, how much of a problem have you had with feeling sad, low, or depressed?

1☐ 2☐ 3☐ 4☐ 5☐

5) Throughout the past week, how much of a problem have you had with feeling worried or anxious?

1☐ 2☐ 3☐ 4☐ 5☐

BODY IMAGE

6) Throughout the past week, how much of a problem have you had with the way your body or body parts looked?

1☐ 2☐ 3☐ 4☐ 5☐

PAIN

7) Throughout the past week, how much of a problem have you had with stomach or abdominal aches and pains?

1☐ 2☐ 3☐ 4☐ 5☐

Use the following scale to answer the questions below.

Scale: 1=none 2=mild 3=moderate 4=severe 5=extreme or could not do

REGULATING DEFECATION

8) Throughout the past week, how much difficulty did you have coordinating and managing bowel movements? (This includes choosing and getting to an appropriate place for bowel movements and cleaning yourself after bowel movements.)

1☐ 2☐ 3☐ 4☐ 5☐

LOOKING AFTER ONE'S HEALTH

9) Throughout the past week, how much difficulty have you had with managing your health? (This includes maintaining a balanced diet.)

1☐ 2☐ 3☐ 4☐ 5☐

INTERPERSONAL ACTIVITIES

10) Throughout the past week, how much difficulty have you had with maintaining personal relationships?

1☐ 2☐ 3☐ 4☐ 5☐

11) Throughout the past week, how much difficulty have you had with performing activities in public?

1☐ 2☐ 3☐ 4☐ 5☐

WORK AND EDUCATION

12) Throughout the past week, how much difficulty have you had with work or household activities?

1☐ 2☐ 3☐ 4☐ 5☐

13) Throughout the past week, how much difficulty have you had with school or studying activities?

1☐ 2☐ 3☐ 4☐ 5☐

The following section will review how you believe aspects of your environment positively influenced your disease symptoms, body functions, and activities of daily life. Use the following scale to answer the questions below.

Scale: N/A= not applicable 1=no positive effect 2=mildly positive effect 3=moderately positive effect 4=very positive effect 5=extremely positive effect

POSITIVE ENVIRONMENTAL FACTORS

14) Throughout the past week, did the medication you take for your Crohn's disease or ulcerative colitis improve or positively affect your symptoms or problems?

1☐ 2☐ 3☐ 4☐ 5☐ N/A ☐

15) Throughout the past week, did the food you consumed improve or positively affect your symptoms or problems?

1☐ 2☐ 3☐ 4☐ 5☐ N/A ☐

16) Throughout the past week, did your family improve or positively affect your symptoms or problems?

1☐ 2☐ 3☐ 4☐ 5☐ N/A ☐

17) Throughout the past week, did health professionals improve or positively affect your symptoms or problems?

1☐ 2☐ 3☐ 4☐ 5☐ N/A ☐

The following section will review how you believe aspects of your environment negatively influenced your disease symptoms, body functions, and activities of daily life. Use the following scale to answer the questions below.

Scale: N/A= not applicable 1=no negative effect 2=mildly negative effect 3=moderately negative effect 4=very negative effect 5=extremely negative effect

NEGATIVE ENVIRONMENTAL FACTORS

18) Throughout the past week, did the medication you take for your Crohn's disease or ulcerative colitis worsen or negatively affect your symptoms or problems?

1☐ 2☐ 3☐ 4☐ 5☐ N/A ☐

19) Throughout the past week, did the food you consumed worsen or negatively affect your symptoms or problems?

1☐ 2☐ 3☐ 4☐ 5☐ N/A ☐

20) Throughout the past week, did your family worsen or negatively affect your symptoms or problems?

1☐ 2☐ 3☐ 4☐ 5☐ N/A ☐

21) Throughout the past week, did health professionals worsen or negatively affect your symptoms or problems?

1☐ 2☐ 3☐ 4☐ 5☐ N/A ☐

The following section will review how benefit from the social security system and health services. Use the following scale to answer the questions below.

Scale: 1=no 2=yes

SOCIAL SECURITY AND HEALTH SERVICES, SYSTEMS AND POLICIES

22) Does the social security system provide you with the benefits you need?

1☐ 2☐

23) Do you receive the healthcare you need?

1☐ 2☐

To the best of your ability, answer to the following questions with the most correct and appropriate answer.

24) In the last week, how many liquid or very soft stools have you had?

Number of liquid/very soft stools: _____

25) What is your current height and weight?

Height (inches) _____
Weight (lbs.): _____

26) Have you lost weight in the last week?

yes ☐ no ☐

27) On average, how many bloody stools do you have per week?

None ☐ A few ☐ A lot ☐

28) Do you have arthritis or arthralgia?

yes ☐ no ☐

Appendix G - Modified Inflammatory Bowel Disease Disability Index: Scoring guide

MODIFIED IBD-DI SCORING GUIDE

Name:	
Email:	
DOB:	
Gender:	
Diagnosis:	
Medications:	
Additional Medical Hx:	

QUESTION 1:	

QUESTION 1	
Rating	**Score**
1=very good	0
2=good	-1
3=moderate	-2
4=bad	-3
5=very bad	-4

QUESTION 2:	
QUESTION 3:	
QUESTION 4:	
QUESTION 5:	
QUESTION 6:	
QUESTION 7:	

QUESTIONS 2–7	
Rating	**Score**
1=none	0
2=mild	-1
3=moderate	-2
4=severe	-3
5=extreme	-4

QUESTION 8:	
QUESTION 9:	
QUESTION 10:	
QUESTION 11:	
QUESTION 12:	
QUESTION 13:	

QUESTIONS 8–13	
Rating	**Score**
1=none	0
2=mild	-1
3=moderate	-2
4=severe	-3
5=extreme/could not do	-4

QUESTION 14:	
QUESTION 15:	
QUESTION 16:	
QUESTION 17:	

QUESTIONS 14–17	
Rating	**Score**
N/A=not applicable	+4
1=no positive effect	0
2=mildly positive effect	+1
3=moderately positive effect	+2
4=very positive effect	+3
5=extremely positive effect	+4

QUESTION 18:	
QUESTION 19:	
QUESTION 20:	
QUESTION 21:	

QUESTIONS 18–21	
Rating	**Score**
N/A=not applicable	0
1=no negative effect	0
2=mildly negative effect	-1
3=moderately negative effect	-2
4=very negative effect	-3
5=extremely negative effect	-4

QUESTION 22:	
QUESTION 23:	

QUESTIONS 22–23	
Rating	**Score**
No	-1
Yes	+1

QUESTION 24:	

QUESTION 24	
Rating	**Score**
0	+1
1–4	-1
5–8	-2
9–12	-3
>12	-4

Question 25: Calculate BMI

$$\text{BMI}=\frac{weight\ (lbs.)}{height\ (in.)^2}\bullet 703$$

Height	
Weight	
BMI	

QUESTION 25:	

QUESTION 25	
Rating	**Score**
≤15	-2
15.1–19.9	-1
20–24.9	0
25–29.9	-1
≥30	-2

QUESTION 26:	

QUESTION 26	
Rating	**Score**
Yes	-1
No	+1

QUESTION 27:	

QUESTION 27	
Rating	**Score**
None	+1
A few	-1
A lot	-2

QUESTION 28:	

QUESTION 28	
Rating	**Score**
Yes	-1
No	+1

SCORE

TOTAL SCORE	
Degree of Disability	**Score**
No Disability	22
Point of Neutrality	0
Minimal Disability	0 to -10
Mild Disability	-10 to -19
Moderate Disability	-20 to -35
Severe Disability	≤-35
Maximum Disability	-80