Use of Probiotics, Prebiotics and Dietary Fibres in Inflammatory Bowel Disease

by

Melissa Priyanthi Silva

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Department of Medicine
University of Alberta

ABSTRACT

Introduction: Inflammatory bowel diseases (IBD) are a group of chronic inflammatory conditions including ulcerative colitis (UC) and Crohn's disease (CD) induced by an interaction between genetic susceptibility, environmental factors, dysbiosis of gut microbiota and an abnormal mucosal immune response. Alternative therapies, such as probiotics, prebiotics and dietary fibre supplements (PPF) are cost-effective, have fewer side effects and can alter the microbial composition of the gut to favour a decrease in gut inflammation. However, these products are relatively understudied with a lack of data on usage patterns. This study aimed to determine factors related to use and awareness of PPF in patients with IBD.

Methods: A cross-sectional study was conducted in patients with a diagnosis of inflammatory bowel disease in the University of Alberta IBD clinic. Using a 20-item survey questionnaire, data on use and awareness of probiotics, prebiotics and dietary fibre supplements and demographic information of their users were collected. Clinical characteristics such as occurrence of flares, age at diagnosis, clinical scores of severity, presence of extra-intestinal disease and objective markers of disease, were collected from charts.

Results: Survey questionnaires were completed by 267 participants with IBD. Ninety-one percent of IBD patients had heard of PPF in their lifetime. Awareness of PPF was associated with female gender ($p<0.05$) and supplement use ($p<0.01$), with advertising through television or radio being the primary source of information. Prevalence of PPF use was 63% in a patient's lifetime and 51% currently (over the last 12 months), with more current users consuming probiotics (46%) in comparison to fibres (12%) or prebiotics (6%). Awareness (OR: 7.7, 95% CI: 2.8-21.5, $p<0.001$), information received from a physician (gastroenterologist or family practitioner; OR: 4.6, 95% CI: 1.3-15.7, $p<0.01$), higher educational status (OR: 2.2, 95% CI: 1.1-4.4, $p<0.023$), intake of a combination of special diets (OR: 3.7, 95% CI: 1.2-11.4, $p<0.05$), supplements (vitamins [OR: 2.2, 95% CI: 1.2-3.8, $p<0.01$], minerals [OR: 2.5, 95% CI 1.5-4.2, $p<0.001$]) and use of other CAMs (OR: 1.8, 95% CI: 1.1-3.0, $p<0.05$) were predictors of PPF use over an IBD patient's lifetime. Ulcerative colitis was the only clinical predictor of current use (OR: 1.8, 95% CI: 1.1-3.0, $p<0.05$). Association with other clinical characteristics such as measures of disease activity, severity and extent was not seen in IBD patients. Danone Activia® yogurt was the most frequently consumed probiotic over the last year, with a lack of approval by Health Canada or proven efficacy for IBD. Participants reported reduction of IBD symptoms as the primary reason for using PPF over the last year with "never users" claiming lack of information from their physician as the motive behind never-use. Though the majority of current users reported receiving the intended benefit of PPF use, almost two thirds of patients experienced no improvement in perceived quality of life in relation to their IBD. However, willingness to spend money on these therapies (probiotic or prebiotic users: $11-50/month) was not affected.

Conclusions: Use of probiotics, prebiotics and dietary fibre supplements is prevalent among IBD patients who choose alternative therapies to manage their disease. Patients frequently choose probiotics to manage their symptoms but may choose strains that are not endorsed by national public health organizations or retain clinical evidence in IBD. Physician suggestion influences patient decision-making regarding use; therefore, greater physician awareness and understanding of supplementary probiotics, prebiotics and fibres is necessary in order to offer evidence-based advice, if available.

PREFACE

This thesis is an original work by Melissa Silva. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Human Research Ethics Board, Project Name “Use of Probiotics, Prebiotics and Dietary Fibres in Inflammatory Bowel Disease”, No. Pro00064575, September 2016. No part of this thesis has previously been published.

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5-ASA	5- Aminosalicylic Acid
CAM	Complementary Alternative Medicine
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CFU	Colony Forming Unit
CI	Confidence Interval
CRP	C-reactive Protein
DASH	Dietary Approaches to Stop Hypertension
DC	Dendritic Cell
DGGE	Denaturing Gradient Gel Electrophoresis
DNA	Deoxyribonucleic Acid
EcN	*Escherichia coli* Nissle 1917
EMR	Electronic Medical Record
FAO/WHO	Food and Agricultural Organization of the United Nations and World Health Organization
FCP	Fecal Calprotectin
FISH	Florescence In-Situ Hybridization
FODMAP	Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols
FOS	Fructo-oligosaccharide
GI	Gastrointestinal
HBI	Harvey Bradshaw Index
HCP	Health Care Provider
HLA	Human Leukocyte Antigen
IBD	Inflammatory Bowel Disease
IBDU	Inflammatory Bowel Disease Unclassified
IL	Interleukin
NCCIH	National Centre of Complementary and Integrative Health

NHP	Natural Health Product
OF-IN	Oligofructose-enriched Inulin
OR	Odds Ratio
PCR	Polymerase Chain Reaction
PPF	Probiotics, Prebiotics and/or Dietary Fibre Supplements
QoL	Quality of Life
qPCR	Quantitative Polymerase Chain Reaction
RCT	Randomized Controlled Trial
RFLP	Restriction Fragment Length Polymorphism
SD	Standard Deviation
SCFA	Short Chain Fatty Acid
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
UCDAI	Ulcerative Colitis Disease Activity Index
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to

INTRODUCTION

1.1 Inflammatory Bowel Diseases: Definition and Etiology

Inflammatory bowel diseases (IBD) are a group of chronic relapsing inflammatory disorders of the intestines that include ulcerative colitis (UC) and Crohn's disease (CD). Approximately 5% of cases do not definitively lie in either category and are defined as IBD-Unclassified (IBD-U; previously known as indeterminate colitis)[1,2]. Symptoms may include abdominal pain, frequent (bloody) diarrhea and rectal bleeding. Extra-intestinal manifestations can be seen in 25-40% of IBD patients and may involve musculoskeletal, dermatologic, hepato-pancreato-biliary, ocular, renal and pulmonary systems[3,4]. Current therapies for IBD include pharmacologic agents that modulate the immune system, such as 5-aminosalicylic acid (5-ASA) compounds, steroids, thiopurines, methotrexate, biologic agents, and surgery in severe cases. These therapies often involve substantial costs, can have serious adverse effects such as malignancy, infections, low bone density or even damage DNA in reproductive cells and do not directly address bacterial dysbiosis in the human gut[5–7].

Although the etiopathogenesis is unknown, the current hypothesis is that IBD is induced by a complex interaction between genetics, environmental factors combined with an excessive immune response and an altered balance in microbiota (dysbiosis)[8]. However, the degree to which each factor contributes to disease development continues to be under study. Recently, advances in DNA sequencing technology have identified

over 200 IBD risk loci, though these loci only account for 13% of CD and 7% of UC genetic variance[9,10]. Additionally, concordance rate studies between identical twins have shown that contribution of genetic factors is only 40-50% for CD and 10% for UC[11]. This suggests that the IBD is a disorder involving not only genetics and immune dysfunction, but external factors, such as environment, as well. Over the past 25 years, industrialization has led to a rise in the incidence of IBD in newly developing nations[12]. This further contributed to the hypothesis that Westernization of environment and lifestyle alters the gut microbiota and associated microbial genes (microbiome), thus inducing chronic intestinal inflammation. Disruption in the microbial balance can occur due to epidemiological factors such as mode of birth (Cesarean vs. vaginal), hygiene, infection, diet, stress, abnormal sleep pattern and antibiotic use in childhood, which are known or presumed causes of chronic immune-mediated diseases, including IBD[13,14]. Dietary modifications may alter the microbial community in the gut, thus warranting investigation in association to IBD. In order to identify new treatment targets and therapeutic strategies for IBD, we must increase our understanding of specific dietary therapies.

Probiotics and prebiotics are considered as alternative treatments for IBD. These therapies have emerged as a step away from costly and potentially toxic or invasive treatment options. In contrast to standard drug therapy, the primary mode of action of probiotics and prebiotics involves alteration of the gut microbiota composition/function that can affect the host immune system leading to reduction of inflammation. Probiotics

and prebiotics are relatively understudied and most of them lack well-powered clinical trials documenting their effectiveness in the treatment of IBD[15].

1.2 Dysbiosis in IBD

The microbiota of the human gastrointestinal (GI) system contains the largest reservoir of microbes in the human body, with over tens of trillions of microorganisms[16]. The host-microbiota interaction is important, with bacteria nearly equalling host cells at a ratio of 1:1[17]. This diverse microbial community consists of numerous species of bacteria, viruses (including bacteriophages), archaea and eukaryotes (including protozoa, yeast and fungi)[18]. These microbiota are responsible for regulating many functions of the host, including metabolizing exfoliated epithelial cells, dietary carbohydrates and mucus and producing metabolites that regulate the function of intestinal epithelial cells, host energy balance, homeostasis of the immune system and hepatic function[19].

Intestinal dysbiosis is defined as an imbalance in structural and/or functional properties of gut microbiota that disrupt host-microbe homeostasis and is implicated in the pathogenesis of many chronic diseases, including IBD[20]. This alteration in the microbial profile involves overgrowth of pro-inflammatory bacteria and/or reduction in composition of beneficial, anti-inflammatory bacteria[19]. Though we know that dysbiosis has a connection to IBD, it remains unknown whether this association is casual or consequential.

Inflammatory bowel diseases are associated with a reduction in the largest phyla found in the gut, *Bacteroidetes* and *Firmicutes*[16]. Both phyla contain microorganisms that can produce metabolites, such as short-chain fatty acids (SCFA: butyrate, acetate and propionate), through carbohydrate fermentation in the gut[16]. Specific examples of beneficial organisms that are suppressed in IBD include *Faecalibacterium prausnitzii, Roseburia intestinalis, Eubacterium rectale, Ruminococcaceae, Lachnospiraceae* and other butyrate-producing organisms[13,21]. Bacterial phyla that increase in numbers in the setting of active IBD are *Proteobacteria* and *Fusobacteria,* which can lead to an overproduction of toxic sulfites and increased oxidative stress[20]. Specific examples of these pro-inflammatory organisms include adherent-invasive *Escherichia coli* and *Shigella* species of the *Enterobacteriaceae* family[13,21]. Dysbiosis occurs through the interaction between intestinal microbes and the abnormal immune response in a genetically susceptible host in IBD. It is important to understand the factors that can ameliorate dysbiosis to improve and reduce microbial immune dysfunction-mediated inflammatory processes in IBD.

1.3 Alternative Therapies for IBD

Current conventional therapies for IBD include pharmaceuticals that target inflammation through modulation of the immune system. Medications such as anti-inflammatories, immunosuppressants and biologic agents are used to induce and maintain remission in patients with active disease. However, failure in the effectiveness of these therapies and/or serious, toxic adverse effects, such as increased susceptibility to infections and

cancer, prompt many patients to seek alternate treatments for their disease[22–25]. The use of non-allopathic therapies such as nutritional interventions or complementary alternative medicine (CAM) among IBD patients is increasing, though they are supported by limited research[26,27]. Probiotics and prebiotics are often included as a category of CAM, thus for the purposes of this study, we will look at CAM use as a predictor to use of probiotics, prebiotics and/or dietary fibre supplements (PPF).

Prevalence of CAM, as an alternative to standard medications, is increasing in patients with chronic disease [28,29]. The National Center of Complementary and Integrative Health (NCCIH) defines CAM as a group of diverse medical and healthcare systems, practices and products that are not presently considered part of conventional medicine[30]. Commonly used types of CAMs include probiotics, prebiotics, massage therapy, chiropractic therapy, faith healing, movement (Tai Chi or yoga), meditation, acupuncture, naturopathy, homeopathy, reflexology, traditional Chinese medicine, Reiki and dietary modifications[29,30]. CAM use is common among adults with IBD, however supporting evidence of their effectiveness in IBD is conflicting[23,31,32]. Table 1-1 demonstrates that over the last twenty years, current CAM use for IBD ranged from approximately 10-65%, whereas current or past use ranged from 20-75% worldwide. CAMs also include the subgroup natural health products (NHP) which include vitamins, minerals and herbal remedies as defined by Health Canada[33]. These products are found naturally and are used to treat disease, maintain health and/or restore regular human functions[34]. Previous studies have shown that the most commonly used NHPs as CAMs in IBD are

Table 1-1: Prevalence in Complementary Alternative Medicine Use in IBD Patients (1998-2016)

Author	Year	n	Country	Sample	Current CAM Use %	Current or Past CAM Use %
Hilsden *et al.*[35]	1998	134	Canada	Clinic	17	51
Hilsden *et al.*[27]	1999	263	Canada	Internet	34	46
Rawsthorne *et al.*[36]	1999	289	International	Clinic	n/a	51
Langmead *et al.*[37]	2002	239	UK	Clinic	28	n/a
Hildsen *et al.* [38]	2003	2828	Canada	National Association	24	47
Burgmann *et al.*[39]	2004	150	Canada	Clinic	n/a	60
Kong *et al.*[40]	2005	311	UK	Clinic	n/a	50
Langhorst *et al.*[41]	2005	671	Germany	National Association	14	51
Bensoussan *et al.*[42]	2006	325	France	Clinic (postal survey)	11	21
Joos *et al.*[43]	2006	413	Germany	National Association	n/a	51
D'Inca *et al.*[44]	2007	552	Italy	Clinic	n/a	28
Langhorst *et al.*[45]	2007	112/994	Germany	National Association (workshop vs. postal survey)	10/14	47/51
Lakatos *et al.*[46]	2010	655	Hungary	Clinic	n/a	31
Bertmoro *et al.*[47]	2010	2011	Italy	Clinic	n/a	24
Fernández *et al.*[48]	2012	705	Spain	Clinic	n/a	23
Weizman *et al.*[49]	2012	380	Canada	Clinic	n/a	56
Rawsthorne *et al.*[50]	2012	309	Canada	Clinic	40	74
Opheim *et al.*[51]	2012	430	Norway	Clinic	n/a	49 (past 12 mo.)
Park *et al.*[52]	2013	366	South Korea	Clinic	n/a	30
Koning *et al.*[31]	2013	1291	New Zealand	National Association, Clinic	n/a	44 (past 12 mo.)
Abitbol *et al.*[53]	2014	767	France	Internet	66	77
Mountifield *et al.*[54]	2015	473	Australia	Clinic	n/a	45
Nguyen *et al.*[55]	2016	392	Canada	Clinic	n/a	62
Oxelmark *et al.*[56]	2016	648	Sweden	Clinic	n/a	48 (past 12 mo.)
Portela *et al.*[57]	2017	442	Portugal	Clinic (postal survey)	12	31

Abbreviations: *IBD* Inflammatory Bowel Disease; *CAM* Complementary Alternative Medicine; *n/a* not available

vitamins and herbal therapies[58]. It is important to note that IBD patients are using a wide variety of CAMs to ameliorate disease symptoms and improve their clinical status[32].

The influence of diet on the gut and intestinal microbiota is a rapidly developing field of interest. The lumen of the GI tract is constantly challenged by food antigens and microorganisms, stressing the importance of the ability of the host immune system in identifying pathogens[59]. In response to such stimuli, the human host mounts an immune response leading to either inflammation or tolerance[60]. Environmental factors, such as diet, can interact with microbiota to modulate inflammation in the gut and thus influence the pathogenesis, natural course and activity of IBD[61]. Dietary modifications may be used in conjunction with other CAMs in the treatment of IBD.

1.4 Probiotics

1.4.1 Definition

Probiotics are defined by the Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO) as live microorganisms which when administered in adequate amounts, confer a health benefit on the host[62]. They can be consumed in the diet through fermented foods (yogurt, kefir, sauerkraut) or on a daily basis in supplement form[63]. General health benefits of probiotics include promoting healthy microbial balance and digestive and immune system function[64]. Probiotics are typically lactic acid bacteria in the gut that have the capacity to withstand gastric, biliary and pancreatic secretions, are non-pathogenic and non-toxic and remain viable during

transit with extended periods of storage[65]. They have been shown to have beneficial properties such as improvement in the integrity of the intestinal epithelial barrier, modulation of the immune system and inhibition of pathogenic enteric bacteria[65–67]. This special group of protective bacteria, originally derived from cultured foods (including milk products), include *Lactobacillus* and *Bifidobacterium*, a non-pathogenic *Escherichia coli* strain, Nissle 1917, *Saccharomyces boulardii*, *Clostridium butyricum* and *Streptococcus salivarius* subspecies *thermophiles*[67].

Probiotics are widely used with increasing evidence of efficacy for treatment of IBD. Increase in bacterial diversity in UC and pouchitis can occur through administration of probiotic bacteria, as evidenced by both experimental and human studies. For example, studies in interleukin-10 (IL-10) knockout mice have shown that first use of *Lactobacillus* spp. and *L. plantarum* prevent the development of spontaneous colitis and attenuation of established colitis, respectively[68,69].

1.4.2 Probiotics as Treatment for Active UC

There are many studies using probiotics as interventional treatment of active UC, as summarized in Table 1-2. *E. coli* Nissle 1917 (EcN) and VSL#3 (a probiotic blend containing *L. acidophilus, L. bulgaricus, L. casei, L, plantarum, B. breve, B. infantis, B. longum* and *S. thermophilus)* have both been proven effective in active UC[70–77].

A single-centre randomized study by Rembacken *et al.* (1999) was conducted using EcN alongside standard therapy and a one-week course of antibiotics to induce remission of

Table 1-2: Summary of RCTs Using Probiotics in Active UC*

Author	Year	Country	Disease	Participants; Duration	Probiotic and dose	Method of Detection	Bacterial Taxa Stimulated or Reduced	Outcome
Rembacken *et al.*[70]	1999	UK	Active UC	116 adults; 12 months	*E. coli* Nissle 1917 (2.5×10^{10} CFU/day) vs. mesalazine (2400 mg/day)			Nonpathogenic strain of *E coli* is as effective as mesalazine in maintaining remission of UC
Ishikawa *et al.*[78]	2003	Japan	Active UC	21 adults; 12 months	Bifidobacteria-fermented milk (*B. breve, B. bifidum, L. acidophilus;* Yakult); 100 ml/day	Culture	↓*B. vulgatus*	Effective and reducing clinical severity of UC
Tursi *et al.*[71]	2004	Italy	Active UC	90 adults; 8 weeks	VSL#3 + balsalazide; 3 g + 2.25 g			Combination of VSL#3 and balsalazide is effective at obtaining remission
Kato *et al.*[79]	2004	Japan	Active UC	20 adults; 12 weeks	*Bifidobacteria*-fermented milk (*B. breve, B. bifidum, L. acidophilus;* Yakult); 100 ml/day	PCR	↑*B. pseudocatenulatum* ↑*B. breve*	Effective at reducing clinical and endoscopic activity
Bibiloni *et al.* [72]	2005	Canada	Active UC	32 adults; 6 weeks **Open label**	VSL#3; 3600 billion CFU/day	PCR, DGGE	↑*Streptococcus thermophilus* ↑*B. infantis*	Effective at inducing remission
Miele *et al.*[73]	2009	Italy	Active UC (newly diagnosed)	29 children; 12 months	VSL#3; 450-1800 CFU/day (weight-based dose)			Reduction in rate of relapse, clinical and endoscopic scores
Sood *et al.*[74]	2009	India	Active UC	147 adults; 12 weeks	VSL#3; 3.6×10^{12} CFU/day)			Effective at improving clinical scores and achieving remission

Author	Year	Country	Disease	Participants; Duration	Probiotic and dose	Method of Detection	Bacterial Taxa Stimulated or Reduced	Outcome
Tursi *et al.*[75]	2010	Italy	Active UC	144 adults; 8 weeks	VSL#3; 3600 billion CFU/day			Effective at decreasing clinical scores (UCDAI) and inducing remission
Ng *et al.*[76]	2010	UK	Active UC	28 adults; 8 weeks	VSL#3; 3600 billion CFU/ day vs. prednisolone 40 mg /day and tapered by 4 mg/week			VSL#3 and steroids induce intestinal DC to lower inflammation
Oliva *et al.*[80]	2012	Italy	Active UC	50 children; 8 weeks	*L. reuteri* ATCC 55730 enema; 10^{10} CFU/day			Improves mucosal inflammation and decreases inflammatory cytokines
Li *et al.*[81]	2012	China	Active UC	82 adults; 2 months	Bifid triple viable capsule (*L. acidophilus, B. bifidum & Streptococcus* spp.); 6 cap/day + 5-ASA; 2 g/day			Reduction in clinical and endoscopic scores and reduced relapse rate
Petersen *et al.*[82]	2014	Denmark	Active UC	100 adults; 8 weeks	*E. coli* Nissle 1917 ± Ciprofloxacin; 2 x 100 mg (2.5-25 x 10^9 CFU/capsule) ± 2 x 500 mg/day			No benefit as adjunct therapy for active UC
Tamaki *et al.*[83]	2016	Japan	Active UC	56 adults; 8 weeks	*B. longum* (BB536); 2-3 x 10^{11} CFU x 3/day			Reduction of clinical scores
Palumbo *et al.*[84]	2016	Italy	Active UC	60 adults; 2 years	*L. salivarius* + *L. acidophilus* + *B. bifidus* BGN4 (Acronelle ®) + mesalazine; dose not specified			Effective over long-term at improving clinical & endoscopic scores

*All studies described are RCTs, except Bibiloni *et al.* (2005) is an open label study, and include adults, except Miele *et al.*(2009) and Oliva *et al.* (2012) which were conducted on children

Abbreviations: *RCT* Randomized Controlled Trial; *UC* Ulcerative Colitis; *CFU* Colony Forming Unit; *PCR* Polymerase Chain Reaction; *DGGE* Denaturing Gradient Gel Electrophoresis; *UCDAI* Ulcerative Colitis Disease Activity Index; *DC* Dendritic Cell; *5-ASA* 5-Acetylsalycylic Acid

active UC over 12 months[70]. One hundred and sixteen patients were randomized to either EcN (n=57) or mesalamine (n=59). Results between treatment groups showed no difference in percentage of patients who achieved remission, induction rates of remission or relapse rates. Therefore, they concluded that the relapse preventing effect of EcN was similar to mesalazine. In contrast, Petersen *et al.* (2014) showed that EcN has no benefit as adjunct therapy in combination with antibiotics in active UC[82]. Though EcN alone cannot induce remission in active UC, evidence shows it may be promising as adjunct therapy.

The effect of VSL#3 in inducing remission of active UC was first proven by Tursi and colleagues in 2004[71]. In this study, VSL#3 and low-dose balsalazide (2.25 g/day) were compared to balsalazide (4.5 g/day) and mesalamine (2.4 g/day) over 8 weeks in 90 patients with mild-to-moderate UC. They concluded that the combination of VSL#3 and low-dose balsalazide was superior at achieving remission of UC quicker than balsalazide or mesalamine alone. These findings were confirmed by the same group in 2010 in a larger group of 144 patients over 8 weeks, in which VSL#3 was proven to decrease clinical activity scores of UC as well as induce remission[75]. In addition, Bibiloni *et al.* (2005) showed in a small, open-label study that high doses of VSL#3 (9×10^9 CFU) can induce remission of active UC[72]. Miele *et al.* (2009) were among the first to demonstrate the efficacy of VSL#3 in the pediatric population[73]. They studied a group of 29 children with newly diagnosed UC and administered VSL#3 (weight-based) versus placebo over one year. Patients responded to VSL#3 as induction therapy with 92.8% on VSL#3 achieving remission, in comparison to 36.4% on placebo. Furthermore, endoscopic and

histologic scores decreased in the VSL#3 group, proving that VSL#3 is effective at inducing remission of UC. Furthermore, Sood and colleagues (2009) also studied the effect of VSL#3 in comparison to placebo in 147 patients with mild-to-moderate UC[74]. These patients were also on concomitant mesalamine, azathioprine or 6-mercaptopurine. Patients on VSL#3 and combination therapy demonstrated improvement in ulcerative colitis disease activity index (UCDAI) scores and clinical symptoms, thus indicating that the efficacy of VSL#3 was equivalent to mesalamine. The most recent RCT by Ng *et al.* (2010) showed that a combination of VSL#3 and corticosteroid taper can also suppress inflammation in active UC by inducing intestinal dendritic cell function to increase anti-inflammatory cytokine production and reduce proinflammatory cytokine production[76]. Though these studies demonstrated efficacy of VSL#3 in active UC, further RCTs have not been performed in nearly a decade.

1.4.3 Probiotics as Maintenance Therapy for UC

Probiotic therapies have been investigated in comparison to standard therapy and placebo in prevention of relapse of inactive UC, as summarized in Table 1-3. EcN is effective as adjunct maintenance therapy for UC[85,86]. A double blinded study conducted by Kruis *et al.* (1997) investigated EcN versus mesalazine in patients with quiescent disease over 12 weeks, with no difference in clinical scores, relapse rates or relapse-free times between the two groups[85]. In 2004, the same group duplicated these results in a larger study population over 12 months, assessing the effect of EcN versus mesalazine on both clinical and endoscopic disease indices[86]. Once again, there was no difference in clinical or endoscopic parameters, relapse rates or relapse-free times. Both studies

concluded that the relapse preventing effect of EcN was similar to mesalazine therapy in UC[85,86]. VSL#3 has also been studied for maintenance of remission of UC. In a small open label study by Venturi *et al.* (1999), administration of VSL#3 alone showed colonization of probiotic bacteria in fecal samples as well as maintenance of remission in a minority of patients[87]. This study demonstrates that VSL#3 may have use as alternate therapy in quiescent UC, though results should be verified in larger controlled studies.

Studies performed in the last ten years have showed that probiotic preparations with *Lactobacillus* spp*., Bifidobacterium* spp*. Streptococcus* spp*. and Clostridium* spp*.* have limited to no effectiveness in maintaining remission of UC in comparison to placebo or standard therapy[88,89]. In a controlled trial by Cui *et al.* (2004), administration of a capsule containing *Bifidobacterium* spp*.* (alongside steroids and sulfasalazine) versus placebo was studied in a small sample of 30 adults over 8 weeks[90]. Results showed that this probiotic strain reduced relapse rates and increased numbers of lactobacilli and bifidobacteria in fecal samples. Though the sample size was small, *Bifidobacterium* spp*.* was effective as adjunctive therapy in preventing relapse. Zocco *et al.* (2006) showed in a larger open-label study that *Lactobacillus rhamnosus* GG was as effective as mesalamine in preventing relapse or prolonging remission of UC, though there was no difference in relapse rates. In contrast, a recent study by Matsuoka *et al.* (2018) showed that *B. breve* fermented milk (Yakult®*)* was not effective in maintaining remission of UC in comparison to placebo[89]. Though probiotic therapy may be as effective as standard therapy in preventing relapse of UC, there remain only a limited number of well powered

Table 1-3: Summary of RCTs Using Probiotics in Inactive UC*

Author	Year	Country	Participants; Duration	Probiotic and dose	Method of Detection	Bacterial Taxa Stimulated or Reduced	Outcome
Kruis *et al.*[85]	1997	Germany	120 adults; 12 weeks	*E. coli* Nissle 1917 (25×10^9 bacteria/day) vs. mesalazine 500 mg/day			As effective as mesalazine in maintaining remission
Venturi *et al.*[87]	1999	Italy	20 adults; 12 months **Open label**	VSL#3 5×10^{11} cells/g; 6 g/day	Culture	↑*S. thermophiles,* ↑*Lactobacillus* spp., ↑*Bifidobacterium* spp.	Useful in maintaining remission in 25% of patients; able to colonize intestine
Kruis *et al.*[86]	2004	Germany	327 adults; 12 months	*E. coli* Nissle 1917; 100 mg of $2.5\text{-}25 \times 10^9$ CFU/day			As effective as mesalazine in maintaining remission
Cui *et al.*[90]	2004	China	30 adults; 8 weeks	Bifid triple viable capsule (BIFICO; *Bifidobacteria* spp.); 1.26 g/day	Culture	↑*Lactobacillus* spp. ↑*Bifidobacterium* spp.	Effective at reducing relapse rate of UC
Zocco *et al.*[91]	2006	Italy	187 adults; 12 months **Open label**	*Lactobacillus* GG + mesalazine; 18×10^9 CFU/day + 2400 mg			Effective at prolonging remission; no difference in relapse rate
Wildt *et al.*[88]	2011	Denmark	32 adults; 12 months	*L. acidophilus* La-5 + *B. lactis* BB-12; 2.5×10^{10} CFU/day			Not effective
Yoshimatsu *et al.*[92]	2015	Japan	60 adults; 12 months	*S. faecalis* T-110 (2 mg) + *C. butyricum* TO-A (10 mg) + *B. mesentericus* TO-A (10 mg) (1 tablet Bio-Three); 9 tablets/day	PCR, T-RFLP, Cluster analysis	↑*Bifidobacterium* spp.	May be effective at maintaining clinical remission
Matsuoka *et al.*[89]	2018	Japan	195 adults; 48 weeks	BFM fermented milk (*B. breve* + *L. acidophilus;* Yakult); $1 \times 10^9 + 10 \times 10^9$	16s rRNA sequencing, PCR	↓*Bifidobacterium* spp.	Not effective

*All studies described are RCTs, except Venturi *et al.* (1999) and Zocco *et al.* (2006) are open label studies

Abbreviations: *RCT* Randomized Controlled Trial; *UC* Ulcerative Colitis; *CFU* Colony Forming Unit; *PCR* Polymerase Chain Reaction; *T-RFLP* Terminal Restriction Fragment Length Polymorphism

trials examining effectiveness of probiotics as adjunct or stand-alone therapies in inactive colitis.

1.4.4 Probiotics for Maintenance of Pouchitis

Probiotics are effective in inducing and maintaining remission of pouchitis, a condition with nonspecific inflammation of the ileal reservoir after pouch surgery for UC. Table 1-4 describes several controlled interventions using probiotics for inactive pouchitis. VSL#3 is clinically effective in preventing pouchitis flares. Gionchetti *et al.* (2000) initially discovered the positive effect of VSL#3 in maintenance of remission of chronic pouchitis and in modulating the gut microbiota through increase of fecal concentrations of lactobacilli, bifidobacteria and *S. thermophiles*[93]. A further study performed by the same group found that VSL#3 had prophylactic benefit and increased quality of life (QoL) in patients with acute quiescent pouchitis[94]. In addition, Mimura *et al.* (2004) determined VSL#3 to be effective at maintaining antibiotic-induced remission of pouchitis and increasing QoL[95]. However, results are conflicting, as Shen *et al.* (2005) showed VSL#3 was ineffective in maintaining remission of antibiotic-dependent pouchitis[96].

Several open label studies have implicated other probiotic therapies as effective in prevention of pouchitis flares. For example, Gosselink *et al.* (2004) showed that oral intake of *L. rhamnosus* GG can be effective in maintaining remission of pouchitis in a larger cohort of 117 patients[97]. First episodes of pouchitis were observed less frequently in patients who had taken the probiotic therapy. Thus, administration of *L. rhamnosus* GG can lead to a delay in onset of disease in patients with quiescent pouchitis. In

Table 1-4: Summary of RCTs Using Probiotics in Inactive Pouchitis*

Author	Year	Country	Disease	Participants and Duration	Probiotic and dose	Method of Detection	Bacterial Taxa stimulated	Outcome
Gionchetti *et al.*[93]	2000	Italy	Quiescent chronic pouchitis	40 adults; 9 months	1 month of antibiotic treatment, then VSL#3; 6 g/day	Culture	*Lactobacillus* spp. *Bifidobacteria* spp. *S. thermophiles*	Effective at preventing flares
Gionchetti *et al.*[94]	2003	Italy	Quiescent acute pouchitis	40 adults; 1 year	VSL#3; 9 x 10^9 CFU/day	Culture, PCR	*S. thermophiles* *Bifidobacteria* spp.	Effective at preventing disease and improving QoL
Mimura *et al.*[95]	2004	UK	Quiescent refractory pouchitis	36 adults; 1 year	VSL#3; 6 g (30 x 10^9 CFU per g)/day	PCR	*S. thermophiles*	Effective at maintaining antibiotic-induced remission and increase in QoL
Gosselink *et al.*[97]	2004	Nether-lands	Quiescent pouchitis;	117 adults; 4 years **Open label**	*L. rhamnosus* GG; 1-2 x 10^{10}/day	Culture	*Lactobacillus* spp.	Delay in onset of first episode of pouchitis
Shen *et al.*[96]	2005	USA	Quiescent antibiotic dependent pouchitis	31 adults; 8 months	VSL#3; 6 g/day (with initial administration of 500 mg of ciprofloxacin)			Not effective; majority of patients discontinued due to relapse/adverse effects
Laake *et al.*[98]	2005	Norway	Quiescent pouchitis;	69 adults; 4 weeks **Open label**	*Lactobacillus* La-5 and *Bifidobacterium* BB-12, both 1 x 10^8 CFU/day	Culture	*Lactobacillus* spp. *Bifidobacteria* spp	Increase in lactobacilli and bifidobacteriae

*All studies described are RCTs, except Gosselink *et al.* (2004) and Laake *et al.* (2005) which are open label studies

Abbreviations: *RCT* Randomized Controlled Trial; CFU Colony Forming Unit; *PCR* Polymerase Chain Reaction; *QoL* Quality of Life

addition, Laake *et al.* (2005), demonstrated that a combination of *Lactobacillus* La-5 and *Bifidobacterium* BB-12 decreased clinical symptoms and endoscopic inflammation after surgery in patients with stable pouchitis[98]. There was also a significant increase in lactobacilli and bifidobacteriae seen in patients on the intervention, proving that probiotics can alter and enrich the microbial flora in pouchitis.

1.4.5 Probiotics for Treatment of Active Pouchitis

High doses of VSL#3 may be clinically beneficial in treatment of active pouchitis (Table 1-5). Kühbacher *et al.* (2006) showed that high doses of VSL#3 (3×10^{11} viable lyophilized bacteria/gram) can increase the diversity and richness of gut microbiota (especially the anaerobic flora), as measured through real time polymerase chain reaction (PCR) and florescence in-situ hybridization (FISH) techniques[99]. The efficacy of high dose VSL#3 (360 billion bacteria/day) in the treatment of mildly active pouchitis over 4 weeks was then evaluated by Gionchetti and colleagues in 2007 [100]. They found that high doses were effective in treating active pouchitis, shown by reduced clinical activity scores. These studies suggest a clinical benefit by induction and maintenance of remission of pouchitis through use of a combination of probiotic strains (VSL#3)[101]. As there is a lack of randomized controlled trials (RCT) within the last decade, further studies should be conducted on the efficacy of probiotics in pouchitis to confirm results.

Table 1-5: Summary of RCTs Using Probiotics in Active Pouchitis

Author	Year	Country	Disease	Participants and Duration	Probiotic and dose	Method of Detection	Bacterial Taxa stimulated	Outcome
Kühbacher *et al.*[99]	2006	Germany	Active pouchitis	36 adults; 12 months	VSL#3; (300 x 10^9 CFU in 6 g/day	FISH, qPCR	*Enterobacteriaceae*	Increase in richness and diversity of gut microbiota
Gionchetti *et al.*[100]	2007	Italy	Active pouchitis	23 adults; 4 weeks	VSL#3 (360 x 10^9 CFU/day)	Culture, PCR	*Lactobacillus* spp. *Bifidobacteria* spp. *S. thermophiles*	High dose is effective at inducing remission of mild disease

Abbreviations: *RCT* Randomized Controlled Trial; CFU Colony Forming Unit; *PCR* Polymerase Chain Reaction; *FISH* Florescence In-Situ Hybridization; *qPCR* Quantitative Polymerase Chain Reaction; *PCR* Polymerase Chain Reaction

1.4.6 Probiotics in the Treatment of Active, Inactive or Post-operative CD

Currently, there is no significant evidence of benefit of probiotics in active, quiescent or post-operative recurrence of CD, as summarized in Tables 1-6 to 1-8. Only a few placebo-controlled trials have examined the effect of probiotics in active CD, as seen in Table 1-6. For example, Schultz *et al.* (2004) demonstrated that *Lactobacillus* GG administration in active CD did not show a significant difference in induction of remission in comparison with placebo[102]. Limited studies have also been performed using probiotics for inactive CD (Table 1-7). Malchow *et al.* (1997) initially demonstrated that EcN versus placebo showed no difference in remission rates of CD[103]. Furthermore, studies by Willert *et al.* (2010) and Boureille *et al.* (2013) demonstrated increased or no difference in rates of relapse in quiescent CD after administration of VSL#3 or probiotic yeast *S. boulardii*, thus negating the use of probiotics as maintenance for CD[104,105].

Emerging evidence of probiotics for prevention of recurrent post-operative CD exists (Table 1-8). Smaller RCTs (n=45–70) using single-strain probiotics *Lactobacillus* GG and *L. johnsonii* LA1 initially showed ineffectiveness in preventing endoscopic recurrence after post-operative resection for CD[106–108]. More recently, a larger multicentre study by Fedorak *et al.* (2015) using VSL#3 for post-operative CD also showed no efficacy in preventing post-operative relapse after 90 days. However, patients who started the intervention within 30 days and remained on this probiotic for 365 days demonstrated lower rates of relapse and decreased inflammatory cytokines. Though these results show promise, there is a need for further investigation for recommendation of probiotics for the treatment of post-operative CD.

Table 1-6: Summary of RCTs Using Probiotics in Active CD

Author	Year	Country	Disease	Participants and Duration	Probiotic and dose	Outcome
Plein *et al.*[109].	1993	Germany	Active CD	20 adults; 2 weeks	*S. boulardii*; 750 mg/day	Reduced bowel frequency
Schultz *et al.*[102]	2004	USA	Active CD	11 adults; 6 months	*Lactobacillus GG;* 2×10^9 CFU/day	Not effective at inducing or maintaining remission
Matthes *et al.*[110]	2010	Germany	Active CD	90 adults; 2 weeks	*E. coli* Nissle 1917 enema; 40 ml vs. 20 ml vs. 10 ml with1 x 10^8 CFU/ml	Dose dependent efficacy was observed in per protocol (but not intention to treat) analysis

Table 1-7: Summary of RCTs Using Probiotics in Inactive CD

Author	Year	Country	Disease	Participants and Duration	Probiotic and dose	Outcome
Malchow *et al.*[103]	1997	Germany	Quiescent CD	28 adults; 1 year	*E. coli* Nissle 1917; $2 \times 2.5 \times 10^{10}$ CFU/day + 60 mg prednisolone	No difference in remission rates
Garcia Vilela *et al.*[111]	2008	Brazil	Quiescent CD	34 adults; 3 months	*Saccharomyces boulardii;* 4×10^8 CFU/day	Some improvement of intestinal permeability
Willert *et al.*[104]	2010	USA	Quiescent CD	38 adults; 1 year	VSL#3	Not effective in maintaining remission, increased rate of relapse
Bourreille *et al.*[105]	2013	France	Quiescent CD	165 adults; 1 year	*S. boulardii*; 1 g/day	No clinical benefit in maintenance of remission after steroids and 5-ASA

Abbreviations: *RCT* Randomized Controlled Trial; *CD* Crohn's Disease; *CFU* Colony Forming Unit; *5-ASA* 5-Acetylsalicylic Acid

Table 1-8: Summary of RCTs Using Probiotics in Post-operative CD

Author	Year	Country	Disease	Participants and Duration	Probiotic/Prebiotic and dose	Outcome
Prantera *et al.*[106]	2002	Italy	Post-op CD	45 adults; 12 months	*Lactobacillus GG;* 2.4 g	Did not prevent recurrence
Marteau *et al.*[107]	2006	France	Post-op CD	98 adults; 6 months	*L. johnsonii* LA1; 4×10^9 CFU/day	Does not prevent post-operative recurrence
Van Gossum *et al.*[108]	2007	Belgium	Post-op CD	70 adults; 12 weeks	L. johnsonii LA1; 1×10^{10} CFU/day	Does not prevent early endoscopic recurrence after ileocecal resection
Fedorak *et al.*[112]	2015	Canada	Post-op CD	119 adults; 1 year	VSL#3	Reduced inflammatory markers and recurrence rates after early VSL#3 administration

Abbreviations: *RCT* Randomized Controlled Trial; *CD* Crohn's Disease; *Post-op* Post-operative; *CFU* Colony Forming Unit

1.5 Prebiotics

1.5.1 Definition

Prebiotics are non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon[113,114]. Established prebiotics include inulin-type fructans (fructo-oligosaccharide [FOS], inulin and oligofructose), galacto-oligosaccharides (GOS) and lactulose[63]. These specific carbohydrates exist under the broader category of dietary fibre, though not all dietary fibres are classified as prebiotics[115]. Their definition has been greatly scrutinized and debated, and, unlike dietary fibres, prebiotics must have a health benefit to satisfy this label. Prebiotics are fermented by intestinal bacteria, leading to production of SCFA such as acetate, butyrate and propionate; important metabolites essential in maintaining gut health through reduction of colonic pH and production of energy to colonocytes[116–119]. Other gastrointestinal benefits of prebiotics include improvement in bowel function, enhanced mucosal immunity, gut barrier integrity and epithelial protection from pathologic gut bacteria[114,120]. Inulin and short chain FOS, GOS and lactulose, in particular, have been shown to increase numbers of endogenous bifidobacteria and lactobacilli, which can have health promoting properties[120].

1.5.2 Efficacy of Prebiotics in Experimental Models

There is evidence of prebiotic efficacy in IBD in animal or *in vitro* gut models. Several studies have demonstrated that inulin and oligosaccharides are effective at reducing inflammation in chemically-induced or genetically engineered rat colitis[118,121,122]. Quantitative PCR techniques have allowed us to examine the effect of prebiotics on modulating the gut microbiota. For example, Koleva *et al.* (2012) demonstrated that administration in FOS or inulin in human leukocyte antigen B27 (HLA-B27) rat colitis model leads to increased total bacteria (FOS-mediated), increased *Bifidobacterium* spp. (inulin-mediated) and decreased *Clostridium* cluster XI (inulin/FOS-mediated)[123]. *In vitro* studies have also examined the effect of prebiotics on modifying mucosal-associated gut bacteria through culture techniques[124].

1.5.3 Prebiotics in Induction or Maintenance of Remission of IBD

There are far fewer prebiotic interventional studies conducted in humans with IBD (Tables 1-9 to 1-11). Most studies have shown that initial administration of prebiotics are associated with decreased disease activity through reduction in clinical scores, inflammation on biopsy, proinflammatory cytokine production (e.g. tumor necrosis factor-α [TNF- α], IL-6 and IL-8), fecal calprotectin and myeloperoxidase levels[125–130]. However, studies have shown that prebiotics do not directly reduce disease activity in CD (Table 1-9)[131,132]. For example, in the largest RCT conducted in 103 adult patients over 4 weeks, Benjamin *et al.* (2011) found that 15 g of FOS versus placebo showed no clinical benefit in patients with active CD[132].

Table 1-9: Summary of RCTs Using Prebiotics in CD*

Author	Year	Country	Disease	Participants and Duration	Prebiotic and dose	Method of Detection	Bacterial Taxa Stimulated or Reduced	Outcome
Lindsay *et al.*[125]	2006	UK	Active CD	10 adults; 3 weeks **Open label**	FOS;15 g	FISH	↑*Bifidobacterium* spp.	Effective at reducing clinical scores and inflammatory markers
Benjamin *et al.*[132]	2011	UK	Active CD	103 adults; 4 weeks	FOS; 15 g			No clinical benefit
Joossens *et al.*[127]	2012	Belgium	Inactive and active CD	67 adults; 4 weeks	Oligofructose-enriched inulin (OF-IN); 10 g	qPCR	↑*B. longum* ↓*Ruminococcus gnavus*	Some improvement of disease activity and increase in *B. longum*
de Preter *et al.* [133]	2013	Belgium	Inactive and active CD	67 adults; 4 weeks	OF-IN; 10 g	qPCR, DGGE	↑*B. longum* ↓*Ruminococcus gnavus*	Higher acetaldehyde and butyrate in OF-IN group. Active patients had differing medium chain fatty acids and p-cresol compared to healthy controls

Table 1-10: Summary of RCTs Using Prebiotics in UC*

Author	Year	Country	Disease	Participants and Duration	Prebiotic and dose	Outcome
Casellas *et al.*[130]	2007	Spain	Active UC	19 adults; 2 weeks	OF-IN (Synergy-1; 12 g/day) + mesalazine (3 g/day) versus placebo	Reduction of fecal calprotectin after administration of Synergy-1
Faghfoori *et al.*[134]	2011	Iran	Quiescent UC	41 adults; 2 months **Open label**	Germinated barley foodstuff; 30 g	Reduction of inflammatory cytokines (TNF-α, IL-6, IL-8)

*Studies are RCTs, except for Lindsay *et al.* (2010) and Faghfoori *et al.* (2011) which are open label studies
Abbreviations: *RCT* Randomized Controlled Trial; *CD* Crohn's Disease; *FOS* Fructo-oligosaccharide; *FISH* Florescence In-Situ Hybridization; *qPCR* Quantitative Polymerase Chain Reaction; *DGGE* Denaturing Gradient Gel Electrophoresis; *TNF* Tumor Necrosis Factor; *IL* Interleukin

Table 1-11: Summary of RCTs Using Prebiotics in Pouchitis*

Author	Year	Country	Disease	Participants and Duration	Prebiotic and dose	Method of Detection	Bacterial Taxa Stimulated or Reduced	Outcome
Welters *et al.*[135]	2002	Netherlands	Active pouchitis	20 adults; **Randomized controlled double blind crossover**	Inulin; 24 g	Culture	↓*B. fragilis*	Effective at decreasing inflammation

*Welters et al (2002) is a double blinded placebo controlled crossover study
Abbreviations: *RCT* Randomized Controlled Trial

Therefore, additional well-powered studies examining microbiological, immunological and clinical effects of prebiotics in CD are required.

In contrast, prebiotics showed promise in the treatment of active UC as adjunct therapy (Table 1-10)[128,130]. In an intervention further described in Section 1.5.4, Furrie *et al.* (2005) demonstrated that short-term synbiotic mixture *B. longum* and prebiotic Synergy-1 (oligofructose-enriched inulin) leads to reduction of clinical and endoscopic disease in patients with active UC (Table 1-12)[128]. A randomized controlled study by Casellas *et al.* (2007) also showed that oligofructose-enriched inulin supplementation combined with oral mesalazine therapy leads to reduction of fecal calprotectin levels in active UC (Table 1-10)[130]. Lastly, Valcheva and colleagues (2012) conducted a small open-label pilot study on UC and showed that administration of 15 g of inulin is associated with increase in *Lachnospiraceae* and *Faecalibacterium* spp. as well as reduction of clinical parameters of inflammation[136]. There is currently a lack of RCTs investigating prebiotics in prevention of relapse of UC. However, an open-label study by Faghfoori *et al.* (2011) showed that 30 g of germinated barley foodstuff (a prebiotic preparation of insoluble dietary fibre and glutamine-rich protein) led to a reduction in inflammatory cytokines in patients with quiescent UC (Table 1-10)[134].

There is limited evidence to support prebiotics as an effective treatment for pouchitis as seen in Table 1-11. Further investigation into the efficacy of prebiotics must be done in order to optimize treatment strategies in pouchitis, as well as UC and CD.

1.5.4 Synbiotics as Treatment for IBD

The combination of prebiotics and probiotics together is termed as synbiotics[137]. Tables 1-12 and 1-13 describe a summary of RCTs using synbiotics as a treatment for IBD. As there is a lack of high quality clinical evidence of prebiotics in IBD (Table 1-9 to 1-11), the future may be in the combination of both prebiotics and probiotics as microbiota altering agents. Synbiotics, rather than prebiotics alone, may achieve beneficial effects by targeting specific probiotic strains of bacteria and ensuring they are present[138]. As previously mentioned, success by Furrie and colleagues (2005) using synbiotics for active UC, leads us to believe that a synergistic effect may be present (Table 1-12)[128]. This study showed that a combination of *B. longum* (2×10^{11} CFU/day) and Synergy-1 (6 grams/day) reduced clinical and endoscopic inflammation after a short term of administration. Additional studies by Federico *et al.* (2009) and Ishikawa *et al.* (2011) showed reduction of inflammatory markers and clinical scores after administration of synbiotics[129,139]. Lastly, a study by Ahmed *et al.* (2013) investigating synbiotics in colitis (colonic CD & UC) did not show clinical benefit or changes in the microflora[140].

Studies on synbiotics as treatment for CD are limited (Table 1-13). Bousvaros *et al.* (2005) showed that a combination of *Lactobacillus* GG and inulin did not show difference in relapse rates of CD in children. However, a study by Steed *et al.* (2010) showed that synbiotic mixture *B. longum* and prebiotic Synergy-1 caused a reduction in clinical scores in CD in a smaller group of adult patients[126]. Additional investigations on the function and effect of synbiotics in IBD are warranted.

Table 1-12: Summary of RCTs Using Synbiotics in UC*

Author	Year	Country	Disease	Participants and Duration	Probiotic/Prebiotic and dose	Method of Detection	Bacterial Taxa Stimulated or Reduced	Outcome
Furrie *et al.* [128]	2005	UK	Active UC	18 adults; 4 weeks	*B. longum* + Synergy-1; 2 x 10^{11}CFU + 6 g/day			Effective at reducing clinical and endoscopic inflammation
Federico *et al.*[129]	2009	Italy	Active UC	18 adults; 8 weeks	*L. casei* B 20160; 1 x 10^{9} CFU + prebiotic combination (arabinogalactan, xilo-oligosaccharide, inulin); 6 g			Reduction of inflammatory cytokines (IL-6 and IL-8)
Ishikawa *et al.*[139]	2011	Japan	Active UC	41 adults; 52 weeks	*B. breve* (Yakult®) + GOS; 1 x 10^{9} CFU + 5.5 g/day	Culture	↑*Bacteroid-aceae* spp.	Effective at improving patient clinical status
Ahmed *et al.*[140]	2013	Denmark	20 Colitis (CD + UC)	20 adults; 8 weeks Double blinded placebo controlled crossover	*4 x 10^{9} L. acidophilus* LA-5, *L. bulgaricus LBY-27, B. animalis, B. lactis* BB-12 (Trevis capsule) + 15 g oligofructose per day	qPCR	No change	No difference in colonic microflora between patients with UC or CD after synbiotic

Table 1-13: Summary of RCTs Using Synbiotics in CD*

Author	Year	Country	Disease	Participants and Duration	Probiotic/Prebiotic and dose	Method of Detection	Bacterial Taxa Stimulated or Reduced	Outcome
Bousvaros *et al.*[141]	2005	USA	Quiescent CD	75 children; 2 years	*Lactobacillus* GG; 1 capsule; (10^{10} CFU + 295 mg inulin)/day			No difference in time to relapse vs. standard therapy
Steed *et al.*[126]	2010	UK	Active CD	35 adults; 6 months	*B. longum;* 2 x 10^{11} CFU/day + Synergy-1; 6 g/day	qPCR	↑*Bifidobacterium* spp. (mucosal)	Significant improvement in clinical outcomes. Reduction of CDAI, histological scores & TNF-α

*All studies are randomized controlled clinical trials including adults, except Ahmed *et al.* (2013) which is a double blind crossover design and Bousvaros *et al.* (2005) which includes children

Abbreviations: *RCT* Randomized Controlled Clinical Trial; *UC* Ulcerative Colitis; *CD* Crohn's Disease; *CFU* Colony Forming Unit; *IL* Interleukin; *qPCR* Quantitative Polymerase Chain Reaction; *CDAI* Crohn's Disease Activity Index; *TNF* Tumor Necrosis Factor

1.6 Dietary Fibre

Dietary fibre was originally defined by Hugh Trowel in 1972 as “the remnants of the plant cell wall that are not hydrolysed by alimentary enzymes of a man”[142]. Over the last few decades, this definition has been extensively debated and modified. Recent definitions of dietary fibre by the American Association of Cereal Chemists and the Food and Nutrition Board of the Institute of Medicine of the National Academy in 2001 highlighted resistance to digestion and absorption in the small intestine as defining characteristics[118]. Eventually, in 2012, Health Canada adopted the current definition of dietary fibre as consisting of carbohydrates (including polyphenols as lignans) with a degree of polymerization of three or more that naturally occur in foods of plant origin that are not digested and absorbed by the small intestine and accepted novel fibres[143]. The health benefits of dietary fibre were popularized by Denis Burkitt as playing a role in lowering the risk of cardiovascular heart disease, obesity, dental caries, vascular disorders and colonic disease such as appendicitis, diverticulosis and cancer[144]. The role of dietary fibre in the etiology of IBD is unclear, with the generalization towards low fibre diets being implicated in the rapid incidence of IBD over the years. A study conducted by Brotherton *et al.* (2016) suggested that a diet low in fibre is responsible for greater risk of a flare in CD[145]. However, conflicting evidence exists as recently reported in a large population based cohort study by Andersen *et al.* (2018) demonstrating that fibre intake (total dietary fibre and fibre from fruits, vegetables and cereals) has no impact on the development of IBD[146]. Therefore, studies on dietary patterns, rather than specific food ingredients, should be conducted in order to arrive at a linear conclusion.

The general population may not know the difference between dietary fibres and prebiotics. Though prebiotics are considered fibre, not all fibres are considered prebiotic[147]. Unlike prebiotics, some dietary fibres do not have the ability to withstand gastric acidity and do not undergo fermentation in the colon. Lastly, not all dietary fibres have a health benefit and selectively stimulate microbiota associated with host health and well-being in accordance with the definition of prebiotics[114].

1.7 Probiotics, Prebiotics and Dietary Fibres: Usage Patterns in IBD Patients

Probiotics and prebiotics are included in the definition of CAM, and studies have shown their use in concordance with other CAMs. The prevalence of probiotic use as non-conventional therapy for IBD is increasing. In a large survey on 2847 Canadian IBD patients, Hilsden *et al.* (2003) found that *L. acidophilus* (a common probiotic) was the most commonly used CAM, though only 19% of patients reported use[38]. In addition, several studies have shown that though 23 – 43% patients use probiotics as a common CAM therapy, homeopathic and herbal remedies (such as turmeric, cercumin, fish oil, aloe vera, slippery elm and other herbs) are used in higher frequency[43,53,54]. Through a survey studying CAM use in 380 Canadian IBD patients, Weizman *et al.* (2012) found that over half of CAM users (54%) used probiotics[49]. Furthermore, a recent study by Nguyen *et al.* (2016) showed a significantly greater proportion of IBD patients using probiotics for their IBD (65%) than for the purpose of general health (46%)[55]. In a study examining use of prebiotics and probiotics in IBD patients (most similar to the current study), Hedin and colleagues (2010) also demonstrated that 52% of patients with IBD used probiotics[148]. Though these studies

confirm that probiotics are consumed frequently by IBD patients, there is a gap in knowledge regarding their isolated use or use in combination with prebiotics.

A limited number of studies have investigated patterns of prebiotic use with a lack of data on use in IBD. In a study conducted by Betz *et al.*(2015) on 200 hospitalized patients with various diseases, 38% reported consumption of prebiotics[149]. Common reasons for prebiotic consumption were overall digestion/gut health and overweight/obesity; however, it is not known if these patients had intestinal disease. Hung *et al.* (2015) showed a small percentage of patients use prebiotics as a supplement for general GI diseases, though the frequency was not provided[29]. Currently, the only study investigating prebiotic use in IBD patients was conducted by Hedin *et al.* (2010) reporting 3% of patients indicate use as alternate therapy for their disease[148]. As this number was negligible, further analysis testing the relationship between prebiotic use and determining factors were not done in this study.

Dietary fibre has been documented in IBD, however studies on use are lacking. Studies on the use of probiotics, prebiotics and dietary fibres as individual or combination therapy are limited, based on our literature search, thus highlighting the need for this research project.

2 STUDY PURPOSE AND OBJECTIVES

2.1 Study Purpose

The purpose of this study was to investigate the prevalence of, and determining factors associated with, the use and awareness of probiotics, prebiotics and/or dietary fibre supplements (PPF) in the IBD population.

2.2 Hypothesis

The hypothesis of this study was that an increase in awareness and disease severity is associated with the use of alternative therapies such as probiotics, prebiotics and/or dietary fibre supplements in IBD patients.

2.3 Objectives

The objectives of the proposed research are as follows:

1) To assess the use and awareness of PPF in IBD patients through a self-administered paper-based survey questionnaire.
2) To determine the factors associated with use and awareness of PPF in IBD patients through a survey questionnaire and review of charts.
    i. Through association analyses between patient demographics and PPF use and awareness.
    ii. Through association analyses between clinical characteristics and PPF use and awareness.

3 METHODS

3.1 Study Design

This cross-sectional study looked at the use and awareness of probiotics, prebiotics and/or dietary fibre supplements in adults with a diagnosis of inflammatory bowel disease (Crohn's disease or ulcerative colitis) to test the study hypotheses. This two-step data collection involved a self-administered twenty-item survey questionnaire followed by a chart review that assessed demographic data, disease characteristics, clinical data, use and awareness of prebiotics, probiotics and/or dietary fibre supplements in IBD patients.

3.2 Participant Characteristics

Study participants were identified as eligible by a gastroenterologist (diagnosis of IBD, adult ≥18 years) during scheduled visits at the University of Alberta Inflammatory Bowel Disease outpatient clinic or BioAdvance® Inviva Infusion centre. Study subjects were then asked to fill out a survey questionnaire in the clinic waiting room either before or after their clinic visit. Adult patients (18 years of age or older) with an established diagnosis of IBD attending the University of Alberta IBD or Infusion Clinic were eligible. Patients were excluded if they could not read or write English fluently. Healthy or non-IBD controls were not included in this study.

3.3 Survey

The self-administered paper-based survey consisted of twenty items in a multiple-choice format. Researchers were careful not to guide or interview patients in this study in order to minimize bias.

The questionnaire (APPENDIX B) was composed of three sections. The first section included standard demographic questions on sex, age, educational level and ethnicity. The second section summarized clinical data (disease diagnosis and duration, current medications and flare frequency) and use of other alternative therapies (dietary patterns, vitamin, mineral, herbal supplement and marijuana use and complementary alternative medicine [CAM] practices). The third section looked at PPF characteristics such as use (lifetime and current), awareness, knowledge source, brand or type currently used, perceived improvement in QoL, benefit intended and received, reason for never-use and monthly expenditure. Timing of use was defined as current (within the last year) or lifetime (including the last year). The structure and format of survey questions were chosen based on consultation with gastroenterologists involved in the study design. Each item of the survey was then verified for wording and structure by an expert statistician in order to maintain accuracy and prevent bias.

3.3.1 Perceived Quality of Life

The relapsing and remitting nature of a chronic disease such as IBD can place stressors in a patient's life. Complications can arise, leading to difficulty with management of and coping with IBD – causing impairment in QoL. Since the early 1990s, factors investigated in relation to health-related QoL in IBD include systemic and bowel symptoms, functional and social impairment and emotional function[150]. Previous studies have shown that as disease severity increases (frequent relapse, clinical activity, need for hospitalization), so does the QoL burden on patients with IBD[151,152]. Therefore, use of alternative therapies such as PPF to ameliorate disease, may have an impact on a patients' health-related QoL.

In the survey questionnaire, patients were asked if they noticed an improvement in QoL after using PPF over the last year. Quality of life was not assessed via a formal validated questionnaire or scoring system in this study. Therefore, any change or improvement in QoL was termed as "perceived". Perceived improvement in QoL was subjective and future research must be conducted with a reliable and validated tool measuring patient improvement in QoL in association with PPF use and awareness.

3.4 Chart Review

A retrospective chart review was conducted by the researcher after participant completion of the survey questionnaire. Charts were reviewed through electronic medical records (EMR) eClinician (EPIC), and WOLF EMR (TELUS Health®). The chart review (APPENDIX C) was comprised of two sections: demographics and disease characteristics. Demographics

collected from charts included age, sex and age at diagnosis. Abstracted disease characteristics included disease activity at the time of survey completion (measured through Partial Mayo scores for UC and the modified Harvey Bradshaw Index for CD), Montreal classification scores, flare frequency, surgical history, current medication list and presence of extra-intestinal manifestations. Objective markers of disease severity such as serum C-reactive protein (CRP) and fecal calprotectin (FCP) levels were also recorded.

3.4.1 Determination of Montreal Classification scores

The Montreal Classification system, formed at the 2005 World Congress of Gastroenterology, involves disease sub-classification scores of IBD[2]. It specifically measures age at diagnosis, disease behaviour, location of CD, and extent and severity of UC. In this study, Montreal classification scores were determined based on most severe presentation per category in the patient's entire disease course (APPENDIX D).

Montreal Classification scores for CD included parameters on age at diagnosis, location and behaviour. Age of diagnosis was documented in three categories: 16 years or younger (A1), 17–40 years (A2) and greater than 40 years (A3) and was abstracted per retrospective endoscopy and/or pathology reports confirming a diagnosis of IBD. Inclusion of a category under the age of eighteen was done to include phenotypes found in early onset CD, which is steadily increasing in prevalence[153]. Disease location was abstracted from charts per guidelines as ileal (L1), colonic (L2) and ileocolonic (L3). In this study, isolated upper GI disease (L4) was also used as a modifier to indicate disease above the ileum (jejunum,

duodenum, gastric, esophageal and/or oral). Disease behaviour was classified as one of inflammatory (B1), stricturing (B2), penetrating (B3) or stricturing and penetrating (B2B3) disease. Inflammatory disease was defined as disease in the absence of strictures and penetration. Perianal disease (p), a modifier added to B1 – B3, was used to describe concomitant disease around the anus, including perianal fistulas, perianal abscesses and anal fissures. This demonstrated a clear delineation from penetrating disease, which included enterocutaneous and entero-entero fistulas only.

Montreal classification scores for UC phenotype were sub-classified by disease extent. Disease extent was defined by isolated rectal involvement (E1), left-sided disease (E2) and pancolitis (E3).

3.4.2 Determination of Harvey Bradshaw Index and Partial Mayo Scores

The Harvey Bradshaw Index (HBI) was created as a simple index of CD activity by R. F. Harvey and J. M. Bradshaw in 1980[154]. It is a numerical index score of disease based on five items:

A. General well-being (0 = very well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible)

B. Abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe)

C. Number of liquid stools per day

D. Abdominal mass (0 = none, 1 = dubious, 2 = definite, 3 = definite and tender)

E. Complications: arthralgias, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissure, new fistula, abscess (score 1 per item)

The scoring template used to calculate HBI scores as part of the chart review was referenced from a guide created by the University of Alberta IBD Clinic (APPENDIX E) based upon Harvey and Bradshaw's scoring index. Extra-intestinal manifestations were also referenced from Item E of HBI. Presence of extra-intestinal manifestations at any point of the patients' disease course was considered.

The Mayo Clinic Index includes clinical symptoms, endoscopic scores, QoL measures and physician global assessment of disease in the assessment of disease activity of UC (APPENDIX F). Elimination of endoscopic scores results in Partial Mayo score, a sub-score assessing inflammation in clinical UC. It involves the following measures of disease activity:

A. Rectal Bleeding (0 = normal number of stools, 1 = 1–2 stools more than normal, 2 = 3–4 stools more than normal, 3 = 5 or more stools than normal)

B. Stool Frequency (0 = no blood seen, 1 = streaks of blood with stool less than half of the time, 2 = obvious blood with stool most of the time, 3 = blood alone passed)

C. Physician Global Assessment (0 = normal [sub scores are mostly 0], 1 = mild disease [sub scores are mostly 1], 2 = moderate disease [sub scores are mostly 1 to 2], 3 = severe disease [sub scores are mostly 2 to 3]

The physician global assessment is based on sub scores, which include a daily record of patient abdominal discomfort and functional assessment, patient performance status and other clinical and physical findings. The sum of all items in the index leads to a total Partial Mayo Index Score which can indicate if a patient is in remission (0–1), has mild disease (2–4), moderate disease (5–6) or severe disease activity (7–9) at the time of presentation.

3.4.3 Definition of a flare and flare frequency

For the purposes of this study, flares were defined as a combination of clinical symptoms and endoscopic and/or histological scores. Clinical symptoms pertaining to a flare included diarrhea ≥ 3 days, obvious blood in the stool, bloating and/or abdominal pain. Constitutional symptoms such as presence of fever > 38° C, loss of appetite, nausea/vomiting, fatigue and change in health status were considered. Flares were also defined as an endoscopic score > 1 and/or evidence of inflammation on histology.

3.5 Sample Size Determination and Power

The estimated number of patients that attend the IBD clinic was 2800. The amount recruited in one year was estimated to be 10% of this patient population, or 280. This sample size was first chosen by the researcher and supervisor as representative of a diverse, general IBD population. In order to recruit a feasible number of patients, sample size was also calculated[155]. A sample size of 287 was calculated when estimating the prevalence of PPF use at 58% (based on proportion of probiotic and prebiotic use studied by Hedin and colleagues) in a population size of 2800[148]. Margin of error was set at 5% with a confidence interval of 93%.

3.6 Consent and Ethics

Participation in this study was voluntary and this was stated in the information sheet and informed consent form (APPENDIX A). Prior to giving consent and filling out the questionnaire, respondents were asked if they had any questions about any risks involving study participation and data collection. Signed consent was obtained to allow access to medical records in order to conduct the chart review. The study protocol and data collection materials were reviewed and approved by the Health Research Ethics Board at the University of Alberta (No. Pro00064575).

3.7 Data Analysis

Study data were collected and managed using REDCap electronic data capture tools hosted by the Women & Children's Health Research Institute[156]. REDCap (Research Electronic Data Capture) is a secured, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) Version 23.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation and a student's *t*-test was used to compare the means between the two groups (i.e. age vs. IBD diagnosis). Categorical variables were presented as proportions and percentages using a 95% confidence interval (CI) with a normal distribution and Chi-square test or Fisher's exact test were used to compare frequencies between the groups (i.e. education vs. current PPF use). To determine possible predictive factors of PPF use, univariate binary logistic regression analyses was performed with PPF use (dichotomized as users and non-users) as the dependent variable of interest. The strength of association between use of PPF and demographic, clinical and PPF characteristics was assessed using the odds ratio (OR). A two-tailed *P* value of less than 0.05 was considered statistically significant.

4 RESULTS

4.1 Population Analysis

In total 280 patients from the University of Alberta Gastroenterology Consultation and Research IBD Clinic and Janssen BioAdvance® Inviva Infusion Clinic provided consent to participate in this study. Thirteen participants were excluded from analysis: four participants were withdrawn based on lack of established IBD diagnosis and nine patients with IBD-U were excluded due to the low number of patients in this group.

4.1.1 Sociodemographic characteristics of the study population

Sociodemographic characteristics of patients are presented in Table 4-1 and associated to IBD diagnosis in Table 4-2. In this study, 267 eligible patients (n=144, 53.9% female) were included. Mean age of participants was 42.6 years (± a standard deviation of 15.7 years), with age of participants ranging from 18 to 77 (Table 4-1). Sixty-eight percent (n=182) had CD and 32% (n=85) had UC. Participants with CD were significantly older than those with UC (44.0 vs. 39.6, $p<0.05$, Table 4-2). Ninety-one percent of the study population was of Caucasian background, and a significantly greater proportion of patients with CD were Caucasian (95% CD vs. 85%UC, $p<0.05$, Table 4-2). The greatest proportion of participants (45%) had achieved education greater than a high school diploma, but less than a 4-year university degree (Table 4-1). There was no significant relationship between IBD diagnosis and gender, age group or educational level achieved, as seen in Table 4-2.

Table 4-1: Sociodemographic Characteristics of the Study Population

Characteristics	n (% of 267)
Type of IBD	
Crohn's disease	182 (68.2)
Ulcerative colitis	85 (31.8)
Age, yr, mean (range)	43 (18-77) [a]
18-35	104 (39.0)
36-50	70 (26.2)
>50	93 (34.8)
Female sex	144 (53.9)
Ethnicity/Race	
Caucasian	244 (91.4)
Visible Minority [b]	23 (8.6)
Education	
High school or less	76 (28.5)
Some college, but ≤ 4 year university degree [c]	119 (44.6)
4 year university degree or greater	72 (27.0)

[a] Frequency expressed as mean and range for age (as a continuous variable)
[b] Visible minority includes Black/African Canadian, First Nation/North American Indian/Métis, Asian, East Indian, Hispanic/Latino and Other ethnicity/race
[c] Includes, but not limited to, associate's degree, diploma certificate, trades certificate and partial fulfillment of a university degree

Abbreviations: *IBD* Inflammatory Bowel Disease

Table 4-2: IBD Type in Association to Sociodemographic Characteristics

Characteristic	CD 182 (66) n (%)	UC 85 (31) n (%)	p-value
Sex			
Female	99 (54.4)	45 (52.9)	0.824
Age, Yr [a]	44.0 ± 15.8	39.6 ± 15.2	**0.036**
Age groups			
18-35 Yr	63 (34.6)	41 (48.2)	0.081
36-50 Yr	49 (26.9)	21 (24.7)	
>50 Yr	70 (38.5)	23 (27.1)	
Ethnicity/Race			
Caucasian	172 (94.5)	72 (84.7)	**0.011**
Visible Minority [b]	10 (5.5)	13 (15.3)	
Education			
≤ High school	57 (31.3)	19 (22.4)	0.133
Some college, but ≤ 4 year university degree [c]	82 (45.1)	37 (43.5)	
≥ 4 year university degree	43 (23.6)	29 (34.1)	

[a] Expressed as mean ± standard deviation

[b] Visible minority includes Black/African Canadian, First Nation/North American Indian/Métis, Asian, East Indian, Hispanic/Latino and Other ethnicity/race

[c] Includes, but not limited to, associate's degree, diploma certificate, trades certificate and partial fulfillment of a university degree

Abbreviations: *IBD* Inflammatory Bowel Disease; *CD* Crohn's Disease; *UC* Ulcerative Colitis

4.1.2 Pharmaceutical and Alternate Therapeutic Characteristics of the Study Population

Patients with IBD often use alternative therapies in conjunction with standard IBD medications. These patients frequently take more than one medication for their disease, thus the cumulative percentage of medications listed in this survey exceeds 100%. We found that the majority of individuals were on biologic therapy at the time of survey (n=157, 59%) as demonstrated in Table 4-3. When comparing disease diagnosis (CD vs. UC) with respect to other alternative therapies (Table 4-4), it was found that UC was significantly associated with use of 5-ASA medications (oral and/or rectal preparations: 65% UC vs. 17% CD; $p<0.001$). In comparison, CD was associated with a higher number of biologic therapies such as adalimumab, infliximab, golimumab or vedolizumab (68% CD vs. 40% UC; $p<0.001$, Table 4-4). Often patients with relapsing disease may undergo surgical resection (CD) or removal of entire colon/colectomy (UC). About thirty percent of the population had past surgical history in their IBD course (Table 4-3). Crohn's disease was associated with a greater prevalence of surgical history in study patients (43% CD vs. 2% UC; $p<0.001$). No significant relationship was seen between IBD type and current or past steroid use, immunosuppressants, antibiotics or presence of no medications.

Sixty two percent of patients indicated that they followed a normal diet (including all food groups) without any modifications. Additional diet categories included exclusion diet (excluding one or more food ingredients, e.g. red meat, dairy, etc.), special diets (including vegan, vegetarian, pescatarian [vegetarian with addition of seafood], gluten-free, lactose-free, low glycemic, DASH [Dietary Approaches to Stop Hypertension] diet, low FODMAP

[Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols] or "trademarked" diets [e.g. Jenny Craig®, Weight Watchers®, South Beach®, Atkins®, Bernstein®, etc.]) or a combination of special diets. There was no relationship between IBD type and diet in our study population.

Supplement use was reported in 76% of the total study population. Within that group, patients utilized vitamins (74%), minerals (52%) and herbal supplements (17%) as seen in Table 4-3. Out of all IBD patients surveyed, 43% were also CAM users. Massage therapy (28%) and chiropractor visits (19%) were the most frequently used types of CAMs used. Though the number of marijuana users was limited in the study population (n=34, 13%, Table 4-3), it was found that CD was related to marijuana use (p=0.021, Table 4-4). There was no significant association between disease diagnosis and supplements or use of other CAMs.

Table 4-3: Therapeutic Characteristics of the Study Population

Characteristics	n (% of 267)
Current Medications [a]	
On IBD Medication (yes)	232 (86.9)
5-ASA (oral ± rectal)	85 (31.8)
5-ASA oral	78 (29.2)
Steroids	10 (3.7)
Immunosuppressants [b]	94 (35.2)
Biologics [c]	157 (58.8)
Antibiotics	8 (3.0)
Rectal 5-ASA	24 (9.0)
No Medications	35 (13.1)
Past steroid use	215 (80.5)
Past surgical history	80 (29.0)
Diet [d]	
Normal	162 (62.3)
Exclusion	43 (16.5)
Special	32 (12.3)
Combination	23 (8.8)
Supplement Users	
Total	204 (76.4)
Vitamins	196 (74.0)
Minerals	137 (51.7)
Herbal	45 (16.9)
CAM Users	116 (43.4)
Types of CAM used	
Massage	74 (27.7)
Chiropractor	51 (19.1)
Yoga	31 (11.6)
Other CAMs [e]	85 (31.8)
Marijuana use	34 (12.8)

[a] Current therapy totals out of 276 do not add up to 100% as patients due to concomitant therapy
[b] Immunosuppressants include thiopurines (azathiopurine, 6-mercaptopurine), methotrexate and cyclosporine
[c] Biologics include adalimumab, infliximab, golimumab, vedolizumab and ustekinumab
[d] Diets include normal (all food groups), exclusion (excluding one or more ingredients), special (vegan, vegetarian, pescatarian, gluten-free, lactose-free, low glycemic, DASH diet with food exclusions, low FODMAP or "trademarked") and combination (≥1 special diet).
[e] Other CAMs include meditation, acupuncture, naturopathy, homeopathy, Reiki, reflexology, faith healing, Tai Chi, Chinese medicine and other unlisted CAMs

Abbreviations: *IBD* Inflammatory Bowel Disease; *5*-ASA 5-Acetylsalicylic Acid; *CAM* Complementary Alternative Medicine

Table 4-4: IBD Type in Association to Therapeutic Characteristics

Characteristic	CD 182 (66) n (%)	UC 85 (31) n (%)	p value
Current Medications [a]			
On IBD Medication	157 (86.3)	75 (88.2)	0.657
5-ASA (oral ± rectal)	30 (16.5)	55 (64.7)	**<0.001**
5-ASA oral	27 (15)	51 (60)	**<0.001**
Steroids	6 (3.3)	4 (4.7)	0.730[e]
Immunosuppressants [b]	71 (39.0)	23 (27.1)	0.057
Biologics [c]	123 (67.6)	34 (40.0)	**<0.001**
Antibiotics	5 2.7)	3 (3.5)	0.712[e]
Rectal 5-ASA	3 (1.6)	21 (24.7)	**<0.001**[e]
No Medications	25 (13.7)	10 (11.8)	0.657
Past steroid use	146 (80.2)	69 (81.2)	0.854
Past surgical history	78 (42.9)	2 (2.4)	**<0.001**[e]
Diet [d]			
Normal	106 (59.6)	56 (68.3)	0.182
Exclusion	35 (19.7)	8 (9.8)	
Special	20 (11.2)	12 (14.6)	
Combination	17 (9.6)	6 (7.3)	
Supplements			
Total	137 (75.3)	67 (78.8)	0.525
Vitamins	135 (74.2)	61 (73.5)	0.907
Minerals	93 (51.7)	44 (51.8)	0.988
Herbal	34 (18.8)	11 (12.9)	0.236
CAM Use [f]	80 (44.0)	36 (42.4)	0.806
Marijuana use	29 (16.0)	5 (5.9)	**0.021**

[a] Current medication totals out of 182 (CD) and 85 (UC) do not add up to 100% due to combination therapy
[b] Immunosuppressants include thiopurines (azathiopurine, 6-mercaptopurine), methotrexate and cyclosporine
[c] Biologics include adalimumab, infliximab, golimumab, vedolizumab and ustekinumab
[d] Diets include normal (all food groups), exclusion (diet with exclusion of one or more ingredients), special (vegan, vegetarian, pescatarian, gluten-free, lactose-free, low glycemic, DASH diet with food exclusions, low FODMAP or "trademarked" diets) and combination (≥1 special diet).
[e] Fisher's Exact Test was used for association analyses when more than 25% of cells had expected counts < 5
[f] Types of complementary alternative therapy included massage therapy, chiropractor visits, yoga, meditation, acupuncture, naturopathy, homeopathy, Reiki, reflexology, faith healing, Tai Chi, Chinese medicine and other various unlisted CAMs

Abbreviations: *IBD* Inflammatory Bowel Disease; *CD* Crohn's Disease; *UC* Ulcerative Colitis; *5*-ASA 5-Acetylsalicylic Acid; CAM Complementary Alternative Medicine

4.1.3 Clinical Characteristics of the Study Population

Table 4-5 summarizes clinical characteristics (age of diagnosis, disease duration, disease activity, flare frequency, CRP, FCP and extra-intestinal manifestations) in the study population and Table 4-6 demonstrates the association between UC or CD and these clinical variables.

The majority of study patients were diagnosed between the ages of 17-40 (64%), had longstanding disease greater than ten years (50%) and presence of disease outside the GI tract (50%, Table 4-5). A diagnosis of CD was found to be significantly associated with an earlier age of disease diagnosis (16 or younger, 20% CD vs. 8% UC, $p<0.05$), longstanding disease (>10 years; 57% CD vs. 35% UC; $p<0.01$) and presence of extra-intestinal manifestations (65% CD vs. 18% UC; $p<0.001$, Table 4-6). Though UC was not associated to complicated disease, a relationship was demonstrated with disease activity as recent flares.

Presence of one or more flares was seen in the majority of patients (51% within 1 year, 72% within 2 years, Table 4-5). Ulcerative colitis was significantly associated with presence of flares and flare frequency as seen in Table 4-6. In this study, UC was related to flares in the last one or two years (one year: 62% UC vs. 46% CD, $p<0.05$; two years: 81% UC vs. 68% CD, $p<0.05$). In addition, UC patients also had higher mean flare frequency versus CD patients within the last two years (UC=1.7 mean flares vs. CD=1.2 mean flares; $p<0.01$).

Table 4-5 includes frequency analysis of bioclinical markers of inflammation abstracted from charts, such as FCP, an objective stool marker of inflammation, and CRP, a serum acute phase inflammatory marker. C reactive protein levels higher than eight (indicating active inflammation) were found in approximately one third of patient charts (34% within 6 months, 42% within 1 year) with mean CRP levels ranging from 16 – 19, respectively. Increased average FCP levels (≥250 µg/g) were found in about 40% of participants with mean average FCP levels between 594 – 614 µg/g within the last six months to the last year. The relationship between IBD diagnosis and markers of inflammation (FCP and CRP) was then determined.

A positive association was found between UC and higher mean average FCP levels within the last six months (UC: 1056.8 ± 2867.5 vs. CD: 433.4 ± 789.6; p=0.05). This is likely due to colonic inflammation present in UC patients. Fecal calprotectin is a useful marker of inflammation, though it is not sensitive in detection of ileal inflammation found in CD. It is important to note that thesis data were based off half of participants who had analyzed FCP levels in charts, which is a limitation. In addition, active patients are more likely to be tested and have a result, thus limiting the data found in charts. Barriers to lab testing, such as living in remote locations, may also affect the availability of data in charts. Presence of active disease, CRP and yearly average FCP levels had no association with either CD or UC.

Table 4-5: Clinical Characteristics of the Study Population

Characteristics	n (% of 267)
Age at diagnosis, yr, mean (range) [a]	29.3 (4-71)
16 or younger	43 (16.1)
17-40	170 (63.7)
40 or older	54 (20.2)
Disease duration (years)	
< 5	70 (26.2)
5-10	64 (24.0)
>10	133 (49.8)
Active disease [b]	80 (30.0)
Presence of flares	
within 1 year	136 (50.9)
within 2 years	193 (72.3)
Mean number of flares within 2 years ± SD (range) [a]	1.4 ± 1.2 [a]
Extra-intestinal manifestations	133 (49.8)
Patients with CRP > 8 [c]	
within 6 months	81 (33.6)
within 1 year	106 (42.2)
Serum CRP values ≥ 8 ± SD [c]	
≤ 6 months	15.8 ± 41.7 [a]
≤ 1 year	19.1 ± 44.1 [a]
Patients with average FCP ≥ 250 µg/g [d]	
≤ 6 months	55 (41.0)
≤ 1 year	66 (42.3)
Mean Average FCP values ≥ 250 µg/g ± SD [d]	
≤ 6 months	613.5 ± 1689.5 [a]
≤ 1 year	594.0 ± 1602.5 [a]

[a] Frequency expressed as mean and range for age and flares (as a continuous variable)
[b] Active disease in ulcerative colitis was determined by a current Partial Mayo Score between 2 to 9 and in Crohn's disease was determined by a current Harvey Bradshaw Index greater than 5.
[c] Reduced subset of patients had CRP values in charts within the last six months (n=141) or last year (n=151)
[d] Reduced subset of patients had FCP values in charts within the last six months (n=135) or last year (n=156)

Abbreviations: *SD* Standard Deviation; *CRP* C-reactive Protein; *FCP* Fecal Calprotectin

Table 4-6: IBD Type in Association to Clinical Characteristics

Characteristic	CD 182 (66) n (%)	UC 85 (31) n (%)	p-value
Age at diagnosis, yr, mean ± SD [a]	28.8 ± 14.2	30.2 ± 13.6	0.458
16 or younger	36 (19.8)	7 (8.2)	**0.044**
17-40	113 (62.1)	57 (67.1)	
40 or older	33 (18.1)	21 (24.7)	
Disease duration (years)			
< 5	38 (20.9)	32 (37.6)	**0.002**
5-10	41 (22.5)	23 (27.1)	
>10	103 (56.6)	30 (35.3)	
Active disease [b]	48 (26.4)	32 (37.6)	0.061
Mean number of flares within 2 years ± SD	1.2 ± 1.2 [c]	1.7 ± 1.3 [c]	**0.007**
Presence of flares within the last year	83 (45.6)	53 (62.4)	**0.011**
Presence of flares within the last two years	124 (68.1)	69 (81.2)	**0.027**
Extra-intestinal manifestations	118 (64.8)	15 (17.6)	**<0.001**
Number of Patients with CRP ≥ 8 [c]			
≤ 6 months	57 (34.1)	24 (32.4)	0.797
≤ 1 year	70 (40.7)	34 (43.0)	0.727
Mean Serum CRP ≥ 8 ± SD			
≤ 6 months	17.3 ± 47.4 [c]	12.2 ± 24.6 [c]	0.378
≤ 1 year	21.6 ± 50.6 [c]	13.7 ± 24.0 [c]	0.185
Number of Patients with average FCP ≥ 250 µg/g [d]			
≤ 6 months	39 (41.1)	16 (41.0)	0.998
≤ 1 year	45 (40.9)	21 (45.7)	0.585
Mean Average FCP ≥ 250 µg/g ± SD			
≤ 6 months	433.4 ± 789.6 [c]	1056.8 ± 2867.5 [c]	**0.052**
≤ 1 year	447.6 ± 831.0 [c]	944.1 ± 2644.9 [c]	0.078

[a] Prevalence expressed as mean ± standard deviation
[b] Active disease in ulcerative colitis was determined by current Partial Mayo Score between 2 to 9. Active disease in Crohn's disease was determined by current Harvey Bradshaw Index greater than 5.
[c] Reduced subset of patients had CRP data in charts within the last six months (CD: n=167, UC: n=74) or the last year (CD: n=172, UC: n=79)
[d] Reduced subset of patients had FCP data in charts within the last six months (CD: n=96, UC: n=39) or the last year (CD: n=110, UC=46)

Abbreviations: *CD* Crohn's Disease; *UC* Ulcerative Colitis; *SD* Standard Deviation; *CRP* C-reactive Protein; *FCP* Fecal Calprotectin

4.1.4 Disease Extent and Activity in the Study Population

Clinical parameters of disease were scored through the Montreal classification system, Harvey Bradshaw Index and Partial Mayo Scoring system in terms of disease location, extent, behaviour and activity as described in Tables 4-7 and 4-8. The majority of participants with CD had isolated ileocolonic involvement (56%) and stricturing phenotype (51%, Table 4-7). Extensive CD can also involve presence of upper GI disease (L4) or perianal involvement (p), which was seen in a minority of the study population (L4: n=38, 21%; p: n=61, 34%).

Extensive pancolonic involvement was seen in the majority of UC study patients (73%, Table 4-8). Most patients were in remission at the time of survey completion, based on HBI for CD and Partial Mayo Scoring for UC (74% CD, 62% UC). In regards to surgical history, 42% (n=77) of all respondents with CD had a history of one or more intestinal resections, with the mean number of resections equal to 1.65. Comparatively, only 2% (n=2) of those with UC were found to have prior history of colectomy throughout their disease course.

Table 4-7: Disease Phenotypes and Clinical Activity in CD Patients

Variable	n (% of 182)
Montreal Classification Score	
Location	
Ileal only (L1)	47 (25.8)
Colonic only (L2)	34 (18.7)
Ileocolonic only(L3)	101 (55.5)
Upper GI involvement (L4 [+ L1, L2 or L3]) [a]	38 (20.9)
Behaviour	
Inflammatory only (B1)	72 (39.6)
Stricturing only (B2)	92 (50.5)
Penetrating only (B3)	42 (23.1)
Stricturing and Penetrating only (B2B3)	15 (8.2)
Perianal involvement (p [+ B1, B2, B3 or B2B3]) [b]	61 (33.5)
Current disease activity (Harvey Bradshaw Index) [c]	
Remission (<5)	134 (73.6)
Mild disease (5-7)	29 (15.9)
Moderate disease (8-16)	16 (8.8)
Severe disease (>16)	3 (1.6)
Surgical history	
Presence of resections	77 (42.3)
Mean total number of resections ± range (n=78)	1.65 (1-6)

[a] L4 = Upper GI modifier
[b] p = perianal disease modifier
[c] Current disease activity was determined Harvey Bradshaw Index, a simple index of Crohn's disease activity
Abbreviations: *CD* Crohn's Disease; *GI* Gastrointestinal

Table 4-8: Disease Phenotype and Severity Scores in UC Patients

Variable	n (% of 85)
Montreal Classification Score [a]	
Extent	
Proctitis (E1)	5 (5.9)
Left-sided (E2)	18 (21.2)
Pancolonic (E3)	62 (72.9)
Current disease activity (Partial Mayo Score) [b]	
Remission (0-1)	53 (62.4)
Mild disease (2-4)	20 (23.5)
Moderate disease (5-6)	10 (11.8)
Severe disease (7-9)	2 (2.4)
Surgical history	
Presence of colectomy	2 (2.4)

[a] Montreal classification scores for severity in UC (S0, S1, S2, S3) were not included in this analysis, as scores are subjective and intra-observer/inter-observer bias exists
[b] Current disease activity was determined by Partial Mayo Index, a simple index of ulcerative colitis disease activity
Abbreviations: *UC* Ulcerative Colitis

4.2 Determinants of PPF Awareness

The awareness of PPF was defined as "having heard" of any one of these therapies at some point in a patient's lifetime. Almost all respondents (n=243, 91%) reported having heard of PPF in their lifetime (Figure 4-1). Most patients reported that they had heard of probiotics (88%) and fibre supplements (73%), with a reduced number reporting awareness on prebiotics (42%) as demonstrated in Figure 4-1. Predictors of PPF awareness are identified in Table 4-9. Females were 2.5 times more likely to be aware of PPF (94% female vs. 87% male; OR: 2.5, 95% CI: 1.1-6.2; $p<0.05$). There was no association between awareness of PPF and other demographics such as age, education or ethnicity.

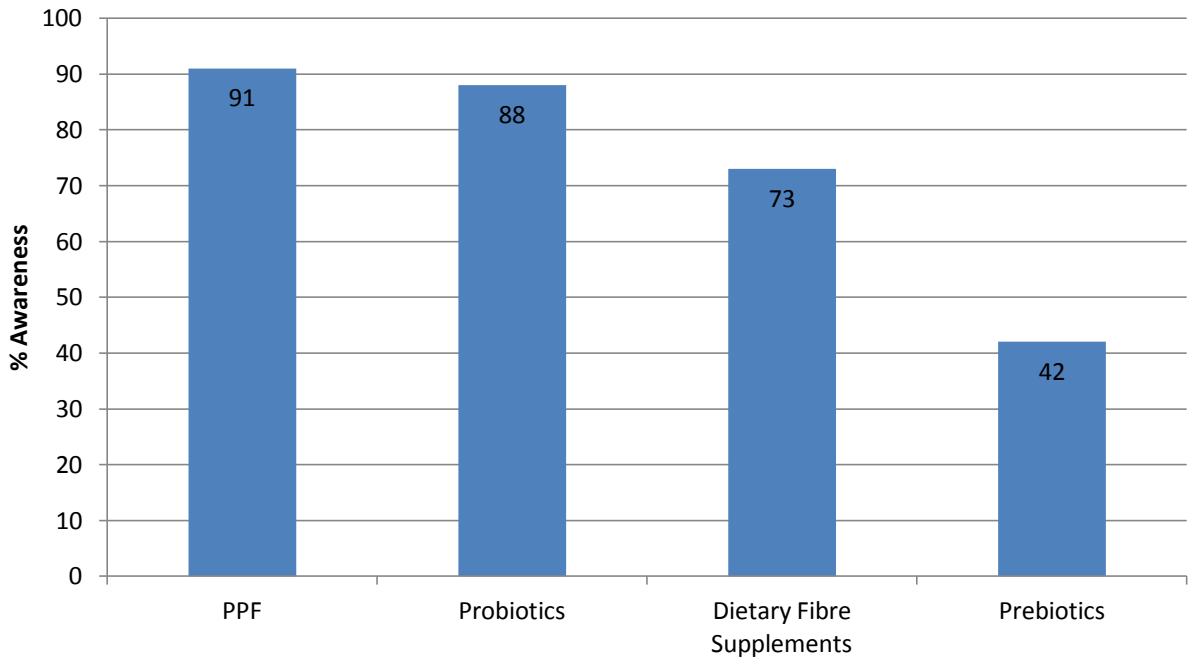

Figure 4-1: Patient Awareness of PPF

Table 4-9: Selected Predictors in Association with PPF Awareness

Variable	Aware of PPF N =243 n %	OR	95% CI	p value
Disease Diagnosis				
Crohn's disease	165 (90.7)	0.9	0.3-2.2	0.769
Ulcerative colitis	78 (91.8)			
Sex				
Female	136 (94.4)	**2.6**	**1.1-6.2**	**0.034**
Male	107 (87.0)			
Age groups				
18-35 yr	98 (94.2)	Ref	-	-
36-50 yr	61 (87.1)	0.4	0.4-1.2	0.111
>50 yr	84 (9.7)	0.6	0.0-1.7	0.307
Ethnicity/Race				
Caucasian	222 (91.0)	1.0	0.2-4.7	0.959
Visible minority [a]	21 (91.3)			
Education				
≤ High school	66 (86.8)	Ref	-	-
Some college, but ≤ 4 year university degree [b]	110 (92.4)	1.9	0.7-4.8	0.204
≥ 4 year university degree	67 (93.1)	2.0	0.7-6.3	0.218
Supplement Use				
Yes	191 (93.6)	**3.1**	**1.3-7.3**	**0.007**
No	52 (82.5)			
CAM Use				
Yes	109 (94.0)	2.0	0.8-4.9	0.139
No	134 (88.7)			
Marijuana Use				
Yes	30 (88.2)	0.7	0.2-2.1	0.489
No	213 (91.8)			

Variable	Aware of PPF N =243 n %	OR	95% CI	p value
Disease Duration				
< 5 years	64 (91.4)	Ref	-	-
5-10 years	59 (92.2)	1.1	0.3-3.9	0.873
>10 years	120 (90.2)	0.9	0.3-2.4	0.780
Flare in the last year				
Yes	119 (87.5)	**0.4**	**0.2-1.0**	**0.041**
No	124 (94.7)			
CRP>8 in 6 months *(n=221)*				
Yes	70 (86.4)	**0.4**	**0.2-1.0**	**0.034**
No	151 (94.4)			
Average FCP>250 in 6 months *(n=124)*				
Yes	51 (92.7)	1.0	0.3-3.9	0.944
No	73 (92.4)			
Surgical History				
Yes	73 (92.4)	1.3	0.5-3.4	0.606
No	170 (90.4)			
Extra-intestinal manifestations				
Yes	120 (90.2)	0.8	0.4-1.9	0.655
No	123 (91.8)			

[a] Visible minority includes Black/African Canadian, First Nation/North American Indian/Métis, Asian, East Indian, Hispanic/Latino and Other ethnicity/race

[b] Includes, but not limited to, associate's degree, diploma certificate, trades certificate and partial fulfillment of a university degree

Abbreviations: *PPF* Probiotics, Prebiotics and/or Dietary Fibre Supplements; *OR* Odds Ratio, *CI* Confidence Interval; *SD* Standard Deviation; *CAM* Complementary Alternative Medicine; *CRP* C-reactive Protein; *FCP* Fecal Calprotectin; *ref* reference category for adjusted odds ratio

Use of supplements was also prevalent in individuals who reported awareness as seen in Table 4-9. Supplement users were 3.1 times more likely to have heard of PPF than those who did not use supplements (vitamins, minerals and/or herbal; OR: 3.1, 95% CI: 1.3-7.3; $p<0.1$). When relating characteristics of the patient's disease to awareness, there was a statistically significant association with inflammation (measured by CRP ≥ 8 over the last six months) and disease flares. High CRP levels had a negative association with awareness (OR: 0.4, 95% CI: 0.2-1.0; $p<0.05$). In addition, a flare in the last year was also negatively associated with awareness (OR: 0.4, 95% CI: 0.2-1.0; $p<0.05$). On sub-analysis with disease diagnosis, the presence of UC combined with flare in the last year was associated with awareness, with no association found in CD patients (data not shown, $p<0.05$). It must be noted that CRP levels were not found in each patient's chart, which was a limitation.

Those who reported awareness of PPF were then prompted to report their source of this information, as seen in Figure 4-2. As marketing for health is abundant, we acknowledged that patients often receive information on alternative therapies from multiple sources. Therefore, subjects were asked to choose one or more sources, if applicable to them. Sources of PPF information included the patient's gastroenterologist, family physician, other health care providers (nurse, dietitian, nurse practitioner, physiotherapist, etc.), pharmacist, advertisements (radio or television), social media (Facebook®, Twitter®, Instagram®, etc.), internet, family and/or friends and other unlisted sources (self-educated, school, etc.). The highest frequency of patients with awareness of PPF had received information from advertisements through radio or television (32%), family and/or friends (30%) and/or the

internet (28%). Data were not collected regarding information on types of advertisements in relation to specific products within this survey.

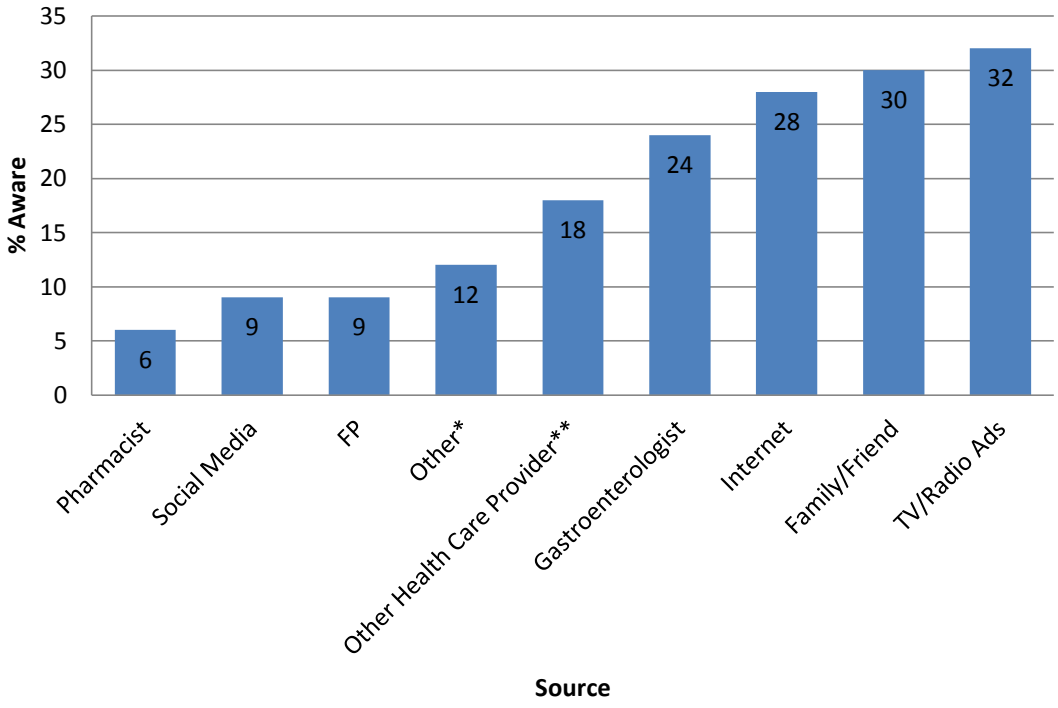

Figure 4-2: Source of Awareness of PPF

*Other sources of information included self-education (reading books/articles), formal (post-secondary) education, alternative practitioners (naturopath, homeopath) and grocery and health food stores
**Other health care providers include dieticians or nurses

Abbreviations: *FP* Family Physician

4.3 Determinants of Probiotic, Prebiotic and/or Dietary Fibre Supplement Use

The use of probiotics, prebiotics and/or dietary fibre supplements was defined by consumption over length of time. Patients were considered "current PPF users" if they had utilized these products within the last 12 months or "lifetime PPF users" if they had utilized these products at any point in their lifetime, including the last year. Figure 4-3 shows that a large percentage of participants (63%) have consumed PPF in their lifetime while about half (51%) reported current use over the last 12 months. Frequency of use per individual product was observed in current users. We found that the majority of current users reported intake of probiotics, while a minority of participants consumed dietary fibre supplements and prebiotics (46% probiotics, 12% dietary fibre supplements, 6% prebiotics, Figure 4-4).

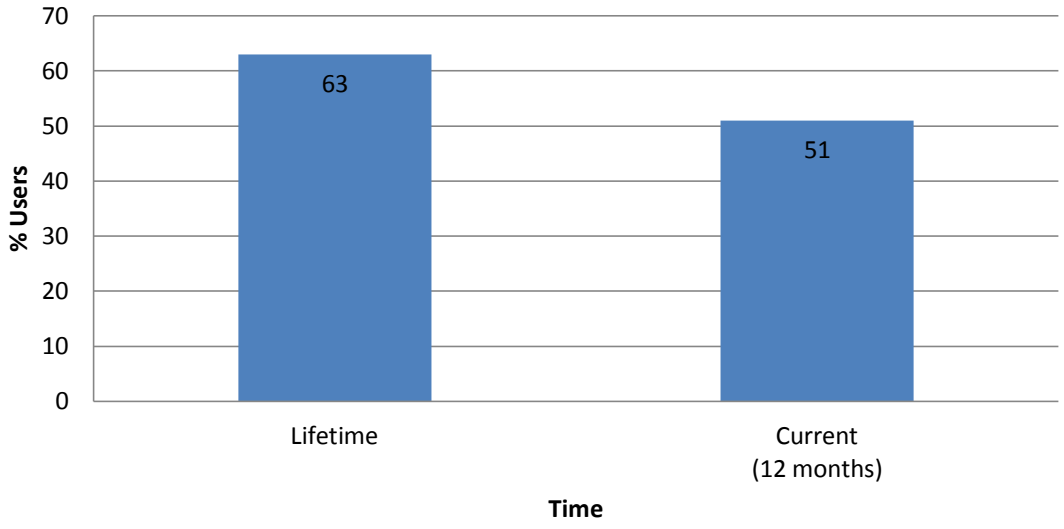

Figure 4-3: Current and Lifetime Use of PPF

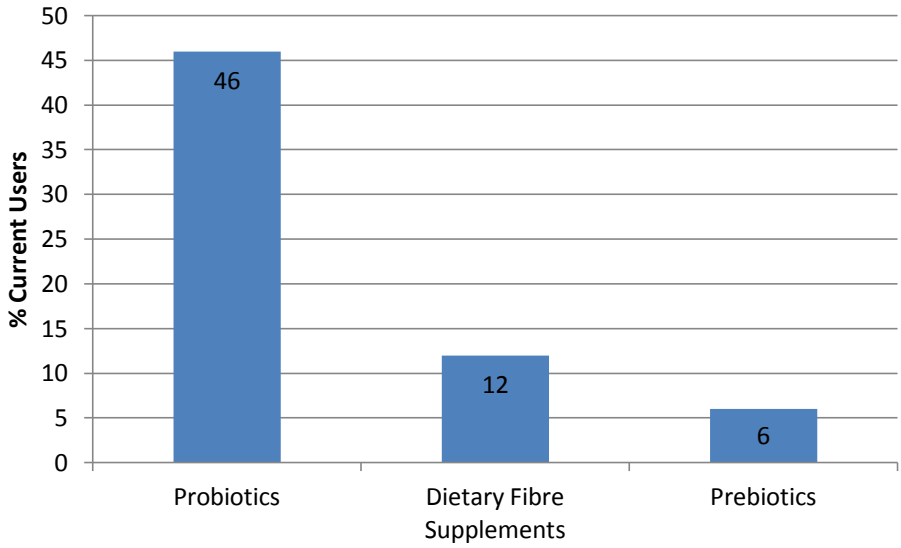

Figure 4-4: Use of Probiotics, Prebiotics or Dietary Fibre Supplements Over 12 Months

4.3.1 PPF Use is Associated with Source of Awareness

The majority of patients that had awareness of PPF had used PPF as described in Table 4-10 (67% lifetime and 55% current). Individuals exposed to information on PPF were approximately six to eight times more likely to consume these products currently or in their lifetime, respectively (current users: OR: 6.0 [95% CI: 2.0-18.2], $p<0.001$; lifetime users: OR: 7.7 [95% CI: 2.8-21.5], $p<0.001$). Interestingly, there were also a smaller percentage of patients without awareness reporting use. This could represent a smaller group of patients that may be using PPF incidentally without knowledge of their contents or properties. As shown above, advertisements, family and/or friends and the internet were the most frequent sources of information for PPF in all IBD patients (Figure 4-2). However, association analysis between awareness and usage identified that advice from a physician had a

relationship with use. Those who had received information from their gastroenterologist or family physician were significantly more likely to have used PPF in their lifetime (gastroenterologist: OR: 2.8, 95% CI: 1.4-5.5, $p<0.01$; family physician: OR: 4.6, 95% CI: 1.3-15.7, $p<0.01$; Table 4-10). There was a trend towards a relationship between receiving information from other health care providers (HCP; i.e.: nurses and dietitians) and total lifetime use as well as information from internet sources and current use, though the odds ratio did not show significance.

Table 4-10: Prevalence of PPF Use in Association to Source of Awareness

	Current PPF Users N=137				Lifetime PPF Users N=168			
Characteristic	**n (%)**	**OR**	**95% CI**	**p value**	**n (%)**	**OR**	**95% CI**	**p value**
Awareness								
Yes	133 (54.7)	**6.0**	**2.0-18.2**	**<0.001**	163 (67.1)	**7.7**	**2.8-21.5**	**<0.001**
No	4 (16.7)				5 (20.8)			
Source of Awareness								
Family/Friend								
Yes	47 (58.0)	1.5	0.9-2.5	0.148	57 (70.4)	1.6	0.9-2.8	0.096
No	90 (48.4)				111 (59.7)			
Internet								
Yes	45 (60.0)	1.6	0.9-2.8	0.076	52 (69.3)	1.5	0.8-2.6	0.175
No	92 (47.9)				116 (60.4)			
Advertisement [a]								
Yes	40 (46.5)	0.8	0.5-1.3	0.279	51 (59.3)	0.8	0.5-1.4	0.399
No	97 (53.6)				11 (64.6)			
Gastroenterologist								
Yes	38 (60.3)	1.6	0.9-2.9	0.102	50 (79.4)	**2.8**	**1.4-5.5**	**0.002**
No	99 (48.5)				11 (57.8)			
Other HCP [b]								
Yes	29 (61.7)	1.7	0.9-3.2	0.116	35 (74.5)	1.9	0.9-3.9	0.071
No	108 (49.1)				133 (60.5)			
Family Physician								
Yes	16 (66.7)	2.0	0.8-4.9	0.115	21 (87.5)	**4.6**	**1.3-15.7**	**0.009**
No	121 (49.8)				147 (60.5)			
Social Media								
Yes	13 (56.5)	1.3	0.5-3.0	0.601	15 (65.2)	1.1	0.5-2.7	0.812
No	124 (50.8)				153 (62.7)			
Pharmacist								
Yes	10 (58.8)	1.4	0.5-3.8	0.522	12 (70.6)	1.4	0.5-4.2	0.499
No	127 (50.8)				156 (62.4)			
Other [c]								
Yes	19 (61.3)	1.6	0.7-3.4	0.237	23 (74.2)	1.8	0.8-4.2	0.167
No	118 (50.0)				145 (61.4)			

[a] Advertisements include radio, television and magazine sources
[b] Other health care provider includes nurses and dieticians
[c] Other sources of information included self-education (reading books/articles), formal (post-secondary) education, alternative practitioners (naturopath, homeopath) and grocery and health food stores
Abbreviations: *PPF* Probiotics, Prebiotics and/or Dietary Fibre Supplements; *OR* Odds Ratio; *CI* Confidence Interval; *HCP* Health Care Provider

4.3.2 Higher Educational Status Predicts Use of PPF

The association of sociodemographic characteristics to the prevalence of using PPF was measured. General sociodemographics, such as sex and ethnicity, did not predict current or lifetime use of PPF. Logistic regression was performed to ascertain the effects of age on the likelihood that participants use PPF, with no statistical significance found. However, education status was found to be a significant predictor of current PPF use (Table 4-11). Patients with a university degree were significantly more likely to have demonstrated use of PPF over their lifetime in comparison to those that had attended high school or less (OR: 2.2, 95% CI: 1.1-4.4; $p<0.05$). An association was not present between educational status and current use.

Table 4-11: Prevalence of PPF Use by Sociodemographic Variables

	Current PPF Users N=137				Lifetime PPF Users N=168			
Characteristic	n (%)	OR	95% CI	p value	n (%)	OR	95% CI	p value
Sex								
Female	80 (55.6)	1.4	0.9-2.3	0.133	97 (67.4)	1.5	0.9-2.5	0.104
Male	57 (46.3)				71 (57.7)			
Age groups								
18-35	55 (52.9)	Ref	-	-	66 (63.5)	Ref	-	-
36-50	33 (47.1)	0.80	0.43-1.46	0.458	41 (58.6)	0.81	0.44-1.51	0.516
>50	49 (52.7)	0.99	0.57-1.74	0.978	61 (65.6)	1.1	0.6-2.0	0.755
Ethnicity/Race								
Caucasian	125 (51.2)	1.0	0.4-2.3	0.931	153 (62.7)	0.9	0.4-2.2	0.812
Visible Minority [a]	12 (52.2)				15 (65.2)			
Education								
≤ High school	37 (48.7)	Ref	-	-	41 (53.9)	Ref	-	-
Some college, but < 4 year university degree [b]	63 (52.9)	1.2	0.7-2.1	0.562	75 (63.0)	1.5	0.8-2.6	0.209
≥ 4 year university degree	37 (51.4)	1.1	0.6-2.1	0.742	52 (72.2)	**2.2**	**1.1-4.4**	**0.023**

[a] Visible minority includes Black/African Canadian, First Nation/North American Indian/Métis, Asian, East Indian, Hispanic/Latino or Other ethnicity/race

[b] Includes, but not limited to, associate's degree, diploma certificate, trades certificate and partial fulfillment of a university degree

Abbreviations: *PPF* Probiotics, Prebiotics and/or Dietary Fibre Supplements; *OR* Odds Ratio; *CI* Confidence Interval; *Ref* Reference category for odds ratio

4.3.3 Diet, Supplement and CAM Use are Associated with Intake of PPF

Standard IBD medications were not predictive of PPF use (Table 4-12). Though the majority of users were on biologic therapy (51.6% current, 63.7% lifetime) at the time of survey completion, this association was not significant. No further association between PPF use and antibiotics, 5-ASA (oral and/or rectal) agents, current steroid use, immunosuppressants or surgery was found. Though past steroid use was prevalent among respondents (80.5%, Table 4-3), it was not related to PPF use.

Alternate therapies for IBD were associated to use (Table 4-12). Interestingly, dietary modifications were a significant predictor of PPF use. Patients who were on a combination of special diets or on a diet with exclusions were more likely to have used PPF in their lifetime (combination: OR: 3.7, 95% CI: 1.2-11.4; $p<0.05$; exclusion: OR: 2.9, 95% CI: 1.3-65; $p<0.01$, Table 4-12). Additionally, a combination of special diets were significantly related to current use (OR: 4.2, 95% CI: 1.5-11.8, $p<0.01$). Binary logistic regression analysis was performed to ascertain diet as a predictor of use, with reference category for all categories being intake of a normal diet, including all food groups.

Supplement use (vitamins and/or minerals and/or herbals) was found to strongly predict lifetime use of PPF (OR: 2.1, 95% CI: 1.2-3.7; $p=0.01$), but not use over the last year. When analyzing supplements by individual category, vitamins were significantly associated with PPF use over lifetime (OR: 2.2, 95% CI: 1.2-3.8; $p<0.01$) or currently (OR: 1.8, 95% CI: 1.0-3.1; $p<0.05$). Intake of mineral supplements also predicted PPF use in a patient's lifetime (OR: 2.5, 95% CI: 1.5-4.2; $p<0.001$) or the last year (OR: 2.4, 95% CI: 1.5-3.9; $p<0.001$).

Table 4-12: Prevalence of PPF Use by Pharmaceutical or Alternative Therapies

Characteristic	Current PPF Users N=137				Lifetime PPF Users N=168			
	n (%)	OR	95% CI	p value	n (%)	OR	95% CI	p value
Current Medications [a]								
On IBD Medication								
Yes	122 (52.6)	1.5	0.7-3.0	0.283	144 (62.1)	0.8	0.4-1.6	0.458
No	15 (42.9)				24 (68.6)			
5-ASA (oral & rectal)								
Yes	50 (58.8)	1.6	0.9-2.6	0.093	54 (63.5)	1.0	0.6-1.8	0.888
No	87 (47.8)				114 (62.6)			
5-ASA oral								
Yes	44 (56.4)	1.3	0.8-2.3	0.284	48 (61.5)	0.9	0.5-1.6	0.764
No	93 (49.2)				120 (63.5)			
Steroids								
Yes	6 (60.0)	1.4	0.4-5.2	0.750[e]	7 (70.0)	1.4	0.4-5.5	0.749[e]
No	131 (51.0)				161 (62.6)			
Immunosuppressants [b]								
Yes	49 (52.1)	1.1	0.8-1.7	0.844	56 (59.6)	0.80	0.5-1.3	0.404
No	88 (50.9)				112 (64.7)			
Biologics [c]								
Yes	81 (51.6)	1.0	0.6-1.7	0.912	100 (63.7)	1.1	0.7-1.8	0.755
No	56 (50.9)				68 (61.8)			
Antibiotics								
Yes	6 (75.0)	2.9	0.6-14.8	0.283[e]	7 (87.5)	4.3	0.5-35.1	0.265[e]
No	131 (50.6)				161 (62.2)			
Rectal 5-ASA								
Yes	16 (66.7)	2.0	0.8-4.9	0.115	18 (75.0)	1.9	0.7-4.9	0.199
No	121 (49.8)				150 (61.7)			
Past steroid use								
Yes	113 (52.6)	1.3	0.7-2.4	0.407	137 (63.7)	1.2	0.6-2.2	0.582
No	24 (46.2)				31 (59.6)			

Past surgical history								
Yes	39 (49.4)	0.9	0.5-1.5	0.680	54 (68.4)	1.4	0.8-2.4	0.233
No	98 (52.1)				114 (60.6)			
Diet [d]								
Normal	75 (46.3)	Ref	-	**-**	91 (56.2)	Ref	-	**-**
Special	18 (56.3)	1.5	0.7-3.2	0.305	23 (71.9)	2.0	0.9-4.6	0.104
Exclusion	25 (58.1)	1.6	0.8-3.2	0.169	34 (79.1)	**2.9**	**1.3-6.5**	**0.008**
Combination	18 (78.3)	**4.2**	**1.5-11.8**	**0.007**	19 (82.6)	**3.7**	**1.2-11.4**	**0.022**
Total Supplements								
Yes	110 (53.9)	1.6	0.9-2.8	0.125	137 (67.2)	**2.1**	**1.2-3.7**	**0.010**
No	27 (42.9)				31 (49.2)			
Vitamins								
Yes	108 (55.1)	**1.8**	**1.0-3.1**	**0.038**	133 (67.9)	**2.2**	**1.2-3.8**	**0.006**
No	28 (40.6)				34 (49.3)			
Minerals								
Yes	84 (61.3)	**2.4**	**1.5-3.9**	**<0.001**	100 (73.0)	**2.5**	**1.5-4.2**	**<0.001**
No	51 (39.8)				66 (51.6)			
Herbal Products								
Yes	27 (60.0)	1.5	0.8-3.0	0.191	31 (68.9)	1.4	0.7-2.8	0.352
No	109 (49.3)				136 (61.5)			
CAM Use								
Yes	66 (56.9)	1.5	0.9-2.4	0.109	82 (70.7)	**1.8**	**1.1-3.0**	**0.021**
No	71 (47.0)				86 (57.0)			
Types of CAM								
Massage								
Yes	39 (52.7)	1.1	0.6-1.8	0.778	50 (67.6)	1.3	0.8-2.33	0.330
No	98 (50.8)				118 (61.1)			
Chiropractor								
Yes	35 (68.6)	**2.4**	**1.3-4.7**	**0.006**	40 (78.4)	**2.5**	**1.2-5.1**	**0.011**
No	102 (47.2)				128 (59.3)			
Yoga								
Yes	18 (58.1)	1.4	0.6-2.9	0.424	20 (64.5)	1.1	0.5-2.4	0.845
No	119 (50.4)				148 (62.7)			
Meditation								
Yes	10 (50.0)	0.95	0.4-2.4	0.903	14 (70.0)	1.4	0.5-3.8	0.496
No	127 (51.4)				154 (62.3)			

Acupuncture	13 (65.0)	1.8	0.7-4.8	0.203	16 (80.0)	2.5	0.8-7.7	0.100
Yes	124 (50.2)				152 (61.5)			
No								
Other CAMs	20 (66.7)	2.1	0.9-4.6	0.070	22 (73.3)	1.7	0.7-4.0	0.210
Yes	117 (49.4)				146 (61.6)			
No								
Marijuana use								
Yes	14 (41.2)	0.6	0.3-1.3	0.214	19 (55.9)	0.7	0.3-1.5	0.373
No	122 (52.6)				148 (63.8)			

[a] Current medication percentages out of 137 (current users) and 168 (lifetime users) do not add up to 100% due to combination therapy
[b] Immunosuppressants include thiopurines (azathiopurine, 6-mercaptopurine), methotrexate and cyclosporine
[c] Biologics include adalimumab, infliximab, golimumab, vedolizumab and ustekinumab
[d] Diets include normal (all food groups), exclusion (diet with exclusion of one or more ingredients), special (vegan, vegetarian, pescatarian, gluten-free, lactose-free, low glycemic, DASH diet with food exclusions, low FODMAP or "trademarked" diets) and combination (≥1 special diet).
[e] Fisher's Exact Test was used for association analyses when more than 25% of cells had expected counts < 5

Abbreviations: *PPF* Probiotics, Prebiotics and/or Dietary Fibre Supplements; *IBD* Inflammatory Bowel Disease; *OR* Odds Ratio; *CI* Confidence Interval; *5*-ASA 5-Acetylsalicylic Acid; CAM Complementary Alternative Medicine; *Ref* reference category for odds ratio

Use of herbal supplements did not have a relationship with PPF.

The majority of PPF users also used CAMs (Table 4-12). This association was significant with CAM users 1.8 times more likely to use PPF in their lifetime (OR: 1.8, 95% CI: 1.1-3.0; $p<0.05$) and no association to current PPF use. Other types of CAM surveyed were massage, chiropractor visits, yoga, meditation, acupuncture and other CAMs (naturopathy, homeopathy, Reiki, reflexology, faith healing, Tai Chi, Chinese medicine or unlisted CAMs). Interestingly, a positive association was also seen between chiropractor visits and PPF use. Participants who were seeing a chiropractor were approximately 2.5 times more likely to use PPF currently or in their lifetime (current users: OR: 2.4, 95% CI: 1.3-4.7, $p<0.01$; lifetime users: OR: 2.5, 95% CI: 1.2-5.1, $p<0.05$). There was no remaining association with PPF use and the other types of CAMs.

In this research project, 12.8% of participants reported regular, or weekly, use of marijuana (Table 4-3). Though marijuana use in conjunction with PPF use was documented (56% lifetime users, 41% current users), no significant association was found (Table 4-12).

4.3.4 Ulcerative Colitis is Associated with PPF Use

Table 4-13 summarizes data on PPF use in association to measures of disease severity, including IBD type, age at initial diagnosis, disease duration, clinical scores, serum and stool markers of inflammation, frequency of disease flare-ups requiring medical or surgical intervention and presence of extra-intestinal disease were collected. The subjective nature

of patient recall required the researcher to verify all survey information through review of medical charts. Ulcerative colitis was 1.8 times more likely to be associated with current PPF use compared to patients with CD (61.2% UC vs. 46.7% CD; OR: 1.8, 95% CI: 1.1-3.0, $p<0.05$). All other clinical characteristics such as disease duration, presence of flares in the last one or two years, flare frequency (not listed in Table 4-13), presence of extra-intestinal manifestations of IBD, disease severity measured by HBI and Partial Mayo scores and disease activity measured by FCP and CRP in the last 6 months or last year did not significantly predict use of PPF currently or in a patient's lifetime.

The Montreal Classification scoring system was used to determine most severe extent, location of UC and CD (Table 4-14 and 4-15). A majority of patients with CD had ileocolonic disease (n=101, 56%) with an stricturing phenotype (n=92, 51%) as shown previously in Table 4-7. When associating disease behaviour to use in CD (Table 4-14), there was no association between ileal (L1), ileocolonic (L2), colonic (L3) or isolated upper GI disease (L4) and use of PPF. In addition, no significant association was seen between an inflammatory, stricturing, penetrating, stricturing and penetrating or perianal disease phenotype and use of PPF. Disease extent was then measured in patients with UC as seen in Table 4-15. The majority of UC study patients had pancolonic disease (n=62, 73%) defined as E3 through the Montreal Classification scoring system, as seen above in Table 4-8. However, association of disease extent in UC with PPF through revealed no relationship through univariate binary regression analysis (Table 4-15).

Table 4-13: Prevalence of PPF Use by Clinical Characteristics

Characteristic	Current PPF Users N=137				Lifetime PPF Users N=168			
	n (%)	OR	95% CI	p value	n (%)	OR	95% CI	p value
Disease diagnosis								
Ulcerative colitis	52 (61.2)	**1.8**	**1.1-3.0**	**0.028**	57 (67.1)	1.3	0.8-2.2	0.339
Crohn's disease	85 (46.7)				111 (61.0)			
Age at diagnosis, yr								
<18	23 (43.4)	Ref	-	-	31 (58.5)	Ref	-	-
18-34	80 (58.4)	1.8	1.0-3.5	0.064	94 (68.6)	1.6	0.8-3.0	0.189
35-50	19 (39.6)	0.9	0.4-1.9	0.698	24 (50.0)	0.7	0.3-1.6	0.393
>50	15 (51.7)	1.4	0.6-3.5	0.470	19 (65.5)	1.3	0.5-3.5	0.533
Disease duration (yr)								
< 5	38 (54.3)	Ref	-	-	45 (64.3)	Ref	-	-
5-10	31 (48.4)	0.8	0.4-1.6	0.499	39 (60.9)	0.9	0.4-1.7	0.689
>10	68 (51.1)	0.9	0.5-1.6	0.669	84 (63.2)	0.9	0.5-1.7	0.874
Active disease [a]								
Yes	40 (50.0)	0.9	0.6-1.6	0.779	49 (61.3)	0.9	0.5-1.5	0.712
No	97 (51.9)				119 (63.6)			
Presence of flares < 1 year								
Yes	70 (51.5)	1.0	0.6-1.6	0.958	83 (61.0)	0.8	0.5-1.4	0.514
No	67 (51.1)				85 (64.9)			
Presence of flares < 2 years								
Yes	101 (52.3)	1.2	0.7-2.0	0.590	123 (63.7)	1.1	0.7-2.0	0.658
No	36 (48.6)				45 (60.8)			
High CRP levels (≥ 8) within 6 months [b]								
Yes	42 (51.9)	1.1	0.6-1.8	0.857	49 (60.5)	0.9	0.5-1.5	0.622
No	81 (50.6)				102 (63.7)			

High CRP levels (≥ 8) within 1 yr [b]								
Yes	52 (50.0)	0.9	0.6-1.5	0.710	61 (58.7)	0.7	0.4-1.2	0.172
No	77 (52.4)				98 (66.7)			
High FCP levels (≥ 250 µg/g) within 6 months [c]								
Yes	33 (60.0)	1.7	0.8-3.4	0.133	41 (74.5)	1.9	0.9-4.0	0.096
No	37 (46.8)				48 (60.8)			
High FCP levels (≥ 250 µg/g) within 1 year [c]								
Yes	38 (57.6)	1.6	0.8-2.9	0.178	46 (69.7)	1.4	0.7-2.7	0.332
No	42 (46.7)				56 (62.2)			
Extra-intestinal manifestations								
Yes	64 (48.1)	0.8	0.5-1.3	0.299	83 (62.4)	1.0	0.6-1.6	0.862
No	73 (54.5)				85 (63.4)			

[a] Active disease in ulcerative colitis was determined by current Partial Mayo Score between 2 to 9. Active disease in Crohn's disease was determined by current Harvey Bradshaw Index of greater than 5.

[b] Reduced subset of users had CRP data in charts within the last six months (current: n=123, lifetime: n=151) or the last year (current: n=129, lifetime: n=159)

[c] Reduced subset of users had FCP data in charts within the last six months (current: n=96, lifetime: n=39) or the last year (current: n=70, lifetime=102)

Abbreviations: *PPF* Probiotics, Prebiotic and/or Dietary Fibre Supplements; *OR* Odds Ratio; *CI* Confidence Interval; *CRP* C-reactive Protein; *FCP* Fecal Calprotectin; *Ref* reference category for odds ratio

Table 4-14: Disease Severity in CD Patients in Association to PPF Use

Characteristic	Current PPF Users with CD N=86				Lifetime PPF Users with CD N=111			
	n (%)	OR	95% CI	p value	n (%)	OR	95% CI	p value
Disease location								
Ileal only (L1)								
Yes	21 (44.7)	0.9	0.5-1.7	0.747	30 (63.8)	1.2	0.6-2.3	0.643
No	64 (47.4)				81 (60.0)			
Colonic only (L2)								
Yes	18 (52.9)	1.4	0.6-2.9	0.419	22 (64.7)	1.2	0.6-2.6	0.622
No	67 (45.3)				89 (60.1)			
Ileocolonic only(L3)								
Yes	46 (45.5)	0.9	0.5-1.6	0.726	59 (58.4)	0.8	0.4-1.4	0.427
No	39 (48.1)				52 (64.2)			
Upper GI involvement (L4) [a]								
Yes	13 (34.2)	0.5	0.2-1.1	0.083	20 (52.6)	0.6	0.3-1.3	0.235
No	72 (50.0)				91 (63.2)			
Disease behaviour								
Inflammatory only (B1)								
Yes	33 (45.8)	0.9	0.5-1.7	0.849	43 (59.7)	0.9	0.5-1.7	0.777
No	52 (47.3)				68 (61.8)			
Stricturing only (B2)								
Yes	44 (47.8)	1.1	0.6-2.0	0.759	59 (64.1)	1.3	0.7-2.4	0.380
No	41 (45.6)				52 (57.8)			
Penetrating only (B3)								
Yes	20 (47.6)	1.0	0.5-2.1	0.892	23 (54.8)	0.7	0.4-1.4	0.346
No	65 (46.4)				88 (62.9)			
Stricturing and Penetrating only (B2B3)								
Yes	8 (53.3)	1.3	0.5-3.9	0.591	9 (60.0)	1.0	0.3-2.8	0.935
No	77 (46.1)				102 (61.1)			
Perianal involvement (p) [b]								
Yes	28 (45.9)	1.0	0.5-1.8	0.878	36 (59.0)	0.9	0.5-1.7	0.698
No	57 (47.1)				75 (62.0)			

[a] L4 = Upper GI modifier. L4 signifies upper GI disease in combination with L1, L2 or L3)

[b] p = perianal disease modifier in combination with B1, B2, B3 or B2B3

[c] Fisher's Exact Test was used for association analyses when more than 25% of cells had expected counts < 5

Abbreviations: *PPF* Probiotics, Prebiotics and/or Dietary Fibre Supplements; *CD* Crohn's disease; *OR* Odds Ratio; *CI* Confidence Interval

Table 4-15: Disease Extent in UC Patients in Association to PPF Use

	Current PPF Use with UC N=52				Lifetime PPF Use with UC N=57			
Characteristic	**n (%)**	**OR**	**95% CI**	**p value**	**n (%)**	**OR**	**95% CI**	**p value**
Disease extent								
Proctitis (E1)	3 (60)	Ref	-	-	3 (60)	Ref	-	-
Left-sided (E2)	6 (33.3)	1.0	-	-	8 (44.4)	1.0	-	-
Pancolonic (E3)	41 (66.1)	1.0	-	-	48 (77.4)	1.0	-	-

Abbreviations: *PPF* Probiotics, Prebiotics and/or Dietary Fibre Supplements; *UC* Ulcerative Colitis; *OR* Odds Ratio; *CI* Confidence Interval; *ref* Reference category for regression analysis

4.4 Types of PPF Used and Impact on Patient Care

4.4.1 Probiotic Users Commonly Consume Activia® Yogurt for IBD

Participants who reported current use of PPF (n=137, 51%) were prompted to answer detailed questions regarding the brand or type of probiotic consumed over the last year, as displayed in Table 4-16. Within the group of current users, a greater number of patients utilized probiotics (n=123, 46%), with less than a quarter of users using dietary fibre supplements (n=33, 12%) and prebiotics (n=17, 6%) over the last 12 months. Out of the 123 patients that used probiotics, 98% (n=121) provided a response on specific brands of probiotics consumed. In this study, we discovered that most probiotic users (42%) with IBD currently consume Danone Activia® yogurt.

Table 4-16: Types/Brands of Probiotics Used in Current Probiotic Users

Probiotic Type/Brand	n (% of 121)
Activia®	51 (42.1)
Probiotic combination [a]	30 (24.8)
Jamieson® Lactobacilli Acidophilus Capsules	9 (7.4)
Illegible/Unknown [b]	8 (6.6)
Align®	4 (3.3)
VSL #3®	4 (3.3)
Florastor®	3 (2.5)
Yoptimal®	1 (0.8)
Bio-K+®	0 (0)
Fem-Dophilus®, Bacid®	0 (0)
Lacidofil®	0 (0)
Mutaflor®	0 (0)
Natrel	0 (0)
Oasis Health Break®	0 (0)
TuZen®	0 (0)
YogActive® cereal	0 (0)
Other [c]	11 (9.1)

[a] Includes a combination of listed probiotic-containing products
[b] Unknown brand or type listed that may or may not contain probiotics
[c] Other probiotics that are not listed

4.4.2 Clinical Efficacy of Probiotics Listed in this Study

Most of the probiotic products listed in this study were referenced from the study conducted by Reid *et al.* (2008) on probiotic products in Canada and their clinical recommendations[157]. Table 4-17 describes each product by probiotic strain, recommended dose, acceptance status by Health Canada, benefit in general health or IBD and detailed summary of clinical evidence. In the current study, patients were asked to identify the type or brand consumed from a list of probiotics including Activia® (*B. animalis*), Align® (*B. infantis*), Bacid® (*L. rhamnosus*), Bio K+® (*Lactobacillus* spp.), FemDophilus (*Lactobacillus* spp.), Florastor® (*S. boulardii*), Jamieson® *L. Acidophilus* capsules (*Lactobacillus* spp.), Lacidophil® (*Lactobacillus* spp.), Mutaflor® (EcN), Natrel® pro (*Lactobacillus* spp., *Bifidobacterium* spp.), Oasis® Health Break with Probiotics (*Lactobacillus* spp., *Bifidobacterium* spp.), TuZen® (*L. plantarum*), VSL#3® (*S. thermophiles, Lactobacillus* spp., *Bifidobacterium* spp.), YogActive® cereal (*L. plantarum*) and Yoptimal® Immuni+ (*Lactobacillus* spp., *Bifidobacterium* spp.).

Activia® yogurt was the probiotic product most frequently consumed by patients in this study. This yogurt contains *B. animalis* DN 117-001 which has been clinically proven to improve intestinal transit time (regularity) in healthy women[157]. However, there was no evidence that this product played a role in modulating intestinal inflammation or improving colonic health in healthy or IBD individuals. Probiotic-containing products clinically proven through peer-reviewed evidence to have benefit for IBD that were included in the survey were Mutaflor® (EcN) and VSL#3, of which 3% of probiotic users consumed in the current

study. In addition, less than half of the products listed were approved by Health Canada. Approved products included Align®, Bio-K+®, Florastor®, TuZen®, and VSL#3, of which only 8% of probiotic users in this study consumed over the last year. Nine out of fifteen of the products listed had a general health or IBD benefit, including Activia®, Align®, Bio K+®, FemDophilus®, Florastor®, Lacidofil®, Mutaflor®, TuZen® and VSL#3®. Furthermore, though these products can be found on Canadian shelves, it is important to note that a limited few have met WHO/FAO guidelines[158].

Table 4-17: Efficacy of Probiotic Products Used in Canada*

Product	Probiotic Strain	CFU/Dose	**Proven Health Benefit?**	**Proven in IBD?**	**Clinical Benefit**
Activia® yogurt, Danone, Canada	*Bifidobacterium animalis* DN 117-001	10^9/100 g	Yes	No	Improves transit times[159]
Align®, Procter & Gamble, USA**	*B. infantis* 35624	1 x 10^9 per cap	Yes	No	Relieves symptoms of irritable bowel syndrome and reduces abdominal bloating in healthy adults. Limited data on reduction of inflammation in UC[160–162]
Bacid®, Aventis Group, Canada	*Lactobacillus rhamnosus*	1 x 10^9 per cap	No	No	No known peer-reviewed data
Bio K+ ® CL1285, Bio K+ Pharma, Canada**	*L. acidophilus* CL1285 *L. casei* LBC80R *L. rhamnosus* CLR2	12.5-50 x10^9 per cap	Yes	No	Helps reduce the risk of *C. difficile* infections in hospitalized patients and those in long term care facilities[163–165]
FemDophilus®, Jarrow Formulas, USA	*Lactobacillus rhamnosus GR-1* *L. reuteri RC-14*	5 x10^9 per cap	Yes	No	Promotes vaginal and urinary tract health in women[166]
Florastor®, Medical Futures Inc, Canada**	*Saccharomyces boulardii lyo* CNCM-I745	5-10 x 10^9 per cap or sachet	Yes	No	Treat and help prevent diarrhea in healthy adults and children. Improves growth and feeding tolerance in formula-fed preterm infants[167–169]
Jamieson® *Lactobacilli Acidophilus* Capsules, Jamieson Laboratories, Canada	*L. acidophilus,* *L. rhamnosus*	1 x 10^9 per cap	No	No	No known peer-reviewed data
Lacidofil®, Xymogen, USA	*L. helveticus R-52* *L. rhamnosus R-11*	2 x 10^9 per cap	Yes	No	Useful as adjunct therapy in promoting GI health and healthy bowel function[170]
Mutaflor®	*Escherichia coli* Nissle 1917	2.5-25 x 10^9 per cap	Yes	Yes	Induction and maintenance of pouchitis and maintenance of remission in UC and many other GI diseases[70,85,86,110,171]
Natrel pro®, Agropur, Division Natrel, Canada	*B. lactis* BB-112 and unknown *Lactobacillus*	1 x 10^9 per 250 ml	No	No	No known peer-reviewed data
Oasis® Health Break with Probiotics, A. Lassonde Inc, Canada	*B. bifidus* *L. acidophilus*	1 x 10^9 per 250 ml	No	No	No known peer-reviewed data
TuZen®, Ferring Pharmaceuticals, Canada**	*L. plantarum* 299v	10 x 10^9 per cap	Yes	No	Treatment of irritable bowel syndrome[172,173]
VSL#3®, VSL Pharmaceuticals Inc, Canada**	*Streptococcus thermophiles* *B. breve* *B. longum* *B. infantis* *L. acidophilus* *L. plantarum* *L. paracasei* *L. bulgaricus*	450 x 10^9 per sachet	Yes	Yes	Prevents pouchitis and induces remission as adjunct treatment in mild-to-moderate ulcerative colitis. Early administration lowered recurrence rates in post-operative CD[72,99,112]
YogActive® cereal, Belgo & Bellas, Canada	*L. acidophilus*	1 x 10^9 per ¾ cup	No	No	No known peer-reviewed data
Yoptimal® Immuni+, Yoplait, Canada	*L. acidophilus* LA-5 *B. lactis* BB-12	1 x 10^9 per 100 g	No	No	No known peer-reviewed data

*Information in table referenced from Reid *et al.* (2010) *Can J Gastroenterol Vol 22 No 2*[157]
**Approved by Health Canada

Abbreviations: *CFU* Colony Forming Unit, *IBD* Inflammatory Bowel Disease, *UC* Ulcerative Colitis; *CD* Crohn's disease; *GI* Gastrointestinal

4.4.3 Prebiotic and Fibre Supplements Used

Table 4-18 demonstrates commonly used prebiotics and fibre supplements in the study population over the last year. The most frequently used prebiotic was FOS (44%), which is contained in products such as BeneFibre® (GlaxoSmithKline, Canada). Psyllium, found in brands such as Metamucil® (Procter & Gamble, USA) was the most commonly consumed dietary fibre supplement by respondents (58%). It is important to note that a limited number of patients utilized prebiotics and dietary fibre supplements as part of their therapeutic regimen.

Table 4-18 Prebiotic and Fibre Supplements Used by IBD Patients

Brand/Type	n (%)
Fibre Supplement (n=34)	
Psyllium (Metamucil®, Natural Brand®, Ultra Fibre®)	19 (57.6)
Combination of fibre supplements	5 (15.2)
Flax (FibreSmart®, Recleanse®)	1 (3.0)
Glucomannan (PGX®)	1 (3.0)
Other [a]	7 (21.2)
Prebiotic (n=17)	
Fructo-oligosaccharide (FOS/Benefibre®)	7 (43.8)
Inulin	4 (25.0)
Inulin/FOS	3 (18.7)
Lactulose	0 (0)
Other [a]	2 (12.5)

[a] not listed
Abbreviation: *IBD* Inflammatory Bowel Disease; *FOS* Fructo-oligosaccharide

4.4.4 Reduction of IBD Symptoms is the Greatest Perceived Benefit of PPF

Inflammatory bowel diseases involve many clinical symptoms such as diarrhea, rectal bleeding, abdominal pain, fatigue, loss of appetite and other systemic problems. The search for alternative therapies for IBD often involves perceived benefits of these products. Common reasons for seeking CAMs as alternate therapy are perceived ineffectiveness, side effects and costs associated with IBD medications, avoidance of steroids, better control of disease and search for the optimum therapy [27,34,58]. Use of CAMs for reasons unrelated to treatment include beliefs that the gastroenterologist thought differently about the causes and treatments of IBD than the patient, emphasis on treating the whole body and advice from family, friends or a physician[29,34,58]. Common reasons for use and perceived benefits of probiotics and prebiotics isolated from other CAMs are not well documented. In a case-control study conducted by Hedin et. al (2010), the majority of IBD patients reported management of IBD as the primary reason for using probiotics[148]. Those who used probiotics for non-related health reasons reported taste preference as their reasoning for use[148].

Expected and observed benefits of PPF use are described in Table 4-19. The majority of patients reported PPF use with the intention to reduce IBD symptoms (n=83, 61%) and to prevent disease flares (n=37, 27%). The lowest number of patients had perceived benefit of PPF to increase appetite (n=5, 4%). Out of the patients who reported actual benefit, two thirds claimed their expected benefit was actually observed (n=70, 67%). Patients also reported perceived benefits of PPF use through an open-ended format as shown in Table 4-20. Responses were centralized around improving health including overall health benefits

such as help with regularity, mental stress and good bacteria production as well as improvement of diet and prevention of *C. difficile* infection.

Table 4-19: Expected and Observed Benefits of PPF Use over the Last Year

	n (%)
Why is PPF beneficial for you? (n=137)	
Reduces symptoms	83 (60.6)
Prevents flares	37 (27.0)
Treats disease	27 (19.7)
Decreases fatigue	13 (9.5)
Improves mood	10 (7.3)
Increases appetite	5 (3.6)
Other [a]	18 (13.1)
Have you received the intended benefit?(n=105)	
Yes	70 (66.7)

[a] Other unlisted self-reported benefits of using PPF
Abbreviations: *PPF* Probiotics, Prebiotics and/or Dietary Fibre Supplements

Table 4-20: Other Perceived Benefits of Using PPF

"I like yogurt"
"They are good"
"Worth a try to help"
"Overall health"
"Dr. Dieleman put me on it"/"Told to try them"
"Treat *C. Difficile*"
"Prevent ulcers"
"Help with regularity"
"Help with mental stress"
"Increase good bacteria"
"To use with antibiotics"
"Improve diet
"No noticeable difference"

Abbreviations: *PPF* Probiotics, Prebiotics and/or Dietary Fibre Supplements

4.4.5 Improvement in Perceived Quality of Life was Not Reported in Patients who Use PPF

In this study, participants were asked to report on perceived improvement in QoL as an outcome after use of PPF over the last year (Figure 4-4). It was found that a large number of current PPF users did not experience a perceived improvement in QoL after use of these therapies (n=81, 59%). When examining perceived QoL in association to each individual product, most prebiotic users (n=10, 59%) reported perceived improvement in QoL, versus fibre users (n=14, 42%) and probiotic users (n=51, 42%), however these results were not significant (prebiotics: p=0.108, fibres: p=0.835, probiotics: p=0.678). No association was found in association to IBD diagnosis. Though the number of patients that did not report a perceived improvement in QoL was high, it is worthy to mention that data on consistency of use was not collected in this study. In addition, patients consumed reduced numbers of products with clinical efficacy, thus potentially having minimal effect on perceived change in quality measurements.

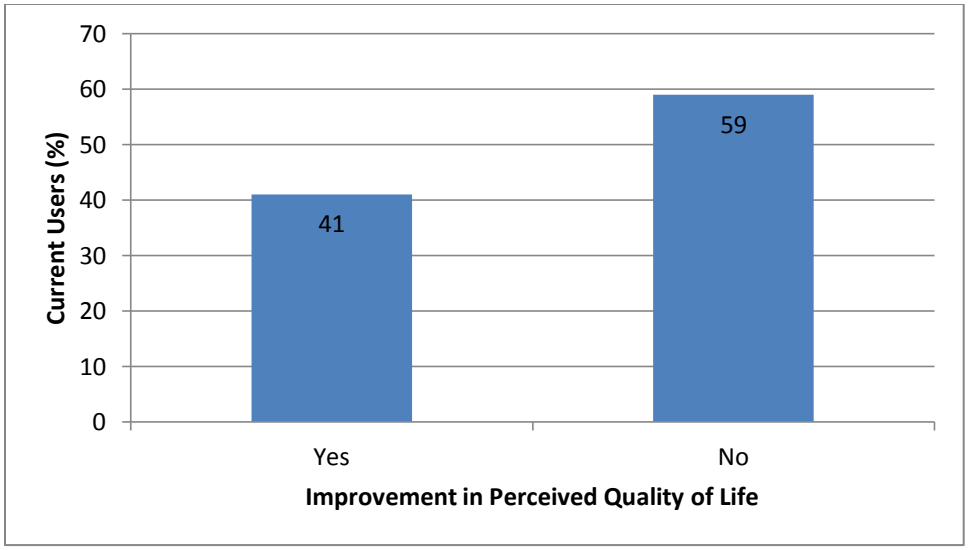

Figure 4-5: Improvement in Perceived Quality of Life with PPF Use Over 12 Months

4.4.6 IBD Patients are Willing to Spend Money on Probiotics, Prebiotics and Dietary Fibre Supplements

Probiotics, prebiotics and dietary fibre supplements vary in cost and dose. For example, 30 sachets of VSL#3 retails for $110 Canadian dollars (450 billion bacteria per sachet) whereas 100 g of Activia yogurt retails for approximately $0.50 Canadian dollars ($5.97/12 100 g cups;1 billion *B. lactis* CNCM I-2494, also known as *B. regularis* per 100 g)[174–176]. The majority of PPF users in this study reported an average monthly expenditure of $11-50 over the last year, though no relationship was found with combined use, as seen in Table 4-21. We then analyzed monthly expenditure by individual prebiotic, probiotic or fibre supplement (Table 4-22). Both probiotic and prebiotic use were significantly associated with monthly expenditures between $11-50 (probiotics: $p<0.05$; prebiotics: $p<0.001$). There was no relationship between fibre supplements and cost.

Table 4-21: Monthly Expenditure on PPF (Combined Category)

Monthly Expenditure ($)	n (%)	P value
1-10	26 (23.4)	0.858
11-50	63 (56.8)	
51-100	14 (12.6)	
100-250	8 (7.2)	

Abbreviation: *PPF* Probiotics, Prebiotics and Dietary Fibre Supplements

Table 4-22: Monthly Expenditure on Probiotics, Prebiotics or Fibre Supplements (Individual Categories)

Monthly Expenditure ($)	Monthly Expenditure n (%)				P value
	$1-10	$11-50	$51-100	$101-250	
Probiotics (n=99)	19 (19.2)	59 (59.6)	13 (13.1)	8 (8.1)	0.030
Prebiotics (n=14)	1 (7.1)	7 (50.0)	1 (7.1)	5 (35.7)	<0.001
Dietary Fibre Supplements (n=31)	9 (29.0)	16(51.6)	5 (16.1)	1 (3.2)	0.548

4.4.7 Lack of Physician Suggestion May Result in 'Never Use' of PPF

Participants who had never used PPF in their lifetime ("never users", n=99) were asked to provide reasons for never-use (Table 4-23). Forty three percent of "never users" did not use PPF as they had never received this information from their physician (n=45, 45%). About one third of never users also reported never-use due to other self-reported reasons such as lack of time and reason to use (data not shown). Reasons for never use were attributed to a combined category of PPF with no data collection regarding never-use per individual product in this survey project.

Table 4-23: Reasons for Never-Use of PPF

Reason for PPF Never-Use	n	% of 99
Lack of physician suggestion	43	43.4
Have not heard	15	15.2
Ineffective	5	5.1
Too expensive	5	5.1
Side effects	3	3.0
Other	33	33.3

Abbreviations: *PPF* Probiotics, Prebiotics and/or Dietary Fibre Supplements

5 DISCUSSION

5.1 Summary of Results

In this study, a self-administered survey questionnaire was used to collect data on demographic, clinical characteristics, awareness and use of PPF in 267 patients with IBD. The second part of this study was a structured chart review involving the collection of clinical variables. Respondent data from the survey were then compared to objective clinical data from charts. Approximately two thirds of respondents had CD and were significantly older than those with UC. Study patients were mostly Caucasian and female and had achieved an education after high school, but not enough to fulfill a 4-year baccalaureate degree. Almost all participants were on one or more medications for their IBD. Biologics were the most commonly prescribed therapy for the entire study population, with UC patients more likely to be on 5-ASA (oral and suppository) and CD on biologic therapies. Participants were more likely to adhere to a normal diet and report supplement use (mostly vitamins). Most participants also reported other CAM use, outside of PPF therapy. Interestingly, presence of CD was associated with marijuana use, though only a small amount of the study population reported use of cannabis. The majority of surveyed participants were found to have longstanding disease with over half of participants receiving an established diagnosis of IBD in adulthood (ages 17-40). Active disease, measured through disease severity indices, was found in nearly one third of respondents at the time of survey and an increase in inflammatory disease markers (measured through CRP and FCP levels) found in less than half of the population over the last six months to a year. Crohn's disease was related

to an increased prevalence of disease duration greater than ten years, extra-intestinal disease and history of surgical intervention in comparison with UC. Patients with CD also exhibited ileocolonic extension with a stricturing phenotype. Ulcerative colitis was related to presence of clinical flares, higher mean flare frequency within the last two years and higher levels of mean average fecal calprotectin over the last six months. Most UC patients were found to have pancolonic disease. At the time of survey completion, the majority of patients were found to be with quiescent disease.

Nearly all IBD patients had heard of probiotic, prebiotics and/or dietary fibre supplements in their lifetime. A majority of patients had heard of probiotics and fibre supplements, with fewer hearing about prebiotics. Females and supplement users (vitamins, minerals and/or herbal) were significantly more likely to have awareness. Presence of clinical flare within the last year and recent CRP levels indicating active disease (CRP ≥ 8 within the last six months) were found to a significant negative association to awareness of these products. There were no further associations between awareness and demographics, alternative therapies or clinical characteristics. Many individuals reported source of their awareness of PPF as advertisements on radio and/or television, family and/or friends or the internet.

Approximately two thirds of IBD patients in this study had utilized PPF over their lifetime, with half reporting current consumption (over the last 12 months). Frequency analysis by individual product revealed higher consumption of probiotics in comparison to prebiotics and dietary fibre supplements over the last year. Increased awareness and information received from physicians (gastroenterologists and/or family doctors) were predictors of use. Higher

educational status, use of supplements (vitamins or minerals) and use of CAMs predicted lifetime use of PPF. Use of mineral supplements, following a combination of special diets or receiving chiropractic care was related to both lifetime and current use. There was no association between gender, age or ethnicity/race, IBD medications, steroid use, herbal supplements, surgical history or marijuana use and use of PPF. A diagnosis of UC predicted current use of PPF. There were no further associations between PPF use and with other clinical characteristics including age at diagnosis, disease duration and activity, flare frequency, levels of CRP and FCP or disease extent/behaviour (as measured through Montreal Classification scoring).

Common brands or types of PPF consumed in users over the last year were Danone Activia® yogurt, FOS and psyllium containing products. A large number of users were found to use a combination of individual products in their therapeutic regimen. However, dosage and efficacy of these products was negligible with lack of clinical benefit of Activia® yogurt or psyllium in IBD. Though FOS is a proven treatment for IBD, very few patients utilized it in our study. In addition, probiotics with proven health benefits for IBD or endorsement by a national public health organization were rarely used by the study population. The most common reason for use of PPF was to mitigate symptoms of IBD. Self-reported benefits of use included reasons centralized around improvement of general or GI-related health. The majority of users received the expected benefit but did not experience an improvement in perceived QoL after use of PPF. Probiotic users spent approximately $11 to $50 Canadian dollars, while prebiotic users spent $100 to $250 per month. Lastly, a minority of patients with IBD have never used PPF (“never users”) during their lifetime. The most common

reason for never use was lack of information from a physician regarding these products. Data were not collected on never-use per individual product in the current study.

5.2 Use of Probiotics, Prebiotics and Dietary Fibre Supplements in IBD Patients

Studies on probiotics and prebiotics as interventional treatment for IBD have been extensively studied in recent years. However, gaps in knowledge remain in usage patterns in IBD patients. Currently, there is a limited number of studies on use of probiotics and prebiotics in adults with IBD. These studies are usually included as part of surveys on use of CAM and do not always report details on usage patterns[31,43,49,51–53,55,56]. Moreover, studies on use are often conducted in pediatric IBD or adult and pediatric non-IBD populations[22,29,184,149,177–183] and very few include prebiotics[29,31,149]. To date, there is only one prior study performed by Hedin et. al (2010) on focused usage patterns of probiotics and prebiotics in IBD patients[148]. However, that study did not include the association between use and detailed clinical characteristics of its IBD study population. To our knowledge, this is the first study investigating patterns of probiotics and prebiotics use in adult IBD patients in association to patient demographics, their clinical characteristics and other alternative therapies.

Patient awareness of PPF is influenced by a variety of health care-related sources. This can include gastroenterologists, family physicians, advertisements on the television or radio, social media and family and/or friends. In the present study, the majority of the study population indicated that they had heard of PPF via advertisements, television or the

internet. Though these sources of information are popular and widespread, they can include products that are not endorsed by Health Canada or lack evidence in treating disease. This may result in lack of clinical benefit, as seen in our study population (no association with disease activity and usage). Patients are likely consuming products that are widely available and advertised, but not tested in IBD. This can be seen as a barrier that physicians must overcome when discussing alternative therapies with IBD patients.

Our study population included IBD patients recruited from specialized IBD and/or infusion clinics. The majority of these patients were on IBD medications at the time of survey, with most CD patients utilizing biologics and UC patients on 5-acetylsalicylic (5-ASA) agents. 5-ASAs are most useful as first-line agents in UC and are effective in inducing and maintaining clinical and endoscopic remission[185,186]. In our study, limited numbers of CD patients used 5-ASA as these medications are not effective for their IBD. 5-aminosalicylates were once widely used in CD, however data on their use in inducing and maintaining remission of disease are conflicting[185]. This could be partially due to the fact that 5-ASA therapies act through topical anti-inflammatory mechanisms in the small bowel and colonic mucosa and do not affect the deeper layers of tissue implicated in the pathogenesis of CD. Based on this evidence, the European Crohn's and Colitis Organization (ECCO) has elected not to recommend the use of 5-ASA medications for active ileal and colonic CD, even if some modest efficacy in mild disease has been demonstrated[187]. Biologic or anti-TNF therapies are newer forms of treatment for IBD that are used in moderate-to-severe disease when other treatments have failed. These medications are infused via intravenous route and have demonstrated effectiveness in both UC and CD. Studies on anti-TNFs in CD are more

extensive with more data supporting recommendation for use in maintenance of remission of luminal inflammatory CD or active CD refractory to corticosteroid use[187]. Evidence of the use of 5-ASA for UC and biologics for CD supports the medication profiles seen in our IBD patients. In addition, the present study involved patients recruited from an academic centre with a specialized IBD outpatient clinic. Sampling from this patient population yielded a diverse group of IBD patients with variations in disease extent, activity and medication profiles. This varied from other studies surveying use of probiotics or prebiotics in IBD patients, where patient recruitment was from the internet, non-random samples or large hospital settings[43,53]. Some CAM studies were based on patients from IBD clinics, though their main focus was not on use, but other factors involving medication adherence[49,55].

The present study found a high prevalence of combined PPF use in IBD patients (63%), which is in line with previous studies looking at general CAM use (46-74%) in IBD patients from North America[27,35,38,39,49,50,55]. Our study showed a high frequency of PPF users (88%) demonstrating probiotic use over the last 12 months. This number was greater than previous studies where probiotics were the most frequent CAM used (19-75%)[38,49,55,148]. The number of probiotic users was also higher than that the Hedin et. al (2010) study, which examined focused use of probiotics or prebiotics in IBD. In this study, 55% of IBD patients used probiotic therapy[148]. Prebiotic use (n=17, 6%) was limited in the current study, a similar trend seen in studies investigating use of prebiotics in IBD patients[148]. Pattern of prebiotic use in IBD has not been investigated prior to the current study, as there have been no studies inquiring this with a small number of patients reporting use in literature. Limited use of prebiotics is likely due to a lack of awareness or understanding of these products. In

addition, to the researcher's knowledge, this is the first study investigating the use of fibre supplements alongside prebiotics, of which 12% of IBD patients reported use over the last 12 months. Future assessment on knowledge of PPF can determine if patients understand the concept of these products, differences in function and application to IBD.

Higher educational levels were associated with use of PPF in comparison to patients who had achieved a high school diploma. This is a pattern seen in previous CAM studies where higher education predicted use [47,49,51,52]. We believe that patients with a university degree may be of higher socioeconomic status, which can affect their ability to afford and use these alternate therapies. Another explanation for this may be that patients with higher education may be more resourceful and knowledgeable in searching for alternative therapies for their disease, especially in settings of treatment failure. Educated patients may also be more involved with their physicians in treatment decisions, thus interactively taking control in management of their IBD. Ineffectiveness in IBD therapies is a reason why many patients search for alternative treatments, though this question was not directly asked in this study.

The use of alternative treatments such as CAM and NHPs were investigated in relationship to PPF use in our IBD population. We found that other CAM users were more likely to use PPF. This association is logical, as probiotics and prebiotics are considered as types of CAM, though CAM usage surveys including PPF are limited. Inflammatory bowel disease patients seeing a chiropractor were also more likely to use PPF in this study. This could be explained as arthralgias are a common manifestation of IBD. Alongside supplementary treatment for disease, patients may be utilizing additional therapy for other manifestations of

IBD. The use of supplements, such as vitamins, was also associated with use of PPF. This trend may be also seen in studies documenting the use of NHPs (such as vitamins, minerals and probiotics) in the setting of illness or disease. For example, a study conducted by Alherbish *et al.* (2011) showed that the most commonly utilized NHPs in patients with acute cardiovascular disease are vitamins and minerals (73%) and other NHPs such as probiotics (35%)[180]. Patient conceptualization of use of vitamins/minerals in comparison to probiotics has been studied. In a multicentre study investigating patient views on probiotics in IBD and irritable bowel syndrome patients, Mercer and colleagues (2013) reported that patients may view probiotics as similar to vitamins due to the method of ingestion and similarity to food[188]. This suggests that patients may be taking vitamins and probiotics simultaneously due to objective similarities in preparation. Though marijuana did not predict PPF use, this alternative treatment was also investigated in relationship to IBD, revealing an association with CD. Evidence of marijuana as a commonly used substance has increased in recent decades. In 2012, the Canadian Community Health Survey recorded that about 42.5% of the household population fifteen years of age or older reported marijuana use over their lifetime and 12.2% reported past-year use[189]. There is also a growing trend toward the use of cannabis as a complementary alternative therapy for sequelae of chronic diseases such as IBD[190,191]. Moreover, the IBD population utilizes marijuana more than the general population[23]. A large population-based cohort study (National Health and Nutrition Examination Survey) showed that IBD patients had an increased lifetime incidence of use of marijuana (67% vs. 60% of those without IBD) with 37% greater odds of first time use increased in IBD patients vs. non-IBD patients[192]. Though the mechanism of therapeutic benefit of marijuana is not clear, it is known that the drug can provide relief of nausea,

diarrhea and abdominal pain and increase of appetite, thus it is an attractive option for alternative therapy of IBD[190,191].

At the time of this writing, no previous study has focused on the use of PPF in relation to objective measures of clinical data from charts. Similar to the Hedin *et al.* (2010) study, a diagnosis of UC predicted use[148]. However, this is the first study in which UC significantly predicted combined use of PPF in IBD. In the current study, we found that UC was associated with frequent disease flares and higher levels of inflammation demonstrated by FCP in comparison to CD. Repeated relapse of IBD can involve numerous visits to the emergency room or clinic, step-up of medications (which can be costly and have adverse effects) and reduction in health-related QoL. This suggests that UC patients with active colonic disease search for alternative therapies to mitigate and treat the sequelae associated with disease flares. However, as this is a cross-sectional study, it is inappropriate to make a direct causal association between use of these alternative therapies and IBD. Study of the association between PPF use and IBD characteristics is particularly relevant as disease activity may fluctuate and lead to complications in the average IBD patient, resulting in distress and reduction in QoL. This significant health burden may result in pursuit of therapies that are cost-effective, safe and commercially available. However, utilization of alternative treatments with clinical evidence of benefit must be assessed in order to optimize treatment for their IBD. In addition, it is unknown if patients understand the difference in function and role of dietary fibres versus prebiotic fibres as treatments for IBD, therefore usage patterns of both products were investigated.

The list of probiotics used was broad and diverse, based on a study looking at clinical recommendations of probiotics for Canadian IBD patients[157]. Though commercially available probiotics were included in this survey, not all were clinically proven or recommended by Health Canada. For example, our study population frequently consumed Danone Activia®, a probiotic yogurt lacking evidence of clinical benefit in gastrointestinal disease or IBD. This suggests that widespread use of probiotics occurs without awareness of strain-specific benefit, a finding commonly seen in other studies in the IBD population[148]. In addition, receiving information on PPF from physicians (gastroenterologists and family practitioners) significantly predicted use. Physician endorsement has the power to influence decision-making strategies by patients on alternative therapies for IBD[54]. Moreover, these findings highlight that physicians may not be necessarily making evidence-based recommendations. Patients who had never used PPF also indicated their reason for never-use was absence of advice from their physician. This suggests that alongside lack of knowledge, physicians may not be recommending these products. As the health industry has a large impact on patient decisions regarding therapy, an in-depth analysis of advertisements or suggestions from physicians should be mandatory. Studies reviewing attitudes on PPF therapies or quality of evidence-based advice by physicians should be performed to ensure validated probiotic health recommendations to patients with IBD.

Frequency of probiotic or prebiotic use by IBD patients is steadily increasing in the effort to improve health-related QoL and to ameliorate symptoms of disease amidst treatment failure or adverse effects of conventional medications. Recommended use is supported by limited evidence of specific strains or types of probiotics and prebiotics as alternative treatment for

IBD. Though extensively used, many probiotics and prebiotics are not yet proven. Physicians must be knowledgeable on probiotics and prebiotics to recommend products that have scientific-based evidence in IBD. Future studies investigating physician perception, knowledge and awareness of prebiotics and probiotics should be conducted to assess how providers are making these treatment decisions. Physician awareness and acceptance of alternative therapies can optimize use. Though physician attitudes may vary regarding alternative treatment, they should be educated and aware of usage patterns within their IBD patient population in order to reinforce and encourage correct utilization of these therapies.

5.3 Strengths

Previous studies have reported the usage of CAM, including prebiotics and probiotics, in the IBD population. For instance, a study conducted by Hedin *et al.* (2010) examined the use of probiotics and prebiotics in 234 IBD participants and 100 healthy controls[148]. Through use of interview-administered questionnaires, this study determined that IBD patients use probiotics to manage their health without knowledge on their evidence or efficacy. The use of prebiotics was negligible, and thus predictive factors were not determined. However, Hedin *et al.* did not assess patient disease history and clinical parameters (disease severity, CRP and/or FCP) of IBD and thus could not identify objective clinical factors associated with use of prebiotics and probiotics. The strength of the current study is the in depth analysis of factors that affect use of PPF, such as patient demographics, alternative therapies and awareness, as well as a detailed chart review collecting objective clinical data that might determine or lead to the search of non-allopathic therapies such as probiotics and

prebiotics. Data on the disease duration, age of diagnosis, frequency of flares, clinical disease scoring, extra-intestinal disease manifestations, CRP and FCP were associated with use of probiotics and prebiotics using Chi-square analyses. To our knowledge, this is the first study that describes the usage patterns and awareness of PPF in association to detailed IBD patient sociodemographics, use of alternative therapies for IBD and clinical characteristics from charts. Previous studies examining the use of these therapies reported low rates of use, no details on usage patterns and used subjective data regarding details on IBD history or current clinical status, therefore increasing the risk of recall bias.

5.4 Limitations

Selection bias arises when the selection of the population sampled is not representative of a random selection of the target population in a study[193]. There was an absence of controls in this study, which did not allow collection of data on PPF use in healthy or non-IBD controls for comparison. Thus, we cannot evaluate PPF use by patients with IBD in comparison to the general population. This group was not included due to risk of sampling bias of patients with chronic disease, as patients were primarily recruited in a clinical setting.

Another weakness is that this study was performed at a single centre at the University of Alberta IBD clinic and/or the BioAdvance® In Viva infusion clinic and thus may not be representative of a general IBD population treated in a community centre. In addition, the majority of patients attending the infusion clinic at the Zeidler Ledcor site were on Remicade with active disease. Medications and disease severity were surveyed and abstracted from

charts, and therefore recruitment was ceased in the infusion clinic in the initial weeks of the study in order to minimize bias.

A confounding factor is a risk factor that may be associated with the exposure of interest but does not have a role in the causal pathway between the exposure and outcome[193]. In this study, time was a confounding factor as the majority of patients had limited time during which they could complete the survey questionnaire. First, the researcher would provide information on the study and obtain consent from the patient. Next, the patient was asked to complete the survey prior to their clinic appointment, in which clinic staff, nurses and other research staff may have approached the patient for clinical care or recruitment into other research studies. This may have had an impact on survey completion and response rate. Patients were encouraged to complete partially filled questions after their clinic appointment, but personal time was a factor in these instances, thus propagating the non-response rate. Questionnaires that did not contain over 50% of responses were discarded.

In this study, quality of life measurement was a limitation as it was assessed subjectively by asking patients if they had experienced an improvement after using PPF over the last year. It is inappropriate to measure QoL without use of a validated or reliable questionnaire tool. Therefore, QoL in this study was termed “perceived” QoL, as it was not objectively measured. Formal measurements with QoL must be done using a validated questionnaire to determine association to PPF use.

Finally, as this study was a cross-sectional study, it is inappropriate to make any causal references between disease severity and use of PPF. A prospective RCT using probiotic and/or prebiotic therapy is required to make conclusions based on efficacy in IBD

5.5 Pitfalls in study design

In the survey questionnaire (APPENDIX B), Section 3 includes questions on awareness and use of PPF. Awareness and current use of each product (probiotic, prebiotic or dietary fibre supplement) were represented in the survey as individual questions. However, lifetime use of PPF was represented as one combined group. Thus, demographic and clinical variables could not be associated to each product individually in the category of lifetime use. To maintain consistency, combined data in one category of "PPF use" was used in association analysis in both current and lifetime users.

The list of probiotics provided to the patients was used based on a study of probiotics used in Canada[157]. The probiotics chosen for this survey did not necessarily have clinical benefit and data was not collected on dose or compliance. Therefore, these findings were not seen in this study.

It is important to understand why patients do not use PPF. Section 3, Question 7 asked participants who have never used PPF reason of never-use of these products as a single combined category. This resulted in a lack of data regarding reason for never-use in either prebiotics, probiotics or dietary fibre supplements as independent variables of interest.

Therefore, it is difficult to make a conclusion based on the relationship between each individual product and reasons for never-use.

5.6 Clinical Relevance

A substantial increase in use of alternative therapies such as probiotics and prebiotics has been seen in the last decade in the IBD population. Emerging studies on efficacy for IBD support the recommendation of use of these products. They are relatively safe and cost-effective and therefore should be used in lieu of or in conjunction with standard IBD medications. Further analysis is required to assess patient knowledge and perception of PPF to understand the purpose of consumption and compare differences based on patient demographics and disease profiles.

5.7 Conclusions

To our knowledge, this study was the first study studying the use and awareness of PPF in IBD in association to objective clinical characteristics. Increased disease severity causes a reduction in health-related QoL, leading to the search for alternative therapies after treatment failure. As many patients are using probiotics to manage IBD, consideration must be taken on their knowledge of which strains have proven efficacy or clinical benefit in IBD. Physician suggestion influences patient decision-making regarding use; therefore greater physician awareness and understanding of supplementary probiotics, prebiotics and/or fibres is necessary in order to offer evidence-based advice. Larger, case-control studies in

a nationally representative sample are necessary to examine the use of probiotics and prebiotics in the general IBD population. These alternative treatments are increasing in prevalence among IBD patients, therefore addressing the need for research on usage patterns in order to optimize treatment strategies.

6 FUTURE DIRECTIONS

6.1 Multivariate Regression Model

Within this study, categorical data was compared between groups using Chi-square analysis or univariate analyses such as binary logistic regression without adjusting for potential confounders. Our next step in determining independent predictors of use is to create a multivariate model. Predictors with a $p<0.2$ in univariate analyses will be used to create this multivariate model using binary logistic regression. This will allow for controlling of confounding variables such as IBD disease subtype or severity of disease. Separate models will be made based on sociodemographics, alternative therapeutic characteristics and characteristics of disease. The results of these analyses will be included in the manuscript on this study.

6.2 Knowledge Assessment of Probiotics, Prebiotics and Dietary Fibres in IBD Patients

The fourth section of the survey questionnaire consisted of questions assessing knowledge of PPF in the study population. These questions were designed as open ended and structured. The aim of conducting a knowledge assessment was to collect data on patient knowledge of the definition and function of these alternative treatments for IBD. Preliminary data involving the knowledge assessment section include high response rates to the question (97% probiotics, 90% fibres, and 87% prebiotics) by the study population. Response rates included IBD patients who indicated no knowledge of these products. The

next step in knowledge assessment is to describe the study population of responders versus non-responders of this question. This will be done through comparison of sociodemographic and clinical characteristics in association to response.

Assessment of patient knowledge on these products will be done through scoring of responses based on similarity to standard definitions in literature[62,113,114,143]. A scoring rubric will be created to delineate consistent criteria for grading each response. Points will be given to correct responses satisfying components of the definition of probiotics, prebiotics or dietary fibre supplements within each patient response. Patient knowledge scores will be associated to demographic and clinical characteristics using Chi-square analyses. As of the current time, knowledge assessment data has been entered into RedCap and will be analyzed within the next step of this research project.

6.3 Relapse Prevention of Ulcerative Colitis Using Synergy-1

6.3.1 Study Design

The present study examines usage patterns of PPF in IBD patients. Our next step is to look at prebiotics in inducing and maintaining remission of IBD. Several studies using prebiotics to treat chronic intestinal disease have been performed in experimental animal models. For example, a diet rich in chicory-derived long-chain inulin combined with oligofructose (Synergy 1) resulted in a reduction of colitis in HLA-B27 transgenic rats[122]. Though animal studies are informative, it is necessary that we study the effect of these products in humans with IBD. We know that well-powered studies investigating the use of prebiotics under a

controlled clinical environment are scarce. A double-blind placebo controlled trial conducted in 2005 by Furrie *et al.* showed a reduction of intestinal inflammation in active UC using a synbiotic preparation (*B. longum* combined with 6 g Synergy 1)[128]. Casellas *et al.* also investigated the effect of Synergy 1 (12 g) versus placebo (maltodextrin) through a prospective RCT and found decreased FCP in patients with mild-to-moderate UC[130]. There are several studies examining various probiotics in the prevention of relapse and maintenance of remission in UC[70,85]. However, there are no previous studies investigating the use of prebiotics or synbiotics for the maintenance of remission in UC[101].

Our next phase in the study was to assess if prebiotics as β-fructans (oligofructose-enriched inulin, Synergy 1, Beneo-Orafti®) can prevent flares in UC patients with a high risk of disease relapse as well as determine their protective mechanisms. The study was designed as a double blind placebo-controlled RCT comparing the relapse rates in Synergy 1 versus placebo (maltodextrin) treated patients. Recruitment for this study has commenced in August 2016 and is ongoing.

Eligible subjects were those who had a confirmed diagnosis of UC, were in clinical and endoscopic remission (confirmed during a screening sigmoidoscopy), and were on stable doses of 5-ASA, biologic or immunosuppressant therapy without presence of gastrointestinal infection or pregnancy. Participants on oral corticosteroids, antibiotics or rectal suppositories with extensive comorbidities were excluded. Detailed exclusion and inclusion criteria can be seen on Figure 6-1. Subjects who passed screening were randomized to receive either 15 g of Synergy 1 or 15 g of placebo maltodextrin for the six-

month interventional period, followed by a six-month observational period. Attendance of visits at month 0 (screening/baseline), month 1, month 3, month 6 (end of study intervention) and month 12 (end of study) with provision of blood, urine and stool were required to continue in the study (Figure 6-2).

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The primary endpoint was the relapse rate of UC. A patient exhibiting a flare clinically or endoscopically would end the study. Secondary endpoints also included changes in time to relapse, compliance and tolerability, mucosal inflammation measured by FCP, Total Mayo score, endoscopic scores and microscopic inflammation scores in colonic biopsies. Side effects of Synergy 1 were estimated to be, but not limited to, excessive flatulence, abdominal rumbling and pain, bloating or diarrhea. Tolerability was assessed based on the patient's ability to tolerate these side effects and their influence on withdrawal rate. The presence of further treatment with oral and rectal suppositories or oral corticosteroids was also an endpoint in this study. Lastly, presence of toxic or severe adverse events or presence of stool pathogens would classify as endpoints as well. Efficacy and protective mechanisms of Synergy-1 to be assessed through fecal and serum analysis include the prebiotic effect on SCFAs, microbiome, cytokine profile and immune response.

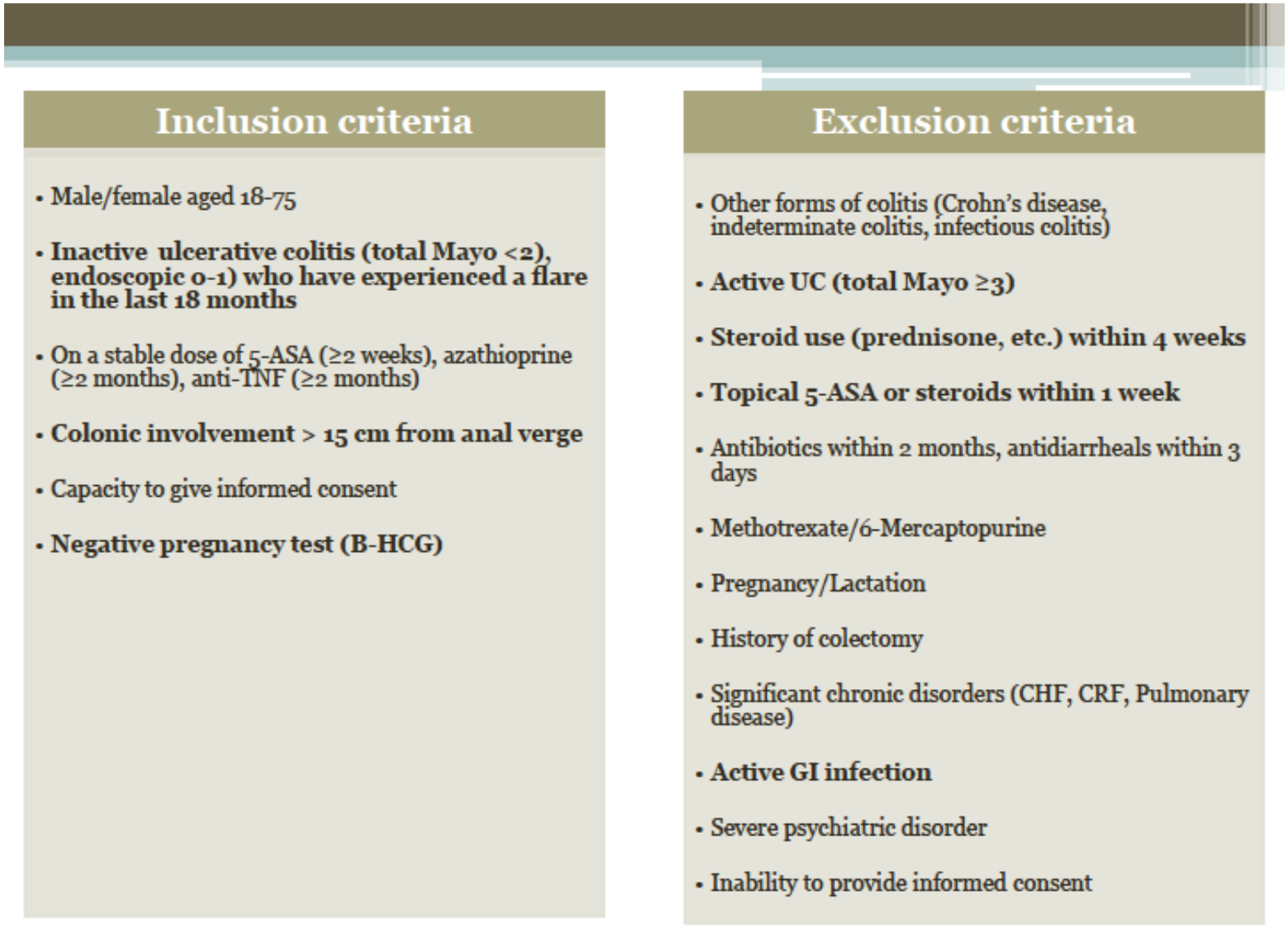

Figure 6-1: Inclusion and Exclusion Criteria for Participants in Relapse Prevention of UC Study

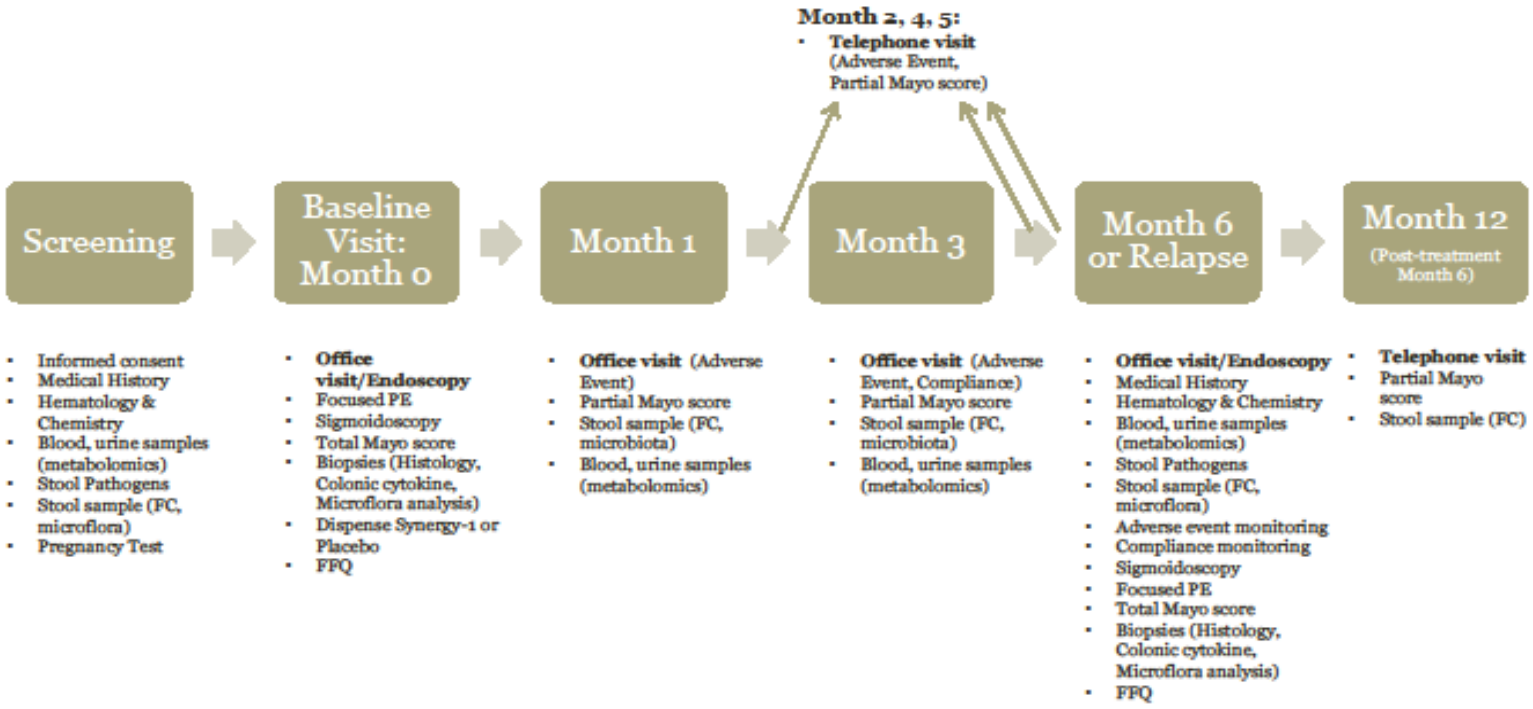

Figure 6-2: Summary of Clinical Parameters Collected per Patient Visit

6.3.2 Clinical Relevance

A prospective study will allow a valid conclusion regarding causation between prebiotics (exposure) in association with a reduction of inflammation (outcome) in IBD. This will allow us to investigate if the use of an effective dose of beta-type fructans that is safe and tolerable can lead to a reduction of inflammation in IBD. This study was modelled off the results of a previous pilot study examining the use of varying doses of Synergy 1 in patients with active UC[136]. This open label study concluded that fructans reduce inflammation in mild-to-moderate UC through specific microflora changes. A well-powered placebo-controlled intervention can assess if a proven dose of prebiotics can reduce relapse of UC in association with modulation of the gut microbiota and reduction of clinical and molecular markers of inflammation.

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APPENDICES

APPENDIX A: Informed Consent and Participation Form

INFORMATION SHEET AND CONSENT

Title of Study: Use of Probiotics, Prebiotics and Dietary Fibres in Inflammatory Bowel Disease

Principal Investigator: Dr. Levinus Dieleman; (780) 492-8691, ext. 2

Co-investigator(s): Melissa Silva

Why am I being asked to take part in this research study?

The current treatment of inflammatory bowel disease (IBD) includes medications such as steroids and other agents that suppress the immune system. These drugs often have many side effects and can be difficult to tolerate. New research has shown that there is a link between the gut and the immune system, which can alter the gut bacteria and lead to inflammation. Supplemental fibres and probiotics are dietary therapies that have shown efficacy in altering the gut-immune system connection to reduce inflammation and to treat or prevent IBD relapses. Some are effective, easier to tolerate, and have fewer side effects than standard medications.

The purpose of our study is to determine how many of our patients are using probiotics, prebiotics and/or dietary fibres, and the reasons behind their use. Our secondary aim is to determine which patients are more likely to use these novel agents, based on IBD disease characteristics.

You are being asked to participate in this study because:

1. You are an adult (18+) with a diagnosis of IBD: Crohn's disease, ulcerative colitis, or indeterminate colitis
2. You attend the IBD and/or infusion clinics at the Zeidler Ledcor Centre at the University of Alberta

Before you make a decision, one of the researchers will go over this form with you. You are encouraged to ask questions if you feel anything needs to be made clearer. You will be given a copy of this form for your records

What is the reason for doing the study?

The purpose of this study is to assess your knowledge and use of probiotics, prebiotics and dietary fibres in inflammatory bowel disease.

What will I be asked to do?

As a participant in this study, you will be asked to fill out a short survey questionnaire on your knowledge and use of probiotics, prebiotics and dietary fibres in inflammatory bowel disease. This survey should take an estimated 8-10 minutes and can be completed during a clinic visit. If you agree to participate in this research study, access to medical records will be required in order to study disease characteristics in relation to this study.

Procedures:

1. First, we will go over this information screening sheet in order to determine your eligibility for this study.
2. If you meet the inclusion criteria, you will be asked to fill out a consent form if you agree to participate.
3. You will then be asked to complete a survey questionnaire before or after your current clinic visit. This should take approximately 10 minutes.
4. After the survey is completed, the researcher will then access your medical records (NetCare, e-Clinician, office charts) to collect information about your disease course.

What are the risks and discomforts?

This study involves completion of a non-interventional survey questionnaire by the participant; therefore, there are no risks or discomforts involved. It is not possible to know all of the risks that may happen in a study, but the researchers have taken all reasonable safeguards to minimize any known risks to a study participant.

What are the benefits to me?

The benefits from participating in this research study will be the knowledge gained in patient utilization of probiotics, prebiotics and dietary fibres as a therapy in inflammatory bowel disease, and their effects on disease activity. This study may help other people with IBD in the future. However, you are not expected to get any benefit from being in this research study.

Do I have to take part in the study?

Being in this study is your choice. If you decide to be in this study, you can change your mind at any time, and it will in no way affect the quality of care or treatment that you are entitled to. As this study involves completion of a survey questionnaire, it is important to know that you do not have to answer any questions that you are not comfortable with. In the event that you choose to withdraw from this study at any point, new health information will not be collected. Contact information will be provided on information sheets, in which you can contact the researcher. You have the option to request for withdrawal of information at any time.

Will my information be kept private?

During this study, we will be collecting data about you. We will do everything we can to make sure this data is kept private. No data relating to this study that includes your name will be released outside of the researcher's office or published by the researchers. Sometimes, by law, we may have to release your information with your name so we cannot guarantee absolute privacy. However, we will make every legal effort to make sure that your information is kept private.

For this study, the investigator or their study staff will require access to your medical record. Personal health records relating to this study will be kept confidential. Data collected in this study will not identify you by name, but instead a coded number. Any personal health information that we get from these records will be only what is needed for the study.

During research studies, it is important that the data we get is accurate. For this reason, your health data, including your name, may be looked at by people from the University of Alberta or the Human Research Ethics Board (HREB).

By signing this consent form, you are saying it is okay for the study team to collect, use and disclose information about you from your personal health records as described above.

After this study is done, health data that was collected as part of the study will be securely stored. At the University of Alberta, we keep data stored for a minimum of 5 years after the end of the study. Additionally, data collected in this study may be used for the purpose of future research, diagnostic management or general information.

If you leave the study, we will not collect new health information about you, but we may need to keep the data already collected.

What if I have questions?

If you have any questions about the research now or later, please contact

Dr. Dieleman (780) 492-8691 ext. 2 OR Melissa Silva (780) 492-0019

If you have any questions regarding your rights as a research participant, you may contact the Health Research Ethics Board at 780-492-2615. This office has no affiliation with the study investigators.

There are no conflicts with respect to funding of this study.

This information sheet is yours to keep.

CONSENT FORM

Title of Study: Use of Probiotics, Prebiotics and Dietary Fibres in Inflammatory Bowel Disease

Principal Investigator(s): Dr. Levinus Dieleman Phone Number(s): (780)-492-8691 ext. 2

Co-Investigator(s): Melissa Silva Phone Number(s): (780) 492-0019

Sub-investigators: Dr. Karen Kroeker
Dr. Brendan Halloran
Dr. Karen Wong
Dr. Richard Fedorak
Dr. Farhad Peerani
Dr. Sander Veldhuyzen Van Zanten
Dr. Dina Kao

	Yes	No	
Do you understand that you have been asked to be in a research study?	☐	☐	
Have you read and received a copy of the attached Information Sheet?	☐	☐	
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐	
Have you had an opportunity to ask questions and discuss this study?	☐	☐	
Do you understand that you are free to leave the study at any time, without having to give a reason and without affecting your future medical care?	☐	☐	
Has the issue of confidentiality been explained to you?	☐	☐	
Do you understand who will have access to your study records, including personally identifiable health information?	☐	☐	

Who explained this study to you? _____

I agree to take part in this study: YES ☐ NO ☐

Signature of Research Participant _____

(Printed Name) _____

Date:_____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee _____ Date _____

**Please sign and return one (1) copy of this page and keep one (1) for your records

APPENDIX B: Survey Questionnaire

Use of Probiotics, Prebiotics and Dietary Fibres in Inflammatory Bowel Disease

This is a non-interventional observational study aimed at assessing your knowledge and use of probiotics, prebiotics and dietary fibre supplements. We are interested finding out use of these alternative therapies in inflammatory bowel disease. Participation in this survey is optional. You must fill out the informed consent form in order to complete this survey. If you agree to participate, a chart review will be completed by the researcher after completion of the questionnaire. Please circle only one selected answer to each question, unless otherwise specified. Please do not skip any of the questions, unless instructed to do so.

This questionnaire will take approximately 8-10 minutes to complete.

Please note: Participation in this survey is optional and requires informed consent. The participant's physician will not know who has or hasn't taken part. Medical care will not be impacted by participation in this research project. Withdrawal is only possible up to submission of the survey. Data in electronic form will be securely stored by researchers on University of Alberta servers and all paper questionnaires will be stored locked cabinets for a minimum of 5 years after the completion of the study.

Principal Investigator: Dr. Levinus Dieleman, IBD Gastroenterologist
Co-Investigator: Melissa Silva, Graduate Student; (780) 492-0019
U of A Research Ethics Office; (780) 492-2615

Identification Number _____

Instructions: Please select one answer, unless otherwise indicated.

Section 1: Demographics

1. Age (on last birthday): _____
2. Gender □ Male □ Female □Other: _____
3. Highest education level achieved: □ Less than Grade 12; please specify highest grade completed _____ □ High School Graduate □ Some College □ Diploma □ Bachelor Degree □ Graduate Degree □ Other _____
4. Ethnicity/Race: □ Caucasian □ Black or African Canadian □ First Nation/North American Indian □ Asian □ East Indian □ Hispanic/Latino □ Other: _____

Identification Number _____

Section 2: Disease Characteristics

1. Do you have diagnosis of one of the following:

□ Crohn's Disease (CD) □ Ulcerative colitis (UC) □ Indeterminate colitis (combination of both CD & UC)

2. How long have you had your disease?

□ Less than 1 year □ 1-2 years □ 3-5 years □ 5-10 years □ greater than 10 years

3. Disease Flares

a. Have you had a disease flare in the last year?

□ Yes □ No

b. If you had a disease flare in the last year, were you treated with corticosteroids (Entocort®/Budesonide)?

□ Yes □ No

4. Are you on a specific diet? (Please mark all that apply):

□ Pescatarian (diet with no animal-based food, except seafood, eggs, dairy and honey)
□ Vegetarian (diet with no animal-based food, except eggs, dairy and honey)
□ Vegan (diet with no animal-based food, including eggs, dairy and honey)
□ Gluten-free (diet excluding the protein gluten)
□ Low glycemic diet (diet including foods that are low in glycemic index, to control blood sugar levels)
□ Lactose-free (diet excluding lactose, a sugar found in milk products)
□ DASH diet (diet rich in fruits, vegetables, low fat or nonfat dairy, used to reduce blood pressure levels)
□ Low FODMAP diet (diet low in Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols, used in Irritable Bowel Syndrome)
□ Special diet (e.g.: Weight-watchers, Jenny Craig, Atkins, Paleo, Mediterranean etc.). Please specify:
_____
□ Diet with certain food exclusions (please list):
_____
□ None (I am on a normal diet, including all food groups)

5. What treatment(s) are you currently taking? (Please mark all that apply):

□ Antibiotics □ Steroids (circle – Prednisone/Budesonide)

□ 5-ASA (*circle* - Asacol®/Salofalk®/Mezavant®) (*circle* – oral/rectal)

□ Thiopurines (azathioprine/Imuran®)/6-Mercaptopurine) □ Methotrexate

□ Vedolizumab (Entyvio®) □ Anti-TNF (Remicade®/Humira®/Simponi®) □ Ustekinumab (Stelara®)

□ I am currently being treated as part of a clinical trial □ None

6. For each type of supplement listed below, please indicate whether you are currently taking it (e.g.: within the last week) and specify which ones you are taking:

a. Vitamins (e.g.: A, B, C, D, Multivitamin, etc.)

□Yes □ No

If yes, which ones are you currently taking? (please list below)

_____
_____
_____

b. Minerals (e.g.: iron, calcium, potassium, magnesium, etc.)

□Yes □ No

If yes, which ones are you currently taking? (please list below)

_____
_____
_____

c. OTC Herbal supplements (e.g.: echinacea, St. John's wort, milk thistle, ginseng, ginkgo biloba, etc.)

□Yes □ No

If yes, which ones are you currently taking? (please list below)

_____
_____
_____

7. Do you regularly use marijuana (e.g.: on a weekly basis)?

□Yes □ No

8. Have you regularly used any of the following complementary alternative therapy (CAM) practices in the past year?

□ Massage □ Chiropractic □ Faith healing □ Yoga □ Meditation □ Acupuncture □ Naturopathy

□ Homeopathy □ Reflexology □Traditional Chinese medicine □ Reiki □ Tai-chi □ Other _____

□ None

Section 3: Probiotics, Prebiotics & Dietary Fibre Supplements

1. Have you heard of the following:

a. Probiotics

□ Yes □ No

b. Prebiotics

□ Yes □ No

c. Dietary Fibre Supplements

□ Yes □ No

2. How did you hear about probiotics/prebiotics/dietary fibre supplements?

□Gastroenterologist □Family physician □Pharmacist □Health Care Provider (Dietician, Nurse, etc.)

□Internet □Social Media (Facebook®, Twitter®, etc.) □Advertisement (Radio, TV, Magazine)

□Family member/Friend

□ Other (please specify):

_____

_____

3. Have you used any probiotics, prebiotics or dietary fibre supplements?

□ Yes □ No (if no, skip to Question #7)

4. Please select which Probiotics, Prebiotics and Dietary Fibre supplements you have used in the <u>past year</u> (please mark all that apply):

a. Probiotics:

Do you use? □ **Yes** □ **No** (skip to 4b)

<u>If you answered yes, which probiotics do you use?</u>

□ Activia® yogurt – *(Bifidobacterium animalis)*
□ Align® – *(Bifidobacterium infantis)*
□ Bio-K+®
□ Fem-Dophilus®, Bacid® – *(Lactobacillus rhamnosus/Lactobacillus reuteri)*
□ Florastor® – *(Saccharomyces boulardii)*
□ Jamieson® L. Acidophilus capsules – *(Lactobacillus acidophilus/Lactobacillus rhamnosus)*
□ Lacidofil® – *(Lactobacillus rosell)*
□ Mutaflor® – (*E. Coli Nissle 1917*)
□ Natrel® – *(Bifidobacterium lactis)*
□ Oasis Health Break® –(*Bifidobacterium bifidus/Lactobacillus acidophilus*)
□ TuZen® – *(Lactobacillus plantarum)*
□ VSL#3® (Probiotic blend of *Streptococcus thermophiles, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus delbrueckii subsp. bulgaricus)*
□ YogActive® cereal – *(Lactobacillus acidophilus)*
□ Yoptimal® – *(Lactobacillus acidophilus/Bifidobacterium lactis)*
□ Other _____

b. Prebiotics

Do you use? □ **Yes** □ **No** (skip to 4c)

<u>If you answered yes, which prebiotics do you use?</u>

□ Benefibre®, Fibre Choice® – *(Inulin)*
□ Lactulose
□ NutraFlora® – *(Fructo-oligosaccharides (FOS))*
□ Other _____

c. Dietary Fibre supplements

Do you use? □ **Yes** □ **No**

<u>If you answered yes, which dietary fibre supplements do you use?</u>

□ Citrucel® – *(Methylcellulose)*
□ FibreSmart®, Recleanse® Fibre Powder – *(Flax)*
□ Metamucil®, Natural Brand® Psyllium seed husk, Ultra Fibre® – *(Psyllium)*
□ PGX® – *(Glucomannan)* □ Unprocessed wheat bran □ Other _____

5. If you use probiotics/prebiotics/dietary fibre supplements, have you noticed an improvement in quality of life over the last year?

□Yes □No

6. Health Benefits of Probiotics/Prebiotics/Dietary Fibre Supplements

a. If you are using probiotics/prebiotics/dietary fibre supplements, or have tried them for Crohn's disease or ulcerative colitis, why are they beneficial for you? (Please mark all that apply, then skip to Question 8)

□ To treat disease □To prevent flares □Reduction of gut-related symptoms (e.g.: bloating, diarrhea, constipation)

□ To decrease fatigue □ To increase appetite □ To improve mood

□ Other (please specify):

_____

_____

b. Have you received the intended benefit?

□Yes □No

7. What is the reason you are <u>not</u> currently using probiotics/prebiotics/dietary fibre supplements?

□ They aren't effective
□ Too expensive
□ My doctor didn't suggest it
□ I have not heard of them
□ Side effects, if so, please specify:

_____

□ Other (please specify):

_____

_____

8. Approximately, how much do you spend per month on probiotics, prebiotics or dietary fibre supplements?

□$0 □$1-10 □$10-50 □$50-100 □$100-250 □>$250

Section 4: Knowledge assessment

***IMPORTANT*: Please fill out each part of this section to the best of your ability. Any information will greatly help the researcher with the study. If you do not know, please indicate so.**

1. Knowledge assessment:

a. In your own words, provide a short description on what you know about **probiotics?**

b. In your own words, provide a short description on what you know about **prebiotics?**

c. In your own words, provide a short description on what you know about **dietary fibre supplements**?

APPENDIX C: Chart Review Form

Study ID _____

Chart Review: Prebiotics and Probiotics in **Ulcerative Colitis**	
Demographics:	
1. Age	_____
2. Sex (circle one)	Male Female
3. Age at diagnosis	_____
Disease characteristics:	
4. Montreal Classification **a. Extension** **b. Severity**	Proctitis (E1)/Left Sided (E2)/ Pancolitis(E3) Clinical remission (S0)/Mild UC (S1)/Moderate UC (S2)/ Severe UC (S3)
5. Partial Mayo Score	_____
6. Surgical History **a. Presence of surgery** **b. Presence of colectomy**	(yes/no) (yes/no)
7. Number of flares in the last two years	_____
8. Current IBD Medications	Oral 5-ASA Immunosuppressants Biologics Prednisone (past/current) Topical therapies
9. Labs **a. CRP > 8 (in the last 6 months)** **b. Average FCP > 250 (in the last 6 months)** **c. CRP > 8 (in the last year)** **d. Average FCP > 250 (in the last year)**	(yes/no) (yes/no) yes/no) (yes/no)
10. Extra-intestinal manifestations	(yes/no)

Study ID _____

Chart Review: Prebiotics and Probiotics in **Crohn's Disease**	
Demographics:	
1. Age	_____
2. Sex (circle one)	Male Female
3. Age at diagnosis	_____
Disease characteristics:	
4. Montreal Classification **a. Extension** **b. Behaviour**	 Ileal (L1)/Colonic (L2)/ Ileocolonic (L3)/Upper GI (L4) Inflammatory (B1)/Stricturing(B2)/ Penetrating (B3)/Perianal (p)
5. Harvey Bradshaw Index	_____
6. Surgical History **a. Presence of surgery** **b. Number of resections**	 (yes/no) _____
7. Number of flares in the last two years	_____
8. Current IBD Medications	Oral 5-ASA Immunosuppressants Biologics Prednisone (past/current) Topical therapies
9. Labs **a. CRP > 8 (in the last 6 months)** **b. Average FCP > 250 (in the last 6 months)** **c. CRP > 8 (in the last year)** **d. Average FCP > 250 (in the last year)**	 (yes/no) (yes/no) (yes/no) (yes/no)
10. Extra-intestinal manifestations	(yes/no)

APPENDIX D: Montreal Classification for IBD

MONTREAL CLASSIFICATION

Age at diagnosis (A)			
A1	16 years or younger		
A2	17–40 years		
A3	Over 40 years		
Location (L)		**Upper GI modifier (L4)**	
L1	Terminal ileum	L1 + L4	Terminal ileum + Upper GI
L2	Colon	L2 + L4	Colon + Upper GI
L3	Ileocolon	L3 + L4	Ileocolon + Upper GI
L4	Upper GI	–	–
Behaviour (B)		**Perianal disease modifier (p)**	
B1*	Nonstricturing, nonpenetrating	B1p	Nonstricturing, nonpenetrating + perianal
B2	Stricturing	B2p	Stricturing + perianal
B3	Penetrating	B3p	Penetrating + perianal

**B1 category should be considered 'interim' until a prespecified time has elapsed from the time of diagnosis. Such a time period may vary from study to study (eg, 5-10 years is suggested) but should be defined in order for B1 behaviour to be considered 'definitive'. GI Gastrointestinal*

The three subgroups of UC defined by extent are:

1. Ulcerative proctitis (E1): involvement limited to the rectum (ie, proximal extent of inflammation is distal to the rectosigmoid junction).
2. Left-sided UC (E2) (also known as distal UC): involvement limited to the portion of the colorectum distal to the splenic flexure.
3. Extensive UC (E3) (also known as pancolitis): involvement extents proximal to the splenic flexure.

Silverberg, MS, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Canadian Journal Of Gastroenterology* 2005;19(Suppl):5A-36A.

APPENDIX E: Harvey Bradshaw Index Scoring Sheet

Modified Harvey Bradshaw Index Assessment for Crohn's Disease Activity

Date:_____
Patient Name:_____
Date of Birth:_____
PHN/ULI:_____

Patient, please complete Questions 1, 2 & 3.

Base your answers on how you felt yesterday.

1. General Well-being (see descriptors)
- ☐ Very well = 0
- ☐ Slightly below Par = 1
- ☐ Poor = 2
- ☐ Very Poor = 3
- ☐ Terrible = 4

☐

2. Abdominal Pain (see descriptors)
- ☐ None = 0
- ☐ Mild = 1
- ☐ Moderate = 2
- ☐ Severe = 3

☐

3. Number of Liquid or Soft Stools per day (Yesterday)

☐

Physician, please complete Question 4

4. Additional Manifestations
- ☐ None = 0
- ☐ Arthalgia = 1
- ☐ Uveitis = 1
- ☐ Erythema Nodosum = 1
- ☐ Aphthous ulcer = 1
- ☐ Pyoderma gangrenosum = 1
- ☐ Anal Fissure = 1
- ☐ New Fistula = 1
- ☐ Abscess = 1

☐

Total Harvey Bradshaw Index score: [sum of all above items]

▒

Remission = <5
Mild Disease = 5-7
Moderate Disease = 8-16
Severe Disease >16

1. General Well-being Descriptors

General well being includes fatigue in the overall rating and how you feel today. Record the worst you have felt today. Compare yourself to someone else of your age, how would they rank their general wellbeing? Below are some descriptors to help you rank your category of general well being.

- **Very Well:** General health is not generally a problem. You're feeling very good or great and under control.
- **Slightly Below Par:** You're getting through things but feeling below par and not normal. Something overall is preventing you from saying " I feel wonderful ". You're feeling good but not great. You can work, socialize, and function on a day to day basis.
- **Poor:** Your symptoms bother you. You occasionally miss work, school, or social activities. You have some embarrassing moments with fecal incontinence. You have diarrhea, abdominal pain, fatigue, and basically just feeling unwell, but you are still able to function. You're getting through the day, doing all your normal stuff but it is a struggle.
- **Very Poor:** Your getting through a part of the day, but can't do you're your normal stuff. You can't attend social events in evening. You sometime leave home from work early. You feel pretty bad and are not doing much activity – only those absolutely necessary. Your symptoms interfere with life considerably, you don't go out or are fearful when out, you miss a lot of school or work. Fecal incontinence happens several times per week.
- **Terrible:** You're unable to function. You can't manage the basics and you're almost bedridden. This is the worse you have ever been. You're not working.

2. Abdominal Pain Descriptors

Abdominal pain may include cramping and discomfort. It does not have to be just "pain" as we know it. Below are some descriptors to help you rank your category of abdominal pain.

- **Mild:** You're aware that the abdominal pain is there but it does not interfere with your life and you continue with activities such as work and pleasure. You feel and hear rumbles, gurgles and cramps.
- **Moderate:** You're aware of your abdominal pain and must alter your activities to manage the pain (ie. lie down to rest, postpone shopping trips until later, and take Tylenol). The pain interferes with your life and daily activities. You may have to miss work or pleasure activities on occasion.
- **Severe:** Your abdominal pain causes you to stop all activity. You are frequently in bed because of the pain, you call in sick to work and cancel all activities.

APPENDIX F: Partial Mayo Scoring Sheet

Partial Mayo Scoring Index
Assessment for Ulcerative Colitis Activity

Date:_____
Patient Name:_____
Date of Birth:_____
PHN/ULI:_____

Patient, please enter number of daily bowel motions you would have when in remission or before your diagnosis or symptoms of ulcerative colitis began. **This number will be Your Normal:** ☐

Patients, please complete Questions number 1 and 2.

1. Stool Frequency (based on the past 3 days)

☐ Normal number of stools	= 0
☐ 1-2 stools more than normal	= 1
☐ 3-4 stools more than normal	= 2
☐ 5 or more stools more than normal	= 3

☐

2. Rectal Bleeding (based on the past 3 days)

☐ No blood seen	= 0
☐ Streaks of blood with stool less than half the time	= 1
☐ Obvious blood with stool most of the time	= 2
☐ Blood alone passed	= 3

☐

Physician, please complete Questions number 3.

3. Physician's Global Assessment (to be completed by Physician)

☐ Normal (sub scores are mostly 0)	= 0
☐ Mild disease (sub scores are mostly 1)	= 1
☐ Moderate disease (sub scores are mostly 1 to 2)	= 2
☐ Severe disease (sub scores are mostly 2 to 3)	= 3

☐

The physician's Global Assessment acknowledges the Sub scores, the daily record of abdominal discomfort and functional assessment and other observations such as physical findings, and the patient's performance status

Total Partial Mayo Index Score [sum of all above items] ☐

Remission = 0-1
Mild Disease = 2-4
Moderate Disease = 5-6
Severe Disease =7-9