Exploring a patient-centred, diet-focused treatment paradigm for Inflammatory Bowel Disease

By

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Thesis submitted for the degree of

Doctor of Philosophy

School of Medicine

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University of Adelaide

November 2021

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Thesis abstract

Introduction

The relationship between diet and inflammatory bowel disease (IBD) is multi-dimensional and complex. Diet is implicated as an environmental factor in disease pathogenesis, however, the interaction between dietary factors and the induction and/or perpetuation of mucosal inflammation is poorly understood. Many people with IBD believe diet and disease are interrelated and subsequently modify their diets in the absence of defined diet therapy, however, this may not improve clinical, nutritional or quality of life (QoL) outcomes. Diet therapy for ulcerative colitis (UC) is under-researched though data proposes the pathogenesis of UC may be a sequelae of interactions occurring between dietary substrate, the gut microbiota and colonic epithelium.

Aims

Therefore, the aims of this thesis were to:

1. Explore dietary beliefs and behaviours of people with IBD and to examine the inter-relationship between diet and QoL.
2. Examine the potential utility of diet therapy with defined mechanistic action in UC.

Methods

A systematic scoping review was firstly undertaken to examine the dietary beliefs of people with IBD and to explore any associations with QoL. Additionally, a systematic review examining the adequacy of dietary fibre intakes and associated factors was performed. Following this, a cross-sectional study examining food-related quality of life (FRQoL) was undertaken to characterise FRQoL and identify any patient- or disease-related predictors of FRQoL in people with IBD. Thereafter, an open label pilot dietary-advice study was undertaken to investigate the tolerability of a novel pathogenically-designed diet (a sulphide-reducing diet) as therapy in people with mild-moderately active UC. The influence on disease activity, bacterial fermentation and patient-reported outcomes were examined. Lastly, in a case series of patients with refractory UC, diet therapy to augment and sustain the efficacy of faecal microbiota transplantation (FMT) was explored.

Results

A complex dietary belief system informing dietary behaviours was identified in people with IBD and a high prevalence of food avoidance and restrictive dietary behaviours. Dietary fibre intakes were inadequate compared to control groups, irrespective of disease activity, and only 10-21% met national fibre recommendations. FRQoL in IBD patients was lowered by restrictive eating behaviours

associated with fear, poor appetite and active disease. However, positive food-related outcomes were associated with surgery. An 8-week sulphide-reducing diet was well tolerated and adhered to, with clinical response occurring in 46%, endoscopic response in 36% and biomarkers of colonic fermentation were successfully modulated. Finally, sustained remission beyond 24-52 weeks was achieved using FMT and diet therapy, where diet may assist in engrafting donor 'healthy' microbiota.

Conclusion

Diet is influential over many important aspects of living with IBD. Restrictive dietary behaviours are associated with poorer FRQoL. A sulphide-reducing diet signals therapeutic potential for UC and as an adjunctive therapy to FMT. Collectively, the studies within this thesis highlight important yet neglected areas of IBD care and identify areas where diet can provide added value, including as a possible therapy for UC. These findings warrant further examination as wide spread integration of diet into conventional treatment of IBD could dramatically change clinical practice, treatment outcomes and QoL for people with IBD.

Thesis declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

The author acknowledges that copyright of published works contained within this thesis resides with the copyright holder(s) of those works. I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Alice Sarah Day

Acknowledgements

Undertaking a Doctor of Philosophy (PhD) and completing my thesis would not have been possible without the support, guidance and energy from my supervisors Professor Jane Andrews, Dr Robert Bryant, and Dr CK Yao.

I would like to acknowledge Professor Jane Andrews for facilitating my undertaking of a PhD and for overseeing my supervisory team. I am highly appreciative of the leadership and collaboration Jane has provided as my primary supervisor, including the essential strategic direction and oversight required to complete this doctorate. Jane has expertly empowered and facilitated my co-supervisors to guide our research projects and has always been available to provide her expertise to our projects.

I am highly appreciative and so thankful of the encouraging support and investment Rob has provided as my supervisor and to the whole higher research degree journey. Rob is highly intelligent, energetic and inspirational. I have learnt so much from his day-to-day support throughout my doctorate. Rob is always positive, encouraging and optimistic, and he has been a wonderful teacher, mentor and friend. I feel extremely fortunate to have had my first research experience within The Queen Elizabeth Hospital Inflammatory Bowel Disease Service which Rob leads and I am proud to be a part of such a dynamic team with broad horizons and new projects ahead.

To CK, my dietitian colleague and supervisor. I am so appreciative of the guidance you have provided me and the sharing of your knowledge and experience in dietary research. I am also grateful for the way you have integrated me into your research network and linked me in with colleagues within your department. You are part of a brilliant research team and inspiring to us here in Adelaide.

I would also like to acknowledge and thank my pseudo-supervisors Dr Sam Costello and Professor Peter Gibson. To Sam, it has been fascinating to watch and learn how your scientific mind investigates, untangles and advances new theories and ideas. Your passion toward investigating the science linking the human colonic microbiota and ulcerative colitis is inspiring and I am extremely grateful to have had your support throughout my doctorate. And to Professor Peter Gibson, my other pseudo-supervisor. Thank you for the guidance and knowledge you have imparted throughout my PhD. From research methodology to data interpretation, presentation, and scientific writing, to introducing me to new collaborative partnerships, you have been instrumental to my higher degree research journey and I am so grateful to you and all my supervisors for your time and dedication to our body of research.

To my husband Anthony and our beautiful children Emily and Lucas. I could not have undertaken this PhD without your unwavering support. Ant, you have enabled me to complete a full-time doctorate

through a challenging pregnancy and turbulent few years of raising two gorgeous, strong-minded, energetic children. This support has extended to me being able to take up long distance running again, secure a job I am passionate about for after my PhD all whilst continuing to enjoy and live our lives with our children to the fullest. This higher degree journey has been so rewarding and enjoyable and you have supported and encouraged me to get the most out of this experience. Your excel spreadsheet and data managements skills and ability to break problems down into sizeable pieces also need commending. This higher degree has been a Day family team project and one I hope will inspire our children to dream, work hard and succeed throughout their lives.

To my parents who provided me with my core values and the best education and life opportunities one could ask for. For always encouraging me to be independent and follow my own path, thank you. I am the person, mother, wife, dietitian and researcher I am today because of you both. Particularly because of you Dad, for picking up the parental reins throughout the last 22 years and guiding me through my secondary, tertiary and now higher degree education. I only wish mum could be here today to have enjoyed the PhD journey with me and seen how her passion for education and learning has been instilled within all her children.

To my three other 'mums' Bronwyn, Corrine & Jane, thank you for stepping in to fill the motherly void after mum died and embracing and loving me as your own. I am so appreciative of all the motherly guidance you have provided me which ensured I never wander too far from my own path. Jane, watching you complete your PhD during my time in England was inspiring and confirmed in my mind after university this would be the path I would eventually take too. Bronwyn, starting and completing this thesis whilst raising Emily & Lucas would not have been possible without the support you have given our little family. Corrine, your wise words about the importance of prioritising family as a working mum were always heard and sometimes a very timely reminder.

Lastly, I would like to sincerely thank both the Central Adelaide Local Health Network Inflammatory Bowel Disease Services at The Queen Elizabeth Hospital and the Royal Adelaide Hospital and The Basil Hetzel Institute. The administrative, medical, nursing and research staff have been instrumental in patient recruitment and supporting our research projects and I am appreciative of all the help I have received.

This degree has been a whole team effort and I am grateful to everyone who has supported me throughout my PhD.

Publications and citations arising from this thesis

Articles published

1. **Day AS**, Yao CK, Costello SP, Andrews JM, Bryant RV. Food avoidance, restrictive eating behaviour and association with quality of life in adults with inflammatory bowel disease: A systematic scoping review. Appetite. 2021 Dec;167:105650. DOI: 10.1016/j.appet.2021.105650. PMID: 34391842.

2. **Day AS**, Davis R, Costello SP, Yao CK, Andrews JM, Bryant RV. The Adequacy of Habitual Dietary Fibre Intake in Individuals With Inflammatory Bowel Disease: A Systematic Review. J Acad Nutr Diet. 2021 Apr;121(4):688-708.e3. https://doi:10.1016/j.jand.2020.12.001

3. **Day AS**, Yao CK, Costello SP, Andrews JM, Bryant RV. Food-related quality of life in adults with inflammatory bowel disease is associated with restrictive eating behaviour, disease activity and surgery: A prospective multicentre observational study. J Hum Nutr Diet. 2021 May 18;n/a(n/a). DOI: 10.1111/jhn.12920.

4. Costello SP,* **Day AS**,* Yao CK, Bryant RV. Faecal microbiota transplantation (FMT) with dietary therapy for acute severe ulcerative colitis. BMJ Case Rep. 2020 Aug 24;13(8):e233135. DOI: 10.1136/bcr-2019-233135. (*joint first authors)

5. Bryant RV, **Day AS**, McGrath KC, Telfer K, Yao CK, Costello SP. Fecal microbiota transplantation augmented by a sulfide-reducing diet for refractory ulcerative colitis: A case report with functional metagenomic analysis. JGH Open. 2021 Jul 29;5(9):1099-1102. doi: 10.1002/jgh3.12623. PMID: 34584982; PMCID: PMC8454482.' (*joint first authors)

Abstracts published

6. **Day, AS**, Yao, CK, Costello, SP., Ruszkiewicz, A., Andrews, JM., Gibson, PR., and Bryant, RV. Evaluation of the tolerance and effect on disease activity of a new dietary strategy (4-SURE diet) for mild-moderately active ulcerative colitis. Journal of Gastroenterology and Hepatology. [https://doi.org/10.1111/jgh.15275]. 2020 2020/11/01;35(S1):191-2.

Articles under review

7. **Day AS**, Yao, CK, Costello, SP., Ruszkiewicz, A., Andrews, JM., Gibson, PR., and Bryant, RV. The novel 4-SURE diet is tolerable, modulates colonic fermentation and has therapeutic potential for mild-moderately active ulcerative colitis: findings of a feasibility study. Submitted for publication to American Journal of Clinical Nutrition, November 2021.

Glossary

5-ASA	Aminosalicylic acid therapy
BCFA	Branched chain fatty acids
BMI	Body mass index
CD	Crohn's Disease
CDED	Crohn's Disease Exclusion Diet
CD-TREAT	Crohn's Disease Treatment with Eating
CoA	Co-enzyme A
CRP	C-reactive protein
DASS	Depression, anxiety stress scale
DRV	Dietary reference value
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th edition
EEN	Exclusive enteral nutrition
FC	Faecal calprotectin
FFQ	Food frequency questionnaire
FODMAPs	Fermentable oligo-, di-, mono-saccharides and polyols
4-SURE diet	FOUR strategies to SUlphide-REduction
FMT	Faecal microbiota transplantation
FRQoL	Food-related quality of life
GSRS	Gastrointestinal symptom rating scale
HBI	Harvey Bradshaw Index
HC	Healthy controls
HRQoL	Health-related quality of life
H_2S	Hydrogen sulphide
IBD	Inflammatory bowel disease
IBDU	Inflammatory bowel disease unclassified

IBW	Ideal body weight
IOIBD	International Organisation of the Study of Inflammatory Bowel Disease
IPAA	Ileal pouch-anal anastomosis
IQR	Interquartile range
NHI	Nancy Histology Index
NO	Nitric Oxide
NSP	Non-starch polysaccharide
OR	Odds ratio
PG-SGA	Patient-generated subjective global assessment
PICOS framework	Population, intervention, comparison, outcome, study design
PRO	Patient reported outcomes
QoL	Quality of life
RS	Resistant starch
UC	Ulcerative colitis
UCEIS	Ulcerative colitis endoscopic index of severity
RCT	Randomised controlled trial
SCCAI	Simple Clinical Colitis Activity Index
SCD	Specific carbohydrate diet
SCFA	Short chain fatty acids
SGA	Subjective global assessment
TNF	Tumour-necrosis factor
VAS	Visual analogue scale

CHAPTER 1

Thesis overview

CHAPTER 1: Thesis overview

Inflammatory bowel disease (IBD), namely Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory, relapsing and remitting diseases of the gastrointestinal tract without a medical cure.[1, 2] The aetiopathogenesis of IBD remains uncertain, however is proposed to relate to genetic predisposition, immune dysregulation, microbial dysbiosis and external environmental exposures including diet and medications.[3, 4] There is renewed interest in the interaction between the compositional and functional shifts of the gut microbiota and innate immunity in IBD and the central role this may play in inflammation.[5] Existing therapies have solely targeted the immune response to the gut microbiota without altering the luminal environment and there is now increasing interest in microbial manipulation as a therapeutic avenue.[6, 7] Diet directly influences the gut microbiota and luminal environment. Therefore, it is plausible that diet has a key role in disease pathogenesis.[8, 9]

Diet is a topic of great significance to people with IBD. Many people with IBD perceive diet to be either an initiating and/or perpetuating factor in disease course.[10, 11] Diet is also reported as the most important psychosocial need affected by IBD.[6-8] However, diet is often overlooked as part of IBD care and a lack of access to evidence-based, individualised dietary advice is frequently reported.[12-14] Dietary advice can be conflicting and this can leave people with IBD vulnerable to dietary misinformation.[15] Subsequently, people with IBD often modify their diet in response to disease-related symptoms, commonly by avoidance or restriction of particular foods or food groups.[16, 17] Restrictive dietary behaviour and dietary inadequacy are associated with poorer clinical and surgical outcomes.[18-22] Less is known about how these behaviours influence quality of life (QoL) though more recently, food-related quality of life (FRQoL) has been identified to be poorer in people with IBD.[23]

Much remains to be understood regarding the role of diet in IBD, particularly in the emerging area of diet therapy, microbial manipulation and strategies to improve quality of life. Accordingly, this thesis was undertaken to explore the dietary beliefs and behaviours of people with IBD and examine the inter-relationship between diet and QoL, including any dietary behaviours that could potentiate a poorer FRQoL or lead to poorer nutritional or clinical outcomes. This thesis also examines the potential utility of a multi-dimensional diet therapy with defined mechanistic action in UC and the role diet may have in augmenting the durability and efficacy of faecal microbiota transplantation (FMT) in UC.

A systematic scoping review of dietary beliefs, dietary behaviours and association with QoL in people with IBD was performed to identify the current dietary perceptions that may inform dietary behaviour, including food avoidance and restrictive eating, and to determine how these behaviours may influence QoL. This study is presented in ***chapter 3***: Manuscript: Day, AS, *et al* 'Food avoidance, restrictive

eating behaviour and the association with quality of life in adults with inflammatory bowel disease: a systematic scoping review', published in *Appetite* August 2021 [impact factor (IF) 3.608].

Unnecessary avoidance or restriction of dietary fibre could have therapeutic implications in IBD as dietary fibres are associated with sustained remission in CD and UC.[24, 25] Therefore, a systematic review examining whether habitual fibre intakes in IBD are adequate was performed. This study is presented in ***chapter 4***: Manuscript: Day, AS *et al* 'The adequacy of habitual dietary fibre intake in individuals with inflammatory bowel disease: a systematic review', published in *Journal of the Academy of Nutrition and Dietetics* April 2021 [IF 4.151].

FRQoL encompasses the psychosocial influence IBD has on eating and drinking, however less is known about the factors that predict a poorer or greater FRQoL. Therefore, a prospective cross-sectional study was undertaken to characterise FRQoL in IBD and identify patient and disease-related predictors of FRQoL. This study is presented in ***chapter 5***: Manuscript: Day, AS *et al* 'Food-related quality of life in adults with inflammatory bowel disease is influenced by restrictive eating behaviour, disease activity and surgery: a prospective multi-centre observational study', published in *Journal of Human Nutrition and Dietetics* May 2021 [IF 3.146].

Microbial metabolites of dietary carbohydrate and protein fermentation are implicated in the pathogenesis of UC. However, a multi-dimensional diet therapy that modulates fermentable dietary substrate to influence excess hydrogen sulphide production at the colonic-luminal interface has not yet been trialled. Therefore, a novel sulphide-reducing diet was piloted to explore tolerability, clinical efficacy and influence on markers of bacterial fermentation in UC. This study is presented in ***chapter 6***: Manuscript: Day, AS *et al* 'The novel 4-SURE diet is tolerable, modulates colonic fermentation and has therapeutic potential for mild-moderately active ulcerative colitis: findings of a feasibility study', submitted for publication to *American Journal of Clinical Nutrition November* 2021 [IF 6.76].

It is biologically plausible that a specific diet may augment the efficacy and durability of FMT by providing a favourable luminal milieu, encouraging engraftment of transplanted microorganisms and restoring luminal homeostasis. A 2-patient case series testing the hypothesis that a sulphide-reducing diet could augment FMT in refractory UC leading to sustained remission was undertaken. This case series is presented in ***chapter 7***: Manuscript #A: Costello, SP, Day, AS *et al* 'Faecal microbiota transplantation (FMT) with dietary therapy for acute severe ulcerative colitis', published in *BMJ Case Reports* August 24th 2020 [IF 0.453] and Manuscript #B: Bryant, RV, Day AS, *et al* ' Faecal microbiota transplantation augmented by a defined dietary strategy for refractory ulcerative colitis: a case report with functional metagenomic analysis', published in *Journal of Gastroenterology Hepatology Open* August 2021 [IF <1].

Lastly, a discussion is presented in ***chapter 8***, summarising and interpreting the findings of this thesis. Collectively, important yet neglected areas of IBD care are highlighted and areas that diet can provide added value to conventional IBD treatment paradigms are proposed, including as a possible therapy for UC. The clinical implications of this body of research, limitations to the current evidence base and future research directions are discussed, contextualising how the body of research presented in this thesis can enhance existing treatment paradigms for people with IBD toward a model of care that optimises control of active disease, improves QoL and positively reframes the relationship between diet and IBD.

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CHAPTER 2

Introduction

CHAPTER 2: Introduction

2.1 Inflammatory bowel disease: epidemiology, pathogenesis and existing treatment paradigms

Inflammatory bowel disease (IBD), namely Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory, relapsing and remitting diseases of the gastrointestinal tract without a medical cure. IBD affects a predominantly younger demographic and is associated with debilitating gastrointestinal symptoms, disability, reduced quality of life and diet-related issues.[1, 2] Currently available therapies are only partially effective and rates of surgery among patients with IBD remains high.[3]

Definitions, clinical presentations and diagnosis

Crohn's disease

CD is characterised by segmental and transmural inflammation which can affect anywhere along the gastrointestinal tract from mouth to anus, with the most common sites of inflammation at the terminal ileum and colon.[4] Disease onset usually occurs between the second and fourth decade of life, with a family history of CD observed in approximately 12% of cases.[4] Clinical presentation of CD varies depending on the site of inflammation, but typically includes abdominal pain, diarrhoea, fatigue and weight loss.[5] Complications of CD include stricturing and penetrating disease (abscess or fistula formation), which affect around half of patients with CD.[4] More than 50% of patients with CD will require at least one surgery within the first 10 years.[3]

Ulcerative colitis

UC is limited to the colon, characterised by mucosal inflammation, which begins in the rectum and extends proximally in continuity.[1, 6] Disease onset usually occurs between 30-40 years of age, with a family history observed in 8-14% of cases.[6] The clinical presentation of UC typically includes diarrhoea, rectal bleeding and fatigue.[5] Approximately 15-20% of patients with UC will require a colectomy.[3, 6]

IBD-unclassified

Up to 5-15% of people diagnosed with IBD have clinical and endoscopic signs of chronic colitis that cannot be further distinguished to either CD or UC. This is twice as common in paediatric-onset IBD than adults.[7] Where binary classification remains undetermined, IBD is labelled as IBD Unclassified (IBDU).[1] There are no distinct clinical or histological features of IBDU however bloody diarrhoea and rectal bleeding are more dominant in clinical presentation.[7]

Extraintestinal manifestations of IBD

Extraintestinal manifestations (EIMs) are observed in up to 50% of people with IBD, often presenting before diagnosis.[8] EIMs can affect eyes, skin, joints or the liver and are more commonly seen in CD than UC. The risk of occurrence increases with disease duration and typically occurs with active intestinal disease.[8] The range of EIMs include peripheral and axial arthropathies, venous thromboembolism, metabolic bone disease, iritis/uveitis, and skin disease (pyoderma granulosum, erythema nodosum) and primary sclerosing cholangitis, a hepatobiliary manifestation of IBD.[1, 8]

Diagnosis

Diagnosis of CD and UC requires a composite assessment of clinical, biochemical, stool, endoscopic, histological and radiological features.[1] A gold standard test for diagnosis does not currently exist.[9] Gastrointestinal infections must be excluded as an initial step in diagnosis. For UC and CD, an ileocolonoscopy with biopsies from inflamed and non-inflamed segments should be obtained. For CD, radiological imaging of the small bowel, including magnetic resonance enterography, is often required to visualise inflammation in areas beyond the reach of the colonoscope.[1, 9] Features of CD on ileocolonoscopy typically include patchy discontinuous inflammation commonly with ileal involvement or perianal lesions. Histological features of CD include granulomas and focal crypt architectural abnormalities along with patchy inflammation.[9] For UC, continuous and confluent inflammation typically extends proximally from the rectum. Mucosal friability, ulceration and spontaneous bleeding are common features. Histological features of UC include focal or diffuse basal plasmacytosis, cryptitis and crypt abscess formation.[1, 9]

Epidemiology of IBD

Historically, CD and UC have been considered diseases of Westernised countries, with the highest incidence and prevalence in Northern America and Western Europe.[5] More recently, an epidemiological shift has been observed with rising rates of IBD in newly industrialised countries of Asia, Africa and South America where incidence rates were low prior to 1990.[10] Australia has one of the highest rates of IBD development with an incidence of 29.3 per 100,000.[11, 12] Australian health systems are significantly impacted by IBD, with direct hospital and pharmaceutical expenses estimated to comprise of >70% of the overall financial burden.[13] Per annum, hospital costs have previously been estimated at $100 million, productivity losses $380 million and total indirect costs $2.7 billion comparable to lifetime costs for cancer and diabetes.[14, 15]

The global rise in the incidence of IBD implicate an environmental influence in disease pathogenesis.[16] These projected trends and figures are unsustainable for health services and further examination of disease pathogenesis and new treatment paradigms are needed.[17]

Pathogenesis of IBD

The aetiopathogenesis of IBD remains uncertain, however is proposed to relate to genetic predisposition, immune dysregulation, microbial dysbiosis and external environmental exposures including diet and medications.[12, 18] There is increasing interest in the interaction between the taxonomic and functional shifts of the gut microbiota and innate immunity in IBD and the central role this may play in modulating inflammation.[19]

In particular, a shift toward pathobionts and a reduction in biodiversity of bacterial species are observed in IBD. Compared to healthy controls, shannon diversity at phylum-level is reduced, with decreases in predominant phyla Firmicutes and expansion of Proteobacteria.[20] Enrichment of up to 6-8 classes of organisms are also observed in CD and UC, including Deltaproteobacteria, a class of sulphate-reducing bacteria.[20-22] These taxonomic, or compositional changes are collectively termed 'dysbiosis' and are associated with potential alterations to metabolic functions, including reduced tolerance oxidative stress, modulation of the immune system, impaired biosynthesis of short chain fatty acids (SCFA) and reduced luminal antimicrobial activities.[20, 23-25] However, the implications of these compositional changes in disease pathogenesis remains poorly understood. It is unclear whether dysbiosis has a casual association with IBD or is a consequence of underlying chronic inflammatory processes.[25] Moreover, variances exist in the microbial signatures of people with CD and UC which suggests the involvement of the gut microbiota in disease pathogenesis could differ for CD and UC.[21]

Pathogenesis of CD

CD is proposed to develop through an interaction between genetic loci, environmental factors and the intestinal microbiota.[4, 18] An abnormal mucosal immune response and defective epithelial barrier function is observed in genetically susceptible individuals, where people with the NOD2 gene are observed to have specific compositional shifts in the gut microbiota.[4, 19, 26] However, genetic predisposition only accounts for 13% of disease heritability and does not explain variance in the phenotypic characteristics of CD, therefore other environmental risk factors are implicated.[4, 27] Smoking is an established risk factor and associated with more severe or refractory CD. This is in contrast to UC where smoking appears to have a protective effect in disease pathogenesis.[26] Early life influences such as breastfeeding in infancy, living on a farm and exposure to pets appear to be protective in the development of CD whereas antibiotic exposure in childhood, infections and use of medications such as nonsteroidal anti-inflammatory drugs appears to increase the risk of CD development.[28, 29] These influences are also known determinants of the gut microbiota and are proposed to influence disease susceptibility by the interaction between the gut microbiota and immune response.[18]

People with CD appear to have lower biodiversity and a less stable microbiota than those with UC.[21, 30] Examination of the microbial signature of CD shows a loss of beneficial microorganisms and a gain of potentially pathogenic microorganisms, with phylum-depletion of Firmicutes and Bacteroidetes and expansion of Proteobacteria phyla.[21, 31] Decreases in Bacteroidetes are associated with reduced oxidative stress tolerance whilst increases in the pathobiont Proteobacteria are associated with inflammatory processes via adherent-invasive capabilities of organisms and decreased synthesis of essential amino acids and associated transporter genes.[19] Furthermore, the Clostridia family appear to be altered in CD. At a species level, decreases in protective *Faecalibacterium prausnitzii,* a butyrate producer of SCFA, are observed, with enrichment of potentially pathogenic, pro-inflammatory species *Ruminococcus gnavus*, *Escherichia coli*, and *Clostridium clostridioforme*.[20, 21, 25, 32] Functional profiling of these compositional changes show downregulation in the expression of SCFAs and decreases in SCFA production. These changes influence the integrity of the epithelial barrier as SCFA are purported to have a key role in decreasing tumour necrosis factor (TNF) production and other pro-inflammatory cytokines in CD.[18, 19, 33]

Pathogenesis of UC

The evidence of a genetic influence in the pathogenesis of UC is weaker than CD, although 8-14% of people with UC will have a family history of IBD.[18] Early life influences including breastfeeding, exposure to animals and living on farms also have a protective association against the development of UC whilst exposure to antibiotics, pollutants and cessation of smoking are negatively associated with the development of UC.[18, 26, 28] Most research to date has focused on immunological mechanisms of disease pathogenesis, which may in fact be the sequelae of interactions occurring between the gut microbiota and colonocytes at the luminal interface with epithelial barrier dysfunction a key feature of UC.[34]

People with UC appear to have heterogeneous microbial profiles. Compositional changes are observed but to a lesser degree than CD.[20, 23] A lower beta diversity is observed compared to healthy controls, indicating more common microbial species between UC and healthy individuals than CD.[35] A depletion of fibre-degrading and SCFA-producing bacteria Lachnospiracae and Ruminococcaceae families with expansion of pro-inflammatory Enterobacteriaceae and Fusobacteriaceae are observed, though these microbial shifts are less than those seen in the microbial signature of CD.[34] Higher levels of sulphate-reducing bacteria from the Desulfovibrio genus, producers of hydrogen sulphide (H_2S), are observed in UC.[36] At a species level, abundance of *Faecalibacterium prausnitzii* is greater in CD, though indistinct from healthy controls, and *Ruminococcus gnavus* is decreased.[35] At a functional level, colonic fermentation of fibre appears to be diminished in quiescent disease and SCFA metabolism defective. On the other hand, colonic production of H_2S in active UC is greater than those

with quiescent disease and in healthy controls indicating a potential implicating role and avenue for therapeutic manipulation. [22, 36-39]

Multiple lines of evidence support the role of H_2S in the pathogenesis of UC, with experimental data suggesting UC may be an 'epithelial disease', consequent to impairment in uptake and oxidation of SCFA butyrate by colonocytes for energy.[40-43] Biochemical injury is hypothesised to occur through exposure to toxic metabolites produced by the colonic microbiota which perpetuates colonic barrier dysfunction and mucosal inflammation in UC.[37, 44-47] These metabolites can impair key metabolic pathways within the colonocytes leading to defective SCFA metabolism and an energy-deprived state for colonocytes (***Figure 2.1***).[42, 43] The energy-starved epithelium has limited ability to perform vital metabolic functions including the maintenance of barrier function.[42, 43]

Experimental data suggest the delivery of dietary protein and fermentable carbohydrates to the colonic microbiota influences the production and detoxification of these harmful metabolites.[45, 47, 48] Carbohydrates are the main sources of dietary substrates for colonic fermentation and production of SCFA.[49] Fermentation of proteins occur in the setting when carbohydrate substrates are depleted and are a major source of microbial metabolites including H_2S, nitrogenous metabolites ammonia, phenol, indole and amine production, BCFAs and to a lesser extent SCFAs.[45, 47, 50] Sulphur proteins and other sources of dietary sulphur are proposed to increase the abundance of sulphate-reducing bacteria, leading to excess production of H_2S gas.[36, 45] However, carbohydrates are preferentially fermented by colonic microbes over proteins. When the supply of fermentable carbohydrates is increased, colonic microbes can 'switch off' protein fermentation, reducing the accumulation of H_2S.[47, 49] Currently accurate, real-time measurement of colonic H_2S production is difficult. However, recent experimental data using novel gas profiling technology to measure H_2S in faecal slurries found slowly and readily fermentable dietary fibres effectively attenuated H_2S gases and were superior to 5-aminosalicylic acid (5-ASA) therapy in this mechanistic action.[48]

Data therefore suggests the manipulation of habitual dietary carbohydrate and protein consumption could influence colonic microbial fermentation processes, thereby reducing accumulation and the potentially harmful effects of excess H_2S and other protein metabolites that are implicated in the development of inflammation and biochemical lesions observed in UC.[42, 51]

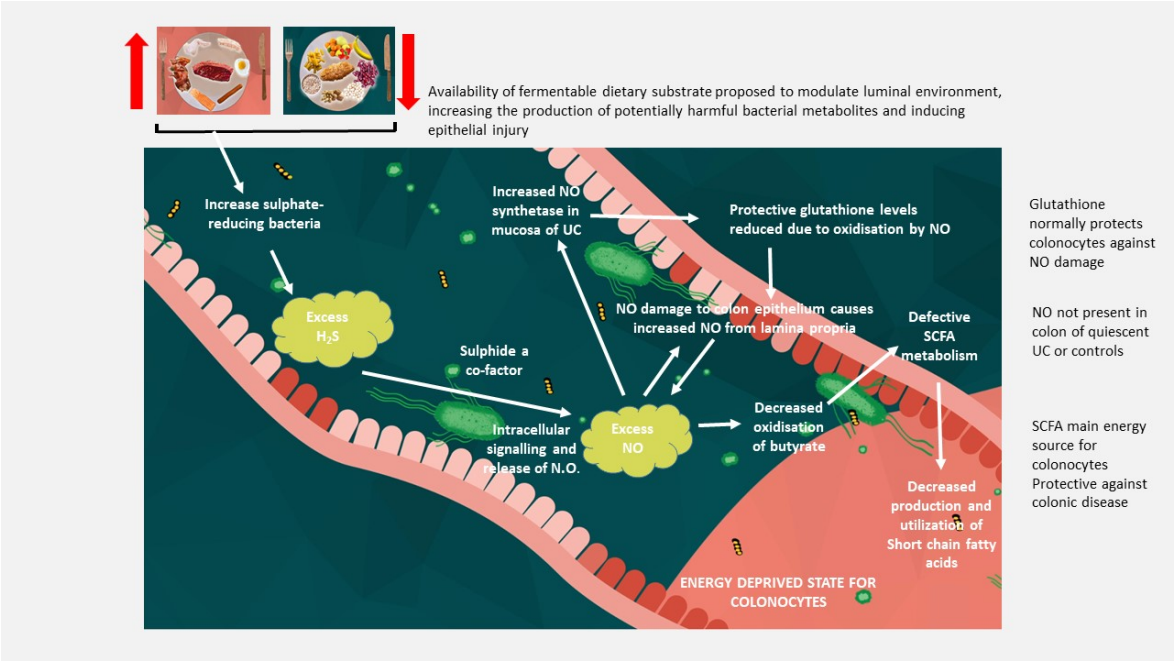

Figure 2.1 Proposed mechanism of how altering fermentable dietary substrate theoretically induces biochemical injury observed in ulcerative colitis.

Legend: *Sulphur and nitrogen pathways are involved in the proposed mechanistic action of sulphur in the pathogenesis of UC. An increase in sources of dietary sulphur and sulphur amino acids are proposed to increase the abundance of sulphate-reducing bacteria, leading to excess production of H_2S gas.[51, 52] H_2S is a co-factor in the intracellular signalling and release of nitric oxide (NO), and NO is proposed to exert multi-pronged effect within the colon including damage to epithelium, suppression of SCFA production and glutathione, both which have a protective effect for colonocytes.[53] This creates an energy-deprived state for colonocytes and the biochemical injury observed is proposed to induce the biochemical lesions seen in UC.[42]*

Diet in the pathogenesis of IBD

Observational data

Widespread adoption of a westernised diet has been implicated as an important factor in IBD susceptibility and may account for current epidemiological trends.[54-57] A westernised diet is characterised by higher consumption of energy-dense foods such as red and processed meats, saturated fats, refined sugars and sweetened beverages, and lower consumption of fruits, vegetables and wholegrains, with more frequent consumption of convenience and processed foods.[56] A limited number of studies examining pre-illness dietary intake have identified an association between higher intakes of fats and animal protein including red meat with risk of developing IBD.[58] Higher intakes of soft drinks, sweetened beverages and a lower intake of vegetables have also been associated with greater risk of UC.[55, 56, 59] Conversely, higher intakes of dietary fibre and fruit appear to have a

protective effect against developing CD and a higher fruit and vegetable intake is positively associated with a lower risk of UC.[60, 61]

In addition to the observational data, having an understanding of the habitual intakes of people with IBD can also inform a deeper understanding of the relationship between diet and disease susceptibility. The diets of people with IBD differ from recommended dietary guidelines, with observational data suggesting habitual fibre intakes are inadequate.[62, 63] Whether this is cause or consequence of disease is unknown. However, the availability of dietary fibre directly influences the composition of protective fibre-degrading bacteria in the colonic microbiota and is essential to SCFA metabolism, therefore may have a pivotal role in IBD pathogenesis.[55, 64] Unfortunately the inconsistencies in observational data limit the interpretability of any association between diet and disease pathogenesis. These may be explained by methodological heterogeneity including in study design, the age of participants being analysed for an association with IBD onset, and a lack of control groups. Furthermore, dietary changes prior to disease diagnosis, recall bias on diet data, heterogeneity in dietary assessment instruments, food composition tables used for data analysis and how nutrients or foods are grouped together for assessment are likely to have influenced data.[27]

Experimental data

Data from human, animal and cell line models collectively implicate a variety of nutrients and food additives in the pathogenesis of IBD (***Table 2.1***). Recent dietary guidance from the International Organisation for The Study of Inflammatory Bowel Disease (IOIBD) attempted to summarise the individual role of dietary components in disease pathogenesis.[65] However, definitive consensus statements were not achieved for many food components due to a lack of high quality dietary trials in human subjects and an imperfect classification system for categorising dietary components for analysis. The IOIBD guidance can be summarised as:[65]

CD. Recommend increasing fruits and vegetables; recommend decreasing saturated and trans fats, emulsifiers, carrageenan, artificial sweeteners, maltodextrin, titanium dioxide.

UC. Recommend increasing omega-3 from fish and food sources; recommend decreasing red and processed meats, dairy fat, palm and coconut oil, saturated and trans fats, emulsifiers, carrageenan, artificial sweeteners, maltodextrins, titanium dioxide.

These dietary recommendations predominantly stem from epidemiological studies and animal data. Therefore, the efficacy of altering disease course by adopting these dietary recommendations in humans with IBD remains largely untested. Furthermore, there is a large body of experimental data relating to differing fermentable fibres, outlined in ***Table 2.1***, absent from review within this guidance,

possibly due to how fibrous food components were grouped together for analysis (fruit and vegetables, refined sugar and carbohydrates, wheat and gluten).[65]

Nonetheless, collectively, there are consistent signals from epidemiological and experimental data that diet has a key role in IBD pathogenesis, plausibly due to how diet interacts with the gut microbiota at the luminal interface.

Table 2.1 Summary of key dietary components proposed to be involved in IBD pathogenesis derived from experimental data in humans, animal and cell-line models.

Dietary component	Purpose / function	Proposed effect or association with IBD	Evidence source
Dietary fibre	Carbohydrates that escape digestion in the small intestine and have a key role in bowel health and function	Fibre-rich habitual diet protective against luminal inflammation in CD[60] Low intake from habitual diet associated with increased risk of disease flare in adults with CD[60]	Human Human
Resistant starch	A fermentable dietary fibre	Attenuates luminal inflammation in colitis[66]	Mice
Non-starch polysaccharide	A slowly fermentable fibre	Increases faecal bulk and normalises gut transit time in combination with resistant starch in UC[37] Germinated barley reduced disease activity scores in UC[67] Psyllium associated with sustained remission in UC[68] Oat bran associated with sustained remission and increased in faecal butyrate concentrations in UC[69]	Human Human Human
Inulin	A fermentable dietary fibre	Increases faecal butyrate concentrations, lowers pH and improves inflammation in pouchitis[70] Increases in fibre-degrading organisms, increases in faecal butyrate and reduction in clinical and endoscopic disease activity in active UC[71, 72]	Human
Gluten	Protein-component of wheat, barley & rye	Increases intestinal permeability in animal studies[73] Reduced occludin expression, induced chronic ileitis in animal studies[73]	Mice Mice
Animal protein	Comprises of amino acids required for protein synthesis and physiological functions	Increased sulphate-reducing bacteria in UC[36] Associated with biochemical lesions observed in UC[66] Associated with increased rates of relapse in UC[74] Not associated with disease flares in CD[75] Impaired ability to sulphate phenols in UC[76]	Human Human Human Mice Human
Saturated fat	Source of energy and essential fatty acids predominantly from animal sources	Increased TNF-α expression, associated with dysbiosis and alterations in bile acid composition[77] Increased intestinal permeability, decreased tight junction proteins expression, and inflammation[78, 79]	Mice Rats/cells

Polyunsaturated fats	Source of energy and essential fatty acids, predominantly from plant sources	Increased inflammation in CD in cell cultures [79]	Cells
Omega 3 fatty acid	Essential fatty acid with anti-inflammatory properties	May reduce T-cell activation and inflammation in UC and CD when consumed from food sources rather than omega-3 supplements[80, 81]	Human
Myristic acid	Source of energy and essential fatty acids, predominantly from dairy, coconut, palm oil	Increased risk of flare in UC[82]	Human
Carrageenan (e407)	Emulsifier / highly sulphated polysaccharide commonly added to processed foods and dairy products	Increases intestinal permeability and epithelial damage[83] Induces biochemical lesions, neoplasia, and ulceration similar to UC[84] Increases rates of relapse in UC[85]	Cells Pigs Human
Carboxymethylcellulose (e466)	Emulsifier / thickening agent commonly added to processed foods and dairy	Increased intestinal permeability[86] Degradation of the mucosal layer[86] Microbial dysbiosis[87]	Mice Mice Cells
Polysorbate-80 (e433)	Emulsifier / thickening agent commonly added to dairy products	Increased mucosal-associated bacteria and mucous layer degradation[88] Increase translocation of pathogenic bacteria, induces colitis[86]	Cell Mice
Maltodextrin / artificial sweetener	Emulsifier / thickening agent commonly combined with sucralose artificial sweetener	Proposed to influence gene expression, colonisation and translocation of pathobionts associated with CD[89, 90]	Cell / Mice
Sulphates/sulphites	Preserving agent added in canned foods, wine, beer, pickled foods to increase stability	Increase production of H_2S by sulphate-reducing bacteria[91] Impairs butyrate oxidation and SCFA metabolism[92] Impairs SCFA beta-oxidation at acyl-CoA dehydrogenase level in colonocytes[93] Associated with increased rates of relapse in UC[74]	Human Human Cell Human
Nitrates/nitrites	Preserving agent added to processed and cured meats to increase stability	Increases nitrite-reducing bacteria and nitric oxide gas[94] Nitric oxide diminishes CoA metabolism in colonocytes and induces biochemical injury similar to UC[53]	Human Human/ cell

Existing treatment paradigms for IBD

Therapeutic aims for IBD

Treatment targets for IBD are evolving. An expanding treatment armamentarium coupled with evidence that resolution of inflammation improves outcomes in patients with IBD has led to ever more ambitious therapeutic targets. Most recent consensus propose recommendations for treating to target in CD and UC.[95] Clinical response, defined as 50% resolution in symptoms such as pain, stool frequency or bleeding, is recommended as an immediate treatment target for CD and UC, with clinical remission, defined as Harvey Bradshaw Index <5 or partial Mayo score <3 with minimal or absence of clinical symptoms, as an intermediate target. Normalisation of CRP and faecal calprotectin can also be used as intermediate treatment targets. Endoscopic mucosal healing, defined as Simple Endoscopic Score-CD <3 or absence of ulcerations and Mayo endoscopic sub score of 0, is recommended as the long-term target. Absence of disability and normalisation of health-related quality of life should also be included as long-term treatment targets. Histological remission has been excluded as a treatment target for CD and UC however can be used as an adjunct marker of deep remission in UC and transmural healing can be used as an adjunct marker of deeper healing in CD.[95]

Patient reported outcomes in IBD

Patient reported outcomes (PRO) offer a patient-centric approach to measuring treatment efficacy and symptom control.[96] Extending beyond gastrointestinal symptoms, PROs measure patient perceptions of general well-being such as mood disorders, impact on QoL, fatigue, work productivity and disability indices, which existing therapeutic targets do not include.[97] PROs can be included in clinical practice and within research protocols to measure global treatment efficacy, including the effect of dietary modifications to manage symptoms of IBD. However, a defined PRO to measure the psychosocial impact of eating and drinking with IBD has not yet been integrated into research examining diet therapy in IBD.[98]

Conventional management of IBD

Treatment algorithms and international consensus statements exist for the conventional management of CD and UC.[1, 95, 99] Oral or systemic corticosteroids are routinely used for remission induction in IBD with clinical response typically occurring within two weeks.[1, 99] Aminosalicylic acid therapies are the foundation therapy for UC, taken orally and/or topically with a 4-week window to observe clinical response.[99, 100] Immunomodulator therapy such as thiopurines (azathioprine or mercaptopurine) and methotrexate are commonly used for IBD patients with clinical response observed within 8-12 weeks.[99] Biologic therapy has evolved the management of IBD considerably. Anti-TNF therapy such as infliximab, anti-intergrin therapy including vedolizumab, and cytokine inhibitors including

ustekinumab are increasingly being used, with time to clinical response varying between 6-12 weeks.[95, 101]

However, these therapies are not wholly effective at inducing and maintaining deep remission in IBD with loss of response occurring over time. Rates of clinical and endoscopic remission are highly variable depending on disease phenotype, type of therapy and route of administration. Higher rates of clinical and endoscopic response (42-79%) are typically observed within the first 1-8 weeks of initiating therapy, with those achieving endoscopic remission tapering to 25-69% at 6-12 months.[101] Therefore, a substantial proportion of patients with IBD will require surgical management.[1]

Surgical management of IBD

In CD, a laparoscopic segmental resection may be indicated for ileocolonic disease that has not responded or failed medical therapy or used as an alternative to anti-TNF therapy in short segment ileocecal disease.[1, 102] In the setting of stricturing disease, a strictureplasty or segmental resection may be indicated. Surgical management may also be required for fistulising disease or to divert the faecal stream in uncontrolled perianal disease.[1] In UC, surgery is recommended when medical management has been optimised and chronic active symptoms persist or in those with acute severe UC who have not responded to rescue therapy. This may include either a curative proctocolectomy with end ileostomy or a restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) which is generally the surgical option of choice.[103] The efficacy of restorative IPAA procedures are high, with conversion rates to an end ileostomy reported as 3.75-5.1% within eight years.[104] QoL following IPAA is generally good.

2.2 Diet therapy for IBD

Diet to treat active disease

Beyond conventional and surgical management, defined diets have been evaluated for induction and maintenance of remission in IBD. EEN is the most widely used diet therapy, with more than 27 randomised-controlled trials evaluating its efficacy as a remission induction therapy for active CD.[105] Hence, EEN offers a steroid-free alternative for remission induction or downgrading disease severity with comparable rates of efficacy to steroids when adhered to.[105] Other whole food diet therapies proposed to modulate pro-inflammatory dietary components or suppress pro-inflammatory mediators (***Table 2.1***) have been trialled however there is a paucity of well-designed studies. The most recent prospectively trialled diet therapies used to treat active CD and UC are summarised in ***Table 2.2***. The efficacy rates for clinical response appear favourable in comparison to the efficacy rates of conventional therapy, however many studies fail to include objective markers of disease activity such as endoscopic scoring and histopathology. Therefore it is possible the reports of clinical efficacy are

related to improvement in functional symptoms rather than treatment of overt inflammation. Furthermore, many studies fail to adequately define the rationale and mechanistic action for food and/or nutrient selection or include an adequate description of the diet and nutrient composition to be able to interpret or replicate the dietary prescription in a high quality, placebo-controlled trial.

Table 2.2 Summary of recent prospectively trialled diet therapies for treatment of clinically active IBD in paediatric or adult populations

Type IBD	Defined diet therapy	Clinical indication	Key dietary characteristics	Proposed mechanistic action	Reported efficacy in trials	Paediatrics (P) Adults (A)	Prospective evidence
CD	Exclusive enteral nutrition	Remission induction; bridging therapy; healing of enterocutaneous fistulas; pre-surgery: downgrading of disease severity or inflammatory strictures	Exclusive use of polymeric or elemental liquid formula for 6-8 weeks. Avoids all food and fluids except water. Allowance for tea or coffee in certain studies	Modulation of luminal environment by removing dietary components proposed to have an inflammatory interaction with mucosa and reducing pathobionts	45-83%	P & A (n=1011)	Randomised Controlled Trials (RCTs)[105]
CD	Crohn's disease exclusion diet + partial enteral nutrition	Remission induction strategy for children with clinically active disease	Selection of 12 food items (including eggs, chicken breast, peeled apple, firm banana) with 50% partial enteral nutrition for 6 weeks followed by 2-phase food re-introduction protocol. Excludes lactose, red meat, food additives, gluten, some fibres (except resistant starch)	Elimination of proposed inflammatory dietary components that can alter intestinal bacteria and impair mucous barrier	75.6%	P (n=73)	RCT[106]

CD	Crohn's disease Treatment with EATing	Remission induction strategy for children with clinically active disease	Includes a selection of low fibre fruits, vegetables and grains, lactose-free dairy, fish and chicken and partial enteral nutrition for 8-weeks	Modulation of the microbiome by altering dietary substrate and creating a luminal environment similar to EEN therapy	60%	P (n=5)	Proof of concept pilot study[107]
CD	Specific carbohydrate diet	Adjunctive therapy for clinically active non-stricturing non-penetrating disease	Includes non-starchy vegetables, lean proteins, homemade yoghurt, honey. Excludes mono and polysaccharides including grains, starches, gluten, refined sugar, most dairy, food additives	Modulation of proposed inflammatory dietary components could alter composition and function of bacteria in intestine including influencing mucosal barrier integrity	29-80%	P (n=16-18)	RCT[108, 109]
CD & UC	Semi-vegetarian diet	Maintenance of clinical remission	Lacto-ovo-vegetarian diet with significant reduction in fish and red meat intake. Includes a selection of traditional fresh and fermented Japanese foods for undefined period of	Elimination of components of a westernised diet proposed modulate beneficial bacteria in intestine	73-94%	A (n=22-92)	RCT [110] and single-group observational study[111]

			time. Excludes refined sugars, processed foods				
CD & UC	Mediterranean diet	Treatment of clinically active disease and maintenance of remission	Includes specific quantities of fruits, vegetables, wholegrains, olive oil, fish, poultry, dairy, legumes, red meats and sweets. No exclusions beyond limited sweets and red meat	Modulation of foods proposed to have an anti-inflammatory effect could correct dysbiosis in intestine, reduce adipose tissue, and improve steatosis of liver	71-78%	A (n=142)	Uncontrolled cohort study[112]
CD & UC	Autoimmune protocol (Paleolethic diet)	Treatment of active disease	Includes daily bone broth, fermented foods, non-starchy vegetables, sweet potatoes, all fruit, meat, chicken, pork, eggs, fish and seafood, nuts and seeds, all fats including coconut products. Excludes wholegrains, gluten, refined sugar, legumes, alcohol, coffee	Modulation of proposed inflammatory dietary components to treat active inflammation in the intestine	40-86%	A (n=15)	Uncontrolled cohort study[113]

UC	Low fat, high fibre diet	Maintenance of clinical remission	Increase fruits, vegetables, grains in preference to other foods. No specific exclusions	Modulation of dietary fat and fibre proposed to have an anti-inflammatory effect	100%	A (n=17)	Parallel crossover study[114]
UC	Low sulphur diet	Remission induction and maintenance of histological remission	Include foods with a low sulphur content including unlimited complex carbohydrates, fats sugars, fruit, specific vegetables, and protein sources with purported low sulphur amino acid content including fish, skim milk, chicken. Reduced red meat. Excludes eggs, cheese, full cream milk, nuts, cruciferous vegetables, foods/drinks with sulphate/sulphite food additives.	Modulation of sulphur-containing foods proposed to reduce sulphide production and metabolism at the colonic-luminal interface	100%	A (n=4)	Uncontrolled cohort study[115]

UC	No-carrageenan diet	Maintenance of clinical remission	Whole foods, unrestricted diet beyond avoiding any foods containing carrageenan food additive followed by rechallenge of carrageenan	Highly-sulphated polysaccharide induces intestinal inflammation and histopathology similar to UC	100%	A (n=12)	RCT rechallenge study[85]

Diet to treat functional-like symptoms in quiescent disease

Approximately 30-40% of individuals with IBD will suffer from concurrent functional gut symptoms.[116, 117] The Low FODMAP diet (fermentable oligo-, di-, mono- and polyols diet) is established as a diet therapy for irritable bowel syndrome. In individuals with IBD, the low FODMAP diet can also lower functional symptom burden, particularly in quiescent disease, but has not been shown to alter inflammatory markers such as faecal calprotectin.[118, 119] The low FODMAP diet temporarily restricts a range of carbohydrates and prebiotic fibres. There are nutritional risks associated with protracted use of this diet therapy in IBD. This includes instituting a diet restrictive in nature in people who already modify other areas of their diet, which could lead to an overly restrictive diet.[120] The potential clinical implications of this include reducing the abundance of gut microbes including immune-regulatory and fructan-degrading Bifidobacteria and SCFA-producer *Faecalibacterium prausnitzii*.[119] Moreover, attempts to follow multiple pieces of dietary advice has been associated with poorer FRQoL in people with IBD.[121]

There are also a vast array of diets lacking any scientific evidence and improvement in objective markers of inflammation available on the internet with claims to improve IBD inflammation and symptoms. Most are restrictive in nature and lack a plan for food re-introduction. These diets tend to encourage long-term restrictive eating behaviour which may increase the risk of dietary inadequacy and associated nutrition-related complications.[122] Furthermore, many of these diets restrict dietary fibre by the exclusion or restriction of complex carbohydrates and wholegrains, fruit, vegetables, legumes and nuts, which may predispose an inadequate fibre intake.[63]

Diet to manage nutritional complications of disease

Beyond the role of diet in disease pathogenesis, CD and UC can have significant impact on nutritional status. People with IBD are already predisposed to nutritional inadequacy during periods of active disease and inflammation by underlying mechanisms including intestinal malabsorption and endogenous losses of nutrients, catabolism and appetite suppression.[123] Restrictive diets may pose additional long-term nutritional risks. These include iron and vitamin B12 deficiency, low calcium intakes and bone disease, low body mass index, malnutrition, and more recently trends in overweight, obesity and sarcopenia.[124-126] Those with more complex disease may also experience electrolyte disturbances and dehydration associated with surgical resection, altered gut anatomy or severe diarrhoea.[123, 124]

Despite the inherent risks of malnutrition in IBD, there is limited data to inform disease-specific nutritional recommendations.[65, 127] Accordingly, recommended energy intakes are similar to a healthy population; 20-30kcal/kg ideal body weight (IBW) for quiescent and active disease. Protein

requirements for quiescent disease are recommended as 1g/kg IBW, increasing to 1.2-1.5g/kg IBW in active disease due to the proteolytic catabolic response to inflammation.[127] However, the evidence for such recommendations are framed from trauma and paediatric CD studies. Hence, an individualised nutrition prescription should take account of disease phenotype, activity, location and anatomy, nutritional status and personal dietary beliefs and behaviours. Dietary recommendations should be tailored accordingly to prevent or treat avoidable nutritional complications.[1, 127]

Nutritional complications and disease outcomes

Poorer nutritional status is associated with poorer clinical outcomes in IBD. Malnutrition is an important indicator of disease activity and is associated with increased in-hospital mortality and poorer IBD prognosis, including more frequent, longer hospital admissions with complications of compromised immune function and infection, and poorer QoL.[128, 129] The presence of sarcopenia is predictive of intestinal resection and surgical morbidity, including delayed wound healing, post-operative sepsis, deep vein thrombosis and increased length of hospital admission.[130, 131] Low lean body mass and sarcopenia independently predict osteopenia and osteoporosis which has important clinical implications for a patient-group susceptible to poor bone health and spinal fractures from steroid use, and low bone mineralisation from inadequate calcium and vitamin D.[132-134]

Diet affects quality of life in IBD

Dietary beliefs and dietary behaviours

Beyond disease pathogenesis, symptom control and nutritional complications, diet represents much more to people with IBD. Diet is reported as the most important psychosocial need affected by IBD yet is often overlooked in consultations with health professionals.[135-137] Many people with IBD believe diet and IBD are interrelated and perceive diet to be either an initiating and/or perpetuating factor in disease course.[125, 138] Dietary beliefs inform dietary behaviours. Subsequently, many patients will modify their diet in response to disease-related symptoms, commonly by avoidance or restriction of particular foods or food groups.[120, 139]

Unfortunately less than 20% of patients reportedly receive formal dietary information to guide food choices soon after diagnosis of IBD.[140] Patients report a lack of access to dietetic support, let alone dietitians trained in IBD, with observational data suggesting 9-48% of people with IBD have seen a dietitian.[141, 142] General dietary advice, often gleaned from internet-based resources lacking scientific rationale, can be conflicting and lacks an individualised approach to disease phenotype, location, disease activity and symptoms.[140, 143, 144] This leaves people with IBD vulnerable to dietary misconceptions, misinformation and to potentially harmful dietary behaviours. These dietary

behaviours are likely to have important nutritional, clinical and psychosocial implications by influencing dietary adequacy and quality, increasing nutritional risk and compromising the pleasures of eating.

Food-related quality of life

The influence diet has on QoL in IBD is a neglected area of research despite diet being a topic of such significance to patients.[98] Food-related quality of life (FRQoL) encompasses the psychosocial impact of eating and drinking with IBD. A deeper understanding of the interaction between dietary beliefs, behaviours and QoL of people with IBD by exploring FRQoL may assist with targeted dietary counselling, promote adherence to diet therapy and prevent avoidable nutrition-related complications. FRQoL has not yet been measured as an outcome of dietary intervention studies however could be a useful marker of whether defined diet therapy has a positive influence on beliefs, behaviour and QoL.

Diet-related research priorities for IBD

The relationship between diet and IBD is multidimensional and complex. Diet has been identified as an international research priority by patients and health professionals (***Figure 2.2***).[145, 146]

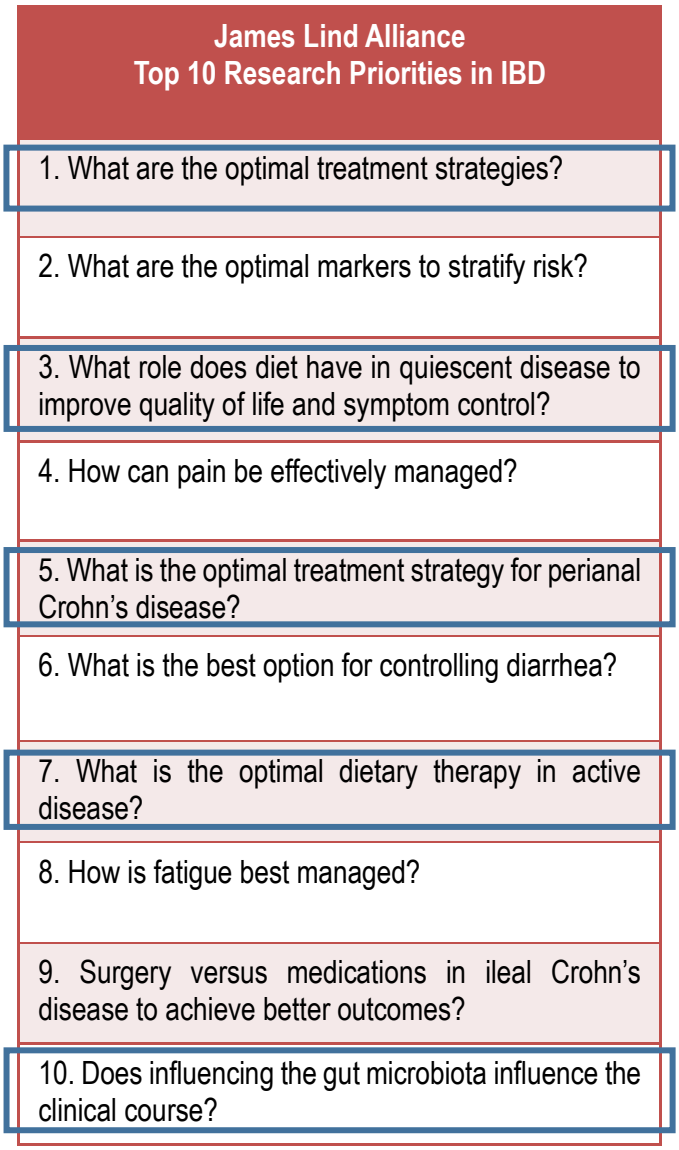

Figure 2.2 Top IBD research priorities highlighting key knowledge gaps including diet in the treatment and management of IBD.

Legend: *Adapted from the top 10 research priority areas for Inflammatory Bowel disease, James Lind Alliance priority setting partnership, 2017.*[145]

As discussed earlier, existing IBD treatment paradigms are not wholly effective and many questions remain unanswered, including the role of diet in treating active disease and the influence of diet on QoL. There is also renewed interest in the involvement of the gut microbiota in IBD pathogenesis and the influence of microbial manipulation on the clinical course of CD and UC.

2.3 The gut microbiota as a therapeutic target in IBD

Therapeutic focus has shifted from modulating the immune response toward microbial manipulation in IBD. While a cause-effect relationship has not yet been established between CD or UC and specific microbes or consortia, modulation of the gut microbiota including FMT and specific diet therapies have shown efficacy for both.[25, 105, 147]

Characterising a healthy gut microbiota

Important features of a healthy gut microbiota

The optimal composition of the human gut microbiota remains largely undefined. Existing compositional and functional profiling of the gut microbiota in healthy individuals provides the fundamental basis for characterisation of gut 'dysbiosis' in disease states.[148] Limitations to this include the significant degree of variation in taxonomy observed in healthy individuals, purported to be influenced by ethnicity, sex, age, diet and health status, and it is likely a significant degree of human gut bacterial diversity with unique functional profiles still remains uncultured.[148-150] Despite this, current evidence suggests important taxonomic features of a healthy gut microbiota include a high taxonomic diversity and a high microbial gene richness.[148]

Influences on the gut microbiota

The development of a healthy microbiota is proposed to be shaped by early life influences including mode of birth, breastfeeding and the introduction of diet.[151] Development and stability of the gut microbiota is reliant on the metabolic cross-feeding of endogenous and dietary substrate. Specific organisms will ferment and degrade substrate to produce essential metabolites for use and survival of other organisms.[151] The colon is the primary site for fermentation with a region-dependent pH gradient which assists in maintaining a diverse and rich ecological balance of phyla, which includes Bacteroidetes, Firmicutes and Proteobacteria.[23, 152]

Key functions of the gut microbiota

Key functions of a healthy gut microbiota are proposed to include maintenance of intestinal barrier function and immune system development through commensal bacteria competitively inhibiting the colonisation of pathobionts. SCFA production and metabolism, primarily through degradation of complex carbohydrates, is another key role along with biosynthesis of vitamins and essential amino acids, promotion of intestinal angiogenesis, promotion of fat storage and modulation of the central nervous system.[148, 151, 153] Taxonomic changes within the gut microbiota are associated with subsequent alterations to these key metabolic functions with functional consequences (***Table 2.3***).

Table 2.3 Functional profiling of key organisms in the gut microbiota of people with IBD

Phylum	Family	Species	Taxonomic shift	Benefit to host	Metabolic function influenced by microbial expansion or reduction
Firmicutes	Lachnospiracae	*Roseburia hominis*	↓ UC	Beneficial	Fibre degradation and butyrate metabolism[20, 34, 154]
		Anaerostipes spp.	↓ CD & UC	Beneficial	Butyrate production[20]
	Ruminococcaceae	*Butyricicoccus spp.*	↓ CD & UC	Beneficial	Fibre degradation and butyrate metabolism[20, 34, 154]
	Clostridiaceae	*Faecalibacterium prausnitzii*	↓ CD & UC	Beneficial	SCFA & butyrate metabolism, anti-inflammatory properties[20]
		Ruminococcus gnavus	↑ CD & ↓ UC	Pathobiont	Production of cytokines, integrity of barrier function, down-regulation of SCFA[18, 19, 33]
		Clostridium clostridioforme	↑ CD	Pathobiont	Production of cytokines, integrity of barrier function, down-regulation of SCFA[18, 19, 33]
	Enterococcaceae	*Enterococcus faecalis*	↑ UC	Pathobiont	Pro-inflammatory specie; induces mucosal injury[155]
Bacteroidetes	Bacteroidaceae	*Enterotoxigenic Bacteroides fragilis*	↑ CD & UC	Pathobiont	Pro-inflammatory cytokine production, oxidative stress tolerance, epithelial cell function [20, 156]
		Bacteroides fragilis	↓ CD & UC	Beneficial	Anti-inflammatory specie; regulation of T-cells and immune system[20, 157]
		Bacteroides coprophilus	↓ UC	Beneficial	SCFA metabolism[147]
Proteobacteria	Desulfovibrionaceae	*Desulfovibrio spp., Desulfuromonas spp*	↑ CD & UC	Pathobiont	Production of H_2S, toxic metabolite, ↓ butyrate metabolism, immune system disruption [20, 36]
	Pseudomonadaceae	*Pseudomonas spp.*	↑ CD	Pathobiont	Epithelial cell damage[20]
	Enterobacteriaceae	*pks+ Escherichia coli*	↑ CD & UC	Pathobiont	Adherent-invasive mucosa-associated organism; DNA damage [158]
		Escherichia coli	↑ CD	Pathobiont	Adherent-invasive species; production of pro-inflammatory cytokines including TNF-α, down-regulates expression of SCFA[18, 19, 33]

		Salmonella spp.	↑ CD	Pathobiont	Adherent-invasive species, immune system disruption[20]

The influence of active inflammation on the gut microbiota

The influence of active inflammation on taxonomic changes in IBD is less clear. Discrepancies between endoscopic and histological classification of active disease, location of mucosal sampling and differences in mucosal versus faecal microbial sampling limits the findings and interpretation of existing microbial analyses.[30] In CD, there does not appear to be a significant difference in taxonomy between inflamed versus non inflamed segments of the bowel and those with quiescent versus active disease.[19, 159] However in UC, abundance of pathobiont families Enterobacteriaceae and Desulfovibrionaceae, Bacteroides genus, and *Enterococcus faecalis* species are positively associated with clinical and endoscopic disease severity.[160] Beyond inflammation, the taxonomic and functional shifts observed in the microbiota of people with IBD also appear to be influenced by other confounding factors including disease duration, pharmacological therapies, diet and endogenous substrate.[161]

Gut microbial manipulation as therapy in IBD

The compositional shifts away from the microbiota of healthy individuals and associated functional consequences (***Table 2.3***) support the notion of gut microbial manipulation as a therapeutic avenue in IBD whereby microbial-targeted therapies would encourage a higher biodiversity and abundance of beneficial organisms.[25, 148]

Microbial shifts associated with conventional IBD therapy

Many existing 'immunocentric' conventional IBD therapies are associated with significant microbial shifts yet the influence of these changes on therapeutic efficacy remain largely unexplored. IBD therapies are modulated into inactive compounds by enzymes metabolised by the gut microbiota. It is therefore plausible the gut microbiota can influence the efficacy of pharmacological therapies.[162] There are differences in microbial diversity and abundance observed between those who respond to pharmacological IBD therapy versus those who do not.[25] For example, clinical response to aminosalicylates and thiopurines are associated with increased biodiversity of Firmicutes and Bacteroidetes phyla with concurrent changes in luminal PH observed.[162, 163] Moreover, during induction of anti-TNF-α therapy, compositional shifts toward the microbial signature of the healthy controls is observed.[164] These microbial shifts and subsequent association with therapeutic efficacy may also be influenced by availability of fermentable dietary substrate and the effect different fibres have on intestinal transit times as well as luminal PH.[165]

Antibiotic therapy

Conventional antibiotic therapy is used in cases of mild-moderately active CD and perianal or fistulising disease with varying levels of therapeutic efficacy. The theoretical mechanism is decreasing potentially pathogenic and pro-inflammatory bacteria or decreasing overall bacterial density however it is also likely broad spectrum antibiotics will deplete beneficial organisms with unintended functional consequences.[1, 25, 31] In UC, small studies have shown that several oral antibiotic therapies are efficacious at inducing remission, however these are not routinely recommended due to the risk of antibiotic resistance and colonisation of pathogenic species.[31, 166]

Probiotic therapy

Probiotics are purported to actively inhibit the colonisation of pathobionts in IBD thereby strengthening the intestinal barrier and modulating the immune response, however they do not have a therapeutic effect in CD.[167, 168] In UC, two probiotics have shown therapeutic efficacy. VSL#3 appears to be effective at inducing remission in active UC and comparable to 5-ASAs in preventing disease relapse.[167] *Escherichia coli Nissle* 1917 probiotic also shows comparable efficacy to Mesalazine therapy in maintaining remission in UC.[169]

Surgical diversion of faecal stream

Surgical diversion of the faecal stream to an ileostomy can often improve severe or refractory ileocolonic and perianal CD.[1, 31, 170, 171] In ileocolonic and perianal disease, clinical response is observed in up to 64%. However, disease reoccurrence rates of 83% are reported after bowel continuity is restored which may indicate an association between luminal content and inflammation.[171] Conversely, diversion of the faecal stream can also be colitogenic through modulation of essential SCFA metabolism required for healthy colonocytes.[25]

Faecal microbiota transplantation

Faecal microbiota therapy (FMT) is emerging as a potential therapy in UC.[147, 172] FMT involves transferring faecal matter from one or multiple healthy people to a recipient with the aim of treating disease.[173] The proposed mechanistic action is to manipulate the colonic microbiota and restore microbial balance with a higher biodiversity of species which will perform vital metabolic functions of a healthy microbiome.[147, 172] In meta-analysis of randomised controlled trials using donor FMT as therapy in UC, superior clinical remission and clinical response rates were observed compared to placebo (Remission: 28%; Placebo: 9%; $p<0.01$; Clinical response: 49%; Placebo: 28%; $p=0.02$).[172] Limited experimental data suggest FMT may also induce a clinical response in active CD, however, this association requires further validation.[174]

More recently, higher rates of remission (38% versus 9%; p=0.03) were achieved using a 3-dose, 1-week induction course of anaerobically prepared pooled donor FMT with sustained remission rates of 42% at 12 months.[147] The higher rates of efficacy are proposed to be related to a greater biodiversity of anaerobic organisms and abundance of Firmicutes, Bacteroidetes and Actinobacteria phyla, Anaerofilum pentosovorans from the Clostridum genus and SCFA-producer *Bacteroides coprophilus* species. Pooled donor FMT is presumed to have a higher biodiversity of species compared to autologous FMT, and oxygen-sensitive viable anaerobes such as *Faecalibacterium prausnitzii* and *Bacteroides coprophilus* are more likely to be preserved through anaerobic preparation.[172] Given diet directly influences microbial diversity and composition in healthy individuals, it remains unknown whether dietary substrates have a key role in augmenting FMT. No studies have also assessed the potential influence of habitual diets of both donor and recipient on engraftment of FMT, highlighting an important area for future research.[64, 173]

Microbial shifts associated with diet therapy

Diet therapy for CD

EEN therapy is associated with compositional shifts in the gut microbiota including decreased abundance of Firmicutes, Bacteroides, Proteobacteriaceae and *Faecalibacterium prausnitzii* species and increases in Bacteroidetes.[175, 176] The mechanistic action of EEN remains unclear but is hypothesised to positively modulate the luminal environment and gut microbiota by minimising the exposure of gut bacteria to food antigens through food exclusion and subsequently downgrading the inflammatory response.[25, 175] Intriguingly, the therapeutic effects of EEN are associated with a shift toward a less diverse microbiota than healthy controls. Active CD is also associated with reduced microbial diversity. This illustrates a contrasting association between lower biodiversity and treatment of inflammation in active CD and raises important questions regarding how and why further reduction in biodiversity treats inflammation and conversely, whether reduced microbial diversity has negative implications.[175, 176] It also raises the question of whether microbial diversity is important or perhaps there is another mechanism that has not been identified yet.

More recently, two experimental whole-food diet therapies have been examined in children with active luminal CD, with signals of therapeutic efficacy associated with potentially beneficial taxonomic changes.[106, 107] The Crohn's Disease Exclusion Diet with 50% partial enteral nutrition (CDED) had similar rates of clinical remission at week 6 compared to EEN (CDED: 80% vs. EEN: 73.5%; p=0.51) but superior tolerability (CDED: 97.5% vs. EEN: 73.6%; p=0.02) and rates of clinical remission (CDED: 75.6% vs. EEN: 45.1%; p=0.01) at week 12.[106]

Key taxonomic changes observed with CDED and EEN included an initial expansion of beneficial Clostridia genus (Firmicutes) and a reduction in Actinobacteria and Proteobacteria phylas with both therapies at week 6. By week 12, further expansion of Clostridia was observed with CDED with a minor, non-significant rebound observed in the EEN group whom resumed an unrestricted habitual diet. A rebound in Actinobacteria and Proteobacteria toward baseline taxa was observed with resumption of a habitual diet in the EEN group however re-introduction of food items in CDED phase two (weeks 7 to 12) sustained the reduction in Proteobacteria and Actinobacteria. These findings suggest both EEN and a food exclusion diet initially expands the abundance of Clostridia genus with concurrent reduction in the abundance of Proteobacteria and Actinobacteria and is associated with clinical remission. However, resumption of an unrestricted diet appears to encourage a degree of dysbiosis and a significant reduction in therapeutic efficacy, whereas an expansion of fibrous foods and animal protein in CDED phase two was not associated with dysbiosis but instead sustained therapeutic efficacy.[106]

The other whole food diet therapy is the Crohn's Disease Treatment with EATing diet (CD-TREAT).[107] This novel pilot study examined the tolerability and metagenomic shifts associated with a whole food diet compared to EEN in healthy adults and rats. Then clinical response and remission rates following the whole foods CD-TREAT diet were observed in children with active luminal CD. Similar therapeutic efficacy to CDED was reported (Clinical response: 80%; Clinical remission: 60%). CD-TREAT was also confirmed to have superior tolerability to EEN and induced compositional and functional shifts in the gut microbiota of healthy adults and rats comparable to EEN. These included a similar shift in β-diversity in adults and a higher Shannon α-diversity with a similar relative abundance of genera were replicated in both EEN and CD-TREAT compared to standard chow in rats.[107]

The therapeutic effects and microbial shifts observed using whole food diet therapies as an alternative to EEN is intriguing. These studies signal the potential of using a whole foods diet as adjunctive or primary therapy for active CD beyond EEN. However, the mechanistic action of these diet therapies and EEN remains poorly understood and evaluation of the therapeutic efficacy remains limited by a lack of objective endoscopic and histological markers of disease activity after therapy. It is also unclear which dietary components are most influential over the taxonomic shifts observed, if any, and whether these microbiota changes are drivers of downgrading inflammation or a consequence of other metabolic processes. [175]

Diet therapy for UC

In comparison to CD, there have been few defined diet therapies for UC that evaluate compositional and functional shifts in the gut microbiota. One single-blind study in mildly active and quiescent UC

patients examined a low-fat higher fibre diet (total fat: 20g/d; total fibre: 25g/d) versus an improved standardised American diet (total fat: 71.5g/d; total fibre: 18g/d) and observed maintenance of remission during the 4-week cross-over study. Additionally phylum-level increases in carbohydrate-degrading Bacteroidetes and increases in the abundance of *Faecalibacterium prausnitzii* were also observed with the intervention diet.[114] Beyond this, experimental research into diet as therapy in UC has predominantly focused on individual dietary components, including supplementing with dietary fibres.[68] These dietary components are associated with compositional and functional shifts in the colonic microbiota.[177]

Germinated barley, rich in resistant starch and likely oligosaccharides, supplemented to habitual diet at 20-30g/d was associated with clinical and endoscopic disease improvement at 4 weeks in mild-moderate UC. An increased abundance of Bifidobacterium, butyrate-producing *Eubacterium limosum*, and a reduction in Bacteroides pathobionts was also observed with increased faecal butyrate concentrations.[67, 178] Germinated barley 20g/d was also associated with sustained remission in patients with UC who were tapering corticosteroids, compared to a control group with no adverse side effects reported.[179]

Supplementing with 15g/d of oligofructose-enriched inulin has been associated with an increased abundance of fibre-degrading Lachnospiraceae and Bifidobacteriaceae organisms. Clinical and endoscopic disease activity decreased and was negatively associated with increases in faecal butyrate production at week 9.[71] Reductions in inflammatory biomarkers at day seven were also observed in another RCT trialling 12g/d oligofructose-enriched inulin in patients with active UC.[72] On the other hand, psyllium had equivalent rates of preventing relapse to mesalamine when habitual diet was supplemented with 20g/d and increased production of faecal butyrate was observed.[180] Other studies have shown psyllium also improves gastrointestinal symptoms in quiescent disease in the absence of measuring disease activity.[68] Similarly, 60g/d of oat bran was associated with sustained remission at three months in quiescent UC and a 36% increase in faecal butyrate concentrations compared to controls without any increased gastrointestinal symptoms reported.[69]

Two prospective observational studies have associated the consumption dietary sulphur-containing amino acids and sulphates with rates of relapse and length of remission in UC.[74, 181] A single, small, uncontrolled study trialled a low sulphur diet in patients with active UC and observed sustained clinical and histological remission at 52 months in all participants.[181] In a prospective cohort examination of patients with quiescent UC, a higher consumption of red and processed meats, alongside dietary sulphur and sulphates from fruit and nuts were associated with increased rates of relapse.[74] Studies have also examined the effects of carrageenan, a highly sulphated polysaccharide used as an

emulsifier. A small randomised controlled trial compared a carrageenan-supplemented diet to a non-carrageenan diet and observed increased rates of relapse in UC with carrageenan supplementation.[85] Similar observations are made in animal models.[84, 182] While none of these studies examining dietary sources of sulphur explored microbial end points, the clinical observations are consistent with the clinical findings of studies that also observe an increased abundance of sulphate-reducing bacteria in active UC.[22, 36, 183]

Collectively, the growing body of experimental data implicates microbial metabolites of dietary carbohydrate and protein fermentation as a target for therapeutic manipulation in UC. Pre-clinical experimental data in animal models and cell lines support this theory.[177] However, these data is yet to be translated into a whole-food diet therapy for UC.

2.4 Summary and research gaps

In summary, much remains to be understood regarding the role of diet in IBD, particularly in the emerging area of diet therapy, microbial manipulation and strategies to improve QoL, particularly those associated with the psycho-social aspects of food. Many people with IBD believe that diet and disease are interrelated and that diet can be used to treat disease. However, self-initiated dietary modifications in the absence of robust evidence may lead to harmful dietary behaviour in the longer-term, negatively influence QoL and may increase the risk of poorer clinical outcomes if nutritional status becomes compromised.

Diet therapy for UC is an under-researched area in comparison to CD despite a growing body of observational and experimental data proposing the pathogenesis of UC may in fact be a sequelae of interactions occurring between dietary substrates, the gut microbiota and colonic epithelium. Collectively, as summerised in ***Figure 2.3*** this presents an exciting avenue for diet research.

2.5 Research question

Rationale

The relationship between diet and IBD is multidimensional and complex. Diet is implicated as an environmental factor in disease pathogenesis yet the interaction between dietary factors and induction and/or perpetuation of mucosal inflammation is poorly understood. People with IBD report modifying their diets in response to symptoms however the clinical, nutritional and psychosocial impact of these dietary behaviours are underexplored.

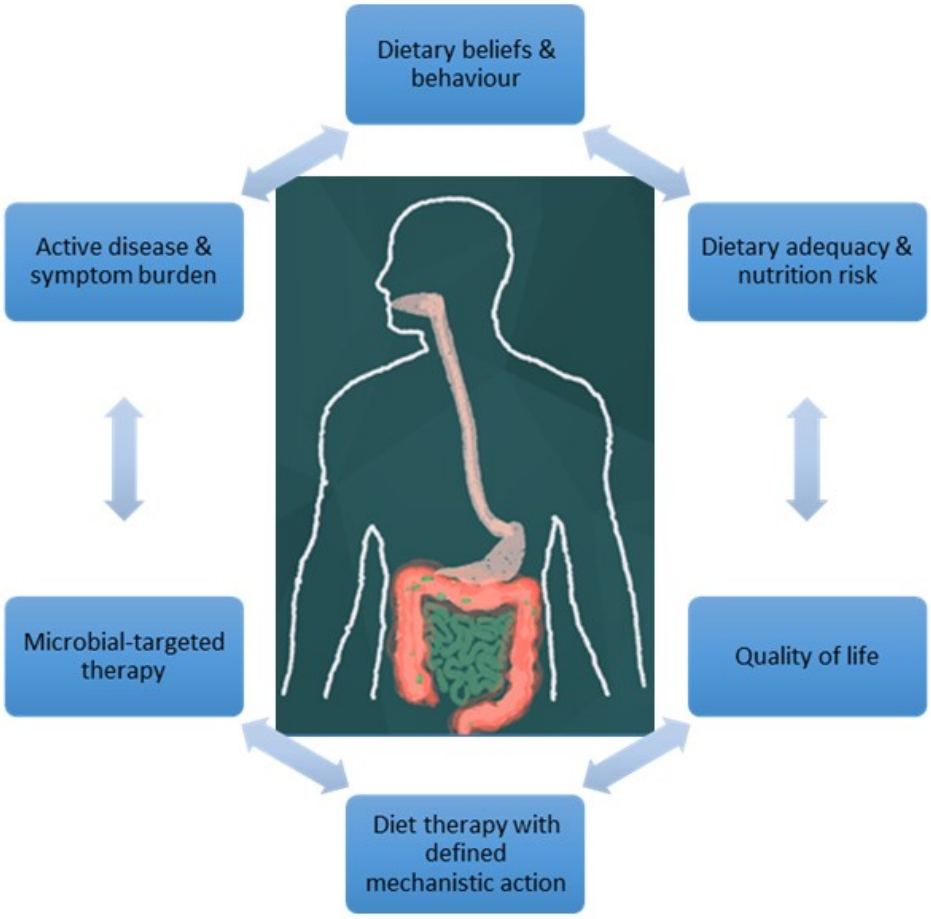

Figure 2.3 Diet-related research gaps in inflammatory bowel disease.

Aim

The overarching aim of this thesis is to explore the dietary behaviours of people with IBD and examine the interrelationship between diet and QoL, and to examine the potential utility of a multi-dimensional diet therapy with defined mechanistic action in UC.

Research objectives

The objectives of this research are to:

1. Examine the dietary beliefs of people with IBD, explore food avoidance or restrictive dietary behaviours and their associations with QoL.
2. Examine the adequacy of habitual dietary fibre intakes of people with IBD and identify factors associated with fibre intake.
3. Characterise and identify any patient or disease-related predictors of FRQoL in people with IBD

4. Investigate the tolerability of a sulphide-reducing diet as therapy in people with mild-moderately active UC and the influence on disease activity, bacterial fermentation and patient-reported outcomes including FRQoL
5. Explore whether a sulphide-reducing diet therapy can augment and sustain the efficacy of FMT in active UC

Research process

Several studies were conducted to address the overarching aim set out for this thesis. The research undertaken can be broadly divided into three inter-related research streams along with a scoping review and systematic review:

1. The first research project involved a cross-sectional evaluation of FRQoL in people with IBD and examined patient and disease-related predictors of FRQoL including food avoidance and restrictive eating behaviours.
2. The second research project prospectively examined the tolerability of a multi-dimensional whole-food, sulphide-reducing diet as therapy for mild to moderately active UC, potential effects on clinical indices, FRQoL, and markers of colonic fermentation.
3. The third research project involved an in-depth two-part case series examining whether a sulphide-reducing diet therapy could augment and sustain the efficacy of FMT in people with refractory UC, including functional metagenomic analysis.

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CHAPTER 3

Food avoidance, restrictive eating and quality of life in inflammatory bowel disease: a systematic scoping review

Published in *Appetite*

August 2021

CHAPTER 3: Dietary beliefs, behaviour and quality of life

Background

Dietary modification is common in people with inflammatory bowel disease (IBD). Access to IBD-specific dietary information or an experienced dietitian for individualised dietary advice is poor.[1] A lack of evidence-based dietary guidance increases the vulnerability and susceptibility of individuals with IBD to internet-based information lacking scientific credibility, and increases the risk of self-directed elimination diets as many believe diet and IBD are interrelated.[2] A lack of adequate support to manage diet during periods of active inflammation or symptoms associated with quiescent disease may be leading to protracted use of highly restrictive elimination diets or food avoidance behaviours.[3]

A greater understanding of the dietary beliefs and behaviours that drive habitual dietary patterns is essential to further an understanding of how diet and IBD may interrelate and to identify areas where earlier dietary counselling could prevent avoidable nutrition-related complications.[4, 5] Furthermore, less is known of how diet affects quality of life (QoL) for those with IBD and whether a positive relationship with food and well-being is being maintained.

The systematic scoping review presented in ***chapter 3*** therefore explores what is known about the dietary beliefs held by individuals with IBD and what informs these beliefs. Potentially harmful dietary behaviours such as food avoidance and restrictive eating are examined and potential risk factors for developing these behaviours are evaluated. The relationship between diet and QoL is examined to determine what is known on this topic.

Statement of authorship

Title of Paper	Food avoidance, restrictive eating behaviour and association with quality of life in adults with inflammatory bowel disease: a systematic scoping review.
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Day AS, Yao CK, Costello SP, Andrews JM, Bryant RV. Food avoidance, restrictive eating behaviour and association with quality of life in adults with inflammatory bowel disease: A systematic scoping review. Appetite. 2021 Dec 1;167:105650. doi: 10.1016/j.appet.2021.105650. Epub 2021 Aug 12. PMID: 34391842.

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Contribution to the Paper	Study concept, study design, literature review, data synthesis and interpretation, drafting of manuscript, corresponding author for journal.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

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Signature		Date	21/010/21

[Manuscript 1]: Food avoidance, restrictive eating behaviour and association with quality of life in adults with inflammatory bowel disease: a systematic scoping review.

Short title: Restrictive eating behaviour in IBD

Key words: Inflammatory bowel disease, dietary behaviour, quality of life

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Disclosure of funding

This work was supported by a Commonwealth Research Stipend administered by University of Adelaide, Australia to ASD as part of a post-doctoral degree.

Conflicts of interest disclosure: none.

There are no conflicts of interests to declare for this study. Here each author has outlined their declarations however none relate to the study design, interpretation of data or writing of the manuscript: ASD has received speaking fees from AbbVie and Chiesi (all paid to employer for research support). CKY has received research support for investigator-driven studies for Ferring Pharmaceuticals, Danone and Yakult Australia. Her department, Department of Gastroenterology, Monash University receives royalties from the sale of The Monash University low FODMAP Diet App. SPC has received advisory, speaking fees or research support from Ferring, Microbiotica, Janssen. Shareholding: BiomeBank. JMA has received speaker's fees, research support, been on advisory boards (all paid to employer for research support) from Abbott, AbbVie, Allergan, Anatara, AstraZeneca, Bayer, Celegene, Celltrion, Ferring, Gilead, Hospira, Immuninc, ImmunsanT, Janssen, MSD, Nestle, Progenity, Pfizer, Sandoz, Shire, Takeda, Vifor, RAH Research Fund, The Hospital Research Fund. RVB has received Grant/ Research support/ Speaker fees (all paid to employer for research support): AbbVie, Ferring, Janssen, Shire, Takeda, Emerge Health.

Data availability statement

The data underlying this scoping review are available within this article, complete with references.

Ethical statement

This study did not require ethics approval as is a systematic scoping review, which synthesises existing peer-reviewed, published data and did not involve human or animal subjects.

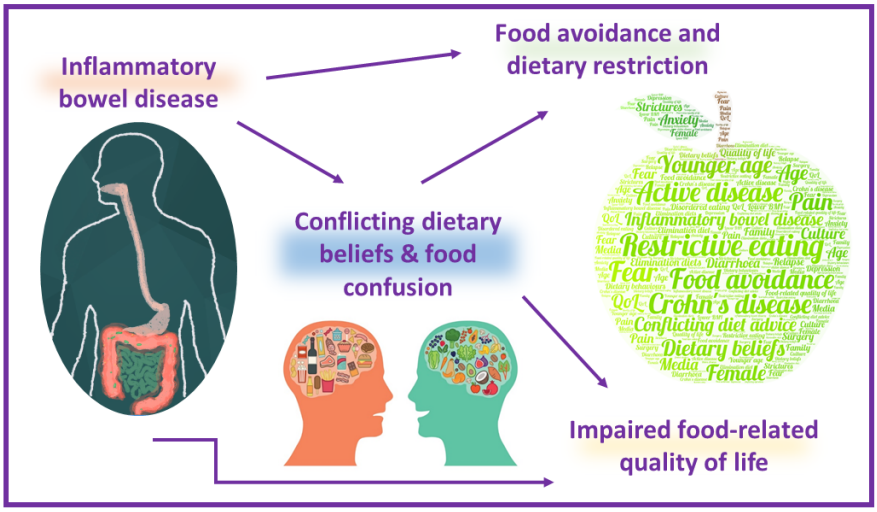
Brief summary

Individuals with IBD believe diet and IBD are interrelated, subsequently dietary modification is common.

The results of this scoping review identify numerous knowledge gaps including:

Food avoidance and restrictive dietary behaviours appear to be highly prevalent in people with IBD. Validated instruments are required to confirm these observations, compare these reported behaviours to habitual dietary intake and examine the influence this has on QoL and nutritional outcomes in IBD.

Graphical abstract



Abstract

Background: Dietary misconceptions and behaviours may worsen outcomes of IBD. This scoping review aims to examine the dietary beliefs and behaviours of individuals with IBD and identify evidence of food avoidance, dietary restriction or disordered eating and any association with QoL.

Methodology: A systematic search of CINAL, EMBASE, MEDLINE was conducted. Primary, peer-reviewed studies in English examining dietary beliefs and dietary behaviours or diet and quality of life in adults with IBD were included. Key dietary terminology was pre-defined.

Results: Twenty-nine studies met inclusion criteria. A range of quantitative self-reported questionnaires (16/29), qualitative interviews (1/29) and mixed methods (7/29) were used to measure dietary beliefs and dietary behaviours. A high prevalence of food avoidance (28-89%) and restrictive dietary behaviours (41-93%) were identified. Factors associated with these behaviours included a diagnosis of Crohn's disease (CD), perceived active disease, female sex, dietary misinformation, and fears of adverse bowel symptoms. Diet and QoL remains largely unexplored in IBD beyond two recent studies demonstrating impairment of food-related quality of life (FRQoL) in IBD.

Conclusion: A high prevalence of self-reported food avoidance and restrictive dietary behaviour exists in people with IBD. The psychosocial impact of IBD-related dietary behaviour is poorly understood. Validated tools with predefined diet terminology and objective markers of disease activity are required to measure dietary behaviour in future prospective studies, using FRQoL as an outcome measure.

3.1 Background / rationale

IBD namely CD and ulcerative colitis (UC), are chronic gastrointestinal diseases of relapsing and remitting nature, characterised by inflammation of the gastrointestinal tract.[6, 7] Periods of active disease and inflammation predispose individuals with IBD to nutritional inadequacy via mechanisms including intestinal malabsorption and endogenous losses of nutrients, catabolism, surgical resection, and appetite suppression with associated insufficient dietary intake.[8] Moreover, many individuals with IBD modify their diet to manage disease-related symptoms, commonly by avoidance or restriction of particular foods or food groups.[2, 9]

Food anxiety and avoidance of foods perceived to cause gastrointestinal symptoms present significant challenges in IBD dietary counselling to ensure diets are nutritionally adequate, particularly as the optimal diets for CD and UC remain unclear. Dietary beliefs are often influenced by past or anticipated gastrointestinal experiences and can be perpetuated by dietary misinformation or a lack of individualised dietary advice, particularly as less than 20% receive formal education after diagnosis.[10, 11] The psychosocial pleasures and enjoyment of eating are at risk of being diminished by anxiety-driven dietary beliefs or behaviours.[8, 12] Existing diet therapies such as exclusive enteral nutrition and Crohn's disease exclusion diet for treating active inflammation in CD and the low fermentable oligo-, di- monosaccharide and polyol (FODMAP) diet for managing functional symptoms in IBD are based on the principles of short-term food exclusion or dietary restriction to achieve therapeutic efficacy.[13, 14] However, the complex nature of these exclusion diets leave people with IBD vulnerable to prolonged dietary restriction if adequate support is not provided by an experienced dietitian, particularly in the food re-introduction phase.[15]

Particular attention to these dietary vulnerabilities is required as a high prevalence of avoidable nutritional deficits and complications exist within IBD cohorts. These include iron and vitamin B12 deficiency, low calcium intake and bone disease, low body mass index and myopenia, malnutrition, and more recently overweight, obesity and sarcopenia. [4, 16, 17] However, examination of dietary behaviours associated with dietary inadequacy, plausibly associated with poorer clinical outcomes, remain uncharacterised.[18] In other chronic digestive diseases such as coeliac disease, food avoidance and disordered eating symptomology are associated with higher levels of anxiety, depression, poorer medication adherence and poorer QoL.[18-21] This is a largely unexplored area in IBD despite comparable levels of psychological distress and poorer QoL.[12, 22]

Objectives and scoping review question

The objectives of this systematic scoping review are therefore to provide an overview of dietary beliefs and dietary behaviours of individuals with IBD, identify factors associated with food avoidance or

restrictive behaviours, and examine whether an association exists between these behaviours and QoL. This review was guided by previously published methodology and the following review questions:[23]

1. What is known about the dietary beliefs and dietary behaviours of individuals with IBD?
2. Is there evidence of food avoidance, dietary restriction or dietary behaviours disordered in nature that may be potentially harmful?
3. What factors predict or are associated with these dietary beliefs and dietary behaviours?
4. Is there any association of such behaviours with QoL?

3.2 Material and methods

This systematic scoping review was undertaken according to preferred reporting items of systematic reviews and meta-analyses extension for scoping reviews (PRISMA-ScR).[23]

Eligibility criteria

The research question and inclusion criteria were developed using a PICOS framework (Population, Intervention, Comparison, Outcome, Study design).[24] Eligible studies were full text peer-reviewed primary studies, in English, and included adults (≥18 years) with a diagnosis of IBD. Included studies must have investigated dietary beliefs or dietary behaviours, examined influences on eating patterns, food avoidance or dietary restriction, or examined a relationship between diet and QoL (***Supplementary material 3.1***). Dietary intervention studies or studies examining beliefs, behaviour or QoL without reference to diet were excluded. Paediatric studies (participants <18 years old) were excluded as influences of parental dietary beliefs and behaviours were beyond the scope of this review.

Search strategy & selection of sources of evidence

A preliminary electronic search strategy was developed to identify key words and MeSH terms to inform the scoping review search strategy. A systematic search of three electronic databases: CINAL, EMBASE, MEDLINE was then conducted from inception until May 2021 using key words and MeSH terms pertaining to 'inflammatory bowel disease', 'diet', 'behaviour', 'attitude', and 'quality of life' (***Supplementary material 3.2***). Duplicates were removed and titles and abstracts were screened using eligibility criteria to remove non-relevant articles, reviews and abstracts. Additional eligible studies were identified through hand searching reference lists. Full text articles were then screened to confirm eligibility.

Data charting: defining key dietary terminology & synthesising results

Data was charted by reviewer ASD into evidence tables that had been pretested for accuracy of data charting before use. Extracted data items included: year, country of origin, study design, research question, methods of data collection, instruments used to measure dietary beliefs and dietary

behaviours, disease activity and objective measurements, dietary behaviours or patterns, reported avoidant, restrictive or disordered dietary behaviours, reported reasons and influences on dietary beliefs or dietary behaviours, previous dietary education, reporting on QoL in relation to diet.

A quality appraisal of included studies is not common methodology within scoping reviews therefore was not undertaken.[23] Instead, to map and synthesise data, PRISMA-ScR checklist including a flow diagram was used. Variable terminology were used within studies to describe dietary beliefs and dietary behaviours without referenced definitions. Therefore, to categorise dietary behaviours into appropriate domains for synthesis, key dietary terminology was predefined in ***Table 3.1*** using definitions from published psychology and dietary behaviour literature. Data were then categorised accordingly and synthesised from evidence tables to answer the review objective and questions.

Table 3.1 Key terms used in current inflammatory bowel disease literature pertaining to dietary beliefs and dietary behaviours

Key dietary terminology	Definition
Dietary belief	A perception or feeling of certainty a food-related issue or truth exists.[25-27]
Dietary behaviour	An action, mannerism, or conduct relating to diet, food or eating.[25-27]
Food anxiety	Fear of consuming an item of food or drink believed to cause an unwanted or adverse symptom.[18, 28]
Food avoidance	Intentional selective or picky eating to avoid specific food items or food groups believed to have an unwanted or adverse effect if consumed.[29]
Dietary restriction, food restriction or restrictive eating	Intentional limitation or omission of certain foods, food groups, limiting number of calories, following a strict eating plan, or intentional skipping of meals, without a methodological approach or plan to reintroduce or substitute foods appropriately.[20, 30]
Food exclusion or elimination	Prescriptive removal of specific foods or whole foods groups from the diet to investigate perceived food intolerances or a therapeutic benefit.[10, 31]
Disordered eating behaviours	Abnormal and unhealthy eating patterns, which deviate from western cultural norms and can include food avoidance, restriction, exclusion or elimination of certain types of food, fasting, binge eating, or skipping meals.[18, 19, 32, 33]
Eating disorder pathology	Binge eating, purging , unhealthy dieting practices such as skipping meals or extreme dietary restriction, and other unhealthy weight control behaviours such as diet pill use or unhealthy or excessive exercise, and / or attitudinal features of eating disorders measured with valid instruments.[34]
Eating disorder	A mental illness defined by cluster of abnormal eating behaviours that meet diagnostic criteria for an eating disorder. The 5 predominant classifications are anorexia nervosa, bulimia nervosa, binge-eating disorder, eating disorders otherwise not specified, and avoidant restrictive food intake disorder.[19, 35]

Avoidant restrictive food intake disorder	According to the Diagnostic and Statistical Manual of Mental Disorders 5th edition criteria (DSM-5 criteria), this eating disorder is characterised by at least one type of the following eating disturbances; food avoidance due to sensory issues, low appetite/limited interest in eating, or fear of experiencing negative gastrointestinal consequences, and not usually associated with preoccupation with body image.[28, 35]

3.3 Results

The search strategy yielded 371 citations (***Figure 3.1***). Following screening and removal of duplicates, 79 full text articles were assessed for eligibility. From these, 29 primary studies exploring dietary beliefs and/or dietary behaviours of adults (≥18 years) with IBD were included. The studies were published between 2004 and 2021 and included 9696 patients with IBD (CD 4881, UC 3884, IBD-unclassified 18, IBD 913). There was a large degree of heterogeneity between the study design and methods of measuring dietary beliefs and behaviours in the included studies Two thirds (20/29) surveyed dietary beliefs and/or dietary behaviours using heterogeneous self-administered questionnaires without predefined dietary terminology,[3, 16, 25, 26, 32, 36-49] whilst the remaining studies (10/29) used clinician-administered questionnaires and/or semi-structured qualitative interview techniques.[21, 50-58] Only two of 29 studies matched IBD subjects to controls for comparative perspectives on dietary beliefs and dietary behaviours.[21, 32] These two studies also examined disordered eating in IBD using validated tools. No studies used the Nine-item Avoidant / Restrictive eating screening tool to identify food avoidance or restrictive eating.[28] Fourteen studies (48%) reported participants had IBD-specific dietary education from a dietitian, though the extent to which this influenced dietary beliefs and dietary behaviours was not reported.[3, 25, 26, 38-40, 44, 46, 48, 50, 52-54] Only one study examined an association between diet and health-related quality of life.[55] Three recent studies explored FRQoL using the validated IBD-specific FRQoL-29 tool.[39, 49, 53]

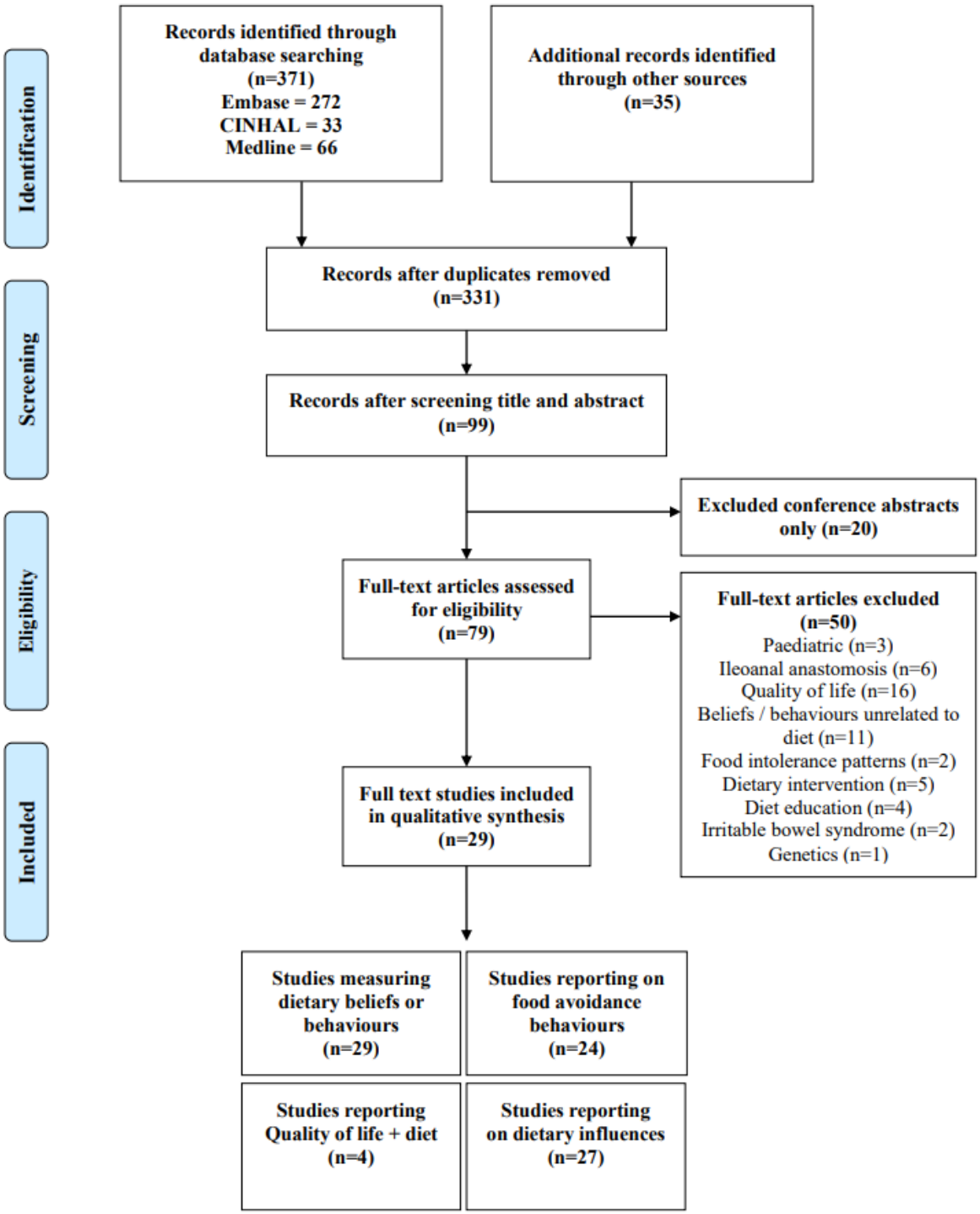


Figure 3. 1 PRISMA-ScR flow chart outlining search methods conducted for scoping review

Dietary beliefs

A dietary belief system mapping complex thoughts and perceptions of individuals with IBD regarding the interrelationship between diet and IBD is outlined in ***Figure 3.2***, informed by the studies reporting ≥50% of the cohort held a particular dietary belief.[3, 16, 25, 26, 37, 38, 40, 41, 44, 47, 48, 51-58]

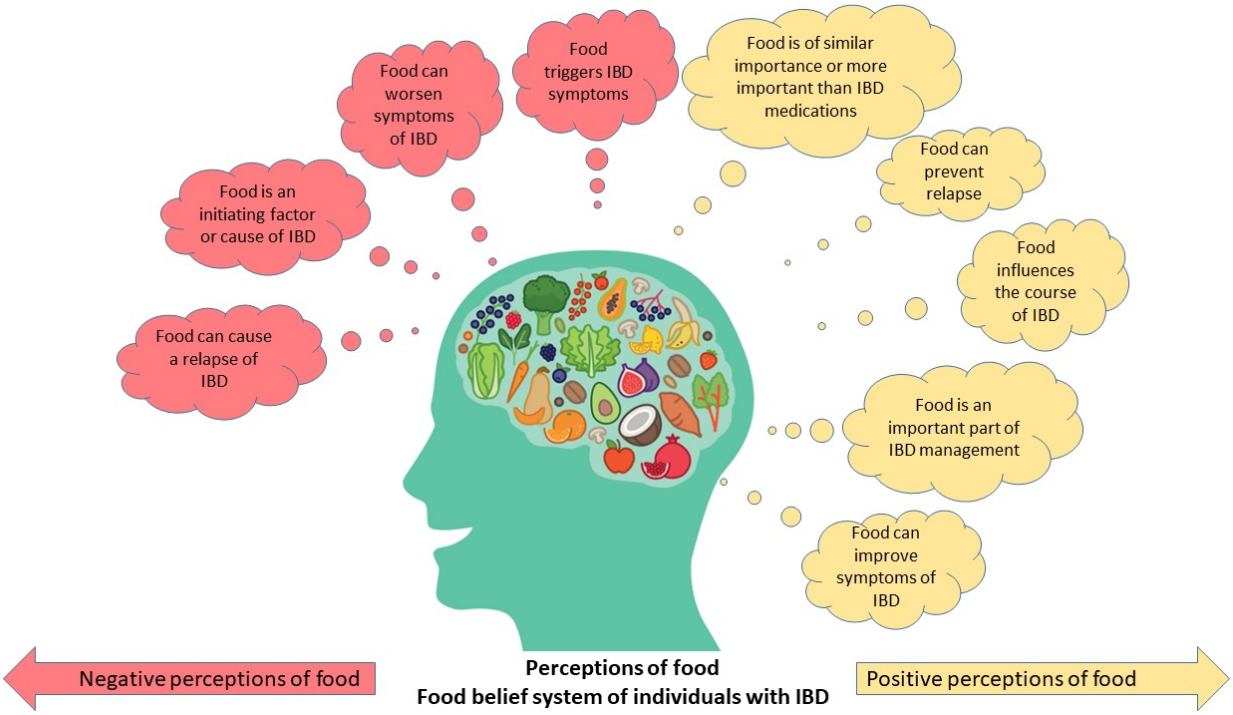


Figure 3.2 Food belief system of individuals with inflammatory bowel disease

Legend. *IBD, inflammatory bowel disease.*

Four studies identified up to 89% of IBD subjects believed diet is of similar or greater importance than medications in IBD management.[25, 38, 42, 44] The most common dietary belief held by 47-79% subjects in 11 studies pertained to specific foods triggering or worsening IBD symptoms.[16, 25, 26, 37, 38, 40, 41, 50, 52, 58] Studies did not differentiate between perceptions of food triggering overt inflammation, symptoms of active disease or concurrent functional symptoms. Up to 90% of participants in 10 studies reported dietary intake influenced disease course or could prevent a relapse, indicating a perceived association between diet improving or worsening disease activity.[3, 26, 38, 40-42, 44, 47, 48, 58]

Dietary behaviours

Dietary behaviours were most commonly reported as food avoidance, dietary restriction, or exclusionary rather than inclusive of certain foods or food groups. Twenty-eight studies (96%) identified that individuals with IBD self-reported at least one of these dietary behaviours, with the most common being food avoidance (***Table 3.2***).[3, 16, 26, 32, 36-52, 54-59] Only two matched-controlled studies used validated instruments to measure disordered eating behaviours.[21, 32]

Table 3.2 Characteristics of included studies that examine dietary beliefs and/or behaviours in individuals with inflammatory bowel disease.

Study (country)	Study design	Method of data collection	Sample size (analysed) % response	Sex	Disease phenotype	Dietary behaviours	Reasons for changing dietary behaviour	Factors identified to influence dietary beliefs and / or dietary behaviours or quality of life	Seen dietitian n (%)
Dietary beliefs and behaviours									
Casanova et al 2017 (Spain)[16]	Multicentre, prospective, observational study with two part design and analysis	Self-administered questionnaire followed by clinician-directed nutrition assessment	1271 (1271; 333)	M 617	CD 761 UC 510	Food avoidance Dietary restriction	To prevent relapse (IBD 75.5%; CD 80% vs. UC 68.8%, p<0.001) Fear of worsening symptoms (IBD 85.7%; CD 89.7% vs. UC 82.4%, p<0.05)	**Disease activity** **Fear** Higher risk of self-imposed food restriction during a flare was associated with: **Treatment** (Treatment with immunomodulator vs. no treatment (OR 1.5 95% CI [1.1-2.1] p value not reported; Systemic steroid treatment during the last year (OR 2.9 95% CI [1.2-6.8])) **Disease duration** (Longer duration (OR 1.03 95% CI: 1.007-1.05) p value not reported) Lower risk of dietary restriction during	-

								flare was associated with: **Older age** (OR 0.98, 95% CI 0.97-0.99) **Male sex** (OR 0.6 95% CI 0.5-0.9) **Phenotype:** UC compared to CD (OR 0.7 95% CI [0.5-0.9]; p ns)	
Cohen et al 2013 (USA)[37]	Cohort study (internet based)	Self-administered semi-quantitative FFQ	6768 (6768; 2329; 4001)	F ~70%	CD 1121 UC 597 UC-P 206 CD-O 405	Food avoidance Dietary restriction	Perception foods worsen or improve symptoms	**Disease phenotype** **Active disease** **Surgery:** stoma or pouch	-
Crooks et al 2021 (United Kingdom)[48]	Cross-sectional multicentre descriptive study	Self-administered questionnaire	255 (255)	M 133	CD 93 UC 154 IBD-U 8	Food avoidance Food exclusion	Belief may prevent relapse (89%) Active disease (31%)	**Sex:** females more likely to avoid foods than males (4.3 vs. 5.2; p=0.02) **Active disease:** those with active disease were more likely to have trialled an exclusion diet (OR 1.95 95% CI [1.13, 3.37]; p=0.02) **Ethnicity**	14%
Crooks et al 2020 (United Kingdom)[3]	Prospective, cross-sectional	Self-administered	208 (208)	M 114 F 94	UC 208	Food avoidance Food exclusion	To prevent relapse (59%)	**Age:** younger individuals were more like to believe diet triggers relapses (mean age 49 vs. 57 years; p=0.001), OR 0.97 95% CI [0.95-0.99], and	ns

	questionnaire based study	questionnaire						were more likely to avoid foods (mean age 52 years vs. 57 years, p=0.04), OR 0.98, 95% CI [0.96-0.99] **Female:** more likely to avoid dietary components to prevent relapse than males (p=0.007) , OR 2.26, 95% CI [1.25, 4.12], and were more likely to use exclusion diets (32% vs. 20% males; p=0.01), and less likely to eat out (p=0.004, OR 2.84 95% CI [1.41-5.75] **Relapse:** relapse in last 12 months was associated with food avoidance (p=0.03; OR 2.01 95% CI [1.08-3.73]	
Czuber-Dochan et al 2020 (UK)[60]	Qualitative study with semi-structured interviews and purposive sampling	In-depth, face to face semi-structured interviews	48 (28)	M 13 F 15	CD 16 UC 12	Dietary restriction	Active disease Loss of appetite during flare Increased appetite due to steroids Fear of exacerbating a flare or symptoms Perceived trigger foods Perceived food intolerance Perceived healthy eating Self-imposed exclusion diet	**Appetite** **Surgery** **Fear / anxiety** **Strictures** **Friends and family** *No noticeable differences between CD and UC observed* **Quality of life:** affected by dietary behaviour	Most (% ns)

							Fear of adverse gut problem outside of home / at work		
De Vries et al 2019 (Netherlands) [38]	Prospective, cross-sectional study	Self-administered 37-item online questionnaire	324 (294)	M 83 F 211	CD 146 UC 148	Food avoidance Food exclusion	Perception to reduce symptoms (76.5%) Perception to control disease (27.4%) Perception to avoid triggering relapse (33%) Perception to end a relapse faster (40.5%)	**Sex:** women more likely to avoid food and use supplements than men (p=0.046) **Disease duration**: more likely to have had dietary advice the longer the disease (p=0.023)	>60%
Dibley & Norton 2013 (UK)[56]	Qualitative interview based study; two part design	Self-administered questionnaire with random sampling following by semi-structured interviews with	3264 (3264; 583; 28)	F 16 (57%)	CD 12 UC 14 IBD-U 2	Food avoidance Dietary restriction	To avoid or manage faecal incontinence	**Fear:** episode of food intolerance in public	-

		purposive sampling							
Holt et al 2017 (Australia)[40]	Cross-sectional study, two-part design	Self-administered online questionnaires (patient and clinician)	1064 (928 patients + 136 clinicians) 24% response rate	F 648	CD 558 UC 315	Food avoidance	Surgery (84.5% vs. 77.1%, p=0.033) Stricturing disease (93%)	**Dietitian**: those who had seen a dietitian were more likely to: consider that diet affected IBD (81.4% vs 72.4% p =0.002), take a supplement / vitamin (76.2% vs. 69.1%, p=0.025) **Disease phenotype:** was not associated with food avoidance rates	46% (More CD had seen Dietitian than UC; 56.1% vs. 40.8%, p<0.001)
Jowett et al 2004 (UK)[50]	Prospective cohort study	Clinician interview of nutrition beliefs, and 107-item validated FFQ	191 (183)	M 93 F 98	UC 183	Food avoidance	Fear of relapse Perception of worsening or improving symptoms Following dietary advice	**Dietary advice** (although only 24 of 60 followed advice received; and those with dietary beliefs did not actually alter their nutritional intake as per the belief)	17 (9%)

Kamp et al (2021) (USA)[47]	Cross-sectional study and 26-item dietary screener	Online questionnaire	147 (147)	M 15 F 132	CD 94 UC 53	Food avoidance	Reduce symptoms (69%) Active disease	**Disease activity**	25%
Kinsey & Burden 2016 (UK)[41]	Cross-sectional study	Self-administered postal questionnaire	416 (156)	M 63 F 93	CD 90 UC 66	Food avoidance	Perceived trigger foods To control symptoms (51%)	ns	ns
Lim, Kim & Hong 2018 (Korea)[57]	Interview based study	Clinician interview followed by clinician administered survey	112 (104)	M 60 F 44	CD 61 UC 43	Food exclusion Dietary restriction	Prevent disease recurrence (45%)	ns	18 (17%) (ns from dietitian or other source) ns advice
Limdi et al 2016 (UK)[25]	Prospective, questionnaire-based study	Self-administered 2-part questionnaire	400 (400)	M 180 F 218	CD 156 UC 205 29 unsure 24 no response	Food avoidance Dietary restriction	Perceived prevention of relapse (68%) Perceived worsening of symptoms (60%)	**Ethnicity**; Asian-British population more inclined to believe diet has role in disease initiation (71% vs 47% other, p=0.005) and plays a more important role than medications (49% vs 28%, p=0.01)	31%

								Disease phenotype; More CD believe diet triggers relapse than UC (67% vs. 53%, p=0.007), affects appetite (87% vs. 66%, p<0.0001), avoid more foods to prevent relapse (77% vs. 63%, p=0.003) **Age**; Below 45 years report a change in appetite since diagnosis (85% vs. 68%, p=0.001) **Sex**; more females reported change in appetite (82% vs. 64%, p=0.001)	
Marsh et al 2019 (Australia)[54]	Prospective cross-sectional study	Clinician administered structured interview, and nutrition assessment	172 (117)	M 53	CD 50 UC 61 IBD-U 6	Food avoidance	Symptoms experience during active disease and remission	**Active disease**	61 (54%)

Nowlin et al 2021 (USA)[58]	Qualitative interview-based study	Semi structured interviews with a clinician	16 (16)	F 11	CD 3 UC 13	Food avoidance Dietary restriction	To control, reduce or manage symptoms during flare Belief induces and / or maintains remission	**Active disease:** poor disease control using conventional therapy **Anxiety/stress**	-
Palant et al 2015 (Germany)[51]	Qualitative interview-based study	Open end narrative interviews	44 (44)	M 20 F 24	CD 25 UC 15 IBD-U 2	Food avoidance Dietary restriction	Perceived symptoms Perceived trigger flare Unsure what to eat Fear of symptom or adverse GI event outside of home Fasting Dietary advice	**Fear** **Uncertainty** **Dietary advice;** misinformation or conflicting information, advice to trial and error foods	-
Prince et al 2011 (UK)[52]	Prospective, structured questionnaire interviews	3-part interviewer administered questionnaire	87 (72) RR 83%	M 32 F 40	CD 47 UC 25	Food avoidance Dietary restriction	Perceived trigger foods Needing to leave the house (managing gut problems)	**Disease phenotype**; CD were two fold more likely to report food or nutrition as important/extremely important compared to UC (p=0.012)	34 (47%)
Tomar et al 2017 (India)[44]	Cross-sectional observational study	Self-administered questionnaire	316 (316)	M 171 F 145	CD 98 UC 218	Food avoidance Food exclusion Dietary restriction	Perceived to prevent a relapse (89.9%) Symptoms during relapse (92.6%)	**Family:** diet considered more important than medications if had fewer family members, p=0.02) **Sex:** more males respondents believe diet is an initiating factor of	44.6% (ns from dietitian or other source)

								IBD (62.7% vs. 44%, p=0.003) and has a more important role than IBD medications (59.41% vs. 47.06%, p=0.031) **Age:** higher mean age associated with a decrease in nutrient intake (p=0.007) **BMI:** BMI<18.5kg/m^2 placed more importance on diet than IBD medications (55.8% vs. 42.3%, p=0.033), believe diet behaviours cause malnutrition/weakness (83.9% vs. 72.7%, p0.038), and more likely to take nutrition supplements (13.5% vs. 4%, p=0.002) **Disease phenotype**: UC made more dietary modification after diagnosis (p=0.04) **Disease activity**: dietary modifications and food avoidance (remission: 92.65% vs. 80.56%, p=0.002; relapse: 94.85% vs. 86.11%, p=0.011)	

Wilburn et al 2017 (UK)[55]	Qualitative interview-based study	Unstructured in-depth interviews	30 (30)	M 12 F 18	CD 30	Food avoidance Dietary restriction	Fear of gut symptoms	**Fear:** episode of food intolerance in public **Quality of life:** affected by dietary behaviour	-
Zallot et al 2013 (France)[26]	Prospective questionnaire-based study	14-item questionnaire	244 (244)	M 96 F 148	CD 177 UC 67	Food avoidance Food exclusion	Fear of relapse 57.8% To avoid relapse 66.8% Decreased appetite during relapse	**Fear** **Appetite** **Dietary advice**	114 (46.7%)
Dietary behaviours									
Bergeron et al 2017 (Canada) [36]	Prospective cross-sectional study	Self-administered questionnaire and 82-item FFQ	313 (245) 63% RR	M 105 F 140	CD 173 UC 72	Food avoidance Food exclusion	To avoid or manage GI symptoms (>75%)	**Strictures**: CD remission: IRR 2.00 95% CI [1.29-3.12, p=0.002] compared to CD active disease: IRR 1.35 95% CI [0.95-1.91, p=0.099]) **Disease activity:** FE rates 69% higher in IBD cohort in active disease compared to remission (p<0.001) **Disease phenotype:** stricturing and non-stricturing CD phenotypes avoided more food items than UC during remission (UC IRR 1.00; CD non-stricturing IRR 1.54 95% CI 1.00-2.38, p=0.049 ; CD stricturing IRR 2.98 95% CI 1.76-5.03, p<0.001)	-

Guadagnoli et al 2019 (USA)[39]	Prospective survey-based study	Self-administered structured surveys	265 (175)	M 23.2% F 76.8%	IBD 95 (IBS 80)	Food avoidance	Perceived symptom management Perceived disease control	**Symptom severity** **Quality of life** affected by dietary behaviour (food-related quality of life)	41 (39%)
Quick et al 2012 (USA)[32]	Prospective study with a matched case control design	Self-administered online survey	2625 (166) (820; DRCHC 164 (IBD 30) + matched HC 656)	ns	IBD 30	Food avoidance Disordered eating	-	**Mental health**: depression (OR 1.04, 95% CI [1.01-1.07; p=0.024]), anxiety (OR 1.04 [1.01-1.08; p=0.013) **Family**: Placed greater value on health than HC (OR 1.54 95% CI [1.20-1.98 p=0.001]), emphasis on maternal weight (OR 1.25 95% CI [1.03-1.51; p=0.025]), greater pressures to eat at mealtimes during childhood (OR 0.74 95% CI [0.63-0.88; p<0.001])	-
Tanaka et al 2009 (Japan)[42]	Prospective questionnaire-based study	Semi-structured interviews, 3-part self-administered	85 (76) 89.4% RR	M 61 F 15	CD 76	Dietary restriction	To manage flare symptoms (70%)	**Bowel resection:** more likely to skip meals to manage signs of flare (Z=-2.826, p=0.005)	-

		questionnaire							
Tanaka et al 2016 (Japan)[43]	Prospective questionnaire-based study	Self-administered 3-part questionnaire	426 (400) 26% RR	M 225	CD 140 UC 260	Dietary restriction	To manage flare symptoms (81.4%)	**Doctor's advice**	-
Vagianos et al 2016 (Canada)[45]	Population-based cohort with control group	Self-administered surveys and in-person interviews	388 (256 at 72 months)	M 159 F 96	CD 135 UC 120	Food avoidance	Perceived trigger foods causing GI upset	**Dietary advice** (15%) **Active disease;** (19-46% for each individual food item) **Food preferences**	-
Walton and Alaunyte 2014 (UK)[46]	Prospective cross-sectional study	19-point self-reported health questionnaire	97 (93)	F 73%	UC 93	Food avoidance Dietary restriction Food exclusion	Symptom management Perception of effect on symptoms	**Media**: 26% sometimes or currently follow diets promoted in the media	22 (27%)

Wardle et al 2018 (UK)[21]	Prospective controlled cohort study with matched pair design	Clinician administered 24hr diet recall automated multiple pass method (AMPM) and 5-part questionnaire	61 (61; CD 30 + HC 31)	M 18 F 12	CD 30	Disordered eating	-	**Food anxiety** **Fear**	-
Whelan et al 2021 (United Kingdom[49]	Prospective questionnaire based study	Self-administered questionnaire and 130-item FFQ	1576 (1221) 77.4%	M 593 F 625	CD 789 UC 432	Food avoidance	Belief food does not agree with IBD or triggers symptoms	**Quality of life:** affected by dietary behaviour (food-related quality of life) **Active disease:** β= -8.2 95% CI [-13.6, -2.8]; p=0.001 **Greater number of disease flares:** 5 flares β= -12.7 95% CI [-19.6, -5.8]; p<0.001 **IBD-related distress:** β= -0.26 95% CI [-0.31, -0.20]; p<0.001	-

								Disease phenotype: Crohn's disease, β= -2.9; 95% CI [-6.22, 0.43]; p=0.11	

Legend: *Inflammatory bowel Disease; IBD, Food frequency Questionnaire; FFQ, Males; M, Females; F, Crohn's Disease; CD, Ulcerative Colitis; UC, Ulcerative Colitis Pouch; UC-P, Crohn's Disease-Ostomy; CD-O, Gastrointestinal; GI, Greater than; >, Percent; Confidence interval; CI, Odds ratio; OR, No; N, Yes; Y, Versus; vs., non-specified; ns, IBD-unclassified; IBD-U*

Food avoidance

Food avoidance was the most commonly reported dietary behaviour, with 27.4-89% of participants in 24/29 studies (83%) (***Table 3.2***) disclosing this behaviour.[3, 16, 25, 26, 32, 36-41, 44-52, 54-56, 58] The main reasons for food avoidance related to the belief avoiding food would prevent a relapse or exacerbation of symptoms (57.8-92.6%). [3, 16, 25, 26, 36, 38, 42-44, 48, 49, 58] Diarrhoea and pain were the main symptoms perceived to improve with food avoidance.[38] One large multicentre Spanish study (n=1271) found food avoidance was more prevalent in CD compared to UC (to prevent relapse: CD 80% vs. UC 68.8%; p<0.001; fear of symptom exacerbation: CD 89.7% vs. UC 82.4%; p<0.05).[16] An Australian observational study (n=928) found food avoidance was more pronounced in those who had undergone surgery (Surgical management: 84.5%; Conservative management: 77.1%; p=0.033) or with stricturing disease (93%).[40] Interestingly, a multicentre study of British South Asians (n=255) reported those who had a co-existing medical condition that required dietary modification (21%) did not avoid a greater number of foods to prevent relapse.[48]

Only six studies surveyed food inclusive dietary behaviours measured in cohorts of up to 400 IBD subjects. If foods were believed to have a beneficial effect, 16-79% individuals with IBD reported they would include more of those foods.[3, 25, 38, 44, 48, 50] Interestingly, in the qualitative, interview-based studies, inclusionary food behaviours were also not commonly reported.

Food exclusion

Engaging in food exclusion behaviour (or food elimination) was self-reported by 29-68% of 1759 individuals with IBD in eight prospective cross-sectional studies (***Table 3.2***). Exclusion diets were followed, predominantly related to the belief they could prevent disease relapse or treat symptoms.[3, 26, 36, 38, 44, 46, 48, 57]. Only two studies identified the types of exclusion diets being used. The most common were lactose-free, gluten-free without co-existence of coeliac disease, low FODMAP, Palaeolithic, the specific carbohydrate diet and the anti-inflammatory diets.[3, 48] Of the studies reporting on exclusion diets, only three disclosed dietitian involvement and only 17-44% used a structured food re-introduction protocol post exclusion diet.[44, 46, 57]

Restrictive eating

Restrictive eating was the second most common dietary behaviour. Within 14 studies (one large cohort study, seven qualitative interviews and six observational studies), 41-93% of 5207 participants described using dietary restriction to manage IBD.[16, 25, 37, 42-44, 46, 51-53, 55-58] Restrictive eating behaviours were perceived to: reduce the risk of bowel obstruction in stricturing disease,[16, 25, 36-46, 50-55, 57] prevent or controlling a relapse,[16, 25, 26, 38, 42-44, 50, 51, 53, 57, 58] control disease activity,[39, 53, 54, 58] aid digestive recovery after surgery,[40] prevent faecal urgency or incontinence,[51-53, 56] help manage poor appetite or be a healthy approach to eating for IBD. [26, 50, 51, 53] The most common reason for

restrictive eating reported in 11 studies of 5001 participants was the perception trigger foods could precipitate a flare of disease or symptoms.[16, 25, 37, 42-44, 46, 51-53, 58] A small number of studies (4/29) identified fear of faecal incontinence or not being able to find a toilet as a primary reason for intentional dietary restriction.[51-53, 56] Prince *et al* 2011 reported 41% of IBD patients (n=72) restricted diet to avoid an embarrassing incident away from home, with no difference between CD or UC (p=0.297).[52] A qualitative study reported food avoidance was used to mitigate loose bowel actions interrupting a full day at work.[51] Five studies reported on disordered eating symptomology in those restricting their diets, including food cravings, living by strict food rules, experiencing food aversions, and a need to control food.[32, 37, 51, 53, 56]

Disordered eating behaviours

Two studies specifically examined and identified disordered eating behaviours in subjects with IBD compared to matched controls.[21, 32] One study (n=61) observed a greater prevalence of binge eating, food craving, and emotional eating in active CD compared to healthy controls.[21] Males and females with CD were more likely to binge eat (CD: 29% vs. controls 3.3%; p=0.008) and had higher binge eating scale scores (10.9±1.9 vs 5±1.0; p=0.01). Another study examining disturbed eating behaviours in young adults (18-25 years old) with diet-related chronic diseases (IBD n=30) identified those with chronic disease were six times more likely to follow a strict dietary regimen than healthy controls (OR 6.84, CI.95 [4.58-10.20] p<0.001), with a two-fold increase in the prevalence of diagnosed eating disorders (OR 1.99, CI.90, [0.91-4.34] p<0.05), and were more likely to misuse medications to control weight.[32]

Influences or factors associated with dietary beliefs or dietary behaviours

The beliefs of how diet and IBD interrelate and perceptions of the relationship between diet and IBD most likely to influence dietary behaviours are outlined in ***Figure 3.2.*** These influencing factors are broad and varied and are sub-categorised into five overarching themes of dietary influence: 1) patient-related characteristics, 2) disease characteristics, 3) information sources, 4) food belief system, and 5) mental health, as outlined in ***Table 3.3***.

Table 3.3 Factors associated with increased risk of food avoidance or restrictive eating behaviours in individuals with inflammatory bowel disease.

Influences on dietary beliefs or dietary behaviours		Factors associated with increased risk of food avoidance or restrictive eating behaviours in individuals with inflammatory bowel disease	Reference
Patient-related characteristics	Sex	Female sex	(3, 16, 25, 38, 48)
	Age	Younger age	(3, 16, 25)
	BMI	Lower BMI (<18.5kg/m^2)	(44)
Disease characteristics	Phenotype	Crohn's Disease	(16, 25, 36, 37, 52)
	Active disease	Flare or more severe symptoms	(3, 36, 37, 44, 45, 47, 48, 58)
		Treatment with Immunomodulators	(16)
		Systemic steroid treatment during the last year	(16)
		Poor disease control using conventional therapy	(58)
		Loss of appetite during flare	(26, 53)
	Disease duration	Longer duration	(16, 38)
		New diagnosis of ulcerative colitis	(44)
	Strictures	Presence of strictures	(36, 53)
	Surgery	Prolonged fasting, conservative dietary management or dietary modification after surgical procedure	(37, 42, 53)
Information sources	Dietary advice	Conflicting information, misinformation or advice to trial and error foods from health professionals	(40, 43, 45, 50, 51, 58)
		Self-initiated trial and error	(48)
	Media	Promotion of diets in media	(46, 48)
		Internet-sourced dietary advice	(48)
	Family	Beliefs, opinions, behaviours of friends and family	(32, 44, 53)

		Maternal weight and dieting behaviours	(32)
		Childhood mealtime pressures	(32)
	Cultural	Cultural beliefs pertaining to pathogenesis and medications	(25)
		Individuals of South Asian heritage who emigrated to Britain	(48)
Food belief system	Dietary beliefs	Self-identified or perceived trigger foods / intolerances / foods that may worsen symptoms	(3, 16, 25, 36-39, 41-46, 48, 50-53, 58)
		Food preferences	(45)
Mental health	Fear	Adverse gut problem	(51, 53)
		Finding public toilet	(55)
		Faecal incontinence in public	(56)
		Worsening symptoms	(16)
		Food aversion	(21)
		Relapse	(26)
	Mood	Depression	(32)
		Anxiety	(32, 58)

Individual characteristics

Sex

Female sex was associated with a change in appetite (82% vs. 64%, p=0.001),[25] a greater prevalence of food avoidance and supplement use.[38, 48] Females were also more like to use exclusion diets and less likely to eat out (***Table 3.3***).[3] Conversely, males tended to have lower incidence of restrictive eating during a flare (OR 0.6, 95% CI [0.5-0.9]).[16]

Age

Younger individuals were more likely to avoid foods, with a marginally lower risk of restrictive eating during a flare associated with older age (OR 0.98, CI 95% 0.97-0.99).[3, 16] More pronounced appetite changes were also observed in adults <45 years age (85% vs. 68%, p=0.001).[25]

Body mass index (BMI) & nutritional status

In a single cross-sectional study, a BMI<18.5kg/m^2 was associated with placing a greater importance on diet than IBD medications (55.8% vs. 42.3%; p=0.033) and the perception dietary behaviours had contributed to malnutrition and muscle weakness (83.9% vs. 72.7%, p=0.038). Those with a lower BMI had increased use of nutrition supplements (13.5% vs. 4%; p=0.002).[44] A multicentre Spanish study (n=333) reported 16% prevalence of malnutrition (subjective global assessment B or C) in CD and UC, and by multivariate analysis, malnutrition was positively associated restrictive eating during a flare (OR 10.3, 95% CI [1.3-78]; p=0.03), however cause or effect was not examined.[16]

Disease characteristics

CD vs. UC

Individuals with CD were two fold more likely to report food or nutrition as important/extremely important compared to UC (p=0.012).[52] A greater number of individuals with CD hold the belief diet triggers disease relapse (CD: 67% vs. UC: 53%; p=0.007) and affects appetite (CD: 87% vs. UC: 66%; p<0.0001). Higher rates of food avoidance in attempt to prevent disease relapse were also observed (CD: 77% vs. UC: 63%; p=0.003).[25] Individuals with CD also reported more unintentional weight loss compared to UC (94% vs 64%; p=0.002).[52] Two recent studies exploring the psychosocial impact of eating in IBD found no statistically significant difference in perceptions between CD and UC.[49, 53]

Disease activity

Active disease was a predictor of restrictive dietary behaviour, with higher rates of dietary restriction (19-46%) and food exclusion (69-95%) reported during periods of active disease and when compared to remission (p<0.001 and p=0.011).[36, 44],[45],[37] A higher degree of self-imposed restrictive eating during a flare were associated with certain treatments in a large multicentre study (n=1271) (immunomodulator vs. no treatment: OR 1.5, 95% CI [1.1-2.1]; systemic steroid treatment during the

last year: OR 2.9, 95% CI [1.2-6.8] p values not reported).[16] Lower risks of restrictive eating during a flare were associated with older age, male sex and UC phenotype. [16]

Stricturing disease

Two studies examining 1000 IBD subjects found stricturing disease in isolation was not a predictor of restrictive eating (27.5% of 928 IBD subjects prescribed biologic therapy).[40, 52] However, a Canadian cohort study reported individuals with stricturing CD in remission were two times more likely to avoid fruits and raw vegetables compared to periods of active disease (CD remission: IRR 2.00 95% CI [1.29-3.12]; p=0.002, CD active disease: IRR 1.35 95% CI [0.95-1.91]; p=0.099]).[36] Furthermore, when compared to UC, both stricturing and non-stricturing CD phenotypes avoided more food items during remission, particularly raw vegetables (UC: IRR 1.00; CD non-stricturing: IRR 1.54, 95% CI [1.00-2.38]; p=0.049; CD stricturing: IRR 2.98, 95% CI [1.76-5.03]; p<0.001) however this study did not report on reasons for food avoidance behaviours.[36]

Disease duration

Longer disease duration was associated with a higher risk of self-imposed restrictive eating during a flare (OR 1.03, 95% CI [1.01-1.05]; p value not reported) and disease duration > 10 years was a predictor of micronutrient deficiencies (p=0.017)[52] and of having received dietary advice (p=0.023).[38][16]

Surgery

Three studies found surgical procedures predicted restrictive eating or food avoidance behaviour, where skipping meals to manage bowel symptoms was a common dietary behaviour (Z=-2.826; p=0.005).[37, 42, 53]

Information sources

Dietary advice

Receiving dietary advice from a health professional was associated with trial and error of foods.[51],[43] Where dietary education was provided, only 40% implemented the dietary advice. Of those who held dietary beliefs about particular foods, 10-39% reported they altered their diet accordingly.[48, 50] Individuals who had seen a dietitian reported an increased awareness about diet and were more likely to consider that diet affected their IBD (81.4% vs. 72.4%; p=0.002) or took nutritional supplements (76.2% vs. 69.1%; p=0.025). However, this study did not examine whether the dietary advice was reflective of current IBD education messages that promote a normal, liberalised dietary intake.[40]

Family

Familial influences within the home environment were associated with disordered eating behaviour. Families of young adults with diet-related chronic diseases were found to place greater value on health

compared to controls (OR 1.54, 95% CI [1.20, 1.98]; p=0.001). There was greater emphasis on weight management within these family environments, particularly if mothers were engaging in weight loss behaviours (OR 1.25, 95% CI [1.03, 1.51]; p=0.025). Increased pressure to eat at meal times during childhood was also reported to influence compensatory disordered eating behaviours as a young IBD adult (OR 0.74, 95% CI 95% [0.63, 0.88]; p<0.001).[32]

Ethnicity

Ethnicity and cultural views were influential over dietary beliefs and behaviours. A study from India observed 77.2% of individuals held the belief specific foods improved symptoms during relapse and >50% believed diet had a more important role than medications in controlling IBD.[44] Coming from a smaller family also influenced the perception managing IBD with diet was important (p=0.02).[44] Two studies of 655 IBD patients found Asian-British ethnicity to be a strong predictor of using dietary restriction to prevent disease relapse (89% vs 67%; p=0.007), where those who had relapsed in the past 12 months were more likely to believe diet was the trigger (OR 1.98, 95%CI [1.17-3.36]; p=0.01).[48] A greater number of individuals of Asian-British ethnicity also perceived diet to be an initiating factor in developing IBD compared to other ethnic groups (71% vs 47% p=0.005).[25]

Media

Only one cross-sectional study (n=93) surveyed the role of media as a potential influence on dietary beliefs and behaviours, finding 26% of individuals with IBD currently or sometimes followed diets promoted in the media.[46]

Mental health

Anxiety, depression & fear

Three studies identified an association between mental health disorders such as anxiety and depression and food avoidance or disordered eating behaviours. A matched controlled study (n=61) observed an increased prevalence of mood disturbances including anxiety and depression between CD and healthy controls (CD: 13.4 ± 1.6 vs. Controls: 7.4 ± 1.5; p=0.01) which were associated with increased binge eating and food craving behaviours.[21] Young adults with diet-related chronic diseases also had significantly higher anxiety and depression scores compared to matched healthy controls, and were more likely to misuse medications to control weight.[32] Those with depression and/or anxiety were more likely to develop an eating disorder (Depression: OR 1.04, 95% CI [1.01-1.07]; p=0.024; Anxiety: OR 1.04, 95% CI [1.01-1.08]; p=0.013). Additionally, six studies identified living with fear of flare or gastrointestinal symptoms was commonly associated with food avoidance or restrictive dietary behaviours.[16, 26, 51, 53, 55, 56]

Association between dietary beliefs, dietary behaviours and quality of life

Only four studies examined QoL in relation to dietary beliefs and behaviours in IBD. Two studies used clinician-directed interviews[53, 55] and two used the validated FRQoL-29 questionnaire.[39, 49] Using unstructured in-depth qualitative interviews and a needs-based model to assess QoL, 30 participants identified nutrition was a fundamental need to their lives, directly affected by CD.[55] Furthermore, restrictive eating and living with the fear of an adverse event or disease relapse negatively influenced their enjoyment of food and QoL and restrictive eating prior to leaving, or while out of the house, was perceived as a necessary dietary routine to avoid an embarrassing adverse event.

FRQoL, defined as the psychosocial impact of eating and drinking with IBD, was explored in three studies.[53] A qualitative study identified five overarching bidirectional themes relating to food, nutrition, eating and drinking with IBD, describing the personal experiences, perceptions and psychosocial impact IBD has on relationship with food and QoL. [53] Two studies of 1316 individuals with IBD measured FRQoL using the validated FRQoL-29 instrument. Whelan *et al* identified impaired FRQoL in 1221 individuals with IBD, with associated inadequate nutritional intakes of key nutrients including fibre and calcium. Recurrent disease flares and greater IBD-related distress were associated with poorer FRQoL.[49] Guadagnoli *et al* compared the FRQoL of those with IBD (n=95) to individuals with irritable bowel syndrome (n=85) and found poorer FRQoL in active IBD which increased during periods of remission.[39] Symptom severity and concurrent use of dietary therapies (i.e. combining multiple different dietary advice or dietary approaches) were predictors of poorer FRQoL in IBD ($p<0.01$), and receiving dietary advice from a dietitian did not translate into improved FRQoL ($p=0.35$).

3.4 Discussion

Summary of evidence

This comprehensive scoping review provides the first systematic mapping of the relationship between dietary beliefs, dietary behaviours and QoL in adults with IBD. Food avoidance and restrictive dietary behaviour were the most prevalent of dietary behaviours, driven by a complex dietary belief system that categorises food dichotomously as problematic or beneficial to IBD. Multiple factors were associated with these dietary behaviours, including a diagnosis of CD or new diagnosis of UC, stricturing CD phenotype, active disease, female sex, anxiety, and having previously received conflicting dietary advice. The psychosocial impact of dietary beliefs and behaviours has been a neglected area of IBD research. More recently, FRQoL has emerged an important, validated patient-reported outcome and is impaired in people with IBD. The heterogeneity of dietary terminology, study design and questionnaires used to examine dietary beliefs and behaviours in IBD are a key finding of this review and highlight an important area for future research which is required to validate these

findings and understand whether early access to individualised dietary education can minimise dietary misinformation, unnecessary dietary restrictions and improve FRQoL.

Food avoidance and dietary restriction has been poorly studied in IBD despite the seemingly high prevalence. The lack of predefined dietary terminology to characterise the dietary beliefs and behaviours of people with IBD are an important finding of this review. A discord exists between how patients believe diet interacts with their IBD, the views of health professionals and available evidence regarding the role of diet imparting susceptibility to IBD. [40, 61] In view of the mapped dietary belief system and high degree of self-reported food avoidance, it would be helpful to see this explored further. Consistent dietary terminology and validated tools are necessary to measure the potential influence of diet on disease activity and symptoms and to minimise the risk of negative bias within the tools being used to measure patient beliefs and behaviours.

Emphatically, this review identifies dietary modification occurs in a response to symptoms. With relatively little evidence for the role of diet in IBD in propagating overt inflammation, the majority of dietary beliefs and subsequent food avoidance are likely the result of functional symptoms rather than active inflammation, particularly as functional symptoms appear to be equally prevalent in deep remission and active disease.[3, 62, 63] Differentiating between and educating on the use of dietary therapies for active disease or concurrent functional symptoms is an important area for dietary counselling. In the absence of defined dietary guidance for CD and UC and a lack of timely access to specialised dietitians, this review identifies how vulnerable people with IBD are to trialling diets derived from internet-based sources to manage symptoms.[2]

A limited number of defined exclusion diets have a therapeutic role in IBD treatment or concurrent symptom management. Clinicians have a responsibility to ensure exclusion diets are clinically indicated, appropriately supervised and based on current scientific evidence. These defined diets have structured food exclusion and dietary re-introduction protocols and long-term attenuated dietary plans.[13, 14, 64] Patients should be selected appropriately for exclusion diet therapy in consultation with a dietitian who can screen for food anxiety and disordered eating risk factors, provide individualised dietary advice and ensure appropriate monitoring to avoid prolonged dietary restriction and nutritional complications.[4, 6, 16, 51] The factors associated with increased risk of food avoidance, restrictive eating or disordered eating symptomology identified in ***Table 3.3*** may help clinicians to identify those suitable for exclusion diet therapy or those whom require a more comprehensive dietary assessment and counselling.

A key finding of this review is the lack of research examining diet and QoL in people with IBD. FRQoL has only recently been identified as is impaired in IBD. Subsequently there has not been any research examining how to improve FRQoL or whether poorer FRQoL affects mental health and nutritional

outcomes in IBD.[49] However, attempting to follow multiple pieces of dietary advice is associated with poorer FRQoL and impaired FRQoL is associated with nutritional inadequacy.[39, 49] These are very important observations with significant clinical implications for IBD dietary education, particularly in view of the high prevalence of food avoidance.

Providing generic or complex IBD dietary education may not serve to improve dietary behaviour, nutritional status or FRQoL. Rather, dietary education should be individualised to disease phenotype, disease activity and location, symptom severity, current nutritional status, and must be clear and simple to follow.[38] The purpose and timing of dietary information is also important. FRQoL should be considered as an outcome measure of patient-centred care and future research into defined therapeutic diets for IBD.[39] In addition to this, non-diet therapies such as psychological-based therapies have an important role in treating food avoidance or restrictive eating behaviours in individuals with gastrointestinal symptoms and may offer complimentary or an alternate approach managing food anxiety and improving QoL.[22]

Limitations of the scoping review

A first limitation of this scoping review is the interpretation of arbitrary and variable terminology used to characterise dietary beliefs and behaviours. This may have led to inaccuracies within the reported prevalence of food avoidance and dietary restriction. Moreover, there was significant heterogeneity within study design and methods of data collection. Therefore findings from this study cannot be generalised beyond this review. However, this importantly highlights the need for validated instruments that use predefined dietary terminology to characterise dietary behaviours in the future. Moreover, these instruments need to differentiate between dietary behaviours during periods of active disease and remission. The association between reported restrictive eating behaviours, habitual diet and objective disease activity requires further investigation. Another limitation of this review is the predominant reporting of negative dietary perceptions in IBD. The 20 observational studies (69%) capturing these views used predefined questions, open to bias by study investigators who may have intended to informally measure dietary behaviours with a negative bias due to the potential nutritional and clinical implications food avoidance has. However, it should be noted the qualitative studies using semi-structured or unstructured interview techniques still captured similar themes and negative perceptions of food and dietary behaviours.

3.5 Conclusion

In summary, this scoping review identifies a high prevalence of food avoidance and dietary restriction amongst individuals with IBD. These findings should be confirmed using validated tools with predefined terminology and objective markers of disease activity to measure dietary behaviour. Diet and QoL is poorly examined in IBD with recent data indicating FRQoL is impaired. Dietary restrictions predispose

individuals with IBD to nutrition-related complications and have a psychosocial influence. Further research into defined diets for quiescent and active IBD are required and investigation into dietary strategies that improve FRQoL is imperative.

Acknowledgements

Thank you to The Queen Elizabeth Hospital Inflammatory Bowel Disease Service and Research Unit supporting this project and to Chris Filosi, Brian Bolado and Sonia Zanatta from the University of South Australia School of Art, Architecture and Design for assistance with images within the graphical abstract.

Author contributions

Guarantor of the article: R.V.Bryant

Author contributions: All authors contributed to the conception and design of the study. A.S.Day performed the literature search and extracted the data. All authors contributed to interpretation of the data. A.S.Day drafted the manuscript and all authors contributed to the revisions and approved the final version of the manuscript.

Disclosure of funding

This work was supported by a Commonwealth Research Stipend administered by University of Adelaide, Australia to ASD as part of a post-graduate degree.

Supplementary tables

Supplementary table 3.1 Inclusion criteria for systematic scoping review examining food avoidance, restrictive eating behaviour and association with quality of life in adults with inflammatory bowel disease.

Inclusion criteria	**Exclusion criteria**
Full text studies	Abstracts, review papers, case studies, articles not undergone peer-review (letters to editor, newspaper article)
Studies in English	Non-English studies
Diagnosis ulcerative colitis, Crohn's disease or inflammatory bowel disease unclassified	No diagnosis inflammatory bowel disease
Subjects ≥18 years old	Subjects <18 years old
Studies investigating dietary beliefs and / or dietary behaviours	Dietary intervention studies
Studies examining influences on eating patterns, food avoidance and dietary restrictions	Studies investigating beliefs or behaviours without reference to diet or food
Studies examining relationship between diet and quality of life or food-related quality of life	Studies investigating health-related quality of life or quality of life without reference to diet or food

Supplementary table 3.2 Example electronic search strategy for systematic scoping review examining food avoidance and restrictive eating behaviours in adults with inflammatory bowel disease and association with quality of life

Database: Ovid MEDLINE

Search Strategy:

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1 colitis/ or colitis, ulcerative/ or proctocolitis/ or inflammatory bowel diseases/ or crohn disease/ or proctitis/ (92908)

2 (inflammatory bowel disease* or ulcerative colitis or crohn* disease or crohn* or colitis or proctitis or inflammatory bowel).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (129218)

3 proctocolitis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1069)

4 1 or 2 or 3 (129461)

5 "diet, food, and nutrition"/ or exp food/ or exp diet/ or eating/ or feeding behavior/ or food preferences/ or appetite/ or nutritional requirements/ or recommended dietary allowances/ or nutritional status/ (1502520)

6 ((diet* or food* or nutri*) adj6 (intake* or behavio?r* or avoidance or restrict* or belief*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (182102)

7 (diet* or food* or nutri* or picky eating or eating habit* or eating behavio?r*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1441068)

8 5 or 6 or 7 (2286139)

9 attitude/ or attitude to health/ or health knowledge, attitudes, practice/ or behavior/ or food preferences/ or habits/ (267510)

10 (attitude* or behavio?r* or habit* or food preference* or preference* or understand* or belief* or knowledge or view* or opinion*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3842216)

11 9 or 10 (3842216)

12 "Quality of Life"/ (181255)

13 (QOL or QoL or (quality adj1 life)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (41812)

14 12 or 13 (194784)

15 4 and 8 and 11 and 14 (66)

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A repeat search strategy was conducted in CINHAL and EMBASE databases with support from the Librarian at The Queen Elizabeth Hospital, Adelaide, South Australia.

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CHAPTER 4

The adequacy of habitual dietary fibre intake in individuals with inflammatory bowel disease: a systematic review

Published in *Journal of the Academy of Nutrition and Dietetics*

April 2021

CHAPTER 4: Habitual fibre intakes in IBD

Background

In ***chapter 3*** of this thesis, a high prevalence of self-reported food avoidance and dietary restriction was identified in individuals with inflammatory bowel disease (IBD), seemingly perpetuated by a complex dietary belief system that dichotomises food as either beneficial or problematic. Food-related quality of life (FRQoL) is compromised in IBD and is lowered by attempts to follow multiple pieces of dietary information.

Historically, low residue or low fibre dietary advice has been recommended for symptom management in IBD.[1, 2] Protracted adherence to a low fibre diet in quiescent disease is not uncommon and fibre advice can cause dietary confusion.[3] More recently, fibre has been recognised for its important health benefits, including a reduced risk of relapse in Crohn's disease (CD) and as the preferred dietary substrate for the colonic microbiota, producing essential short-chain fatty acids (SCFA) and detoxifying potentially harmful metabolites of protein fermentation.[4-6] However, avoidance of fibre-rich core food groups such as fruits, vegetables and wholegrains is common in CD and ulcerative colitis (UC). This may be causing more harm than benefit to disease pathogenesis.[4, 7-9] Furthermore, these dietary patterns may be contributing to a higher consumption of foods with lower nutritional value leading to other health-related issues including the rising trends in overweight and obesity.[10]

Therefore, the systematic review in ***chapter 4*** examined whether individuals with IBD consume adequate dietary fibre and explored factors associated with habitual fibre consumption. Habitual fibre intakes were compared to healthy control (HC) groups and respective national dietary fibre guidelines to determine fibre adequacy and any association between potential influencing factors such as disease activity or phenotype.

Statement of authorship

Title of Paper	The adequacy of habitual dietary fibre intake in individuals with inflammatory bowel disease: a systematic review.
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	**Day AS**, Davis R, Costello SP, Yao CK, Andrews JM, Bryant RV. The Adequacy of Habitual Dietary Fibre Intake in Individuals With Inflammatory Bowel Disease: A Systematic Review. J Acad Nutr Diet. 2021 Apr;121(4):688-708.e3. doi: 10.1016/j.jand.2020.12.001.

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Overall percentage (%)	70%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

iv. the candidate's stated contribution to the publication is accurate (as detailed above);

v. permission is granted for the candidate in include the publication in the thesis; and

vi. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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[Manuscript 2]: The adequacy of habitual dietary fibre intake in individuals with inflammatory bowel disease: a systematic review.

Short title: Fibre intake in IBD

Keywords: habitual fibre intake, dietary fibres**,** inflammatory bowel disease, nutritional adequacy, disease activity

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Funding sources / financial disclosures:

Nil funding.

Conflicts of interest disclosure:

ASD has received speaking fees from AbbVie and Chiesi paid to employer for research support.

RD has no conflicts to declare.

CKY has received research support for investigator-driven studies for Ferring Pharmaceuticals, Danone and Yakult Australia. Her department, Department of Gastroenterology, Monash University receives royalties from the sale of The Monash University low FODMAP Diet App.

SPC has received advisory, speaking fees or research support from Ferring, Microbiotica, Janssen. Shareholding: BiomeBank.

JMA has received speaker's fees, research support, been on advisory boards for Abbott, AbbVie, Allergan, Anatara, AstraZeneca, Bayer, Celegene, Ferring, Gilead, Hospira, Immuninc, ImmunsanT, Janssen, MSD, Nestle, Progenity, Pfizer, Sandoz, Shire, Takeda, Vifor, RAH Research Fund, The Hospital Research Fund.

RVB has received Grant/ Research support/ Speaker fees (all paid to employer for research support): AbbVie, Ferring, Janssen, Shire, Takeda, Emerge Health.

Acknowledgements:

No acknowledgements.

Research snapshot

Research question:

Do individuals with IBD consume adequate dietary fibre, and what factors are associated with habitual fibre consumption?

Key findings:

In this systematic review of 26 studies with 4164 participants with IBD, individuals with IBD were found to eat less total fibre than recommended national dietary guidelines and less total fibre than control populations. Heterogeneous and inconsistent data conflicted regarding factors associated with fibre intakes and this warrants further investigation.

Practice implications

What is the current knowledge on this topic?

Westernised diet, including lower intakes of fruits, vegetables and wholegrains have been implicated in IBD course. Fibre restriction is thought to be widespread in IBD however has not been thoroughly investigated.

How does this research add to knowledge on this topic?

This systematic review of 26 studies identifies individuals with IBD consume less fibre than healthy populations. Fibre intakes are also inadequate compared to respective national fibre guidelines, irrespective of whether disease is quiescent or active.

How might this knowledge impact current dietetics practice?

The findings of this systematic review highlight the importance of assessing fibre intakes for all individuals with IBD when taking a diet history. Early identification of inadequate fibre intake provides the opportunity for dietary counselling regarding optimisation of dietary fibre during periods of both active and quiescent disease to achieve recommended fibre intakes.

Abstract

Background: Dietary fibre may influence disease course in individuals with IBD, yet there is a paucity of understanding of habitual fibre intakes.

Objectives: To identify studies measuring fibre intakes of individuals with IBD, compare the adequacy of fibre intakes to control groups or respective national dietary guidelines, and examine factors associated with fibre consumption.

Methods: Five electronic databases; MEDLINE, CINAHL, SCOPUS, PROQUEST and COCHRANE LIBRARY were systematically searched using search terms; "inflammatory bowel disease", "Crohn's disease", "ulcerative colitis", "dietary intake" and "fibre" until December 2019, with hand searching of reference lists. Primary studies were included if fibre intakes were measured in participants 18 years or older, with confirmed IBD, with or without comparison to a control.

Results: A total of 2105 publications were identified, and 26 met inclusion criteria. Total fibre intake of 4164 participants with IBD ranged broadly (9.9±7.8g/d to 21.0±10.5g/d). Most (18/26) used cross-sectional study design with a large degree of heterogeneity in tools measuring fibre intake. Sixty-six percent of studies comparing participants with IBD to control groups found participants with IBD consumed significantly less fibre than controls. Four studies reported <10-21% of IBD participants met their national fibre recommendations. Data conflicted regarding an association between disease type, disease activity or rate of relapse and fibre intake.

Conclusions: Individuals with IBD consume less fibre than healthy populations. Fibre intakes are inadequate compared to respective national fibre guidelines. Interpretation of factors associated with fibre intakes were limited by data quality and conflicting results. Future research is required into factors associated with fibre intake and whether increasing fibre intakes can influence disease course and behaviour.

4.1 Introduction

Diet, in particular widespread adoption of a westernised diet, has been implicated as an important factor in IBD susceptibility and may account for current epidemiological trends.[11-14] Recent intervention studies and prospective data indicate dietary intake influences disease course.[15-17] Increased intakes of red and processed meats, sweetened beverages, and lower intakes of fruits and vegetables are associated with risk of increased disease activity.[9, 15, 17, 18]

Despite the intuitive importance of diet on gastrointestinal illness, there is a paucity of understanding of factors shaping dietary habits of individuals with IBD. Studies have shown >70% of individuals with IBD attempt elimination diets as a strategy to control gastrointestinal symptoms.[3, 19, 20] These diets are often highly restrictive, with avoidance of fibrous food groups.[20-23] Unfortunately, beyond healthy eating guidelines or exclusive enteral nutrition for active CD, there are few defined dietary strategies for individuals with IBD to induce or maintain disease remission, although emerging CD diets that modulate components of core food groups, including fibres, show potential.[17, 20, 24]

Consuming adequate dietary fibre supports the beneficial, multifaceted role fibres have in digestive function. This includes assisting gut transit, laxation, stool formation, providing substrate for bacterial degradation and fatty acid production, and in shaping gut microbial composition and function.[16, 25] Dietary fibres are fermentable carbohydrates, generally defined as carbohydrates that are not hydrolysed or absorbed in the upper part of the gastrointestinal tract.[25] The large bowel is the principle site for fibre to be fermented into metabolites by communities of gut microbes.[26] While an association between fibre intake and aetiology of IBD has not yet been found, higher intakes of fermentable dietary fibres have been associated with favourable functional shifts in microbiota thereby altering UC disease course.[16, 27] Conversely, lower intakes of fermentable fibres have been associated with structural changes in the gut microbiota, less favourable for overall colonic health.[28]

Daily fibre targets for individuals with IBD do not differ from population dietary guidelines.[3, 29] In Australia, the recommended total fibre intakes are 25g/d for women and 30g/d for men, consumed from a wide variety of sources.[30] Nevertheless, clinicians still frequently recommend a low fibre or low residue diet (~10g/d fibre) to individuals with IBD for management of inflammatory-related gastrointestinal symptoms.[1, 19] However, outside of stricturing CD there is a lack of reliable evidence to suggest low fibre or low residue diets are therapeutically beneficial, or whether this advice is even necessary in a cohort known to restrict foods or whole food groups.[22] A recent systematic review found no valid reason for individuals with IBD to restrict fibre.[29] Despite this and the potential detriments of continued and prolonged restriction of dietary fibre on digestive function, numerous individuals with IBD may follow these diets long term.[3]

The habitual dietary fibre intake in individuals with IBD has not yet been systematically reviewed. These data are necessary to understand whether fibre intakes are adequate or whether fibre is being restricted. This systematic review therefore aims to identify studies measuring habitual dietary fibre intake of individuals with IBD, compare the adequacy of fibre intakes to HC groups or respective national dietary guidelines, and examine factors associated with fibre intake.

4.2 Materials & methods

The methods of this systematic review were undertaken in line with the preferred reporting items for systematic reviews and meta-analyses guidelines by two independent reviewers, with agreement on predefined methodology.[31]

Eligibility criteria

The research question and study inclusion criteria were developed using the patient, intervention, comparator, outcomes, study design (PICOS) framework.[32] The PICOS research question was 'Do individuals with IBD consume adequate dietary fibre, and what factors are associated with habitual

fibre consumption?' The PICOS components of this question were reflected in the study inclusion criteria (***Table 4.1***).

Search strategy

Five electronic databases; MEDLINE, CINAHL, SCOPUS, PROQUEST and COCHRANE LIBRARY were systematically searched until December 11th 2019 using a predefined search strategy. A range of search terms and synonyms were used to identify articles for inclusion, "inflammatory bowel disease", "Crohn's disease", "ulcerative colitis", "dietary intake" and "fibre" (***Figure 4.1***). The search was limited to human studies published in English.

Study selection

For inclusion, studies were primary studies that measured dietary intakes of individuals aged 18 or older, with diagnosed IBD, and reported on fibre intake in grams per day (***Table 4.1***). Dietary intervention studies, including those examining fibre supplements, were excluded. All citations obtained from the electronic database search were exported into EndNoteX9, where duplicate articles were removed. Titles and abstracts were screened by two authors using the pre-established inclusion and exclusion criteria (***Table 4.1***). Full text articles were obtained for relevant studies then re-screened for a second time to determine eligibility. Reference lists of included articles were then hand searched to identify any additional appropriate articles. For any differing opinion in study eligibility, two authors discussed independent findings and reached a consensus.

Data extraction

Data were extracted independently by two authors into piloted evidence tables. Data included disease phenotype, disease activity, methods of dietary assessment, fibre intakes, and contributions from different fibrous foods (***Table 4.1***). Extracted data was sufficient therefore it was not necessary to contact authors for additional information.

Quality assessment

Studies were quality assessed for validity, reliability and bias using Academy of Nutrition and Dietetics (Academy) quality criteria checklist for primary research by two independent reviewers.[33] The quality of each study was assessed by determining the relevance and applicability of study outcomes before proceeding to appraise the validity of the study. The key methodological areas considered included a clearly stated research question, selection of study participants, whether study groups were comparable, management of withdrawals, blinding, clear outline of interventions, relevant outcomes and valid measurements, and appropriate statistical analysis. As per Academy quality assessment guidelines, each study was given a quality grade of either negative (poor quality, key areas not addressed), neutral (key areas not of poor or high quality), or positive (study has addressed key areas,

introduction of bias, and generalisability) (***Table 4.2***).[33] The two authors completed independent quality assessments for each study and for any differing opinion, a consensus was reached through discussion (***Table 4.3***). The combined strength of evidence from all studies is reflected in the discussion and conclusion statement.

4.3 Results

Study selection

The systematic database search with additional hand searching yielded 2432 citations. (***Figure 4.2***). A total of 2105 titles and abstracts were screened following removal of duplicates and 75 full text articles were assessed for eligibility by two independent reviewers. From these, 26 studies evaluating habitual fibre intake in participants with IBD between 1983 and 2019 were included in this review.

Population, comparators and factors associated with habitual fibre intake

Of the 26 studies included, habitual fibre intake was measured for 4164 participants with IBD (2221 CD, 1448 UC, and 495 IBD-Unclassified) (***Table 4.2***). The sample size of studies varied widely; nine studies included >100 IBD participants,[4, 15, 21, 23, 34-38] whereas six included <50 IBD participants.[39-44] Many studies (15/26) only recruited IBD participants from one site.[36-42, 44-51]

Twelve studies (12/26) compared a total of 1137 IBD participants (five CD studies with 450 participants, two UC with 100 participants, and five included 587 CD, UC and IBDU participants)) to HC groups (total 2548 HC participants) all either matched to age and sex or with no significant difference between groups (***Table 4.2)***.[34-36, 40, 41, 43, 45-48, 51, 52] Seven studies (7/26) compared the total fibre intake of participants with IBD to associated national dietary guidelines.[7, 40, 43, 46, 47, 53, 54] Of the 14 studies (14/26) without HC groups, disease phenotype, disease activity, clinical remission status, intentional food exclusion, sex and nutritional status were examined for potential association with dietary fibre intakes.[4, 7, 15, 21, 37-39, 42, 44, 49, 50, 53-55] Disease activity differed across studies. Ten studies (10/26) included participants with quiescent disease,[15, 35, 36, 38, 39, 41, 46, 52, 55, 56] while 14 included active and quiescent disease.[7, 21, 23, 34, 37, 42, 44, 45, 47-50, 53, 54] Four studies (4/26) examined fibre intake and patterns of relapse in UC.[21, 42, 49, 50]

The majority of studies (18/26) had cross-sectional design.[35-41, 43-48, 51-54, 57] A further six were prospective cohort studies,[13, 15, 42, 49, 50, 55] one a retrospective cohort study,[4] and one had mixed methodology (***Table 4.2***).[23] The majority of studies (18/26) compared fibre intakes between groups using comparison of means. Five studies adjusted for confounders using multivariate analysis.[4, 15, 40, 49, 51]

Study quality

Of the 26 studies, 3 were given a positive quality grade[15, 34, 49] and 23 were given a neutral quality grade using Academy quality criteria checklist (available at www.jandonline.org).[4, 7, 21, 23, 33, 35-42, 44-48, 50, 52-55] The most common reasons for a neutral quality grading related to methods of statistical analysis or reporting, or a lack of validated, reliable measures for study outcomes (***Table 4.3***). Meta-analysis of included studies was not possible due to heterogeneity and disparities in methodology and quality.

Measuring dietary fibre intake

Five methods of capturing habitual dietary fibre intake were used (***Table 4.4***). The most common methods of assessment were food frequency questionnaires (FFQ) (10/26), seven of which were validated FFQ,[15, 21, 23, 34, 41, 42, 45, 47-49] or 3-day food diaries (5/26).[37, 46, 50, 53, 55] A 7-day weighed food diary was only used in three studies.[36, 41, 54] Alternative methods, including 24-48hr dietary recall (5/26) [7, 40, 41, 43, 44] and dietary history questionnaires (4/26) [4, 35, 38, 39] were also used. One study used FFQ, 7-day food diary, and a 24-hour recall to measure dietary fibre and reported no statistical difference between these methodologies (mean nutrient data reported).[41] Twenty-four studies measured total fibre intake while four studies measured consumption of specific sub-types of fibres.[34, 38, 48, 49]

Fibre intake of IBD participants compared to associated national dietary guidelines

Total fibre intake of individuals with IBD broadly ranged from a mean of 9.9g ± 7.8 standard deviation (SD) to 21.0g ± 10.5 (***Table 4.4***). Seven studies (7/26) compared the total fibre intake of participants with IBD to their respective national dietary fibre recommendations (***Table 4.4***), with four studies reporting on percentage intakes within IBD cohort (***Figure 4.3***).[43, 46, 47, 52-54, 57] Two Canadian studies reported inadequate fibre intakes for participants with IBD compared to Canadian dietary guidelines (CD: 16.91 ± 0.95g/d; and CD: 13.3 ± 9.3g/d and UC: 13.5 ± 5.6g/d respectively, compared to recommendations for men 30-38g/d, women 21-25g/d).[40, 54, 58] Another French study found >80% of participants with CD do not meet fibre recommendations (25g/d) in France.[46] Guerreiro *et al* 2007 examined Portuguese CD participants and similarly found 80.3% consumed less fibre than the respective dietary reference intake.[47] Moreover, >90% of UC participants (n=93) in the United Kingdom consumed a mean intake of only 11g/d compared to British dietary reference value (DRV) of 18g/d.[57] Similarly, Lomer *et al* 2004 reported 91 British CD participants had mean fibre intakes of 12 ± 5g/d compared to British DRV.[52] Additionally, an Icelandic study including UC and CD participants reported fibre intakes for both IBD subtypes were lower than their national recommendations (17.5g ± 6.7g/d vs. 23g/d, p value not reported).[53] Irrespective of disease type or activity, all seven studies

showed a vast majority of IBD participants were not meeting national fibre recommendations (***Table 4.4***).

Fibre intakes of individuals with IBD compared to HC populations

Overall.

Twelve studies (12/26) compared fibre intake of participants with IBD to HC. Eight cross-sectional studies found statistically significant differences in fibre intake between participants with CD and/or UC compared to HC (***Table 4.4***).[23, 34-36, 41, 45, 47, 52] Two large cross-sectional studies found a significantly lower fibre intake in IBD participants compared to HC (CD: 16.4g/d ± 1.6, UC: 15.5g/d ± 1.2, HC: 20.1g/d ± 2.4, p<0.0001; IBD: 21.5g/d (17.2-35.3), HC: 24.1g/d (20.2-28.9); p<0.05).[45, 51] Principi *et al* 2018 reported fibre intake in 150 IBD participants, even while in remission, was significantly lower than HC (IBD: 11.9g/d ± 4.7, HC: 15.5g/d ± 8.3, p<0.01).[36] Looking specifically at contributions from whole food groups to fibre intakes, Opstelten *et al* 2019 found HC ate significantly more vegetables than participants with IBD (148g/d (median inter quartile range (IQR) 95.8-200) vs. 60.9g/d (median IQR 41-94.6); p<0.05) (***Table 4.4***).[23] D'Odorico *et al* 2001 reported similar findings, including lower fruit intakes in participants with CD and UC.[45]

Crohn's Disease.

Six studies (6/26) compared fibre intakes of CD participants with HC. Of two studies comparing quiescent CD to HC, Filippi *et al* 2006 measured fibre intake using a 3-day food diary and found no significant difference in fibre intake (CD: 16.7g/d ± 1.2, HC: 14.7g/d ± 0.9, p value not reported).[46] In contrast, Lomer *et al* 2004 measured fibre intakes using a 7-day food diary in a larger cross-sectional study and reported CD participants had a significantly lower fibre intakes than HC (CD: 12.0g/d± 5.0, HC: 14.0g/d ± 5.0, p=0.001).[52]

The other four studies included participants with both quiescent and active CD. Disease activity was not independently analysed against HC and fibre intakes, and findings were disparate. Brauer *et al*. found no significant difference in fibre intake between 23 CD and 65 HC (CD: 13.3g/d ± 9.3, HC: 15.3g/d ± 6.9), however two larger cross-sectional studies did find significantly lower fibre intake amongst CD participants (CD: 21.0g/d± 10.5, HC: 32.2g/d ± 13.7, p=0.02; CD: 62.3-74.9% <20g/d, HC: 51.5-51.7% <20g/d, p=0.011).[35, 40, 47] Wardle *et al* examined 24-hour dietary intake in 30 participants with active or quiescent CD and found HC had a higher intake of dietary fibre (CD: 18.9g ± 2.1, HC=23.4 ± 2.3, p value not reported).[43]

Anderson *et al* specifically measured intakes of fermentable fibres in active and quiescent CD compared to HC, and found higher intakes of oligofructose and fructans in both HC and quiescent CD groups (Oligofructose: active CD: 2.8g/d (IQR 1.8), quiescent CD: 3.5g/d (IQR 2.2), HC: 3.8g/d (IQR

2.1) p=0.001), (Fructans: active CD: 2.9g/d (IQR 1.8), quiescent CD=3.6g/d (IQR 2.1), HC: 3.9g/d (IQR 2.1) p<0.001).[34] Wheat-based products provided the highest percentage contributions of both fructans and oligofructose in those with active CD. Whereas HC consumed significantly more fructans and oligofructose from a broader range of plant-based foods compared to all participants with CD, irrespective of disease activity (p<0.001).

Ulcerative colitis.

Four studies (4/26) compared the fibre intake in UC participants with HC; three studies included participants with active and quiescent disease. Similarly to CD, the results of these studies conflict. One small cross-sectional study found no significant difference in total fibre intake between 11 UC participants of mixed disease activity and 65 HC (UC: 13.5g/d ± 5.6, HC: 15.3g/d ± 6.9).[40, 48] Another cross-sectional study specifically examined soluble and insoluble fibres and found no significant difference in intake between groups (soluble fibre: UC: 3.1g/d ± 1.0, HC: 2.9g/d ± 1.2; insoluble fibre: UC: 9.9g/d ± 2.7, HC: 8.6g/d ± 3.0).[48]

Conversely, a much larger cross-sectional study showed participants with quiescent UC (n=101) had significantly lower intakes of total fibre compared to HC (n=129) (UC: 71.7-88.9% <20g/d, HC: 51.5-51.7% <20g/d, p=0.0004).[35] Additionally, another study using three methods to measure dietary intake in 42 participants with quiescent disease, showed total fibre intake in UC participants was significantly lower than HC (UC: 9.0g/d ± 4.0, HC: 32.0g/d ± 7.0, p= 0.0001), finding UC participants eat less fruits, vegetables, grains and legumes (***Table 4.4***).[41]

Factors associated with dietary fibre intakes of individuals with IBD

Disease type.

Fourteen studies (14/26) reported on fibre intake in participants with IBD, without comparison to HC (***Table 4.4***). Two studies (2/26) examined the difference in fibre intake between participants with CD and UC. A Japanese cross-sectional study of 388 UC and CD found no significant difference in total fibre intake between disease types (total fibre: UC: 12.1g/d ± 4.6, CD: 11.0g/d ± 5.0).[38] In contrast, a large retrospective Canadian study evaluated fibre intakes by quartiles and found participants with UC were 2.6 times more likely to be in the highest quartile for fibre intake when compared to participants with CD (OR: 2.63, 95% CI: 1.91-3.62).[4]

Disease activity.

Aghdassi *et al* 2007 compared participants with quiescent (n=43) and active CD (n=41) and found no significant difference in total fibre intake between groups. There was however, a trend toward a lower fibre intake in those with active CD (active: 14.9g/d ± 1.18, quiescent: 18.3g/d ± 1.28, p=0.052).[54] It is important to note that this study used clinical symptom scores rather than objective markers to

interpret IBD disease activity.[54] Two studies examined soluble and insoluble fibre to determine whether intakes of fibre sub-types and disease activity were associated. Neither study found a statistically significant difference in intake between groups, although both used unvalidated dietary assessment tools.[48, 49]

Rate of relapse.

Four prospective cohort studies (4/26) included participants with quiescent UC and observed the incidence of relapse over time. Total fibre intakes did not significantly differ between participants who maintained remission and those who relapsed (***Table 4.4***). Rates of relapse were not associated with contributions from specific fibrous food groups or intakes of soluble/insoluble fibre (***Table 4.4***).[15, 42, 49, 50] Interpretation of data is limited by unvalidated FFQs.[48, 49]

Food avoidance and malnutrition.

Two studies (2/26) investigated whether fibre intake differed between groups who reported food avoidance (e.g. fruits and vegetables) and those who reported an unrestricted diet. However, no differences in total fibre intake were identified between groups in either study (***Table 4.4***).[13, 37] A small cross-sectional study found malnourished IBD participants (evaluated by a dietitian using subjective global assessment) consumed significantly less total fibre per day than nourished participants (malnourished: 14.2g/d $\pm$ 8.2, nourished: 20.8g/d $\pm$ 5.6, p= 0.013).[44] Pieczynska *et al* observed dietary fibre intakes of less than 20 grams per day were more prevalent in malnourished UC participants or those at risk of malnutrition than well-nourished UC participants, whereas nutritional status was not associated with differing fibre intakes in CD.[35]

Nine studies sub-analysed which foods or food groups contributed to total fibre intake.[4, 21, 23, 34, 40-42, 45, 50] Two studies observed no difference in intake of wholegrains between participants with UC and CD (Wholegrains: CD: 3.3g/d ± 2.8g/d, UC: 3.7g/d ± 2.5g/d and CD:1.0oz eq/d ± 1.4oz eq/d, UC=1.0oz eq/d ± 1.6 oz eq/d (p values not reported).[4, 40] Additionally, Brauer *et al* also observed no difference in intakes of fruits and vegetables (Fruit: CD: 0.9g/d ± 1.0g/d, UC: 1.8g/d ± 2.7g/d; Vegetables: CD: 2.6g/d ± 2.2g/d, UC: 3.3g/d ± 1.7g/d) (p values not reported).[40] However, both D'Odorico *et al* and Rosman-Urbach *et al* observed participants with UC and CD had lower fibre contributions from fruits, vegetables and legumes compared to HC (Fruits: CD: 150.8g/d ± 52.0g/d, UC: 147.6g/d ± 62.0g/d, HC: 201.0g/d ± 41g/d ($p<0.01$); Vegetables: CD: 149.0g/d ± 20.0g/d, UC: 136.1g/d ± 34.0g/d, HC: 166.5g/d ± 53g/d ($p<0.05$) and Fruits: UC<2 serves/d, HC: 5 serves/d; Vegetables: UC<2 serves/d, HC>6 serves/d; Legumes: UC mean intake: 11.2g/d ± 6.6g/d, HC: 21.9g/d ± 6.9g/d (p=0.0001).[41, 45] Similarly, Opstelten *et al* reported IBD participants had lower fibre contributions from vegetables than HC (IBD median: 60.9g (inter quartile range (IQR) 41-94.6), HC: 148g (IQR 95.8 – 200) $p<0.05$, but found no significant differences in intakes of fruit (IBD: 157g (IQR

80.5-226), HC: 212g (IQR 83-238) or cereal (IBD: 56g (IQR 33.1-87.4), HC: 54.9g (IQR 32.5 – 93.6) p value not reported.[23]

Anderson *et al* observed significant differences in intakes of fibrous food commodities contributing fructans and oligofructose to the diet of individuals with CD compared to HC. Higher intakes of fructans and oligofructose derived from wheat sources were observed in participants with active CD compared to those with quiescent CD and UC, with >80% participants consuming <1% fructans and oligofructose from vegetable and fruit sources (Fructans: active CD median: 69.6g (interquartile range (IQR) 40.6), quiescent CD: 62.8g (IQR 37.5), HC: 57.9g (IQR 34.3), p=0.003; Oligofructose: active CD: 70.5g (IQR 39.8), quiescent CD: 64.6g (IQR 34.6), HC: 57.9g (IQR 34.3), p=0.005).[34]

4.4 Discussion

Summary of main findings

This systematic review of 26 studies identified that although data is inconsistent, larger and higher quality studies (66%) found fibre intakes were lower in participants with IBD than HC or were inadequate compared to respective national fibre recommendations, regardless of disease activity. Data conflicted regarding any associations between disease activity, disease type or risk of relapse and fibre intake. Interpretation of findings and the capacity to draw firm generalisable conclusions is limited by small sample sizes, a lack of diversity in sample populations, and heterogeneity in study methodology. This review illustrates the lack of quality data regarding whether participants with IBD are eating enough fibre and any factors associated with habitual fibre intake.

Interpretation

Fibre restriction is widespread in IBD. Walton & Alaunyte 2014 reported almost half of the UC cohort actively avoided fibrous foods such as fruits and vegetables.[7] Similarly, Brotherton *et al* identified 29.6% CD also avoided high fibre foods.[4] The reasons for fibre restriction in individuals with IBD are multifactorial, thought to be influenced by dietary beliefs, self-guided elimination diets, advice from health professionals, or information from the internet.[59] Additionally, with irritable bowel syndrome coexisting in 39% of individuals with IBD, functional symptoms could be driving lower fibre intakes, though existing data does not support this theory.[28, 60, 61] It is also observed that HC populations have inadequate fibre intakes compared to respective national guidelines highlighting a broader public nutrition issue requiring targeted dietary education to this area of dietary inadequacy.[28, 61, 62]

The long-term implications of inadequate fibre intake amongst individuals with IBD are not well understood, however it is known a reduced fibre intake may diminish diversity of the gut microbiota.[3, 25] A diet low in total fibre is also likely to be low in readily fermentable fibres, such as oligosaccharides and resistant starch.[63] Fermentation of these fibres by colonic bacteria results in the production of

SCFA, an important energy source for colonic mucosal cells, while also attenuating negative effects of protein fermentation.[64] Altering substrate for healthy colonic fermentation is associated with structural changes to the microbiota and has the potential to promote inflammation in individuals with IBD, a cohort identified to lack diversity compared to HC.[28, 65-68]

There is growing interest in the differing physicochemical properties of fibres, their nutritional functionality, and how these influence health outcomes.[69] Most studies in this review assessed only total dietary fibre intake without reference to fibre subtypes. Where reported in 3 studies, fibre subtypes were labelled as 'soluble or insoluble', which is a suboptimal and an inconsistent approach to fibre categorisation. Further research is needed to better understand the fermentable properties of different fibres and the significance of their functionality on IBD disease course.[70] In addition to this, more comprehensive and updated data is required in food composition tables to enable analysis of differing contributions of fibres subtypes from specific foods.[71]

Inadequate fibre intakes in individuals with IBD are an important area for nutrition intervention by an experienced IBD dietitian. Goals of dietary management and optimisation of fibre intakes for individuals with IBD should include improving overall quality of diet while also managing symptoms of active disease, strictures, or concurrent functional symptoms.[20] This is also an important area for future research.[72] Further high-quality prospective research is required not only to better measure habitual fibre intake in a large cohort, but to understand factors associated with habitual dietary fibre intake in IBD, before examining whether total fibre intake or intake of specific types of fermentable fibres have a bearing on microbial constitution and function, disease activity and clinical course.[73, 74]

Limitations

Limitations of this systematic review need to be acknowledged. Although a broad search was performed to capture all available data, study quality was relatively poor with heterogeneous methodology which limited meta-analysis of included studies and influenced bridging this important knowledge gap regarding habitual fibre intakes in IBD.[71]

Methods of measuring dietary fibre varied, most subjective, self-reported and without repeated measurements that would otherwise reduce bias and more accurately reflect varying habitual intakes.[75] The weighed food diaries used in eight studies may provide more accurate data as they are typically more representative of a habitual diet than 24-hour recalls or FFQ. However, these methods still rely on reporting accuracy by participants and can be burdensome to complete if required to weigh all food and fluid consumed.[76] While FFQ are simple to use, usually self-administered and therefore cost effective, this frequently used dietary assessment method can have cultural limitations and lacks the ability to detect the influence of dietary beliefs and behaviours on eating patterns and

food choice and therefore intake of fibrous foods, compared to an interview with a trained clinician.[75, 77]

Differences in disease activity and limited use of validated indexes and objective assessment of disease activity hindered capacity for inter-group comparisons and further analysis of an association between fibre intakes and disease activity. Other potential factors that could be associated with dietary fibre intake such as disease duration, IBD surgery, hospitalisation, or corticosteroid use were also not able to be comprehensively assessed due lack of data. Further to this, only 35% of the studies examined included >100 IBD participants, and most studies recruited from single centres (57% studies). Therefore, data was difficult to interpret as other associated factors may not be reflected in these samples.

4.5 Conclusions

In summary, despite heterogeneous and inconsistent data, this systematic review illustrates individuals with IBD eat less total fibre than recommended national dietary guidelines and less than control populations, irrespective of disease activity. This is an important first step in evaluating what is known about habitual fibre intakes in IBD, however, factors associated with fibre intake require further investigation as this review has identified many limitations preventing further synthesis and appraisal of current evidence.

Figures

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions (R) From inception to December 11th 2019		
#	**Searches**	**Results**
1	inflammatory bowel diseases/ or colitis, ulcerative/ or crohn disease/ or proctocolitis/ or colitis/	86450
2	("Inflammatory bowel disease*" or (ulcerative adj1 colitis) or proctocolitis or colitis or (Crohn* adj1 disease)).tw,kf.	104452
3	or/1-2	118453
4	dietary fibre/ or prebiotics/ or exp Oligosaccharides/	98787
5	(fibre* or fibre* prebiotic* or inulin or Resistant starch or Pectin* or Guar gum or Psyllium or Ispaghula or Beta glucan* or Beta-glucan* or oat* or wheat bran or wheat-bran or lignin or flax* or cellulose or Sterculia or Methylcellulose or Oligosaccharide* or Oligo-saccharide* or FODMAP* or fructan* or Fructo-oligosaccharide* or Galacto-oligosaccharide* or Galactooligosaccharide*).tw,kf.	205641
6	or/4-5	280290
7	diet/	144780
8	FOOD/	30657
9	(diet* or nutri* or food*).tw,kf.	1067306
10	7 or 8 or 9	1104056
11	6 or 10	1340616
12	(intake* or consumption or consume or amount or eat or ingest).tw,kf.	880450
13	11 and 12	267152
14	3 and 13	1361
15	exp Animals/ not Humans/	4486179
16	(rat or rats or mice or murine or mouse or rodent* or pig or pigs or swine or bovine or horse* or equine or monkey*).ti.	1636197
17	15 or 16	4755997
18	14 not 17	1103
19	limit 18 to english language	982
	Total number of citations:	**982**
EBSCOhost Research Databases- CINAHL		
#	**Searches**	**Results**
S21	S18 NOT S19	151
S20	S18 NOT S19	152
S19	TI (rat or rats or mice or murine or mouse or rodent* or pig or pigs or swine or bovine or horse* or equine or monkey*)	29,827
S18	S5 AND S17	162
S17	S15 AND S16	34,619

S16	TI ((intake* or consumption or consume or amount or eat or ingest)) OR AB ((intake* or consumption or consume or amount or eat or ingest))	91,461
S15	S9 OR S14	158,453
S14	S10 OR S11 OR S12 OR S13	152,335
S13	TI ((diet* or nutri* or food*)) OR AB ((diet* or nutri* or food*))	137,811
S12	(MH "Nutrients")	1,768
S11	(MH "Food")	7,895
S10	(MH "Diet")	30,574
S9	S6 OR S7 OR S8	10,446
S8	TI ((fibre* or fibre* prebiotic* or inulin or "Resistant starch" or Pectin* or "Guar gum" or Psyllium or Ispaghula or "Beta glucan*" or "Beta-glucan*" or oat* or "wheat bran" or "wheat-bran" or lignin or flax* or cellulose or Sterculia or Methylcellulose or Oligosaccharide* or Oligo-saccharide* or FODMAP* or fructan* or Fructo-oligosaccharide* or Galacto-oligosaccharide* or Galactooligosaccharide*)) OR AB ((fibre* or fibre* prebiotic* or inulin or "Resistant starch" or Pectin* or "Guar gum" or Psyllium or Ispaghula or "Beta glucan*" or "Beta-glucan*" or oat* or "wheat bran" or "wheat-bran" or lignin or flax* or cellulose or Sterculia or Methylcellulose or Oligosaccharide* or Oligo-saccharide* or FODMAP* or fructan* or Fructo-oligosaccharide* or Galacto-oligosaccharide* or Galactooligosaccharide*))	5,630
S7	(MH "Prebiotics")	603
S6	(MH "Dietary Fibre") OR (MH "Oligosaccharides") OR (MH "Polysaccharides")	5,648
S5	S1 OR S2 OR S3 OR S4	7,882
S4	TI (("inflammatory bowel disease*" or (ulcerative N1 colitis) or proctocolitis or colitis or (crohn* N1 disease))) OR AB (("inflammatory bowel disease*" or (ulcerative N1 colitis) or (crohn* N1 disease)))	5,877
S3	(MH "Crohn Disease")	2,725
S2	(MH "Colitis, Ulcerative")or (MH colitis)	2,555
S1	(MH "Inflammatory Bowel Diseases")	2,554
S1	Limiters – Language: English	
	Total number of citations:	**151**
	Scopus Database	
#	**Searches**	**Results**
1	TITLE-ABS-KEY ((fibre* OR fibre* AND prebiotic* OR inulin OR "Resistant starch" OR pectin* OR "Guar gum" OR psyllium OR ispaghula OR "Beta glucan*" OR beta-glucan* OR oat* OR "wheat bran" OR wheat bran OR lignin OR flax* OR cellulose OR sterculia OR methylcellulose OR oligosaccharide* OR oligo-saccharide* OR fodmap* OR fructan* OR fructo-oligosaccharide* OR galacto-oligosaccharide* OR galactooligosaccharide*or AND diet* OR nutri* OR food*)) AND TITLE-ABS-KEY ((intake* OR consumption OR consume OR amount OR eat OR ingest)) AND TI	

	TLE-ABS-KEY (("Inflammatory bowel disease*" OR (ulcerative W/1 colitis) OR proctocolitis OR colitis OR (crohn* W/1 dise ase))) AND NOT TITLE ((rat OR rats OR mice OR murine OR mouse OR rodent* OR pig OR pig s OR swine OR bovine OR horse* OR equine OR monkey*)) AND (LIMIT-TO (LANGUAGE , "English "))	
	Total number of citations:	**109**
ProQuest Database		
#	**Searches**	**Results**
1	noft((fibre* OR fibre* prebiotic* OR inulin OR "Resistant starch" OR Pectin* OR "Guar gum" OR Psyllium OR Ispaghula OR "Beta glucan*" OR Beta-glucan* OR oat* OR "wheat bran" OR wheat-bran OR lignin OR flax* OR cellulose OR Sterculia OR Methylcellulose OR Oligosaccharide* OR Oligo-saccharide* OR FODMAP* OR fructan* OR Fructo-oligosaccharide* OR Galacto-oligosaccharide* OR Galactooligosaccharide* OR diet* OR nutri* OR food*)) AND noft((intake* OR consumption OR consume OR amount OR eat OR ingest)) AND noft(("Inflammatory bowel disease*" OR (ulcerative NEAR/1 colitis) OR proctocolitis OR colitis OR (Crohn* NEAR/1 disease))) NOT ti(8 (rat OR rats OR mice OR murine OR mouse OR rodent* OR pig OR pigs OR swine OR bovine OR horse* OR equine OR monkey*)) Exclude: Trade Journals and Magazines Limit to: English Language	
	Total number of citations:	**946**
Cochrane Library		
#	**Searches**	**Results**
1	'(fibre* or fibre* prebiotic* or inulin or “Resistant starch” or Pectin* or “Guar gum” or Psyllium or Ispaghula or “Beta glucan*” or Beta-glucan* or oat* or “wheat bran” or wheat-bran or lignin or flax* or cellulose or Sterculia or Methylcellulose or Oligosaccharide* or Oligo-saccharide* or FODMAP* or fructan* or Fructo-oligosaccharide* or Galacto-oligosaccharide* or Galactooligosaccharide* or diet* or nutri* or food*) in Title Abstract Keyword AND (intake* or consumption or consume or amount or eat or ingest) in Title Abstract Keyword AND ("Inflammatory bowel disease*" or (ulcerative NEAR/1 colitis) or proctocolitis or colitis or (Crohn* NEAR/1 disease)) in Title Abstract Keyword NOT 8 (rat or rats or mice or murine or mouse or rodent* or pig or pigs or swine or bovine or horse* or equine or monkey*) in Title Abstract Keyword - (Word variations have been searched)	
	Total number of citations:	**244**

Figure 4.1 Complete search strategy.

Legend: *Conducted including the search terms used and number of citations retrieved from each electronic database for the systematic review investigating habitual fibre intake of individuals with inflammatory bowel disease.*

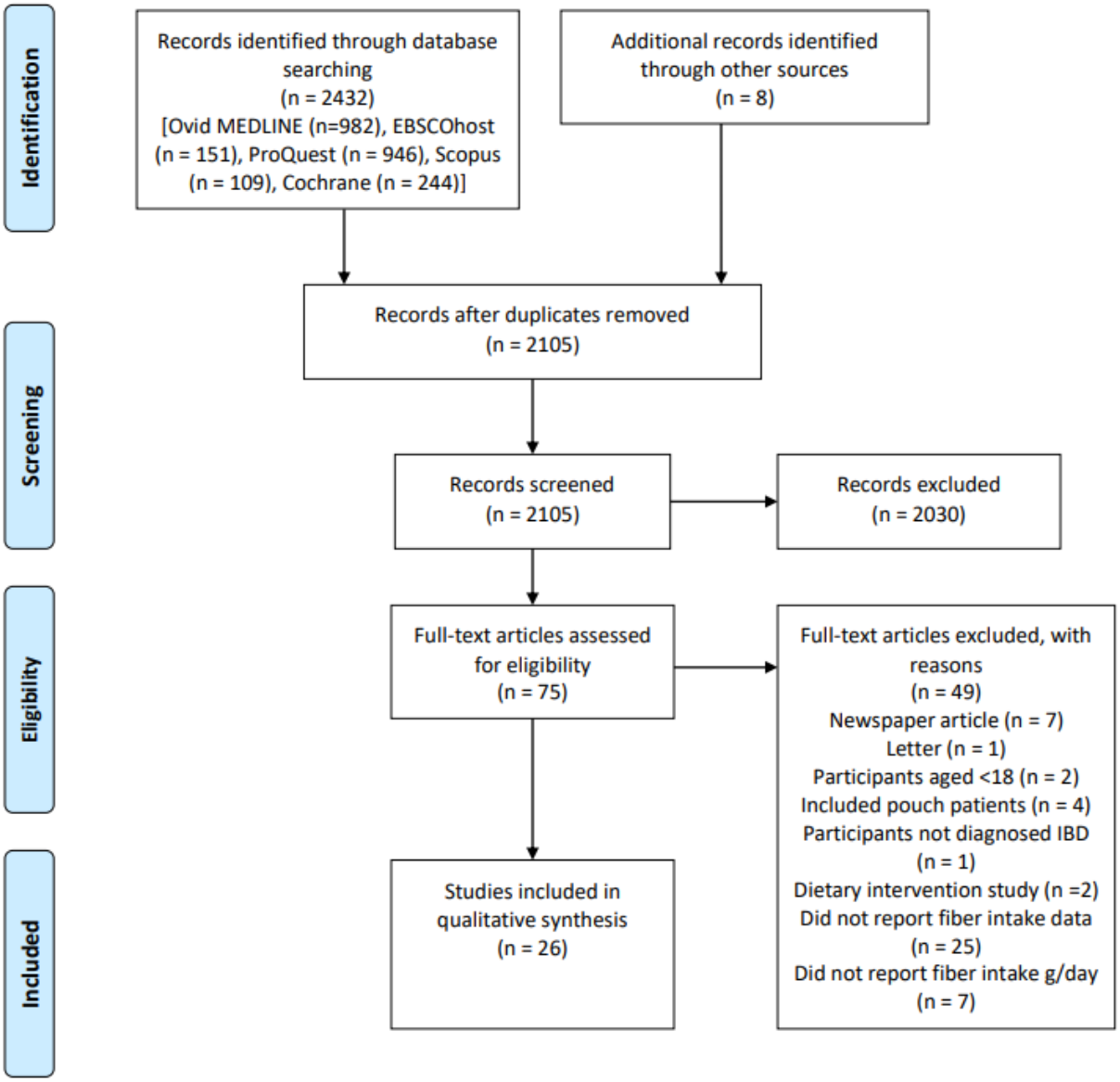

Figure 4. 2 PRISMA flow chart

Legend: *Outlines search methods conducted for systematic review investigating habitual fibre intake of individuals with inflammatory bowel disease.*

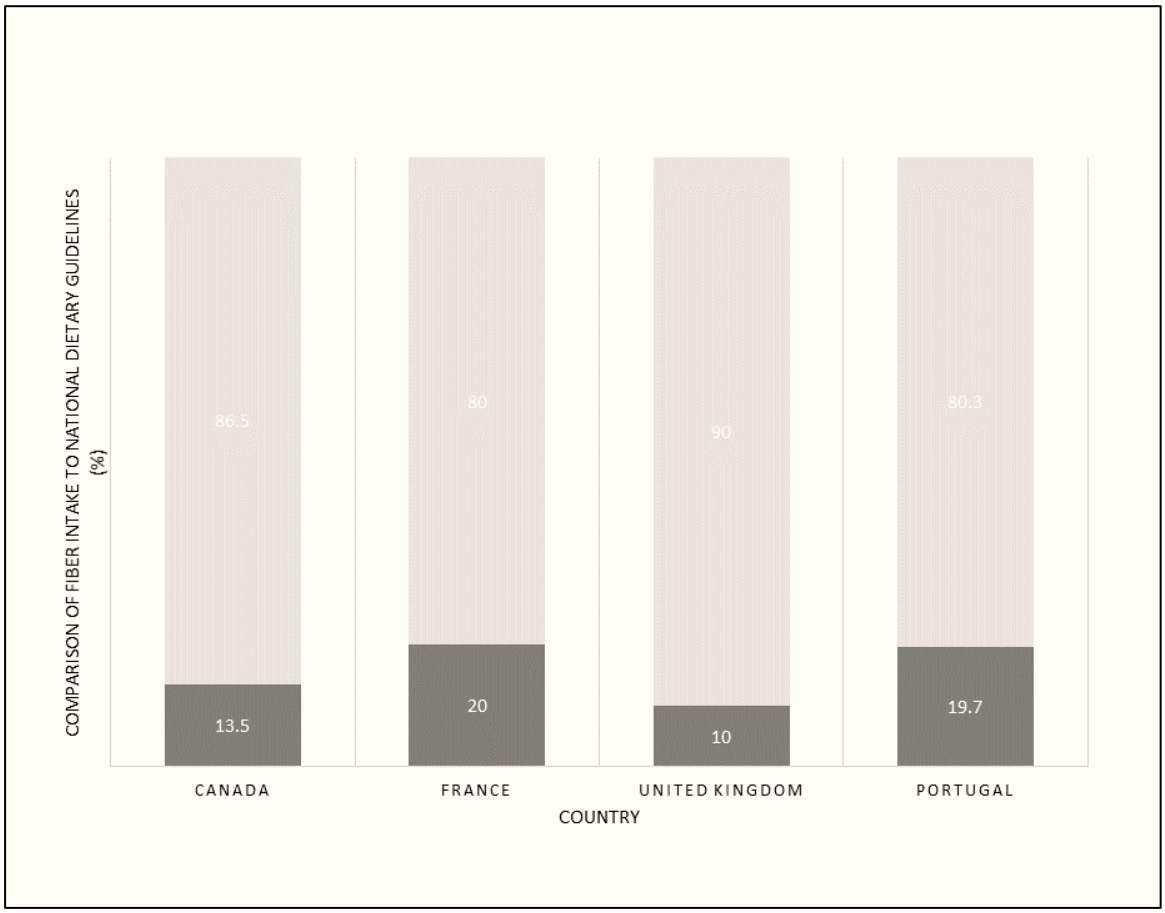

Figure 4. 3 Habitual fibre intakes of individuals with inflammatory bowel disease compared to population dietary fibre guidelines.

Legend: *[a]Data derived from population based studies providing data on fibre as a percentage of total intake[7, 46, 47, 54]*

% with adequate daily fibre intakes[a]

% with inadequate daily fibre intakes[a]

Tables

Table 4.1 Established inclusion and exclusion criteria and data extracted for systematic review investigating habitual dietary fibre intake in individuals with inflammatory bowel disease.

PICOS[a]	Inclusion criteria	Data extracted
Patient	Inclusion: Human participants, ≥ 18 years old, diagnosed with Crohn's Disease or Ulcerative Colitis before study enrollment. Exclusion: Animal studies, children ≤18 year's old, pregnant women, patients with an ileal anal pouch.	Number of patients recruited, age, sex, IBD[b] phenotype, disease type, disease activity, location of recruitment.
Intervention	Inclusion: Studies measuring usual dietary fibre intake (using tools such as food diaries, food frequency questionnaires or 24-hour dietary recalls) Exclusion: Dietary intervention studies where fibre intakes are prescribed, controlled or restricted, studies where fibre supplementation has been provided.	Dietary assessment tool used to measure fibre intake in grams per day, timeframe dietary intake was measured, sub type of dietary fibre measured.
Comparator	Inclusion: Studies with or without control groups, studies with or without national dietary fibre guidelines, studies comparing fibre intakes between IBD phenotype or disease activity.	Number of subjects in control group, age, sex, location of recruitment, whether control group matched for age and sex, country of dietary fibre guideline
Outcomes	Studies reporting on fibre intake in grams per day, dietary sources providing fibre in habitual diet, relevant study end points (remission rates, rates of relapse, disease activity).	Total fibre intake and intakes of fibre sub-types reported in grams per day, contributions from different fibrous foods, other variables identified as having an association with dietary fibre intake (nutritional status, gastrointestinal symptoms, food beliefs, food exclusions followed). Comparison of end point data between groups.
Study design	Inclusion: Primary studies. Exclusion: Review articles, expert opinions, newspaper articles, and letters.	Authors, publication details, type of study design. Full text or abstract.

Legend: *[a]PICOS, patient, intervention, comparator, outcome, study design; [b]IBD, inflammatory bowel disease.*

Table 4.2 Characteristics of 26 studies included in systematic review which report on habitual dietary fibre intake in individuals with inflammatory bowel disease.

	Sample size		Inflammatory Bowel Disease		Study design	
Authors Year Country	**Number of patients**	**Healthy controls[a]**	**Disease activity**	**Index reported**	**Design**	**Quality rating and grade[33]**
Aghdassi *et al* 2007[54] Canada	74 CD[b]	-	43 CD quiescent / 31 CD active	CDAI[c]	Cross-sectional	Level D Neutral (∞)
Anderson *et al* 2015[34] United Kingdom	197 CD	106 HC[d]	99 CD quiescent / 98 CD active	HBI[e]	Cross sectional	Level D Positive (+)
Brauer *et al* 2013[40] Canada	23 CD 11 UC[f] 15 IBS[g] 36 other GI[h]	65 HC *all female*	23 CD quiescent 11 UC not specified	CDAI UC not reported	Cross-sectional	Level D Neutral (∞)
Brotherton *et al* 2016[4] United States of America	1130 CD 489 UC / IBD[i]-unclassified	-	1130 CD quiescent 489 UC / IBD-unclassified quiescent	CDAI SCCAI[i]	Retrospective cohort	Level B Neutral (∞)
D'Odorico *et al* 2001[45] Italy	33 CD 43 UC	386 HC	23 CD quiescent / 10 CD active 28 UC quiescent / 15 CD active	CDAI Powell-Tuck	Cross-sectional	Level D Neutral (∞)
Dhingra *et al* 2017[49] India	97 UC	-	79 UC quiescent / 18 UC relapsed	UCDAI[k]	Prospective cohort	Level B Positive (+)
Filippi *et al* 2006[46] France	54 CD	25 HC	54 CD quiescent	CDAI	Cross-sectional	Level D Neutral (∞)
Glabeska *et al* 2019[55] Poland	56 UC	-	56 UC quiescent	Mayo / Rachmilewitz / endoscopy	Prospective cohort	Level B Neutral (∞)
Guerreiro *et al* 2007[47] Portugal	78 CD	80 HC	78 CD quiescent or mildly active	HBI	Cross-sectional	Level D Neutral (∞)

Jowett *et al* 2004a[21] United Kingdom	183 UC	-	183 UC quiescent	SCCAI	Prospective cohort	Level B Neutral (⇔)
Jowett *et al* 2004b[15] United Kingdom	183 UC	-	87 UC quiescent / 96 UC relapsed	SCCAI	Prospective cohort	Level B Positive (+)
Kawakami *et al* 2007[48] Japan	58 UC	29 HC	21 UC quiescent / 8 UC active	Truelove and Witts	Cross-sectional	Level D Neutral (⇔)
Keshteli *et al* 2017[42] Canada	20 UC	-	13 UC quiescent / 7 UC relapsed	Partial Mayo	Prospective cohort	Level B Neutral (⇔)
Lim *et al* 2014[44] South Korea	15 CD 26 UC	-	15 CD quiescent 26 UC active (15 UC mild / 9 UC moderate / 2 UC severe)	CDAI Truelove and Witts	Cross-sectional	Level D Neutral (⇔)
Lim *et al* 2018[37] South Korea	61 CD 43 UC	-	75 IBD quiescent / 29 IBD active	Not reported	Cross-sectional	Level D Neutral (⇔)
Lomer *et al* 2004[52] United Kingdom	91 CD	91 HC	91 CD quiescent	Not reported	Cross-sectional	Level D Neutral (⇔)
Opstelten *et al* 2018[23] Netherlands	91 CD 68 UC 6 IBD-unclassified	1469 HC	135 IBD quiescent / 30 IBD active	Endoscopy Invalidated index	Cross-sectional and longitudinal prospective cohort	Level B Neutral (⇔)
Piecyznska *et al* 2018[35] Poland	61 CD 101 UC	129 HC	61 CD quiescent 101 UC quiescent	CDAI Mayo score	Cross-sectional	Level D Neutral (⇔)
Principi *et al* 2018[36] Italy	84 CD 66 UC	100 HC	84 CD quiescent 66 UC quiescent	HBI Partial Mayo	Cross-sectional	Level D Neutral (⇔)
Ripoli *et al* 2010[50] Brazil	65 UC	-	24 UC quiescent / 41 UC relapsed	SCCAI	Prospective cohort	Level B Neutral (⇔)
Rosman-Urbach *et al* 2006[41]	42 UC	37 HC	42 UC quiescent	Not reported	Cross-sectional	Level D Neutral (⇔)

Israel						
Tanaka *et al* 2007[39] Japan	26 UC	-	26 UC quiescent	Not reported	Cross-sectional	Level D Neutral (ø)
Vidarsdottir *et al* 2015[53] Iceland	43 CD 35 UC	-	Cohort reported as predominantly quiescent	Not reported	Cross-sectional	Level D Neutral (ø)
Wada *et al* 2015[38] Japan	156 CD 232 UC	-	156 CD quiescent 232 UC quiescent	CDAI CAI[l]	Cross-sectional	Level D Neutral (ø)
Walton & Alaunyte 2014[7] United Kingdom	93 UC	-	93 UC not specified	Not reported	Cross-sectional	Level D Neutral (ø)
Wardle *et al* 2018[43] United Kingdom	30 CD	31 HC	30 CD active	FC[m], endoscopy, imaging	Cross-sectional	Level D Neutral (ø)

Legend: *[a]Healthy control groups either matched for age and sex or no statistical difference between groups; [b]CD, Crohn's disease; [c]CDAI, Crohn's disease activity index; [d]HC, healthy control; [e]HBI, Harvey Bradshaw index; [f]UC, ulcerative colitis; [g]IBS, irritable bowel syndrome; [h]GI, gastrointestinal; [i]SCCAI, simple clinical colitis activity index; [j]IBD, inflammatory bowel disease; [k]UCDAI, ulcerative colitis disease activity index; [l]CAI, Lichtiger clinical activity index; [m]FC Faecal Calprotectin.*

Table 4.3 Academy of Nutrition and Dietetics Quality Criteria Checklist scores and overall ratings for studies included in systematic review.[33]

		Validity questions[b]										
Author(s) Year	**Relevance questions[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Quality[c]**
Aghdassi *et al.* 2007[54]	Y[d]	Y	N[e]	U[f]	N	U	NA[g]	Y	U	Y	Y	Ø[h]
Anderson *et al.* 2015[34]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	U	+[i]
Brauer *et al.* 1983[40]	Y	Y	U	U	N	Y	NA	Y	Y	U	Y	Ø
Brotherton *et al.* 2016[4]	Y	Yes	U	Y	NA	U	U	U	Y	Y	U	Ø
D'Odorico *et al.* 2001[45]	Y	Y	N	U	N	U	Y	U	U	U	U	Ø
Dhingra *et al.* 2017[49]	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	+
Filippi *et al.* 2006[46]	Y	Y	Y	Y	U	U	Y	Y	U	U	U	Ø
Glabeska *et al.* 2019[55]	Y	Y	U	U	N	N	N	N	Y	N	Y	Ø
Guerreiro *et al.* 2007[47]	Y	Y	U	U	N	U	Y	Y	U	U	U	Ø
Jowett *et al.* 2004a[21]	Y	Y	Y	Y	Y	U	U	Y	U	Y	U	Ø
Jowett *et al.* 2004b[21]	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	+
Kawakami *et al.* 2007[48]	Y	Y	N	U	N	U	U	U	U	N	N	Ø

Keshteli *et al.* 2017[42]	Y	Y	U	Y	U	U	Y	Y	U	Y	Y	Ø
Lim *et al.* 2014[44]	Y	Y	U	Y	Y	U	Y	Y	U	U	Y	Ø
Lim *et al.* 2018[37]	Y	Yes	U	U	Y	U	Y	U	U	U	Y	Ø
Lomer *et al.* 2004[52]	Y	Y	U	Y	Y	Y	Y	U	U	Y	U	Ø
Opstelten *et al.* 2018[23]	Y	Y	U	Y	U	U	Y	U	Y	Y	Y	Ø
Pieczynska *et al.* 2018[35]	Y	Y	U	U	N	U	Y	U	U	U	Y	Ø
Principi *et al.* 2018[36]	Y	Y	U	Y	N	U	Y	Y	U	Y	U	Ø
Ripoli *et al.* 2010[50]	Y	Y	U	U	Y	U	Y	Y	U	U	U	Ø
Rosman-Urbach *et al.* 2006[41]	Y	Y	U	Y	N	U	Y	U	U	U	U	Ø
Tanaka *et al.* 2007[39]	Y	Y	U	NA	N	U	Y	U	U	Y	Y	Ø
Vidarsdottir *et al.* 2016[53]	Y	Y	U	Y	N	U	Y	U	Y	Y	Y	Ø
Wada *et al.* 2015[38]	Y	Y	Y	Y	Y	U	U	U	U	U	U	Ø
Walton & Alaunyte 2014[7]	Y	Y	U	NA	N	U	Y	U	U	Y	Y	Ø
Wardle *et al.* 2018[43]	Y	Y	U	Y	N	N	N	Y	Y	Y	Y	Ø

Legend: *[a]Four relevance questions are included in the Quality Criteria Checklist: 1) Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? 2) Did the authors study an outcome of interest (dependent variable) or topic that the patients/clients/population group would care about? 3) Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice? 4) Is the intervention or procedure feasible? Possible answers include yes (Y), no (N), unsure (U), not applicable (NA);*

[b]Ten validity questions are included in the Quality Criteria Checklist: 1) Was the research question clearly stated? 2) Was the selection of study subjects/patients free from bias? 3) Were study groups comparable? 4) Was the method of handling withdrawals described? 5) Was blinding used to prevent introduction of bias? 6) Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described? 7) Were outcomes clearly defined and the measurements valid and reliable? 8) Was the statistical analysis appropriate for the study design and type of outcome indicators? 9) Are conclusions supported by results with biases and limitations taken into consideration? 10) Is bias due to study's funding or sponsorship unlikely?

[c]Final rating for each study as agreed by both reviewers (A.S.D. and R.D.) are reported. An assignment of the overall quality criteria checklist rating is provided as follows: Negative (-): If most (6 or more) of the answers to the 10 validity questions are 'no,' the report should be designated with a (-) symbol. Neutral (Ø): If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (Ø) symbol. Positive (+): If most of the answers to the above validity questions are "yes" (including criteria 2, 3, 6, 7 and at least one additional "yes"), the report should be designated with a (+) symbol.

[d]Y, yes; [e]N, no; [f]U, unsure; [g]NA, non-applicable; [h]Ø, neutral; [i]+, positive.

Table 4.4 Methods used to measure habitual dietary fibre of individuals with inflammatory bowel disease and factors associated with fibre intake

	Methods of measuring fibre intake		Fibre intake *Quiescent vs. active disease*				Fibre intake *Other comparators*			
Study reference	**Dietary assessment tool**	**Type of fibres**	**Unspecified (g/d)[a]**	**Quiescent (g/d)**	**Active (g/d)**	**Relapse (g/d)**	**National dietary guidelines**	**Control groups (g/d)**	**Significance between groups**	**Factors associated with fibre intake**
Aghdassi *et al* 2007[54]	7-day food diary	Total fibre	CD[b] 16.91g/d ±[c] 0.95[d]	18.3g/d ± 1.28[d]	14.9g/d ± 1.18[d]	-	Canada Men 30-38g/d Women 21-25g/d	-	Active vs.[e] quiescent CD (p=0.052) 86.5%[f] CD reported not meeting dietary reference intake for fibre	Active CD associated with lower fibre intake
Anderson *et al* 2015[34]	1-week validated 23-item FFQ[g]	Fructans Oligosaccarides	-	CD: Fructans 3.6 (2.1)[h] CD: Oligofructose 3.5 (2.2)[h]	CD: Fructans 2.9 (1.8)[h] CD: Oligofructose 2.8 (1.8)[d]	-	-	Fructans 3.9 (2.1)[h] Oligofructose 3.8 (2.1)[h]	Quiescent CD and control vs. active CD Fructans p<0.001 Oligofructose p=0.001	Active CD associated with lower fermentable fibre intake
Brauer *et al* 1983[40]	48-hour recall conducted by dietitian	Total fibre	CD:13.3 ± 9.3[d] UC[i]: 13.5 ± 5.6[d]	-	-	-	Canada: Men 30-38g/d Women 21- 25g/d	15.3 ± 6.9[d]	CD and UC vs. control (no p value)	CD and UC associated with lower fibre intakes
Brotherton *et al* 2016[4]	1-month online 26-item	Total fibre	-	CD: 16.0g/d ± 6.5[d]	-	-	-	-	Quiescent CD vs. quiescent UC	CD associated with lower fibre intake

	validated questionnaire			UC: 18.0g/d ± 7.4[d]					(OR[k]: 2.63 95% CI[l]: 1.91-3.62), (no p value)	
D'Odorico*et al* 2001[45]	Daily, weekly, annual intake by validated 99-item FFQ completed with researcher	Total fibre	CD: 16.4 ± 1.6[d] UC: 15.5 ± 1.2[d]	-	-	-	-	20.1 ± 2.4[d]	CD and UC vs. HC p <0.0001	CD and UC associated with lower fibre intake
Dhingra *et al* 2017[49]	Daily and weekly intake by open ended invalidated semi-quantitative FFQ	Total fibre Soluble and insoluble fibre	-	UC maintained remission: Total fibre 9.9g/d ± 7.8[d] Soluble fibre: 2.4g/d ± 1.7 Insoluble fibre 7.4± 6.1	-	UC relapsed: Total fibre 10.6g/d ± 5.5[d] Soluble fibre 2.6g/d± 1.5 Insoluble fibre 7.9± 4.0	-	-	UC remission vs. relapse Total fibre in remission vs. relapse (p=0.79) Soluble fibre remission vs. relapse (p=0.69) Insoluble fibre remission vs. relapse (p=0.73)	Rate of relapse not associated with fibre intake
Filippi *et al* 2006[46]	3-day food diary	Total fibre	-	CD: 16.7 ± 1.2[d]	-	-	France 25g/d	14.7 ± 0.9	CD vs. HC No significant difference (no p value)	CD not associated with differing fibre intake

Glabeska *et al* 2019[55]	3-day weighed food diary	Total fibre	**U**C Tenesmus: 5-14g/d[i] UC Flatulence: 5-13g/d[i] UC constipation: 5-14g/d[i]	-	-	-	-	-	UC groups based on symptoms No significance difference between groups (no p value)	UC symptoms not associated with differing fibre intakes
Guerreiro *et al* 2007[47]	12 month intake by validated semi-quantitative 86-item FFQ	Total fibre	CD: 21.0 ± 10.5[d]	-	-	-	Portugal DRI[m]	32.2 ± 13.7[d]	CD vs. control (p= 0.02)	CD associated with lower fibre intake
Jowett *et al* 2004a[21]	Validated 107-item FFQ	Total fibre	UC avoiding F&V[n]: 16.7g/d[o] UC unrestricted diet-: 16.3g/d[p]	-	-	-	-	-	UC with reported dietary restriction vs. UC without reported dietary restriction (p=0.97)	Unrestricted diet not associated with increased fibre intake
Jowett *et al* 2004b[15]	Validated 107-item FFQ	Total fibre	-	UC maintained remission: 16.3g/d[c]	-	UC relapsed: 16.4g/d[c]	-	-	UC remission vs. relapse (p=0.954)	UC relapse not associated with differing fibre intake

Kawakami *et al* 2007[48]	1-week FFQ	Soluble and insoluble fibre	UC soluble fibre: 3.1 ± 1.0[d] UC insoluble fibre 9.9 ± 2.7[d]	UC soluble fibre: 3.1 ± 1.1[d] UC insoluble fibre 10.0± 2.8[d]	UC soluble fibre: 2.9 ± 0.8[d] UC insoluble fibre 9.6± 2.6[d]	-	-	Soluble fibre 2.9 ± 1.2[d] Insoluble fibre 8.6± 3.0[d]	Quiescent UC vs. active UC vs. control No significant difference (no p value)	UC disease activity not associated with differing intakes of soluble or insoluble fibre
Keshteli *et al* 2017[42]	12 month intake by validated self-administered, semi-quantitative FFQ	Total fibre	-	UC maintained remission: 16.1g/d (13.5-26.0)[h]	-	UC relapsed: 14.1g/d (9.7-22.2)[h]	-	-	UC remission vs. relapse (p=0.32)	UC relapse not associated with differing fibre intake
Lim *et al* 2014[44]	Three 24-hr recalls conducted by dietitian	Total fibre	IBD[p]: 18.1g/d ± 7.5[d] Nourished IBD: 20.8g/d ± 5.6[d] Malnourished IBD: 14.2g/d ± 8.2[d]	-	-	-	-	-	Nourished vs. malnourished (p=0.013)	Malnutrition associated with lower fibre intake
Lim *et al* 2018[37]	3-day food diary	Total fibre	IBD: 8.8g/d ± 5.7[d]	-	-	-	-	-	IBD unrestricted diet vs. food exclusion (p=0.547)	Unrestricted diet not associated

			Food exclusion group: 8.4g/d ± 5[d] No food exclusion group: 9.5g/d ± 7.9[d]							with increased fibre intake
Lomer *et al* 2004[52]	7-day weighed food diary	Total fibre	CD: 12.0 ± 5.05[d]	-	-	-	United Kingdom 18g/d DRV[q]	14.0 ± 5.05[d]	CD vs. control (p=0.001)	CD associated with lower fibre intake
Opstelten *et al* 2018[23]	1-month validated self-administered, semi-quantitative FFQ	Total fibre	IBD: 21.5 (17.2-25.3)[h]	Non-relapse IBD: 21.5g (17.4-24.9)[h]	-	Relapse IBD: 21.3g (16.9-25.9)[h]	-	24.1 (20.2-28.9)[h]	IBD vs. control -2.19 95% CI -3.05-1.32 (p <0.05) IBD Relapse vs. non-relapse 3.65 95% CI 1.44 – 9.26 (p=0.085)	IBD associated with lower fibre intake Relapsing IBD associated with lower fibre intake
Pieczynska *et al* 2018[35]	1-month validated cross-check dietary history conducted by dietitian	Total fibre	-	<20g/d: CD nourished 62.3%	-	-	-	<20g/d: Control group for CD 51.7% Control group for UC 51.5%	CD vs. control (p=0.011) CD vs. nutritional status (not significant, no p value)	CD and UC associated with lower fibre Poorer nutritional status in UC

				CD risk of / malnutrition 74.9% UC nourished 71.7% UC risk of / malnutrition 88.9%					UC vs. control (p=0.0004) UC vs. nutritional status (p=0.028)	associated with lower fibre intake
Principi *et al* 2018[36]	7-day food diary	Total fibre	-	IBD: 11.9 ± 4.7[d] CD: 11.9 ± 4.6[d] UC: 11.6 ± 0.65[d]	-	-	-	15.5 ± 8.35[d]	IBD remission vs. control (p<0.01)	IBD in remission associated with lower fibre intake
Ripoli *et al* 2010[50]	3-day food record	Total fibre	-	UC 12.9g/d ± 8.27[d]	UC 12.44g/d± 9.23[d]	-	-	-	UC remission vs. active UC (p=0.835)	Active UC not associated with differing fibre intake
Rosman-Urbach *et al* 2006[41]	Validated FFQ, 7-day food diary and 24-hr recall conducted with dietitian	Total fibre	-	UC: 9.0 ± 4.0[d]	-	-	-	32.0 ± 7.05[d]	UC remission vs. control (p=0.0001)	UC in remission associated with lower fibre intake

Tanaka *et al* 2007[39]`	1-month validated self-administered diet history questionnaire	Total fibre	-	UC males: 11.8g/d ± 4.6[d] UC females: 12.6g/d ± 6.6[d]	-	-	-	-	UC male vs. UC female (no p value)	Sex not associated with lower fibre intake in UC
Vidarsdottir *et al* 2015[53]	3-day food diary including two weekdays and one weekend day	Total fibre	IBD: 17.5g/d ± 6.7[d]	-	-	-	Iceland 23g/d	Icelandic dietary survey 2011 17g/d	IBD vs. control (no p value)	IBD associated with lower fibre intake
Wada *et al* 2015[38]	150-item self-administered diet history questionnaire	Total fibre Soluble & Insoluble fibre	-	IBD: 11.7g/d ± 4.7[d] UC: 12.1g/d ± 4.6[d] CD: 11.0g/d ± 5.0[d]	-	-	-	-	IBD vs. UC vs. CD (no p value)	Disease type not associated with differing fibre intake
Walton & Alaunyte 2014[7]	24-hour recall	Total fibre	UC: 11g/d[i]	-	-	-	United Kingdom DRV 18g/d	-	UC vs. DRV ($p<0.001$)	UC associated with low fibre intake
Wardle *et al* 2018[43]	24-hour dietary recall	Total fibre	CD: 18.9 ± 2.1[d]	-	-	-	United Kingdom 18g/d DRV	23.4 ± 2.3[d]	p value not reported	Sex CD males: 21.2 ± 3.0[d] CD females: 15.9 ± 2.6[d]

Legend: *[a]g/d, grams per day; [b]CD, Crohn's Disease; [c]±, plus or minus; [d]Mean ± SD, standard deviation; [e]vs., versus; [f]%, percent; [g]FFQ, food frequency questionnaire; [h]Median (Inter Quartile Range); [i]Mean; [j]UC, ulcerative colitis; [k]OR, odds ratio; [l]CI, confidence interval; [m]DRI, dietary reference intake; [n]F&V, fruits and vegetables; [o]Median; [p]IBD, Inflammatory bowel disease; [q]DRV, dietary reference values*

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CHAPTER 5

Food-related quality of life in adults with inflammatory bowel disease is associated with restrictive eating behaviour, disease activity and surgery: a prospective multi-centre observational study

Published in *Journal of Human Nutrition and Dietetics*

May 2021

CHAPTER 5: Food-related quality of life in IBD

Background

The food avoidance and restrictive dietary behaviours presented in ***chapter 3*** are known to influence health-related quality of life (HRQoL), however, the psychosocial impact of eating and drinking has been a neglected area of inflammatory bowel disease (IBD) research. The examination of diet and IBD has typically focused on diet and disease pathogenesis or diet to manage symptoms or nutrition-related complications. Patient-reported outcomes (PRO) are influencing conventional treatment paradigms to include patient-centric measures of treatment efficacy and symptom control.[1] Despite diet reported as the primary psychosocial need affected by IBD, until recently, there had not been a specific outcome measure for determining how diet and quality of life (QoL) are affected by IBD.[2, 3]

The food-related quality of life (FRQoL) instrument directly measures a patient's perspective of how QoL is being influenced by daily food-related challenges including co-existing dietary beliefs and dietary behaviours. A more in-depth understanding of FRQoL and factors associated with poorer or greater FRQoL could assist with more targeted, individualised dietary counselling for the patient to improve the overall QoL and wellbeing of people with IBD.

This multi-centre prospective cross-sectional study aimed to characterise the FRQoL of individuals with IBD across three tertiary IBD services in South Australia and comprehensively examine patient- and disease-related predictors of FRQoL including any association between food avoidance and restrictive eating behaviour and psychological distress.

Presented in this chapter is manuscript #3 entitled *Food-related quality of life in adults with inflammatory bowel disease is associated with restrictive eating behaviour, disease activity and surgery: a prospective multi-centre observational study*, published in Journal of Human Nutrition 2021.

Statement of authorship

Title of Paper	Food-related quality of life in adults with inflammatory bowel disease is associated with restrictive eating behaviour, disease activity and surgery: a prospective multi-centre observational study
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	**Day, AS**, Yao, CK, Costello, SP, Andrews, JM, Bryant, RV. Food-related quality of life in adults with inflammatory bowel disease is associated with restrictive eating behaviour, disease activity and surgery: A prospective multicentre observational study. J Hum Nutr Diet. 2021; 00: 1– 11. https://doi.org/10.1111/jhn.12920

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Contribution to the Paper	Study concept, study design, data acquisition, data analysis and interpretation, drafting of manuscript, corresponding author for journal.		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

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Contribution to the Paper	Contributed to study concept and design Data acquisition Support with data analysis and interpretation Critical review and revisions of manuscript		
Signature		Date	26.5.21

[Manuscript 3] Food-related quality of life in adults with inflammatory bowel disease is associated with restrictive eating behaviour, disease activity and surgery: a prospective multi-centre observational study.

Short title: Food-related quality of life in IBD.

Key words: Inflammatory bowel disease, food-related quality of life, diet, dietary restriction

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Author contributions: All authors contributed to the conception and design of the study. ASD, RVB, SPC and JMA assisted with recruitment. ASD collected data. ASD, RVB, CKY and JMA contributed to

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Ethical considerations:

This study was approved by Central Adelaide Local Health Network (CALHN) Human Research Ethics Committee (HREC/16/RAH/24, R20160202) and informed consent was obtained from all participants.

Acknowledgements:

Thank you to Nicky Carney for administrative support, Patricia Kaazan, Amanda Lim, Serena Martin and Sangwoo Haan for assistance with data collection and Suzanne Edwards for statistical support.

Sources of support:

The Queen Elizabeth Hospital Inflammatory Bowel Disease Service and Research Unit and Royal Adelaide Inflammatory Bowel Disease Unit.

Disclosed funding:

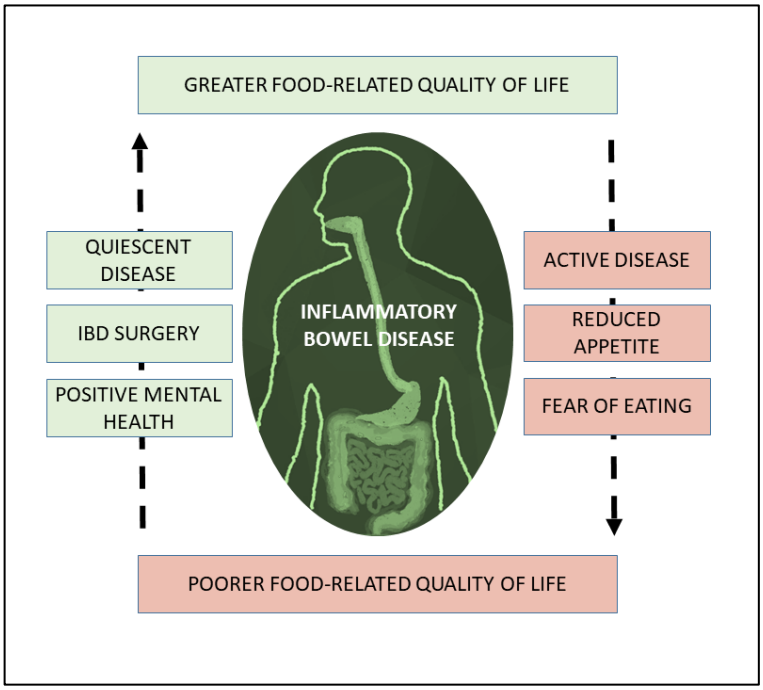
This work was supported by a Commonwealth Research Stipend administered by University of Adelaide, Australia to ASD as part of her post-doctoral degree.

Key highlights

- An important inverse relationship between FRQoL, restrictive eating and active disease in people with IBD exists
- Individuals with clinically active disease whom experience greater symptom severity have poorer FRQoL
- Individuals more fearful of eating or with a poorer appetite had a greater tendency to avoid foods and/or restrict their diets, associated with poorer FRQoL

- Attention is drawn to positive food-related outcomes of surgery and the strong relationship between FRQoL, QoL and psychological distress

Graphical abstract



Abstract

Background: Measuring FRQoL quantifies the psychosocial impact of eating and drinking. FRQoL and associated factors are not well explored in people with IBD, despite IBD being a chronic disease affecting the digestive tract. This study aims to characterise and identify any patient or disease-related predictors of FRQoL in individuals with IBD.

Methods: Adults with a formal diagnosis of IBD were recruited to a prospective multicentre cross-sectional study between April 2018 and December 2019. Participants completed questionnaires measuring FRQoL (FRQoL-29), clinical disease activity (Harvey Bradshaw Index (HBI), Simple Clinical Colitis Activity Index (SCCAI)), restrictive eating behaviour (NIAS), mental health (DASS-21) and other patient and disease-related variables. A multivariable regression was performed to identify factors associated with FRQoL.

Results: One hundred and eight participants completed the questionnaires (39 Crohn's disease (CD), 69 ulcerative colitis (UC)). The mean FRQoL was 79 (95% CI 75, 84) (poor 29, superior 145). Poorer FRQoL was observed in those with restrictive eating behaviour associated with fear of a negative consequence from eating ($p<0.0001$) and reduced appetite ($p<0.030$). Greater FRQoL was observed in those with lower disease activity ($p<0.0001$) and previous IBD surgery ($p=0.024$). FRQoL was not

associated either way by IBD phenotype, duration, or gender. The majority of participants obtained their dietary information from the internet (60%) or gastroenterologist (46%).

Conclusion: FRQoL in people with IBD is poorer in those with restrictive eating behaviours and clinically active disease. Interestingly, it was greater in those with previous IBD surgery. Further research is required to validate these associations and explore longitudinal effects of poor FRQoL on patient outcomes and potential strategies for prevention or management of impaired FRQoL in IBD.

5.1 Introduction

IBD, including CD and UC, are lifelong incurable diseases of the gastrointestinal tract.[4] Both have significant impact on activities of daily living due to their associated symptom burden.[5] These symptoms are widely variable depending on disease location, severity and phenotype but commonly include pain, fatigue, abdominal discomfort, reduced appetite, faecal urgency, and bloody diarrhoea.[6, 7] IBD is known to cause disruption across multiple domains of HRQoL, including psychological, social, sexual, and cultural well-being as well as enjoyment of food.[8] Psychological distress and restricting dietary intake are associated with poorer HRQoL in IBD and gastrointestinal diseases, however in IBD less is known about any association between mental health, restrictive eating and FRQoL, which directly measures of the psychosocial impact of eating and drinking.[2, 3, 9, 10]

People living with IBD rate diet as the most important psychosocial need affected by IBD.[9-11] Additionally, diet is a primary behavioural factor manipulated to control disease and symptoms.[12-14] However, as the role of diet and specific dietary components in disease pathogenesis remains unclear and evidence base for dietary therapies limited, dietary advice is often conflicting.[15-17] This predisposes those who believe diet has a key role in IBD management to engage in unnecessary dietary restrictions.[18-20] Avoidance of perceived dietary triggers can cause social withdrawal and isolation.[11, 13] Up to 75% of individuals report foods affect their IBD whilst 20% of patients avoid eating out at restaurants for fear of symptoms or unknown foods triggering relapse.[13, 20, 21] Beyond poorer HRQoL, restricted food intake is associated with poorer nutritional status, loss of lean muscle mass, fatigue, diminishing overall well-being, lower mood and anxiety, and worse surgical outcomes in both CD and UC.[22-24]

Recent data in 1221 people with IBD indicated recurrent disease flares and worse IBD-related distress were associated with poorer FRQoL, which itself was independently associated with lower intakes of fermentable fibres and calcium.[25] An inverse relationship between FRQoL, IBD disease activity and symptom severity and attempts to follow multiple pieces of dietary advice has also been established.[26] However, a more in-depth understanding of what is associated with FRQoL could assist more targeted dietary counselling, adding value to patient-centred care and improving overall QoL in those with IBD.

Therefore, the aim of this study was to characterise FRQoL and identify any patient or disease-related predictors of FRQoL in individuals with IBD in a multi-centre cross-sectional study.

5.2 Methods

Study population

This was a prospective observational study conducted across three tertiary IBD centres in Adelaide, South Australia between April 2018 and December 2019. Adults ≥18 years old with a formal diagnosis of IBD were invited to complete a two-part questionnaire. Recruitment occurred via advertising in outpatient clinics, infusion centres and established IBD service emailing lists. Individuals were ineligible to participate if unable to give informed consent, had impaired capacity to complete questionnaires, were not consuming an oral diet containing food (e.g. on exclusive enteral nutrition or total parenteral nutrition), were on a therapeutic diet for another medical condition that required dietary modification beyond general dietary guideline principles, or were pregnant or breastfeeding.[27]

Study variables

Demographic and disease-related variables

Demographic and disease-related data were recorded and included age, gender, disease type, Montreal phenotype, disease duration, inflammatory biomarkers (faecal calprotectin and serum C-reactive protein), previous IBD surgery, medications, smoking status, and body mass index (BMI). Sources of dietary information and access to previous dietary education were also collected.

Food-related quality of life

FRQoL was assessed using the validated FRQoL-29 questionnaire.[2] This is a disease-specific tool that measures the psychosocial aspects of eating and drinking, including pleasure, maintaining social activities and achieving nutritional adequacy. This self-reported tool includes 29 questions measured on a 5-point likert scale, giving a total sum score of 145 (minimum 29, maximum 145). Categories with cut off values for FRQoL-29 are not available however a higher sum score indicates greater FRQoL, whilst FRQoL of healthy volunteers has previously been reported as 123, SD 16.5.[2]

Clinical disease activity

Disease activity was assessed using HBI for CD and SCCAI for UC with previously defined cut off values for clinical disease activity. A HBI score >4 was used to define active disease in CD whereas in UC, a SCCAI score >2 defined active disease.[28]

Restrictive eating patterns

Nine-item Avoidant/Restrictive Food Intake disorder screen (NIAS) was used to measure restrictive eating patterns.[29] This multidimensional tool includes nine questions across three domains of eating

patterns (appetite, fear and picky eating). Each question is measured on a 6-point likert scale, with domain scale scores of minimum 0, maximum 15 and an overall NIAS scale score totalling 45. A higher scale score for each domain indicates greater restrictive eating behaviour. In the absence of categorical cut-off values, median reference scores for representative eating behaviour from an adult population in the initial validation study can be used as a comparator: picky eating 3 (inter quartile range (IQR) 1, 7), appetite 3 (IQR 0, 7), fear 0 (IQR 0, 3), total NIAS score 14 (IQR 7, 21).[29]

Mental health

The Depression Anxiety Stress Scale-21 (DASS-21) was used to measure dimensions of mental health.[30] This 21-item questionnaire includes seven questions for each dimension: depression, anxiety, stress, measured on a 4-point likert scale (minimum 0, and maximum 42). There are numerically different categories for normal, mild, moderate, severe and extremely severe psychological distress for each dimension. However overall DASS-21 score is out of 126, with a higher score indicating a greater degree of psychological distress: 0-77 normal, 78-87 mild, 87-95 moderate, 95-98 severe and 98-100 extremely severe distress.

IBD-related quality of life

The IBD-Control-8 instrument was used to measure PROs of perceived disease control.[31] This is a brief 8-item self-reported QoL outcome measure that captures the patient perspective on how symptoms of active disease are affecting their QoL. Each question has a binary answer of 0 to 2 points. There are not categories for poorer or greater QoL however a score ≥13 correlates with quiescent disease, a lower symptom burden and greater QoL, whilst a lower sum score indicates a poorer self-reported QoL and poorer perceived disease control.

Sample size & statistical analysis

The primary analysis was to examine FRQoL-29 scores in individuals with IBD. Thereafter, predictors of FRQoL were identified by performing a multivariable linear regression. Secondary planned analyses included comparing FRQoL of individuals with quiescent and clinically active disease and investigating correlations between FRQoL and mental health. A sample size calculation was performed using data from the initial FRQoL-29 tool validation paper.[2] This was initially performed based on the precision of the confidence interval for the mean. A required sample size was calculated to be 44, which resulted in an IBD group 95% confidence interval for FRQoL-29 sum score (79.1, 99.9) that did not overlap with the 95% confidence interval for the asthma control group (120.7, 130.1). However, to allow for the use of a multivariable linear regression whilst avoiding problems of sparse data, a sample size of n=100-120 was required for approximately 10-12 covariates (predictors and confounders).[32] For this reason, the final sample size was n=108 after allowing for dropouts. Demographic and disease-related

variables were reported as descriptive data. Univariate analyses were then performed between variables and the dependent variable FRQoL to identify factors associated with FRQoL using independent t-tests and univariate linear regressions for categorical and continuous data. An initial multivariable regression was then performed to identify predictors of FRQoL, including those covariates with $p<0.20$ on univariate analysis. Backwards elimination was performed until all covariates in a final multivariable model had a p value<0.2.[33] Mental health status and QoL were excluded from multivariate analysis as similar instruments Hospital Anxiety Depression Scale and IBD-Questionnaire were used in the construct validation of the FRQoL questionnaire.[2] Instead, correlations between FRQoL, mental health and QoL were analysed using Pearson's correlation coefficient and scatter plots. A statistically significant p value was considered to be $p<0.05$.

Data analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), IBM SPSS Statistics Version 26.0 (IBM, Armonk, NY) and Graph Pad Prism Version 9.0 (GraphPad Software, San Diego, CA, USA). All authors were involved in study data analysis and approved the final manuscript for publication.

Ethical considerations

This study was approved by Central Adelaide Local Health Network Human Research Ethics Committee with reference number HREC/16/RAH/24, R20160202 and informed consent was obtained from all participants.

5.3 Results

Study population

One hundred and twenty-two participants were enrolled in the study. Fourteen had partial or uncompleted questionnaires. Therefore with a response rate of 89%, 108 participants who completed both parts of the questionnaire were included in the analysis (***Figure 5.1***). Detailed demographic and clinical characteristics of these participants are presented in ***Table 5.1***. The majority of the cohort had UC (64%) and there was almost equal distribution of those with quiescent (48%) and active (52%) disease. Of IBD therapies, oral 5-aminosalicylates (45%) and biologics (42%) were most common, and eight percent were on no IBD therapy. Of participants who had previous IBD surgery, 18% had CD and 4% had UC. Approximately one third of participants had previously seen a dietitian for IBD-specific dietary education (30.6%). Most accessed dietary information from the internet (60%), their gastroenterologist (46%) or friends and family (27%), with only 5% reporting they had never accessed any dietary information. Thirty-seven percent were unconfident in making food choices for their IBD.

Food-related quality of life of individuals with IBD

Participants reported a mean FRQoL score of 79 (95% CI 75, 84) with poorer FRQoL observed in individuals with clinically active disease (IBD-active: 70 (95% CI 64, 75); IBD-remission: 90 (95% CI 85, 95); p<0.0001) (***Figure 5.2***). Individuals with UC had poorer FRQoL compared to CD (UC: 75 (95% CI 71, 80); CD: 87 (95% CI 78, 95); p=0.009), irrespective of disease activity. Individuals with active UC were also observed to have poorer FRQoL than those in clinical remission (UC-active: 69 (95% CI 63, 74); UC-remission: 88 (95% CI 82, 94); p<0.0001). This appeared likely to also be the case in those with CD although statistical significance was not reached (CD-active: 74 (95% CI 52, 96); CD-remission: 91 (95% CI 83-100); p=0.066). ***Figure 5.3*** presents the negative linear association between FRQoL and clinical disease activity in CD and UC. Further information outlining patient perceptions of the psychosocial impact of clinically quiescent and active IBD on eating and drinking, measured by the FRQoL-29 tool, can be found in ***Supplementary table 5.1***.

Restrictive eating behaviour

The overall mean restrictive eating behaviour score for the IBD cohort was 12.6 (95% CI 11.1, 14), with no significant difference observed between CD and UC (CD: mean 13 (95% CI 10.2, 15.8), UC: 12.3 (95% CI 10.6, 14); p=0.673). On examination of domains of restrictive eating patterns, participants with IBD reported mean picky eating behaviour scores of 4.2 (95% CI 3.6, 4.8), fear of a negative consequence from eating 4.5 (95% CI 3.7, 5.2) and reduced appetite 4.1 (95% CI 3.4, 4.8). Mean scores were higher than reported NIAS reference scale scores, particularly for fear of eating. There were no significant differences within each domain observed between CD and UC.

Psychological distress

Participants reported a mean DASS-21 score of 22 (95% CI 18.4, 25.6), within normal range for psychological distress. Depression and anxiety scores were also within normal range; depression: 6.8 (95% CI 5.4, 8.2); anxiety: 5.2 (95% CI 4.1, 6.3). Stress scores were numerically higher than anxiety and depression however remained within range: 10.1 (95% CI 8.5, 11.6). There were no significant differences observed between CD and UC for total DASS-21 and individual domain scores.

Quality of life

The mean IBD-Control-8 score for participants was 10.2 (95% CI 9.5, 11). In comparison to IBD-Control-8 reference values, participants with CD and UC both reported poorer QoL associated with symptoms of active disease. QoL was lower in UC compared to CD (UC: 9.5 (95% CI 8.5, 10.4); CD 11.5 (95% CI 10.4, 12.7); p=0.008).

Factors associated with FRQoL-29 scores

In univariate analyses, FRQoL positively correlated with lower psychological distress (r^2=0.12, p<0.0001), greater perceived disease control (r^2=0.32, p<0.0001) and lower restrictive eating behaviour (r^2=0.27, p<0.0001) *(**Table 5.2**)*. Depression, anxiety and stress sum scores each inversely related to FRQoL-29 scores (***Figure 5.4***)

In a multivariate model comprised of patient and disease-related variables, the FRQoL-29 sum score was associated with disease activity, previous IBD surgery and restrictive eating behaviour, associated with changes in appetite and fear, after adjusting for all other variables in the model (adjusted R^2=0.48), but not associated with disease phenotype (***Table 5.3***). Quiescent disease was positively associated with FRQoL, with a mean score 15.3 points higher than those with active disease. A history of previous IBD surgery was also positively associated with FRQoL; those with prior resectional surgery had a mean FRQoL-29 score 8.8 points higher than those without resection. Two domains of the restrictive eating behaviour assessment were negatively associated with FRQoL. For every single point increase in appetite-related restrictive eating behaviour, mean FRQoL-29 scores lowered by a point, whilst those who restricted their diets due to fear of experiencing gastrointestinal discomfort or an adverse gastrointestinal symptom had a mean FRQoL-29 score 2.6 points lower for every single point increase in fear-driven restrictive eating behaviour.

5.4 Discussion

This comprehensive, multi-centre dietary study provides a detailed picture of how patient and disease-related factors associate with FRQoL. We have identified an important inverse relationship between FRQoL, restrictive eating and active disease in people with IBD. Individuals more fearful of eating or with a poorer appetite had greater tendency to avoid foods and/or restrict their diets, with a consequent reduction in FRQoL, whilst those with clinically active disease and greater symptom burden had poorer FRQoL. Conversely, those who had surgical resection of their IBD had greater FRQoL, possibly due to a lower symptom burden enabling a more liberal diet.[34, 35] Findings from this study also confirm a strong relationship between FRQoL, QoL and psychological distress.

Our data adds to the current evidence that poorer FRQoL exists in those with clinically active disease or more frequent flares, whom experience greater symptom severity.[25, 26] In the absence of defined cut off values categorising poorer or greater FRQoL, findings can be compared to previous studies. Our FRQoL-29 sum scores are similar to those reported in a recent large multi-centre study by Whelan *et al* and lower than healthy volunteers and asthmatics in the initial FRQoL-29 validation study (***Figure 5.2***).[2, 25] Our data confirm FRQoL-29 sum scores are consistently lower in participants with active IBD and greater in those with quiescent disease.[2, 25, 26] A lower FRQoL-29 sum score indicates

psychosocial pleasures of eating and drinking have diminished, social activities affected with social withdrawal more likely, and dietary intake at risk of being inadequate. Confirmation of the inverse relationship between FRQoL and clinical disease activity importantly highlights a subgroup of people with IBD who may benefit from proactive dietary counselling to improve QoL and minimise risks associated with an inadequate diet. Measuring FRQoL should now be repeated at different time points and when a change in disease activity occurs to test responsivity of the FRQoL-29 tool.

The strong relationship between FRQoL and restrictive eating behaviour is a novel, understandable finding of this study. Restrictive eating behaviour driven by fear of a negative gastrointestinal experience or increased gastrointestinal discomfort and poorer appetite were both associated with reduced FRQoL. Conceivably a bidirectional relationship between food, disease activity and symptom burden may exist, perpetuating restrictive eating behaviour and lowering FRQoL. This is of clinical significance as restrictive dietary behaviour is likely to increase the risk of poorer clinical outcomes associated with inadequate dietary intake and malnutrition. This includes sarcopenia, low bone density and bone disease, micronutrient deficiencies, impaired surgical recovery, longer hospital stays and disability.[23, 36-38]

The NIAS instrument was selected to screen for restrictive eating behaviour primarily because it measures domains of eating behaviours driven by fear and changes in appetite, both common in IBD, and other instruments validated in IBD populations do not exist.[12-14, 39] Active CD has previously been associated with poorer appetite, dietary restriction, disordered eating behaviour and poorer mental health. In our study, similar observations were associated with poorer FRQoL, although phenotypic differences were less clear.[7, 24] Future validation of NIAS in an IBD cohort would be useful as its unique construct to measure individual domains of restrictive dietary behaviour are highly relevant to this population. Moreover, use of both NIAS and FRQoL-29 instruments in clinical practice may assist in earlier identification of restrictive eating thoughts or behaviours, particularly in those exhibiting greater food-related psychological distress, allowing more timely dietary intervention and pro-active counselling to minimise avoidable nutrition-related complications of IBD and improve FRQoL. Specifically, Whelan *et al* identified lower intakes of a broad range of essential macro and micronutrients in those with poorer FRQoL, including calcium, phosphorous, magnesium, vitamin C and non-starch polysaccharide carbohydrate.[25] These nutrients relate to core groups of foods commonly avoided by individuals with IBD such as fruits, vegetables, wholegrains, and calcium-rich foods, all identified as either clinically and nutritionally important to include or as having a protective effect in IBD.[20, 40-42]

Surgical management of IBD was associated with a greater FRQoL, consistent with other literature reporting those who have undergone surgery or have ostomies eat a more liberal diet and have greater QoL.[34, 35] Whilst different surgical procedures are associated with different clinical and QoL outcomes, this typically relates to improved control of disease-related symptoms where those who require surgery usually have more complex or severe disease, often having failed medical therapy.[43] For those with unresected stricturing or stenosing disease, dietary intake may also be more limited due to fibre avoidance.[44] Equally, this finding could be related to a higher proportion of participants with CD phenotype and disease located more proximally to the colon where symptom burden can be less. This interesting finding should be explored in future perioperative research that includes measuring habitual dietary intake to validate an association between surgery, liberalisation of diet and FRQoL.

Several key limitations of this study must be discussed. Firstly, inferences of causal effects between FRQoL and active disease, restrictive eating or surgery cannot be made as this was a prospective cross-sectional study without a control group. Furthermore, response bias may have occurred as individuals who replied to advertising may have a greater interest in food or perceived food-related problems. Secondly, this observational study was not powered to make direct comparisons between CD and UC, however signals from univariate analyses that individuals with UC have poorer FRQoL and poorer perceived disease control and QoL than CD are a novel study finding, warranting further exploration. UC is often perceived as the 'less severe' disease, with a lesser amount of literature on associated nutritional risks and dietary management, despite most changes in bowel habits being related to the colon.[45] Additionally, individuals with UC are more likely to avoid foods or restrict their diets and less likely to receive dietary counselling from a dietitian.[6, 39] This highlights an important area to explore further to ensure people with UC are not being nutritionally neglected. Thirdly, coexisting functional symptoms were not measured despite a reported prevalence of 30-40% in IBD.[46, 47] Poorer FRQoL has previously been observed in those with irritable bowel syndrome therefore it is possible coexisting functional symptoms could have influenced study outcomes.[26] Lastly, psychological distress and QoL could not be examined as a predictive factor due to the construct of the FRQoL-29 tool. The DASS-21 instrument is not validated in IBD, though broadly used in clinical practice, and was selected based on its construct to measure three key areas of psychological distress observed in IBD in one tool.[48] Similarly, the NIAS-fear scale had constructs similar to DASS-21 therefore direct associations between restrictive eating behaviour and psychological distress were not made.

5.6 Conclusion

In summary, this study identifies restrictive eating patterns and active disease as risk factors for poorer FRQoL in people with IBD and draws attention to positive food-related outcomes of surgery. Further

research examining whether FRQoL can be improved if these risk factors are managed are now required, including whether pro-active access to an IBD specialist dietitian for dietary counselling is a critical part of this. Moreover, research into defined dietary management strategies that influence disease activity, reduce symptom burden, minimise unnecessary restrictive eating behaviour and improve psychosocial experiences of eating and drinking with IBD are required. These studies should be designed with methodological rigour to overcome the challenges of blinding in diet studies. This includes developing sham diets for placebo control arms of dietary trials. Further to this, FRQoL is an essential domain of QoL to measure in all future IBD dietary research and based on our findings, also warrants further exploration in perioperative IBD studies.

Transparency Declaration: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported. The reporting of this work is compliant with STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

Data availability statement: The data underlying this original article are available within this article, complete with references.

Conflicts of interest disclosure: There are no conflicts of interests to declare for this study.

Figures

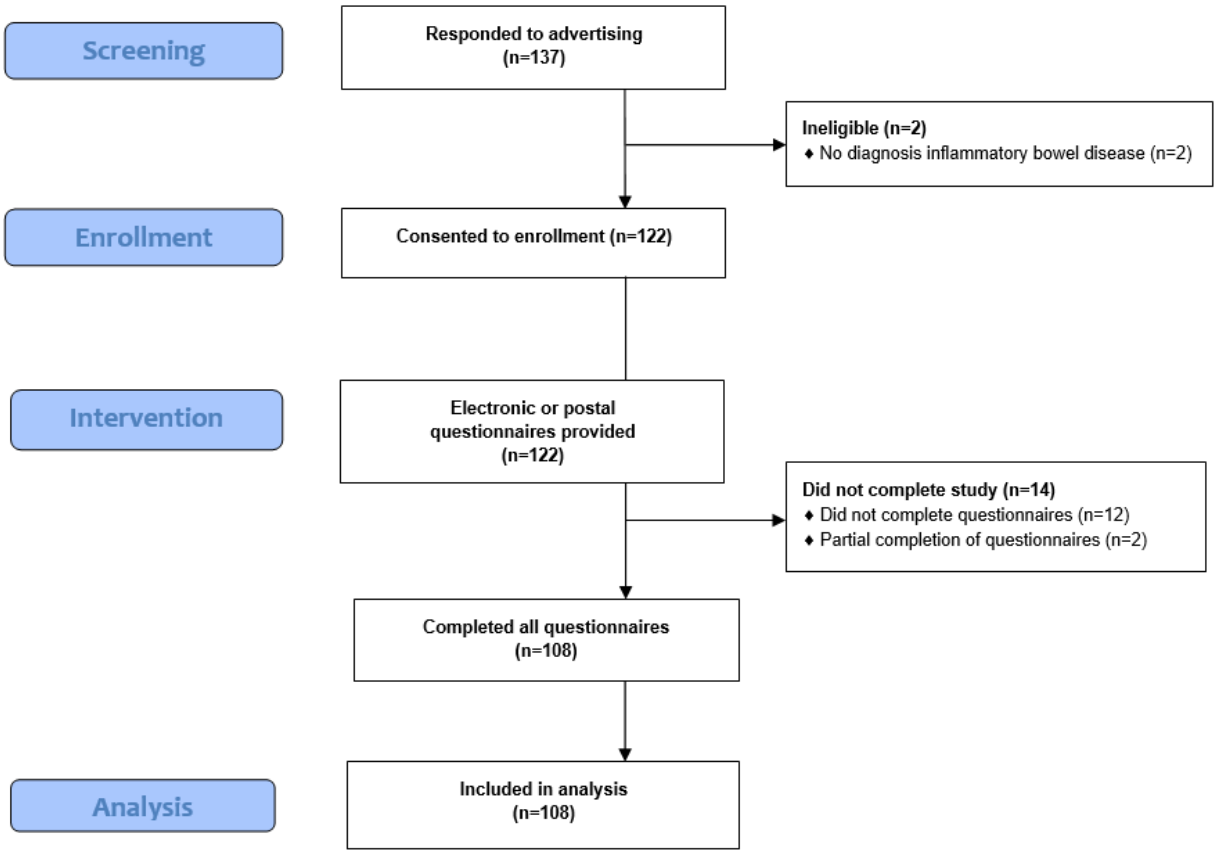


Figure 5.1. Recruitment, enrolment and completion of prospective, observational multicentre study examining food-related quality of life in individuals with inflammatory bowel disease

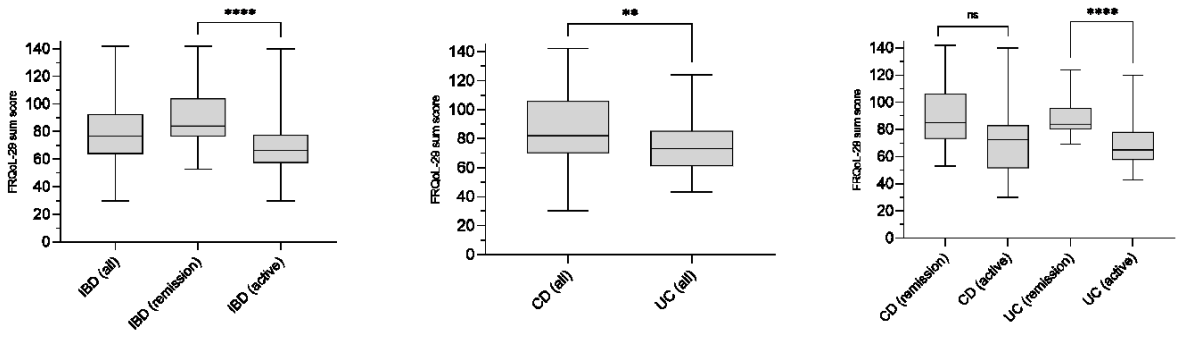


Figure 5.2 *Box plots of the mean food-related quality of life scores of individuals with inflammatory bowel disease by phenotype and disease activity*

Legend: *Whiskers represent minimum to maximum values. In the absence of references ranges and cut off values for FRQoL-29, this data can be compared to data from the initial validation study where FRQoL-29 scores of healthy volunteers (n=117) was mean 123, SD 16.5, asthmatics (n=100) mean 125.4, SD 24.1, and patients with IBD (n=314) mean 89.5, SD 28.6.(2) FRQoL-29, food-related quality of life 29-item questionnaire; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; ****, p<0.0001; **, p<0.001; ns, non-significant p value.*

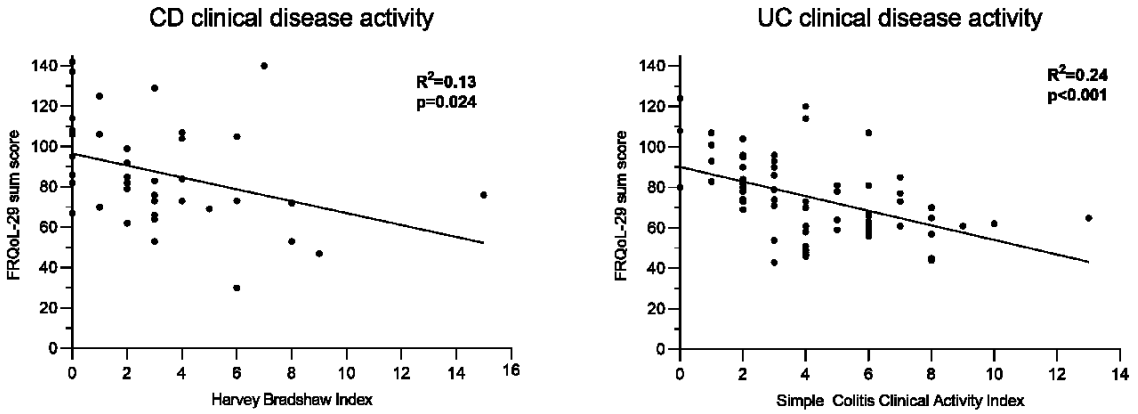


Figure 5.3 *Scatterplots with regression line demonstrating the relationship between food-related quality of life and disease activity*

Legend: *In individuals with Crohn's Disease (n=39) and ulcerative colitis (n=69). CD, Crohn's disease; UC, ulcerative colitis; FRQoL-29, food-related quality of life 29-item questionnaire.*

Figure 5. 4 *Scatterplots with regression line demonstrating the linear relationship between food-related quality of life and mental health covariates in individuals with IBD*

Legend: *Concurrent validity of FRQoL-29 tool was established by correlating sum scores with other validated questionnaires that measured similar constructs. The mental health tool used was Hospital Anxiety and Depression Scale. Based on this, mental health was not used in the multivariable model where FRQoL was the dependent variable as there was an expected association between mental health and FRQoL, as outlined in these simple linear regressions of total and subscale sum scores of DASS-21. FRQoL-29, food-related quality of life 29-item questionnaire; DASS-21, Depression, anxiety, stress scale 21-item questionnaire.*

Tables

Table 5. 1 Demographic and disease-related characteristics of patients with inflammatory bowel disease participating in food-related quality of life survey (n=108)

Characteristic	**Total (n=108)**
Disease type, n (%)	
Crohn's disease	39 (36)
Ulcerative colitis	69 (64)
Female, n (%)	61 (56)
Age, years, mean (SD)	43.6 (15.2)
Age at diagnosis, years, mean (SD)	33.6 (15.7)
Disease duration, years, mean (SD)	10.1 (9.6)
Body Mass Index (kg/m^2), mean (SD)[a]	26.3 (5.9)
Montreal location, n (%)	
L1, ileal	12 (31)
L2, colonic	6 (15)
L3, ileocolonic	16 (41)
L4, isolated upper disease	3 (8)
Montreal behaviour, n (%)	
B1, inflammatory	19 (49)
B2, stricturing	11 (28)
B3, penetrating	9 (23)
Perianal disease, n (%)	9 (23)
UC extent, n (%)	
E1, proctitis	11 (16)
E2, left side	32 (46)
E3, extensive	26 (37)

Previous IBD surgery, n (%)	22 (20)
Smoking status, n (%)	
Never	70 (65)
Current	8 (8)
Previous smoker	29 (27%)
Current IBD treatment, n (%)	
None	9 (8)
Corticosteroids	18 (17)
Oral 5-aminosalicylates	49 (45)
Topical 5-aminosalicylates	23 (21)
Immunomodulators	42 (39)
Biologics	45 (42)
Combination therapy	18 (17)
Clinically active disease, n (%)	56 (52)
HBI (>4)	10 (9)
SCCAI (>2)	46 (42)
Inflammatory markers, median (IQR)	
Faecal calprotectin[b]	157 (23, 632)
C-reactive protein[c]	2.6 (0.8, 7.0)

Legend: *[a]Incomplete dataset for BMI (38 CD and 63 UC); [b]Faecal calprotectin measured within 6 months prior to study, not used to define active disease, incomplete dataset, n=87; [c]C-Reactive protein measured within 6 months prior to study, not used to define active disease, incomplete dataset, n=99; IBD, inflammatory bowel disease; HBI, Harvey Bradshaw Index; SCCAI, Simple clinical colitis activity index*

Table 5. 2 Univariate analyses of the patient and disease-related variables

Independent variable (directionality)	Mean difference (95% CI of the difference)	Chi square	P value
Disease type (Crohn's disease)	11.6 (3.2, 20.1)	7.23	0.007
Disease activity (remission)	20.4 (12.9, 27.9)	28.57	<0.0001
Age	0.4 (-0.2, 0.3)	0.89	0.766
Gender (male)	-1.9 (-10.3, 6.6)	0.18	0.669
Disease duration	-0.5 (-0.5, 0.4)	0.42	0.837
Seen a dietitian previously (no)	2.3 (-6.8, 11.4)	0.25	0.620
Accessed dietary information on internet	3.3 (-5.4, 11.9)	0.54	0.461
Smoking status (no)	-11.8 (-27.7, 4.1)	2.13	0.150
IBD surgery (no)	-10.1 (-20.4, 0.1)	3.75	0.053
Overall psychological distress (DASS-21)	-0.4 (-0.6, -0.2)	15.24	<0.0001
Depression	-1.0 (-1.5, -0.4)	11.73	0.001
Anxiety	-1.2 (-1.9, -0.5)	11.67	0.001
Stress	-0.9 (-1.4, -0.4)	11.80	0.001
Overall restrictive eating behaviour (NIAS)	-1.5 (-2.0, -1.1)	40.59	<0.0001
Appetite	-2.4 (-3.4, -1.3)	18.85	<0.0001
Fear of eating	-3.4 (-4.4, -2.5)	53.35	<0.0001
Picky eating	-1.6 (-2.9, -0.3)	6.09	0.140
Perceived disease control and quality of life (IBD-Control 8)	3.2 (2.4, 4.1)	51.68	<0.0001

Legend: *The dependent variable is food-related quality of life sum scores in individuals with inflammatory bowel disease and the independent variables are listed. The directionality of the association of each independent variable with FRQoL is identified within brackets. Data expressed as mean difference (95% CI of the difference) and Chi square. Univariate analyses of independent*

variables was performed prior to a multivariate regression to identify factors associated with FRQoL in individuals with inflammatory bowel disease. The directionality of the association with FRQoL is presented within brackets. FRQoL, food-related quality of life; DASS-21, Depression anxiety stress score 21 item questionnaire; NIAS, nine item avoidant/restrictive screen; IBD, inflammatory bowel disease.

Table 5. 3 Results of the multivariable analysis of the association between patient and disease-related variables and food-related quality of life sum score in individuals with inflammatory bowel disease.

Predictors (directionality)	Mean difference (95% CI of the difference)	β	P value	Adjusted R squared
Disease activity (remission)	15.3 (9.1, 21.4)	-0.34	<0.0001	0.484
Previous IBD surgery (yes)	8.8 (1.2, 16.3)	0.16	0.024	
NIAS Appetite (restrictive behaviour)	-1.1 (-2, -0.1)	-0.17	0.030	
NIAS Fear of eating (restrictive behaviour)	-2.6 (-3.5, -1.7)	-0.44	<0.0001	

Legend: *Backwards elimination of variables to a p value <0.2 was used. Statistical significance was set at p<0.05. IBD, inflammatory bowel disease; NIAS, nine item avoidant/restrictive screen*

Supplementary table

Supplementary table 5. 1 Patient perceptions of the psychosocial impact of eating and drinking with inflammatory bowel disease, measured using a five-point Likert-type response scale within a validated FRQoL-29 questionnaire.

	Perceptions	5-point Likert scale	IBD-remission n (%)	IBD-active n (%)	P value
Q1	I have regretted eating and drinking things which have made my IBD symptoms worse	Strongly agree	7 (13)	13 (23)	0.201
		Agree	18 (35)	26 (46)	
		Neither agree nor disagree	9 (17)	7 (12)	
		Disagree	12 (23)	8 (14)	
		Strongly disagree	6 (12)	2 (4)	
Q2	My enjoyment of a particular food or drink has been affected by the knowledge that it might trigger my IBD symptoms	Strongly agree	6 (12)	25 (45)	<0.0001
		Agree	24 (46)	21 (37)	
		Neither agree nor disagree	7 (13)	4 (7)	
		Disagree	13 (25)	3 (5)	
		Strongly disagree	2 (4)	3 (5)	
Q3	My IBD has meant that I have had to leave the table while I am eating to go to the toilet	Strongly agree	1 (2)	5 (9)	<0.0001
		Agree	7 (13)	26 (46)	
		Neither agree nor disagree	5 (10)	10 (18)	
		Disagree	23 (44)	11 (20)	
		Strongly disagree	16 (31)	4 (7)	
Q4	I have not been able to predict how long it will take for my body to respond to something I have had to eat or drink due to my IBD	Strongly agree	1 (2)	10 (18)	<0.0001
		Agree	12 (23)	30 (54)	
		Neither agree nor disagree	18 (35)	11 (20)	

		Disagree	15 (29)	4 (7)	
		Strongly disagree	6 (11)	1 (2)	
Q5	Certain foods have triggered symptoms of my IBD	Strongly agree	11 (21)	21 (37)	0.059
		Agree	27 (52)	17 (20)	
		Neither agree nor disagree	7 (13)	13 (23)	
		Disagree	3 (6)	4 (7)	
		Strongly disagree	4 (8)	1 (2)	
Q6	My IBD has meant that I have been nervous that if I eat something I will need to go to the toilet straight away	Strongly agree	3 (6)	13 (23)	0.020
		Agree	13 (25)	21 (37)	
		Neither agree nor disagree	14 (27)	8 (14)	
		Disagree	13 (25)	9 (16)	
		Strongly disagree	9 (17)	5 (9)	
Q7	I have avoided having food and drink I know does not agree with my IBD	Strongly agree	18 (35)	23 (41)	0.825
		Agree	22 (42)	22 (39)	
		Neither agree nor disagree	3 (6)	5 (9)	
		Disagree	6 (11)	4 (7)	
		Strongly disagree	3 (6)	2 (4)	
Q8	I have felt relaxed about what I can eat and drink despite my IBD[a]	Strongly disagree	0 (0)	7 (12)	0.003
		Disagree	12 (23)	22 (39)	
		Neither disagree nor agree	7 (13)	10 (18)	
		Agree	24 (46)	12 (21)	
		Strongly agree	9 (17)	5 (9)	
Q9		Strongly disagree	0 (0)	2 (4)	0.027

	I have felt in control of what I eat and drink in relation to my IBD[a]	Disagree	6 (11)	16 (29)	
		Neither disagree nor agree	7 (13)	12 (21)	
		Agree	29 (56)	21 (37)	
		Strongly agree	10 (19)	5 (9)	
Q10	I have struggled to eat the way that is best for my IBD because of other commitments during the day	Strongly agree	5 (10)	8 (14)	0.044
		Agree	5 (10)	15 (27)	
		Neither agree nor disagree	10 (19)	13 (23)	
		Disagree	25 (48)	13 (23)	
		Strongly disagree	7 (13)	7 (12)	
Q11	I have been frustrated about not knowing how food and drink will react with my IBD	Strongly agree	1 (2)	15 (27)	<0.0001
		Agree	15 (29)	19 (34)	
		Neither agree nor disagree	10 (19)	14 (25)	
		Disagree	21 (40)	3 (5)	
		Strongly disagree	5 (10)	5 (9)	
Q12	I have had to concentrate on what I have been eating and drinking because of my IBD	Strongly agree	2 (4)	13 (23)	0.001
		Agree	22 (42)	30 (54)	
		Neither agree nor disagree	8 (15)	7 (12)	
		Disagree	15 (29)	4 (7)	
		Strongly disagree	5 (10)	2 (4)	
Q13	I have been worried that if I eat I will get symptoms of my IBD	Strongly agree	2 (4)	14 (25)	0.001
		Agree	16 (31)	25 (45)	
		Neither agree nor disagree	10 (19)	7 (12)	
		Disagree	15 (29)	7 (12)	

		Strongly disagree	9 (17)	3 (5)	
Q14	I have felt the way that I eat and drink for my IBD has affected my day to day life	Strongly agree	0 (0)	7 (12)	<0.0001
		Agree	15 (29)	31 (55)	
		Neither agree nor disagree	9 (17)	12 (21)	
		Disagree	25 (48)	3 (5)	
		Strongly disagree	3 (6)	3 (5)	
Q15	The way I have had to eat for my IBD has restricted my lifestyle	Strongly agree	0 (0)	6 (11)	<0.0001
		Agree	5 (10)	21 (37)	
		Neither agree nor disagree	18 (35)	14 (25)	
		Disagree	25 (48)	12 (21)	
		Strongly disagree	4 (8)	3 (5)	
Q16	I have had to concentrate on what food I buy because of my IBD	Strongly agree	2 (4)	14 (25)	0.005
		Agree	25 (48)	29 (52)	
		Neither agree nor disagree	8 (15)	6 (11)	
		Disagree	12 (23)	4 (7)	
		Strongly disagree	5 (10)	3 (5)	
Q17	It has been on my mind how my IBD will be affected by what I eat and drink	Strongly agree	7 (13)	13 (23)	0.030
		Agree	25 (48)	36 (64)	
		Neither agree nor disagree	6 (12)	2 (4)	
		Disagree	11 (21)	3 (5)	
		Strongly disagree	3 (6)	2 (4)	
Q18		Strongly agree	1 (2)	12 (21)	<0.0001
		Agree	10 (19)	24 (43)	

	My IBD has prevented me from getting full pleasure from the food and drink I have had	Neither agree nor disagree	12 (23)	7 (12)	
		Disagree	22 (42)	10 (18)	
		Strongly disagree	7 (13)	3 (5)	
Q19	I have felt that I need to know what is in the food I am eating due to my IBD	Strongly agree	5 (10)	17 (30)	0.070
		Agree	22 (42)	19 (34)	
		Neither agree nor disagree	7 (13)	8 (14)	
		Disagree	13 (25)	7 (12)	
		Strongly disagree	5 (10)	5 (9)	
Q20	I have felt that I have had to be careful about when I have eaten because of my IBD	Strongly agree	2 (4)	11 (20)	0.033
		Agree	23 (44)	29 (52)	
		Neither agree nor disagree	9 (17)	5 (9)	
		Disagree	14 (27)	7 (12)	
		Strongly disagree	4 (8)	4 (7)	
Q21	I have had to be more aware of what I am eating due to my IBD	Strongly agree	6 (12)	17 (30)	0.028
		Agree	31 (60)	29 (52)	
		Neither agree nor disagree	2 (4)	5 (9)	
		Disagree	10 (19)	3 (5)	
		Strongly disagree	3 (6)	2 (4)	
Q22	I have missed being able to eat or drink whatever I want because of my IBD	Strongly agree	4 (8)	20 (36)	0.001
		Agree	14 (27)	19 (34)	
		Neither agree nor disagree	14 (27)	5 (9)	
		Disagree	14 (27)	6 (11)	
		Strongly disagree	6 (12)	6 (11)	

Q23	I have felt that I would like to be able to eat and drink like everyone else	Strongly agree	4 (8)	25 (45)	<0.0001
		Agree	17 (33)	15 (27)	
		Neither agree nor disagree	18 (35)	9 (16)	
		Disagree	9 (17)	4 (7)	
		Strongly disagree	4 (8)	3 (5)	
Q24	I have been happy to eat and drink around people I do not know despite my IBD[a]	Strongly disagree	0 (0)	4 (7)	0.180
		Disagree	6 (12)	7 (12)	
		Neither disagree nor agree	9 (17)	13 (23)	
		Agree	26 (50)	18 (32)	
		Strongly agree	11 (21)	14 (25)	
Q25	I have felt that I have been eating and drinking normally despite my IBD[a]	Strongly disagree	0 (0)	10 (18)	0.011
		Disagree	9 (17)	12 (21)	
		Neither disagree nor agree	15 (29)	14 (25)	
		Agree	19 (37)	14 (25)	
		Strongly agree	9 (17)	6 (11)	
Q26	I have found it hard not knowing if a certain food will trigger IBD symptoms	Strongly agree	4 (8)	14 (25)	0.002
		Agree	15 (29)	27 (48)	
		Neither agree nor disagree	17 (33)	8 (14)	
		Disagree	13 (25)	5 (9)	
		Strongly disagree	3 (6)	2 (4)	
Q27	My IBD has meant I have had to make an effort to get all the nutrients my body needs	Strongly agree	3 (6)	16 (29)	0.007
		Agree	21 (40)	22 (39)	
		Neither agree nor disagree	12 (23)	11 (20)	

		Disagree	14 (27)	5 (9)	
		Strongly disagree	2 (4)	2 (4)	
Q28	I have felt that I have not known how my IBD will react to food or drink	Strongly agree	4 (8)	10 (18)	0.003
		Agree	16 (31)	32 (57)	
		Neither agree nor disagree	11 (21)	4 (7)	
		Disagree	19 (37)	9 (16)	
		Strongly disagree	2 (4)	1 (2)	
Q29	My IBD has meant that I have had to work hard to fit my eating habits in around my activities during the day	Strongly agree	1 (2)	10 (18)	0.001
		Agree	9 (17)	19 (34)	
		Neither agree nor disagree	13 (25)	14 (25)	
		Disagree	24 (46)	10 (18)	
		Strongly disagree	5 (10)	3 (5)	

Legend: *Categorical data is presented as frequency (percentage) and the difference between groups (IBD-remission n=52 and IBD-active n=56) is analysed using Chi-square test or Fisher's Exact test. A correction factor was not applied due to the exploratory nature of the study without the need to present conservative p values. Where any cell in the contingency table has n<5, the P value is presented from the Fisher's Exact test P-value. For all other values, the Chi-Square test P value is presented.* [a]*, reverse scoring; FRQoL-29, food-related quality of life 29-item questionnaire.*

CHAPTER 5 REFERENCES

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CHAPTER 6

Examining diet as therapy in ulcerative colitis

Submitted to *American Journal of Clinical Nutrition*

November 2021

CHAPTER 6: Examining diet as therapy in ulcerative colitis

Background

The body of research presented in ***chapters 3, 4 and 5*** illustrate the importance of furthering research into diet therapies for inflammatory bowel disease (IBD). Food avoidance and dietary restriction are associated with poorer food-related quality of life (FRQoL) and may be unnecessarily compromising nutritional status. Inadequate intakes of dietary fibre may also have significant implications in IBD pathogenesis. Diet therapies are appealing for many reasons. Patients have shown they are motivated to make dietary changes to control disease. Diet therapy is a relatively cost effective therapeutic strategy without risk of immunosuppression, infection and malignancy. Diet therapies are advancing for Crohn's disease (CD) whilst ulcerative colitis (UC) has been largely neglected despite a growing body of observational and experimental evidence implicating dietary factors with its effects on the microbial and immune compartment within the colon. One such hypothesis is the toxic microbial metabolites of colonic fermentation may be impairing key metabolic pathways and contribute to biochemical injury, loss of epithelial barrier function and the ensuing mucosal inflammation observed in UC.

The prospective open label feasibility study presented in this chapter is the first study to examine the tolerability, acceptability and therapeutic efficacy of a multidimensional sulphide-reducing diet strategy for mild-moderately active UC. This diet strategy draws together more than 40 years of observational and experimental data indicating the inflammation observed in UC could be downgraded by modulating carbohydrate and protein fermentation to supress production of excess hydrogen sulphide (H_2S) at the colonic-luminal interface, thereby restoring essential short chain fatty acids (SCFA) metabolism for colonocytes. Furthermore, this whole-food diet therapy was evaluated for dietary adherence, influence over FRQoL, and its proposed mechanistic actions on faecal biomarkers of fermentation.

Statement of authorship

Title of Paper	The novel 4-SURE diet is tolerable, modulates colonic fermentation and has therapeutic potential for mild-moderately active ulcerative colitis: findings of a feasibility study
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Submitted to American Journal of Clinical Nutrition November 2021

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Contribution to the Paper	Contributed to study concepts and design, data acquisition, data analysis and interpretation, drafting of manuscript, corresponding author for journal.		
Overall percentage (%)	70%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

vii. the candidate's stated contribution to the publication is accurate (as detailed above);

viii. permission is granted for the candidate in include the publication in the thesis; and

ix. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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[Manuscript 4]: The 4-SURE diet is tolerable, modulates colonic fermentation and has therapeutic potential for mild-moderately active ulcerative colitis: findings of a feasibility study

Short title

4-SURE diet for ulcerative colitis

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Author declarations of personal interest

ASD has served as a speaker for Emerge Health and AbbVie (fees paid to employer for research support). CKY has received research funding from Atmo Biosciences, Ferring Pharmaceuticals, Danone and Yakult Australia. Her Department financially benefits from the sales of a digital application, booklets and on-line courses on the FODMAP diet. SPC has received advisory, speaking fees or

research support from Ferring, Falk, Microbiotica, Janssen. SPC owns shares in BiomeBank. AR has no disclosures. JMA has served as a speaker, a consultant and an advisory board member for, and has received research funding from, Abbott, AbbVie, Allergan, Anatara, AstraZeneca, Bayer, Celgene, Falk, Ferring, Gilead, Hospira, Immunic, ImmunsanT, Janssen, MSD, Nestle, Progenity, Pfizer, Sandoz, Shire, Takeda, Vifor, RAH Research Fund, The Hospital Research Fund with all monies received by her department for research support. PRG has served as consultant or advisory board member for Anatara, Atmo Biosciences, Novozymes, Falk Pharma and Takeda. He has received research funding from Atmo Biosciences. He holds shares in Atmo Biosciences. His Department financially benefits from the sales of a digital application, booklets and on-line courses on the FODMAP diet. He has published two educational/recipe books on diet. RVB has served as a speaker, a consultant and an advisory board member for (all fees paid to employer for research support), and has received research funding from AbbVie, Ferring, Janssen, Shire, Takeda, Dr Falk, Emerge Health. RVB owns shares in BiomeBank.

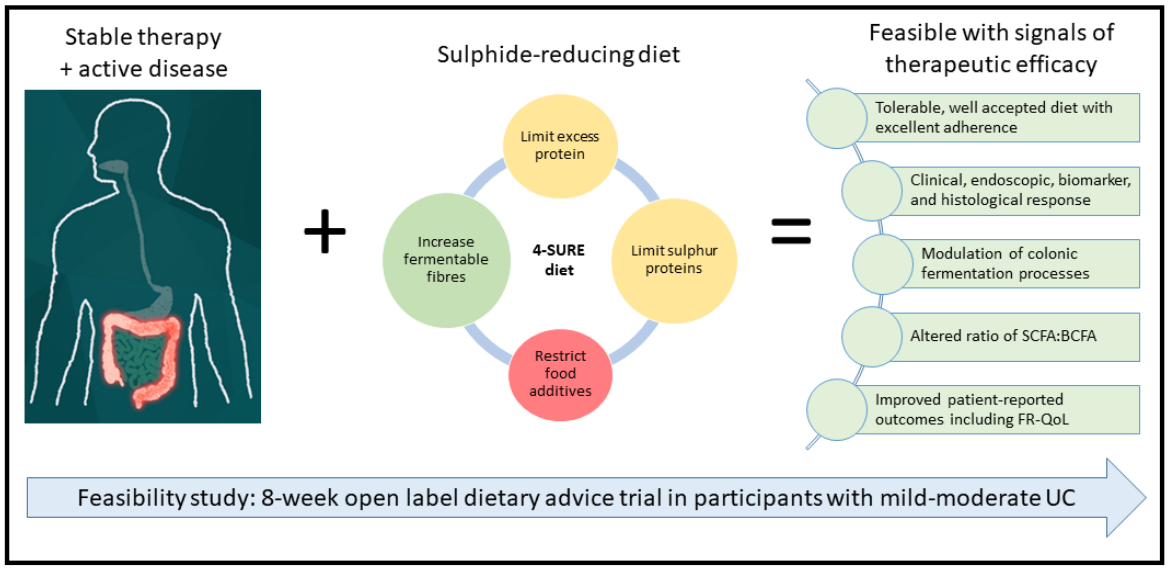
Guarantor of article

Dr Robert V Bryant takes responsibility for the integrity of the work as a whole, from inception to published article.

Author contributions

ASD, RVB, SPC, JMA, CKY and PRG contributed to the study concept and design. RVB, CKY, SPC and JMA provided study supervision. ASD, RVB, SPC and AR contributed to the acquisition of data and data analysis. RVB obtained study funding. ASD and RVB completed the statistical analysis with statistician support. All authors contributed to the interpretation of the data. ASD, RVB and CKY drafted the manuscript; RVB, JMA, SPC, CKY, PRG provided critical revision of the manuscript for important intellectual content. All authors approved the final version of the article, including the authorship list.

Graphical abstract



Abstract

Background & aim: Diet therapy may bridge the therapeutic gap in UC. The novel 4-SURE diet (4-strategies-to-SUlphide-REduction), designed to modulate colonic fermentation and production of excess hydrogen sulphide, was examined in a feasibility study for acceptability, clinical efficacy and effects on microbial end-points.

Methods: Patients with mild-moderately active UC were advised to increase intake of fermentable fibres, restrict total and sulphur proteins and avoid specific food additives for 8-weeks. Measures included tolerability (100-mm visual analogue scale (VAS) with 100-mm being intolerable), self-reported adherence, clinical and endoscopic response (reduction in partial Mayo ≥2 and Mayo endoscopic sub-score ≥1), modulation of faecal characteristics including markers of protein and carbohydrate fermentation, and FRQoL (IBD-FRQoL-29).

Results: 28 patients with UC, mean age 42 (range 22-72) years, 15 female, 3 proctitis, 14 left-sided and 11 extensive, were studied. Prescribed dietary targets were achieved overall. The diet was well tolerated (VAS:19 (95% CI 7, 31) mm) with 95% adherence. Clinical response occurred in 13/28 (46%) and endoscopic improvement in 10/28 (36%) ($p=0.02$). Two (7%) worsened. Excretion of SCFA increased from 13.5 (7.4, 21.7) to 22.9 (14.1, 37.2) mmol/d ($p<0.0001$), whilst the proportion of branched-chain to SCFA were numerically suppressed from 4.9% (3.7, 6) to 3.6% (2.6, 4.5) ($p=0.007$). FRQoL improved by 10 points (4, 16) ($p<0.001$).

Conclusions: The 4-SURE dietary strategy is considered acceptable by patients with mild-moderate UC and meets prescribed dietary and faecal targets. Given signals of therapeutic efficacy, further evaluation of this diet is warranted.

Trial registration number: Australian New Zealand Clinical Trials Registry ACTRN12619000063112.

Key words

Ulcerative colitis, hydrogen sulphide, diet, fibre, fermentation

6.1 Introduction

The global rise in incidence of UC implicates an environmental trigger.[1] Dietary intake is proposed as a key environmental contributor to epidemiological trends, in particular a Western diet, high in animal protein, processed foods and low in fibre.[1, 2] However, in the setting of established UC, beyond observational studies there is limited evidence for specific therapeutic diet strategies.[3]

Excessive colonic production of H_2S and nitric oxide are implicated in UC pathogenesis.[4, 5] These gases can impair key metabolic pathways leading to defective SCFA metabolism and an energy-deprived state for colonocytes.[6, 7] This so called 'biochemical injury' in UC contributes to a loss of epithelial barrier function and ensuing mucosal inflammation.[6, 7] Modern western dietary patterns observed in patients with UC create a colonic environment likely to be permissive of nitrogenous metabolites and excess H_2S production as variation in fermentable dietary protein and carbohydrate reaching the colon influences microbial production.[2, 8-11] Also contributing to colonic H_2S accumulation is intake of inorganic sulphur (sulphates/sulphites) and nitrates/nitrites and, to a lesser extent, endogenous substrate.[12, 13] High doses of sulphated dextrans, including food additive carrageenan, induce histopathological features typical of human UC with associated microbial changes in mouse models.[14, 15]

Most available therapies for UC target the mucosal immune system, without concurrent modulation of the dysbiotic gut microbiota typically observed.[16, 17] This may account for the substantial therapeutic gap that exists in UC, with high rates of treatment failure and colectomy despite an expanding immune therapy armamentarium.[16] A limited number of studies have demonstrated the therapeutic potential of modulating dietary sulphate to induce clinical response in UC.[18, 19] Observational data also show an association between dietary sulphate intake and rates of clinical relapse.[3] Further to this, experimental data using faecal gas profiling technology has detected superior suppression of H_2S production by readily fermentable fibres compared to 5-aminosalicylic acid (5-ASA) therapy.[20] This supports earlier observations suggesting colonic bacteria preferentially ferment carbohydrate and signal a mechanism to 'switch off' protein fermentation, a major source of microbial nitrogenous metabolites and H_2S, thereby supressing excess production.[10, 21]

A multidimensional dietary strategy designed with the aim of less animal protein and increased fermentable fibre intake has the potential to manipulate sulphide metabolism at the colonic-luminal interface. Beyond signals from murine studies, this novel approach to dietary modulation in UC has not yet been trialled.[15, 22] Moreover, it is unknown if higher intakes of fermentable fibres are tolerable in active UC.[21] Therefore, this real-world feasibility study aimed to investigate the tolerability and

acceptability of the 4-SURE diet in patients with mild-moderately active UC and to explore its effects on disease activity, bacterial fermentation and patient-reported outcomes including FRQoL.

6.2 Materials and methods

Participants

Adults (≥18 years old) with an established diagnosis of UC and mild-moderately active disease were recruited between August 2018 and December 2019 from IBD Services. Included were those with a total Mayo score of 3-10 with a Mayo endoscopic sub-score score ≥1; stable dose or no existing UC therapies for defined periods (≥4 weeks for no medication, 5-ASAs, oral prednisolone <20 mg/day; ≥8 weeks for immunomodulatory therapy; ≥12 weeks for biologics). Exclusion criteria were pregnancy or breastfeeding, prior colonic surgery, significant medical or cognitive/psychiatric comorbidities, evidence of active infection and/or antibiotic therapy within past 4 weeks, dual antiplatelet therapy or anticoagulant therapy, habitual vegan or lacto-vegetarian diet, and inability to provide informed consent.

The study was approved by Central Adelaide Local Health Network Human Research Ethics Committee (HREC/16/RAH/24, R20160202). The study protocol was registered with Australian New Zealand Clinical Trials Registry (ACTRN12619000063112).

Study protocol

This was a prospective, 8-week open-label feasibility study examining real-world application of 4-SURE dietary-advice. Potential participants either self-referred in response to newsletter advertisements or via a member of their treating team were then screened for eligibility by telephone. If deemed likely to be eligible, they were invited to provide written consent and complete a baseline screening flexible sigmoidoscopy. Thereafter, participants were enrolled and completed a 14-day run-in period with collection of prospective information on baseline diet, clinical symptoms and quality of life (QoL). A 48-hour stool collection was also performed on baseline diet. Participants then attended a baseline study visit with a research dietitian during which 4-SURE dietary education was provided, advising how to shop, cook and prepare meals for the 8-week intervention. Participants were seen in person on two further occasions at weeks 4 and 8, as per study protocol (***Supplementary material 6.1***).

Assessment visits and data collection

Baseline data collection included patient demographics, Montreal disease distribution, clinical disease activity assessment, past and current therapy for UC, recent hospitalisations and global nutrition assessment. Prior to each study visit, a prospective 3-day weighed food diary and stool collection were

completed, and laboratory tests (serum C-reactive protein, full blood count) performed. In addition, micronutrients (iron studies, B_{12}, folate, calcium, vitamin D) were measured at weeks 0 and 8.

Study endpoints

Primary endpoint

Overall tolerability and acceptability of the 4-SURE diet were measured using five 100-mm VAS. Each assessed differing domains of tolerability and acceptability (overall tolerability, dietary knowledge, ease of purchasing study foods, ease of preparing meals, overall ease of following 4-SURE diet) where 0 = excellent and 100 = extremely difficult.

Secondary endpoints

Dietary adherence was measured semi-quantitatively using weekly self-reported checklists and assessment of 3-day food diaries. Always adherent to the diet was defined as 76-100%, frequently adherent 51-75%, sometimes adherent 26-50% and rarely/non-adherent 0-25%. Excellent adherence was defined as the sum score of always and frequently adherent.[23] Dietary data were estimated using weighed food diaries and analysed for macro and micronutrient intake and adequacy using Foodworks program (Xyris Software Pty Ltd; Queensland, Australia). Inorganic sulphur and FODMAP data were estimated using published food tables and the Monash FODMAP database.[24] United States (US) Department of Agriculture food composition data were used to measure intake of sulphur proteins. Food composition data to measure intake of carrageenan, nitrates/nitrites do not exist therefore this could not be assessed beyond self-reported dietary adherence.

Clinical response was defined as reduction in partial Mayo score ≥2 and clinical remission partial Mayo ≤1.[25] Endoscopies were video-recorded using Provation® software. Endoscopic response was defined as reduction in Mayo endoscopic score ≥1 and endoscopic remission Mayo endoscopic score = 0.[25] Additional scoring by Ulcerative Colitis Endoscopic Index of Severity (UCEIS) was performed due to the responsiveness of this tool whereby endoscopic response was defined as a reduction in UCEIS ≥2 and endoscopic remission UCEIS ≤1.[26] Overall improvement in disease activity was defined as reduction in total Mayo score ≥3 and overall remission total Mayo ≤2.[25] Tissue biopsies from the most severely diseased segment of the colon were taken during each endoscopy and scored by a single Pathologist using the Nancy Histological Index (NHI). Histological response was defined by a ≥1-point reduction in NHI score and histological remission NHI = 0.[27]

Other outcomes explored included change in serum and faecal markers of inflammation. Improvement in global gastrointestinal symptoms were measured at each visit, defined by a reduction in Gastrointestinal Symptom Rating Scale (GSRS) subscale scores (1, no discomfort, to 7, very severe discomfort, giving a total sum score of all subscales 13-91).[28] The impact of the 4-SURE diet on quality of life (QoL) markers were assessed at each visit using IBD-Control-8 and IBD-FRQoL-29

questionnaires. Change in perceived IBD control defined by change in IBD-Control-8 score (score 0, poorer QoL, score ≥13-16 = quiescent disease and greater QoL) was measured along with change in FRQoL, defined by an increase or decrease in FRQoL sum score (minimum/poor 29, maximum/greater 145).[29, 30]

As faecal sulphide cannot be accurately measured as a study endpoint, surrogate markers associated with carbohydrate and protein fermentation such as molar ratios of SCFA and branched chain fatty acids (BCFA) and output of ammonia (NH3) were used in this feasibility study.[31, 32] Lastly, adverse events, including disease flare requiring escalation of therapy or need for hospital admission, were assessed at each visit.

4-SURE dietary-advice

The four central strategies of the diet were: (a) to achieve an intake of 10-15 g/d of resistant starch (RS) and 5 g/d slowly-fermentable non-starch polysaccharide whereby dietary advice targeted a variety of food sources rich in RS1-RS3 including from wholegrains and retrograded sources of RS and supplemental non-starch polysaccharide psyllium was also utilised in addition to fruits, vegetables, nuts and legumes; (b) to ensure total protein intake from animal and plant sources was limited to 75-90 g/d (≤1.2 g/kg for females and males); (c) to restrict the intake of sulphur-containing amino acids to ≤1.5-2.0 g/d; and (d) the avoidance of sulphite/sulphate, nitrite/nitrate and carrageenan food additives. An additional aim was to ensure the intake of total FODMAPs were not increased with a specific focus on reducing excess fructose, sorbitol and mannitol intake to offset a potential increased intake of total oligosaccharides. The diet incorporated a 1-week set meal plan including a 3-day adaptation period where levels of fermentable fibres were gradually increased to minimise potential functional gut symptoms.

Participants received 30-minutes of individualised dietary education and were advised to eat to appetite within dietary parameters. A 4-SURE diet manual and recipe book were provided. A brief telephone review by the research dietitian was conducted at the end of week 1 to promote adherence when participants transitioned from the set meal plan to self-application of dietary advice. Participants were provided with a contact email for dietary support between reviews at weeks 4 and 8.

Faecal collection and assessment

Participants completed a 48-h stool collection in the 2-days prior to each visit. Stools passed into a blue sterile bag were immediately placed into a supplied -21°C portable freezer. After delivery, stool samples were stored at -80° C until defrosted for measurement of stool weight and consistency as per established methods, before homogenising, aliquoting and storing at -80°C until further assessment.[33-35]

Detailed methodology of faecal assessment can be found in ***Supplementary material 6.2***. Briefly, faecal pH was measured at 25°C using a Fisher Scientific Accument AE150 pH meter (ThermoFisher Scientific, Waltham, Massachusetts, U.S.A)[33, 34] and faecal water content assessed using a microwave drying method.[33, 34, 36] Faecal concentrations of SCFA were measured via gas chromatography and faecal output of SCFA were calculated as previously described.[31, 33, 35] Faecal ammonia was measured in duplicate using an enzymatic assay (Megazyme rapid ammonia assay, K-AMIAR, Bray, Ireland) after protein precipitation and filtration as previously described.[37]

Statistical analysis

Estimated tolerability of 5-ASA therapy for remission induction of active UC was used to inform a power calculation in the absence of preliminary dietary therapy data.[38] This feasibility study was therefore powered to detect a significant difference in the primary outcome with 15 participants (alpha=0.05, 80% power), with an estimated sample size to allow for dropouts calculated as 25-30. The primary analysis was by intention to treat (ITT) (n=28). A subsequent per-protocol (PP) analysis (n=24) was performed on secondary outcomes. Imputation of continuous variables was obviated by complete data accrual. Descriptive data are presented as mean (95% confidence interval (CI)) or median (interquartile ranges (IQR)) for continuous variables. Categorical data are presented as frequency (%). Paired t-test and Wilcoxon signed-rank statistical tests were used to compare continuous dietary intake variables and faecal characteristics. A p-value ≤0.05 was considered statistically significant. False discovery rates (FDR) were calculated to minimise Type 1 error. An adjusted linear mixed-effects model was used to investigate the association between tolerability variables (with logarithm transformation). An unstructured covariance structure was used to adjust for repeated measurements over time. Backwards elimination was used until all covariates in the model had a P value <0.5.[39] Data were analysed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), IBM SPSS Statistics Version 26.0 (IBM, Armonk, NY) and Graph Pad Prism Version 9.0 (GraphPad Software, San Diego, CA, USA). All authors had access to analysed data, inputted into decision and approved final decision regarding data for publication.

6.3 Results

Of 92 screened, 28 UC patients from three tertiary IBD service in South Australia were enrolled and commenced the 4-SURE intervention diet. Patient flow is shown in ***Figure 6.1***. Four participants (14%) breached study protocol with medication changes during the trial (two participants after week 4 required escalation of therapy due to increased symptoms of disease, one commenced Predsol enema on day 2, and one unintentionally ceased medications due to bushfire evacuation). They were not withdrawn as they continued the diet. Baseline characteristics for the cohort are summarised in ***Table 6.1***.

Tolerability and acceptability

The 4-SURE dietary strategy was well tolerated and accepted with a median overall tolerability of 19 (IQR 7, 32) mm at week 8 (***Figure 6.2***). No differences in scores were observed between week 4 and 8. The other domains of tolerability also scored similarly. Age, anxiety, depression and FRQoL were not associated with any domain.

Dietary adherence

Twenty-six (93%) participants completed weekly dietary adherence checklists. Of these, 65% reported being always adherent to key dietary parameters and 30% reported frequent adherence. All participants reported always reading food labels and avoiding 4-SURE food additives. Only 3/26 (12%) reported rarely adhering to one or more central dietary strategies at least once during the study.

Analyses of weighed food diaries are shown in ***Table 6.2***. A 20% reduction in total protein intake (95% CI 5.6, 31.3) g/d was observed between baseline and week 8 (p=0.007), but not for sulphur proteins. The intake of inorganic sulphur tended to fall by 24% (12.2, 626.1) mg/d (p=0.042). Marked increases in total fibre (<0.0001), RS (<0.0001) and galacto-oligosaccarides (p=0.007) were seen without consistent changes in overall FODMAP intake. A reduction in energy occurred without subsequent change in BMI (p=0.0461). All other nutrients remained similar to baseline intake with the exception of reduction in B_{12}.

Disease activity

The changes in key indices of disease activity are shown in ***Figure 6.3***. A clinical response was observed in 13/28 (46%) and endoscopic improvement in 10/28 (36%), whether expressed as UCEIS or Mayo endoscopic sub-score. Two (7%) had worsening of symptoms and endoscopic disease activity, which included the participant who commenced Predsol enema on day 2. Histology improved in 12/28 (43%) and worsened in 6/28 (21%). Serum C-reactive protein did not change. Median faecal calprotectin levels reduced by 131µg/g (p=0.02).

Of patient-reported outcomes, perceived disease control improved by 43% according to IBD-Control-8, from 7 (IQR 4, 13) to 10 (7, 13; p<0.0001). The most troublesome gastrointestinal symptoms at baseline and an overall 24% reduction in symptom burden by week 8 (p=0.002) are shown in (***Figure 6.4a and 6.4b***). FRQoL score increased from 69 (95% CI 61, 77) at baseline to 79 (71, 88) at week 8 (p=0.001).

The PP analysis showed 33% of participants had a clinically and statistically significant reduction in total Mayo score (***Table 6.3***). There was also consistent and clinically relevant improvement in faecal calprotectin and all patient-reported outcomes.

Faecal characteristics

As shown in ***Table 6.4***, faecal weight increased by 35% (95% CI 30, 122) g/d (p=0.002) during the dietary intervention without changes in the number of stools per day, faecal water content or pH. Faecal concentrations of SCFA increased by 17% (1.5, 26.9) µmol/g whilst reductions in BCFA concentrations failed to reach statistical significance after FDR correction (p=0.04). However, the total daily output of SCFA increased by 69% (p=0.0001). Outputs of butyrate, acetate and propionate all increased similarly (p≤0.001). While concentrations and daily output of ammonia and BCFA did not significantly change, the ratio of BCFA:SCFA fell (p=0.007), just failing to reach statistical significance after FDR correction.

Comparison of those with and without response in overall disease activity

Post-hoc analyses were performed comparing the eight participants with reduced overall disease activity at week 8 with the 20 without. The 4 participants who breached protocol with additional medications did not have an overall response therefore were included in the non-responder group for post hoc analysis. In terms of dietary intake, responders tended to habitually consume more protein at baseline than non-responders and reduced protein intake by 31% (95% CI 6.3, 57; p=0.02) compared with 15% (-2.5, 28.9; p=0.09) in non-responders (***Supplemental material 6.3***). There were no differences in baseline intakes or change in consumption achieved by dietary education in sulphur proteins, inorganic sulphur, total fibre or RS observed between the two groups. Faecal characteristics in responders versus non-responders are shown in ***Supplemental material 6.4***. No consistent patterns of changes in faecal metabolite responses were observed.

Adverse events

There were three adverse events recorded during this study related to worsening of disease requiring escalation of therapy. Additionally, one participant reported an increased in gastrointestinal symptoms during menstruation only. Another reported an oral tingling sensation and a further four participants reported increased bloating and wind, all self-attributed to consumption of legumes. Two reported cold and flu symptoms.

6.4 Discussion

The novel sulphide-reducing diet (4-SURE diet) for UC is based on the premise that excess colonic H_2S production can be modulated by diet and is implicated in the pathogenesis of UC. This feasibility study is the initial step in testing the safety and tolerability of this novel diet therapy. The 4-SURE diet was well tolerated and acceptable as a dietary therapy by patients with UC. High levels of dietary adherence were achieved through dietary education akin to real-world clinical practice. The 4-SURE diet modulated fermentation in the colonic luminal environment and showed signals of clinical efficacy, inducing both clinical response and endoscopic mucosal healing, hypothesised to result from

manipulation of sulphide metabolism. Collectively, this feasibility study shows the 4-SURE diet is an acceptable dietary strategy by patients with active UC and signals a potential therapeutic effect in mild-moderately active UC, which warrants further evaluation in a randomised-controlled trial.

The 4-SURE diet was considered an acceptable dietary prescription as it was well tolerated, easy and inexpensive to purchase, prepare and follow. This is plausibly explained by the design of this whole-foods diet, which is not restrictive in nature, and self-implemented with ease away from the home. Moreover, the 4-SURE diet is positively framed to 'include more of, or less of' and therefore is devoid of negative dietary connotations associated with exclusion or restriction of foods. This feasibility study also demonstrated an intake of dietary fibre from a wide variety of foods across all food groups and above national fibre recommendations of 25-30g/d, inclusive of RS >12g/d, is well tolerated in the presence of active disease. The sustained tolerability of an increased intake of fermentable fibres and concurrent reduction in gastrointestinal symptoms is in contrast to previous studies reporting worsening flatulence and abdominal discomfort.[40, 41] It is possible that reduced intake of excess fructose and mannitol may have contributed to tolerability and improvement in any coexisting functional gastrointestinal symptoms, known to be prevalent in approximately 27% of individuals with UC.[42]

The success of the 4-SURE diet central strategies, details of which remain intentionally limited for a future randomised-controlled trial, was carefully addressed by assessment of adherence and actual food intake via interrogation of checklists and food diaries. Modification of carbohydrate intake was uniformly successful. The intake of fibre in general and RS specifically were markedly increased without a change in total carbohydrate or starch intake. This suggests participants were able to replace low fibre carbohydrates for specific fibre-rich alternatives as advised. FODMAP intake was largely unchanged and planned restriction of polyols was achieved with reduction of mannitols. The two-fold increase in galacto-oligosaccharides was anticipated with an increase in RS-containing foods.

Modification of protein intake was variably successful although measured consumption did significantly fall overall. The majority of patients had a baseline intake already within the targeted range, set according to nutritional guidelines for active inflammation.[43] Interestingly, post-hoc analysis of those whose disease responded very well to the diet showed a higher baseline protein intake, which reduced by a greater amount (nearly one-third) during the dietary intervention compared with non-responders. Like protein, baseline sulphur protein intake was within targeted range for most, but again, the reduction in responders was greater. However, calculation of the content of sulphur proteins in food was dependent upon US data; how accurately such a database applies to Australian foods is untested.

Measurement of other targeted dietary changes, in particular reduced inorganic sulphur and carrageenan intake from food additives, were limited to qualitative assessment of participant reading of food labels and self-reported adherence, rather than by objective quantification. Whilst dietary

counselling of reading food labels is a real-world approach to modifying dietary intake, interpretation of this dietary change on clinical response is limited. The numeric reduction in energy intake was expected with a shift toward a whole-foods diet with reduction in processed foods with additives; however, BMI remained unchanged over 8-weeks likely due to the individualised advice recommending eating to appetite. An untargeted reduction of B_{12} intake was observed, but anticipated with a reduction in animal protein, and intake remained adequate. Non-completion of adherence checklists was not reported to negatively influence self-reported dietary adherence.

The 4-SURE diet was designed to achieve specific changes to the distal colonic environment, which can be interrogated by faecal analysis. Unfortunately, accurate and reproducible measurement of H_2S production in vivo or in freshly passed faeces, and as previously reported, was too impractical.[20] For this reason, surrogate markers were used. Since H_2S and other nitrogenous metabolites are largely produced by faecal microbiota from the fermentation of protein and this can be markedly inhibited by increasing carbohydrate fermentation, products of such fermentation (SCFA, BCFA and ammonia) were used as surrogate markers.[20] Since the increased fibre intake reflected a marked increase in the faecal volume, the production of such molecules was better evaluated as the daily output rather than concentration.

Indeed, preferential carbohydrate rather than protein fermentation was indicated by a marked increase in SCFA excretion without a concomitant increase in excretion of BCFA or ammonia. This is congruent with previous studies showing higher levels of RS (>16-39 g/d) are required to achieve increased SCFA concentration and excretion.[10, 34, 35] Moreover, the four-fold increase in RS was sufficient to increase SCFA excretion, despite carbohydrate metabolism purportedly being abnormal in UC.[10, 34, 35, 44] There are also signals from the post hoc analysis of responders that butyrate utilisation increased with expected reductions in butyrate observed. Thus, within the limitation of interpretation of biomarkers, targeted changes in colonic luminal environment were achieved.

There is a lack of data informing protein recommendations for active UC.[43] In keeping with our hypothesis and the overall response observed by those who had a greater reduction in protein intake, protein requirements for active UC may be lower than 1.0-1.2g/kg given inflammation is confined only to the colonic mucosa. It is plausible a lower protein prescription may then contribute to a lower sulphur amino acid intake and invariably lower faecal concentrations and outputs of protein fermentation by-products, including nitrogenous metabolites ammonia, BCAA, and H_2S. Speculatively, this could explain the trends observed in faecal ammonia concentrations and outputs that failed to achieve statistical significance. Decreased ammonia concentrations suggest a degree of suppression of protein fermentation may have occurred. This observation was also made in those who responded to the dietary intervention. The increases in ammonia output with concurrent increases in butyrate in non-

responders may also reflect decreased ammonia absorption in the colon though this does not explain the trends in suppression of BCFA:SCFA observed in the non-responders.[10, 35] Collectively, these findings suggest a lower total protein intake in active UC may be required to see a significant change in these surrogate markers.

The novel 4-SURE diet showed signals of therapeutic efficacy as it not only led to improved patient-reported outcomes, but also objective improvement in endoscopic criteria and faecal calprotectin. The proportion of patients with clinically significant improvement was greater than might be anticipated through placebo effects only, although endoscopic appearances were not centrally-read.[45] There was discrepancy between endoscopic mucosal healing and histopathology, but such a discord is well recognised in clinical trials and may relate to sampling error, limited responsiveness of the Nancy score, and perhaps a longer time to histological healing beyond endoscopic mucosal healing.[46, 47]

The prospect of diet as therapy for UC is appealing, and is plausibly adjunctive to conventional therapies targeting the immune system by concurrently manipulating the gut microbiota and colonic environment. Moreover, a whole-food balanced dietary strategy is safe in the longer term, lacking risks of infection and malignancy that plague immunosuppressive therapy.[48] Further studies are required to understand the response time, particularly endoscopic and histological, for remission induction in UC using diet therapy.

This study is the first to examine and show FRQoL improves with a dietary intervention in UC. This is an important outcome of a potential diet therapy as FRQoL is impaired in IBD and may be lower in active UC.[49] Provision of dietary education and direction coupled with the flexibility of the whole-food, non-restrictive 4-SURE diet are likely explanations for the improved FRQoL observed, even in those who did not clinically respond. The diet provided participants with structured dietary parameters designed to minimise the psychosocial burden of eating and drinking, notably poorer in UC.[50] This novel finding confirms FRQoL as an important outcome measure for future dietary studies, particularly where two diets can be compared.

The current study had limitations. Interpretability of secondary clinical endpoints is limited by a lack of power and placebo control. Further to this, the accuracy of evaluating the dietary data is limited by available food composition databases, particularly for measuring sulphur proteins and food additives. Therefore, collectively, the signals of efficacy including post-hoc differences observed must be interpreted with caution, requiring further evaluation in a higher-quality placebo-controlled dietary trial. Lastly, absence of centralised reading of endoscopy may have influenced endoscopic scoring and reporting bias.[51] Study strengths include the comprehensive assessment of baseline diet and success of changes instituted by dietary education, the assessment of faecal biomarkers that mechanistically reflect the success of dietary manipulation in the absence of accurate and reproducible measures of

H_2S, and careful documentation of endpoints including tolerance and acceptability, as well as subjective and objective clinical markers.

Key learnings from this feasibility study not only span patient responses to the diet, effect on disease behaviour and provision of data needed to power future randomised controlled trials, but also include how the diet might potentially be improved. The main area of contention is the targeted protein intake including sulphur proteins and whether the ratio of animal to plant proteins requires further evaluation. Conceivably, total protein intake could be lower without compromising nutritional status. A higher ratio of plant proteins, also rich source of carbohydrate, may assist in achieving microbial end-points. Alternatively, the post-hoc findings suggest pre-treatment evaluation of protein intake might be a means of personalising the diet.

In conclusion, the 4-SURE dietary strategy can be taught to achieve both dietary and faecal biomarker targets, is well tolerated and acceptable as a dietary prescription in patients with mild-moderately active UC and improves FRQoL. Patients already manipulate their diets and patients and clinicians alike have voiced dietary strategies for UC as a top research priority.[52] The associated clinical, endoscopic and biomarker response highlights the potential of the 4-SURE diet to reduce the degree of colonic inflammation. The study findings provide a sufficient signal of efficacy with mechanistic rationale such that the 4-SURE diet should be subject to randomised controlled evaluation.

Funding

This work was partly supported by Gastrointestinal Society of Australia FICE Grant, The Hospital Research Foundation Project Grant, and Commonwealth Research Stipend administered through the University of Adelaide.

Acknowledgements

We would like to acknowledge and contribution and involvement of the following services and individuals in this study: The Queen Elizabeth Hospital Inflammatory Bowel Disease Service, Basil Hetzel Institute, Dr James Fon, Dr Karmen Telfer, Dr Samuel Forster, Dr Naomi Cook, Bronwyn Hutchens, Dr Bron Lett, Rachel Davis, Serena Martin, Sangwoo Han, Dakota Rhys-Jones and Suzanne Edwards.

Data availability statement

The following data will be made available after publication of this manuscript to any researcher who provide a methodologically sound proposal. This may include request for study protocol or statistical plan, or de-identified participant data for meta-analysis.

Figures

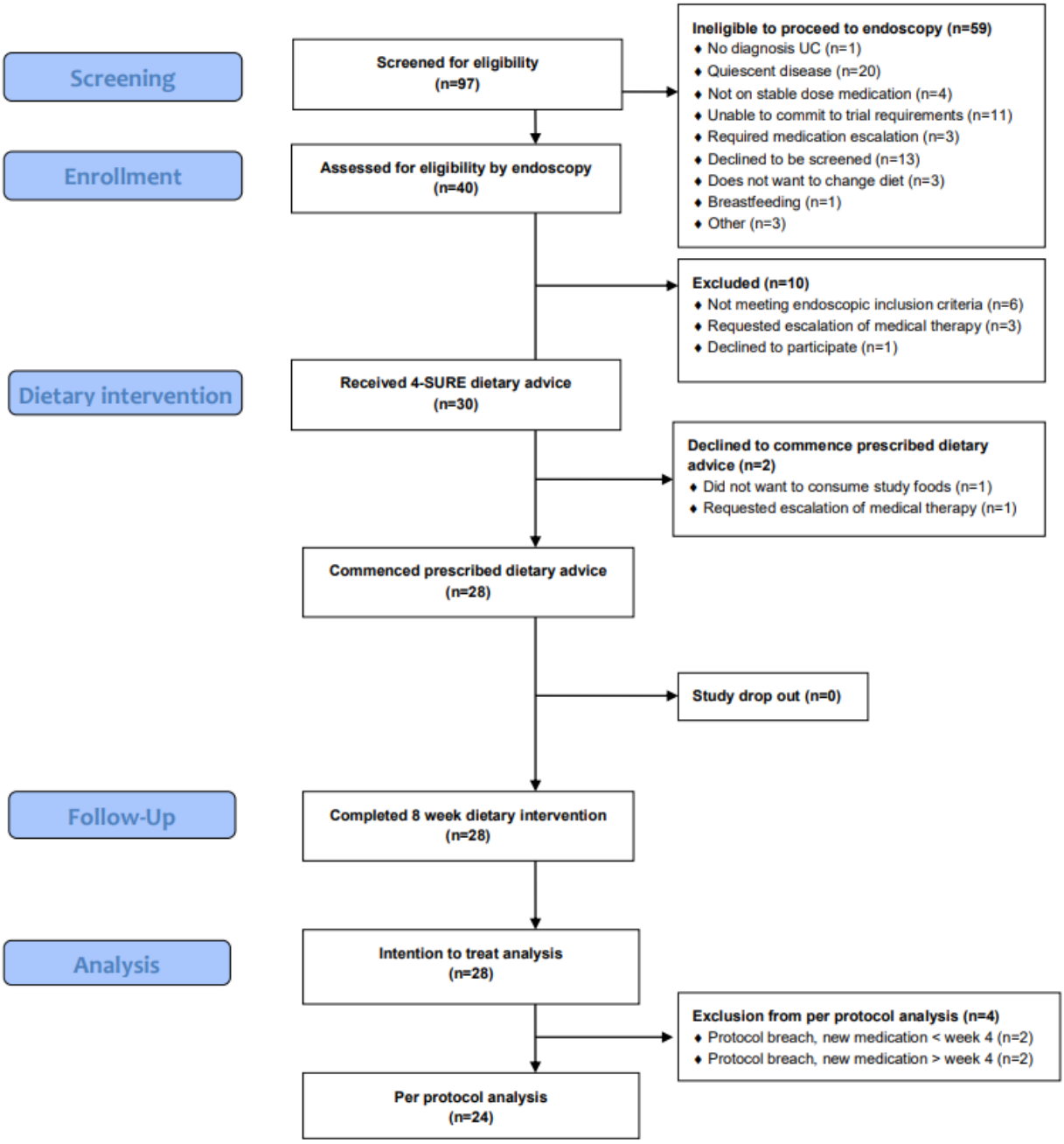


Figure 6. 1 Pilot dietary–advice study flow diagram.

Legend: *Participants (n=28) with mild-moderately active ulcerative colitis were prescribed the 4-SURE diet for 8 weeks.*

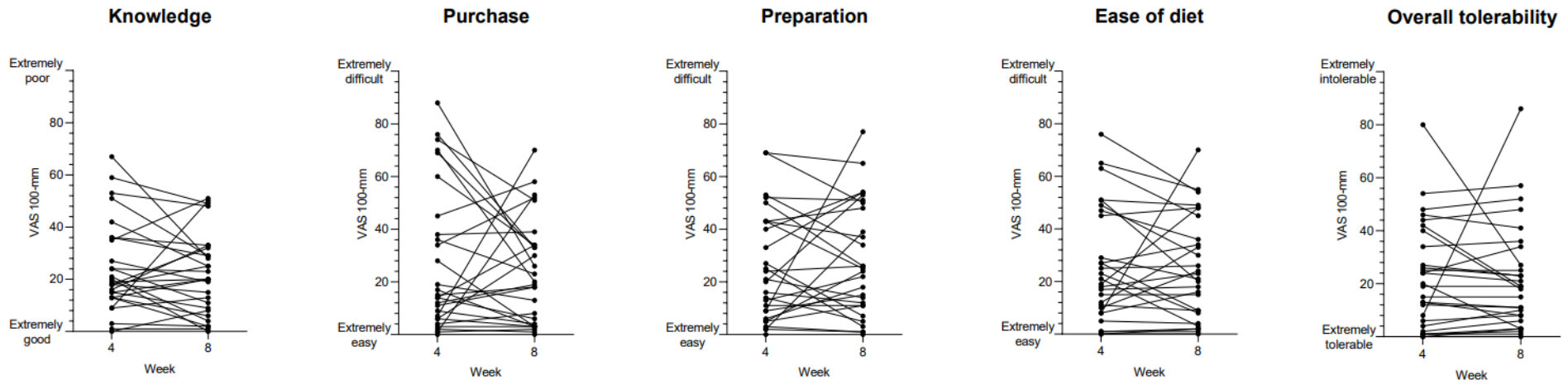


Figure 6. 2 Tolerability and acceptability of the 4-SURE dietary strategy.

Legend: *Five domains of tolerability and acceptability were measured using 100-mm visual analogue scales at week 4 and end of study in 28 participants with mild-moderately active ulcerative colitis. There was no significant change in any index over time (Wilcoxon signed-rank test).*

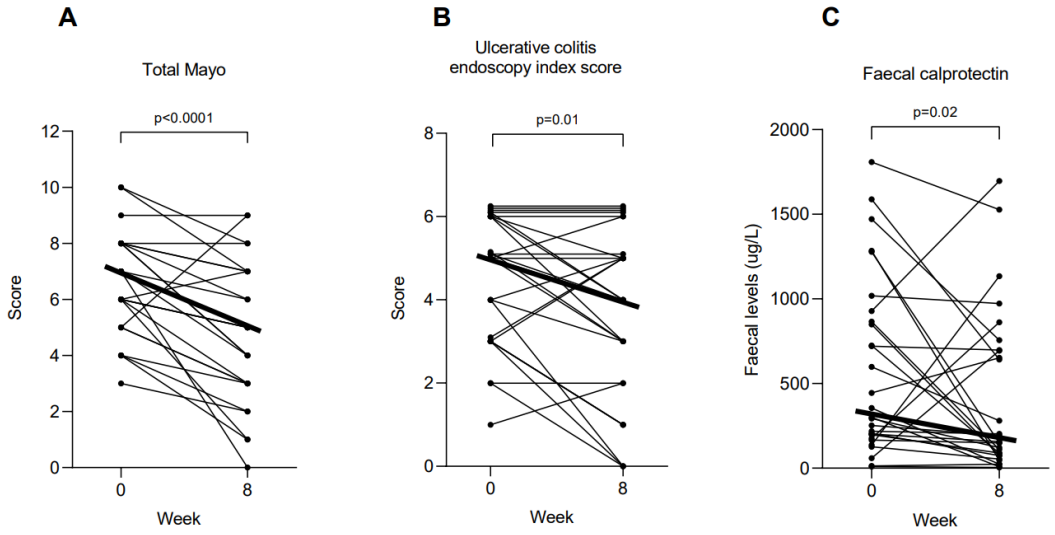


Figure 6. 3 *Change in disease activity and individual response to 4-SURE dietary intervention.*

Legend: *Results are analysed using paired t tests for parametric data and Wilcoxon signed Rank test for non-parametric data, with median line of best fit.* ***(A)*** *Total Mayo score used to measure overall response.* ***(B)*** *Ulcerative colitis endoscopy index score used to measure endoscopic response.* ***(C)*** *Faecal calprotectin used as an inflammatory biomarker.*

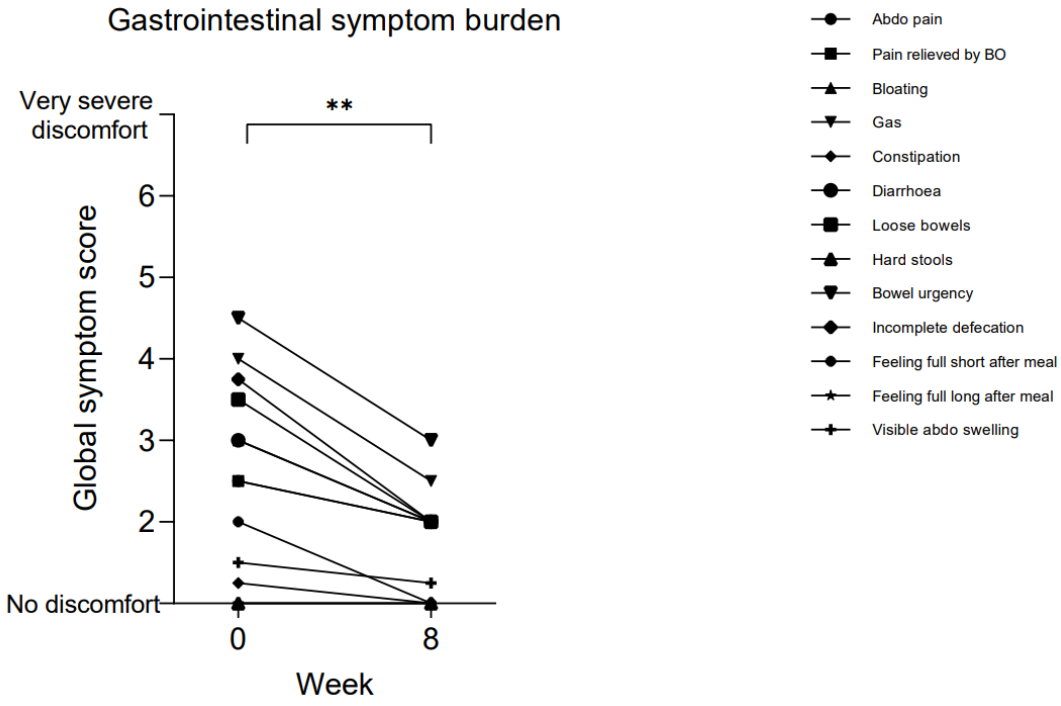


Figure 6. 4a *Gastrointestinal symptom burden of participants with mild-moderately active ulcerative colitis and influence of 4-SURE on symptom burden.*

Legend: Symptoms measured using GSRS instrument and results are presented as median change in scores and analysed using Wilcoxon signed-rank test.

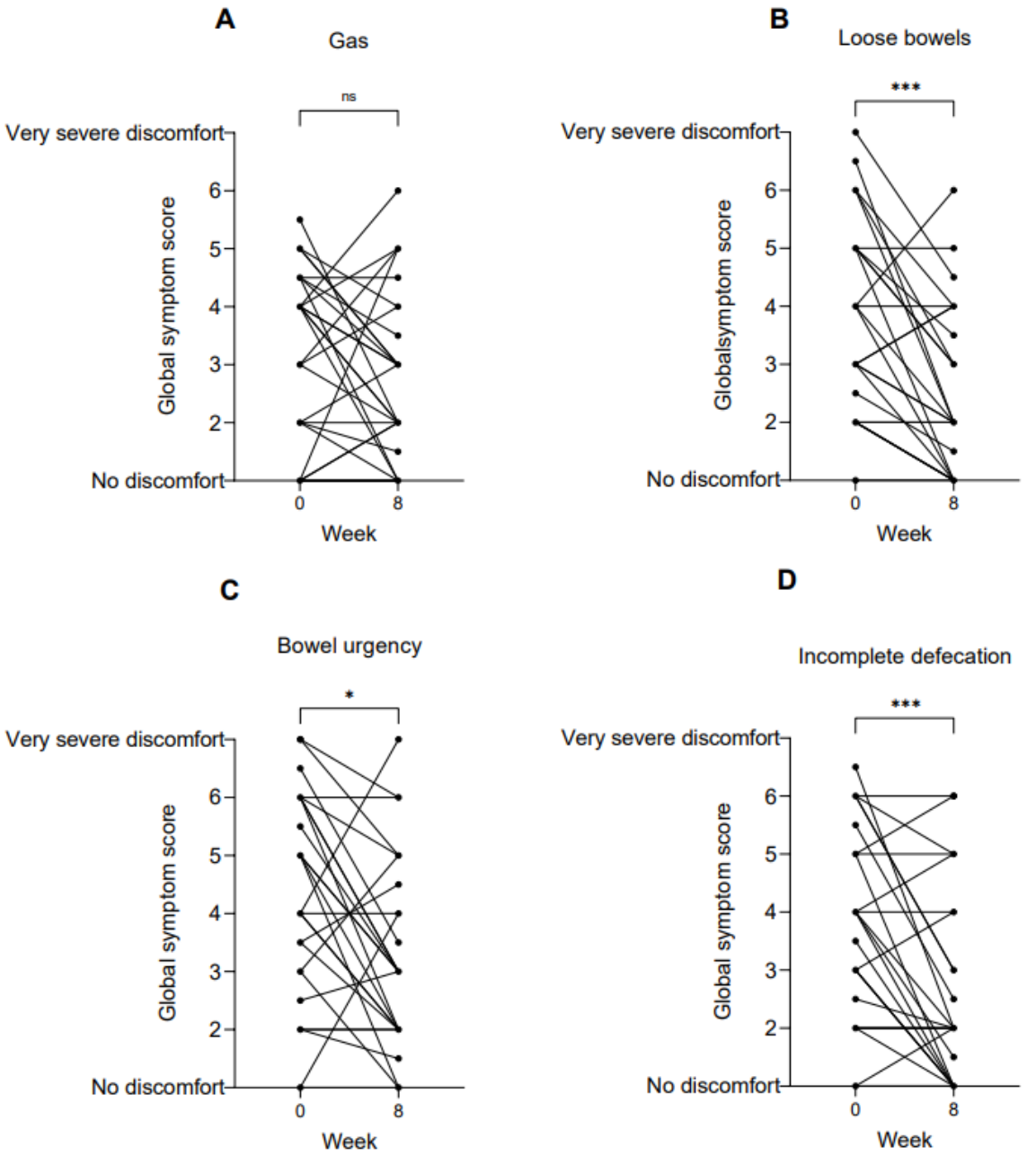


Figure 6. 4b Change in most troublesome gastrointestinal symptoms following the 4-SURE diet

Legend: *Symptom burden measured using the Gastrointestinal Symptom Rating Scale. Individual scores and response are presented and analysed using Wilcoxon signed-rank test. (**A**) Discomfort associated with gas and wind. **(B)** Discomfort associated with loose bowels. **(C)** Discomfort associated with urgency to use bowels. **(D)** Discomfort associated with a sense of incomplete emptying of bowels.*

Tables

Table 6. 1 Baseline characteristics of participants (n=28)

	Characteristics	Ulcerative colitis (n=28)
Demography	Age, years, median (interquartile range (IQR))	42 (32, 54)
	Age range, years	22-72
	Female n (%)	15 (54)
	Active smoker n (%)	0 (0)
	Disease duration, years, median (IQR)	8 (3, 13)
	Body mass index (BMI), kg/m^2, median (IQR)	25.1 (22.5, 28.1)
Disease distribution, n (%)	Proctitis (E1)	3 (11)
	Left sided (E2)	14 (50)
	Extensive (E3)	11 (39)
Disease activity median (IQR)	Total Mayo score • Partial Mayo score Mayo endoscopic sub-score • Mayo 1, n (%) • Mayo 2, n (%) • Mayo 3, n (%)	7 (6, 8) 5 (4, 5) 2 (2, 2) 2 (7) 20 (72) 6 (21)
Ulcerative colitis therapy, n (%)	No medications	4 (14)
	Corticosteroids • Prednisolone (stable dose <20 mg/d) • Budesonide (oral/topical)	3 (11) 3 (11) 0 (0)
	5-aminosalicylic acid drug • Oral only • Topical only • Oral + topical	18 (64) 10 (35.7) 8 (28.5) 8 (28.5)
	Immunomodulators • Methotrexate • Thiopurine	4 (14) 0 (0) 4 (14)
	Biologics • Infliximab • Vedolizumab	6 (21) 2 (7) 4 (14)
	Immunomodulator + biologic	0 (0)

Table 6. 2 Mean daily nutritional intake of participants (n=28).

		Week 0 (Baseline diet)	Week 8 (4-SURE diet)	P value
Energy, kcal		2108 (1847 – 2369)	1806 (1616 – 1996)	0.032
Protein, g	Total	**91 (79 – 103)**	**72 (64 - 81)**	**0.007**
	Total g/kg	**1.2 (1.1 - 1.4)**	**1 (0.9 – 1.1)**	**0.004**
	Total sulphur protein	1.7 (1.4 – 2.0)	1.5 (1.2 – 1.8)	0.427
	Methionine	1.1 (0.9 – 1.3)	1 (0.8 – 1.2)	0.476
	Cysteine	0.5 (0.4 – 0.6)	0.5 (0.4 – 0.6)	0.482
Inorganic sulphur, mg		1337 (1054 – 1619)	1018 (805 - 1230)	0.042
Fat, g	Total	**95 (82 - 107)**	**72 (61 – 83)**	**0.006**
Carbohydrates, g	Total	202 (174 – 229)	201 (178 – 223)	0.931
	Sugars	76 (63 – 89)	73 (64 – 83)	0.703
	Starch	127 (107 – 147)	126 (108 – 144)	0.901
	Resistant starch	**2.8 (2 – 3.7)**	**12.6 (10.7 – 14.4)**	**<0.0001**
	Fibre	**21.5 (18.2– 24.8)**	**34.4 (30.2 – 38.6)**	**<0.0001**
	Total FODMAPs[a]	14.7 (6.7- 21.9)	15.7 (8.5 – 33.1)	0.633
	Oligosaccharides • Fructans • Galacto-oligosaccharides	4.3 (3.3 – 5.3) 3.3 (2.5 – 4.2) **0.9 (0.7 – 1.2)**	5.2 (4.1 – 6.3) 3.5 (2.8 – 4.1) **1.7 (1.1 – 2.3)**	0.094 0.766 **0.007**
	Lactose †	7.4 (1.8 – 12.8)	8.6 (3.5 – 19.4)	0.210
	Excess fructose	**1.2 (0.8 – 1.5)**	**0.7 (0.5 – 0.9)**	**0.007**
	Sorbitol	0.7 (0.5 – 1.9)	0.5 (0.3 – 0.6)	0.100
	Mannitol	**0.6 (0.4 – 0.7)**	**0.2 (0.1 – 0.3)**	**<0.0001**
Micronutrients	Iron, mg	11.7 (10 – 13.3)	12.4 (11 – 13.8)	0.343
	B_{12}, µg	**4 (2.6 – 5.2)**	**1.4 (1 – 1.9)**	**<0.0001**
	Calcium, mg	760 (621– 899)	826 (688 – 964)	0.442

Legend: *Data are means (95% CI) compared using paired t-test except where indicated. Statistically significant differences* ***in bold*** *after adjusting for multiple comparisons using FDR. †non-parametric data analysed using Wilcoxon signed rank test and presented as median (95% CI)*

Table 6. 3 Secondary study outcome measures by per protocol analysis.

	Per protocol analysis (n=24)				
Outcome measure	**Remission n (%)**	**Response n (%)**	**Week 0**	**Week 8**	**P value**
Total Mayo score	4/24 (17%)	8/24 (33%)	6 (5, 8)	4 (3, 6)	<0.0001
Partial Mayo	7/24 (29%)	12/24 (50%)	4 (3, 5)	3 (1, 4)	<0.0001
Mayo endoscopic	4/24 (17%)	9/24 (38%)	2 (2, 2)	2 (1, 2)	0.013
UCEIS†	6/24 (25%)	9/24 (38%)	5 (3, 6)	4 (2, 5)	0.0084
Nancy Histology Index	4/24 (17%)	9/24 (38%)	2 (2, 3)	2 (1, 3)	ns
Faecal calprotectin, µg/g			400 (181, 996)	175 (59, 741)	0.022
C-reactive protein, mg/L			3 (1, 5)	2 (1, 5)	ns
Gastrointestinal Symptom Rating Scale, (13-91)			34 (25, 36)	22 (18, 35)	<0.0001
IBD-Control 8, (0-16)			8 (6, 9)	11 (9, 12)	<0.0001
FRQoL, (29-145)			66 (57, 79)	78 (67, 91)	0.0008

Legend: *Data presented as median (inter quartile range) for clinical interpretation. Clinical response data compared using paired t-test or Wilcoxon signed-rank test. †UCEIS, ulcerative colitis endoscopy index score*

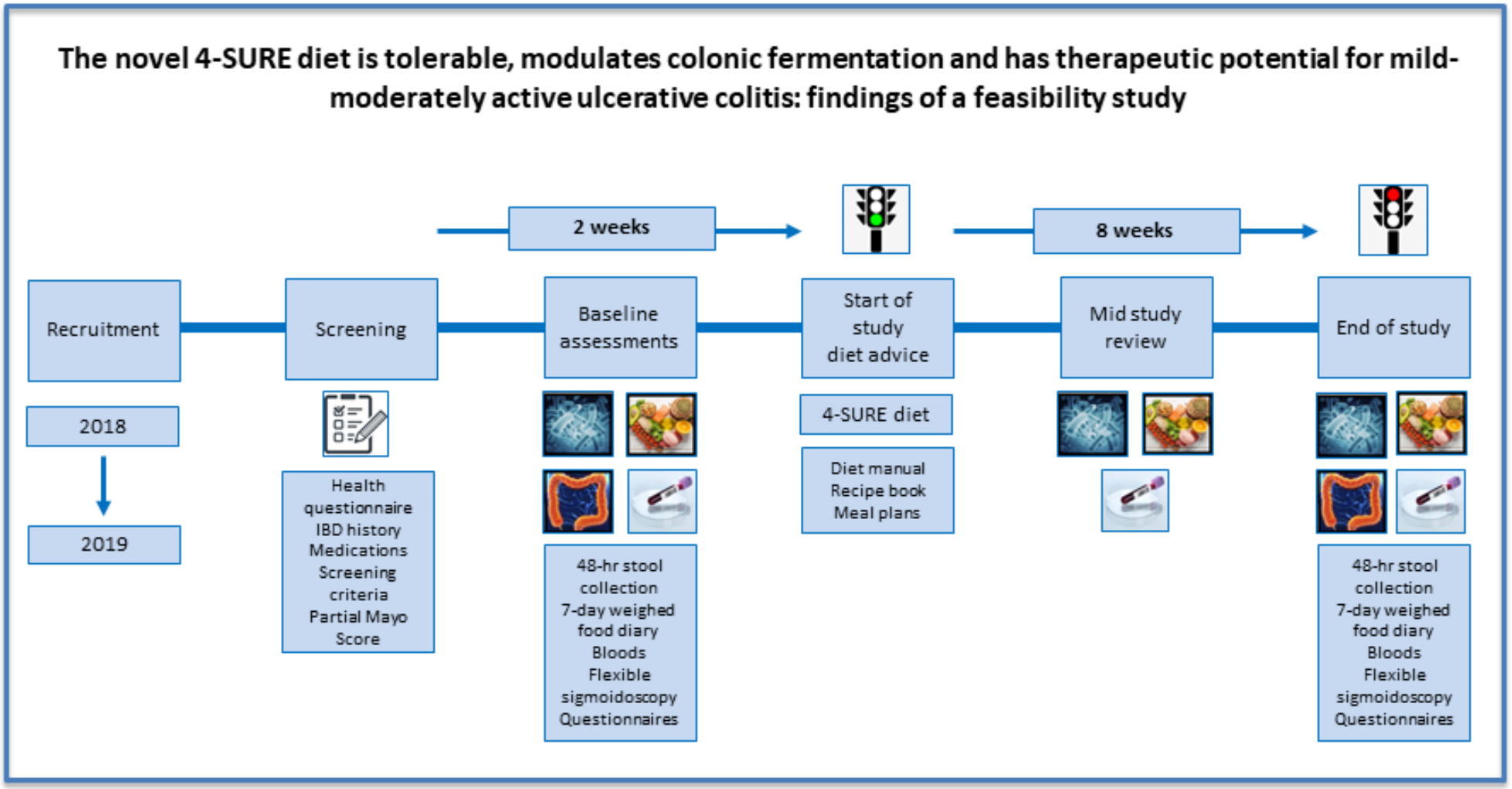
Table 6. 4 Faecal biomarkers within homogenates of 48-h stool collections in participants (n=28) during baseline (pre-intervention) and 4-SURE dietary periods.

Faecal characteristic		**Week 0 (Baseline diet)**	**Week 8 (4-SURE diet)**	**P value**
Bowel frequency, times/day†		3 (2, 4)	2 (1, 4)	0.30
Faecal weight, g/day	Wet	218 (178, 296)	294 (249, 383)	0.002
	Faecal water content, %	81.6 (78.9, 84.2)	81.3 (79.1, 83.6)	0.78
	Faecal pH	6.6 (6.4, 6.9)	6.6 (6.3, 6.8)	0.99
SCFA concentration, µmol/g	Total	76.1 (62.8, 89.4)	88.8 (75.6, 102)	0.08
	Butyrate	15.1 (11.9, 18.4)	16.8 (13.7, 19.9)	0.31
	Acetate	46.4 (38.2, 54.6)	56.1 (47.1, 65.2)	0.04
	Propionate	13.2 (10.7, 15.8)	14.7 (11.1,18.4)	0.34
	Valerate	1.2 (0.8, 1.5)	0.9 (0.6, 1.1)	0.03
	Caproate	0.2 (-0.003, 0.3)	0.2 (-0.0006, 0.5)	0.35

Proportion of total SCFA, %	Butyrate	19.2 (17.3, 21)	19.0 (16.7, 21.3)	0.82
	Propionate	17.7 (15.8, 19.6)	16.6 (14, 19.2)	0.16
	Acetate	61.3 (59.3, 63.3)	63.1 (60.1, 65.7)	0.10
BCFA concentration, μmol/g	Total	3.3 (2.5, 4.2)	2.7 (2.1, 3.4)	0.04
	Isobutyrate	1.6 (1.3, 2)	1.4 (1, 1.7)	0.11
	Isovalerate	1.7 (1.2, 2.2)	1.3 (1, 1.7)	0.02
Proportion of BCFA to SCFA, %		4.9 (3.7, 6)	3.6 (2.6, 4.5)	0.007
Ammonia concentration, μmol/g		26.7 (21, 32.2)	21.5 (16.8, 26.1)	0.06
SCFA output, mmol/day	Total†	13.5 (7.4, 21.7)	22.9 (14.1,37.2)	0.0001
	Butyrate†	2.2 (1.3, 4)	4.2 (2.4, 6.6)	0.0001
	Acetate†	8.5 (4.8, 12.9)	13.5 (8.2, 21.5)	0.001
	Propionate†	2.3 (1.4, 3.2)	3.2 (1.9, 5.9)	0.002
	Valerate†	0.1 (0.05, 0.3)	0.17 (0.01, 0.3)	0.70
	Caproate	0.002 (0.001, 0.03)	0 (0,0.003)	0.65
BCFA output, mmol/day	Total†	0.5 (0.4, 0.8)	0.6 (0.5, 0.7)	0.40
	Isobutyrate†	0.3 (0.2, 0.4)	0.3 (0.2,0.3)	0.40
	Isovalerate	0.2 (0.1, 0.4)	0.3 (0.1, 0.2)	0.50
Ammonia output, mmol/day[a]		4.3 (2.3, 8.3)	4.9 (3, 8)	0.60

Legend: *Results presented as mean (95% CI) unless otherwise specified, analysed using paired tests and subjected to correction using FDR. †non-parametric data analysed using Wilcoxon signed rank test and presented as median (95% CI)*

Supplemental materials



Supplemental figure 6. 1 Study flow chart

Supplemental material 6.2. Detailed methodology for faecal assessment

Faecal measures of protein and carbohydrate fermentation included faecal PH, stool weight, faecal water weight, SCFA, BCFA and NH3. Faecal samples were collected at week 0, 4 and 8. Participants were provided with a Waeco© 28L portable freezer and stool collection kits (blue sterile bag) and completed a 48-hour stool collection at week 0 and 8 for metagenomic analysis.[40] At week 4, participants provided a single morning stool sample for mid-study microbiota analysis. Participants were advised to avoid urine contamination and faecal samples were sealed and immediately placed in the Waeco freezer at -21°Celcius for up to 5 days before being transferred to -80°Celcius Thermo Fischer Freezer for storage. Stool consistency was measured using Bristol Stool Chart and stool weight recorded for each sample, with a total stool weight per 48hrs calculated as per established methods.[33, 34] Stool samples were was processed and aliquoted via two processes. For microbiome analysis, the first stools collected at each time point were aliquoted in their frozen state to minimise aerobic loss of bacteria. For analysis of other metabolites, all remaining stool per time point was defrosted and homogenised in a sterile beaker under a fume hood. Multiple aliquots were then taken and refrozen in -80° celcius for storage.

Faecal water content

Aliquots of 3g homogenised faecal sample defrosted overnight at 4C, and rehomogenised using a clean spatula.[34, 36] A 50mm glass watch dishes (Technos pty LTD, Thornbury, Victoria, Australia) were numbered and had their weights recorded using a precision balance (A&D Weighing, Thebarton, Adelaide, South Australia, Australia). Between 1 and 3 grams of faecal sample was weighed out on a watch dish, distributed evenly, and the initial weight recorded. The samples were then heated in a standard household microwave (Panasonic, Kadoma, Osaka, Japan) for 30 minutes at 100W followed by 10 minutes at 300W after which they had their weight recorded again as per previously established methods.[36] The samples then underwent a further 5 minutes of heating at 300W and were weighed again. This final step was repeated until each sample weighed the same twice in a row. Faecal water weight was then calculated.[36]

Faecal pH

Faecal PH was measured using a Fisher scientific accument AE150 pH meter (ThermoFisher Scientific, Waltham, Massachusetts, U.S.A). A 10g sample of homogenized stool was collected and stored at -80C until ready to be measured. Samples were thawed at 4C overnight and then rehomogenised with a clean spatula. The pH meter was calibrated with standard solutions of pH 4 and pH 7 as per the manufacturer's instructions. The thawed samples were then placed into a 40C water bath and a thermometer inserted until the samples reached 23C. The pH probe was then inserted and the pH taken once the sample reached 25C as per previously established methods.[33, 34]

Faecal SCFA

Thawed faecal material was spiked with three times the volume of internal standard (1.68 mM heptanoic acid), homogenized and centrifuged (2000 g, 10 mins, 4 °C). After centrifugation, 300 µL of supernatant was added to a 0.2 µL filter vial containing 10 µL of 1 M phosphoric acid. The vials were then analysed for SCFA content via gas chromatography. Samples were analysed using an Agilent GC6890 coupled to a flame-ionisation detector (FID), with helium used as the carrier gas. An Agilent FFAP column (30 m x 0.53 mM (internal diameter) x 1.00 µM (film thickness)) was installed for analysis. A splitless injection technique was used, with 0.2 µL of sample injected. A constant flow rate of 4.0 mL/min was used on the column. Upon injection, the oven was initially held at 90 °C for 1 minute, then raised to 190 °C at 20 °C/min and held for 3 minutes. Samples were run in triplicate to ensure accurate and replicable data were obtained. A CV <10% within triplicate samples was used as a quality control measure. SCFA concentrations were calculated against a four-point standard curve containing acetic acid (17.49 µmol/mL), iso-valeric acid (2.71 µmol/mL), valeric acid (2.74 µmol/mL), caproic acid (2.38 µmol/mL) and heptanoic acid (0.84 µmol/mL) made up in filtered ultra-pure water. All acid standards were purchased from Sigma-Aldrich and of analytical grade (≥99% purity).

Faecal ammonia

Briefly, thawed faecal material was homogenised with an equal volume of 1 M perchloric acid (Sigma-Aldrich, Castle Hill, NSW, Australia) and centrifuged at 2000 g for 10 minutes. The resulting faecal supernatant was further clarified by centrifugation at 13,000 g for 5 minutes, then alkalised by addition of 215 µL 1 M potassium hydroxide. The solution was filtered through a 0.22 µm filter and analysed at 340 nm in a plastic cuvette on a Genesys 10s UV-Vis spectrophotometer (Thermofisher scientific, Massachusetts, USA). Concentrations were determined from a five-point calibration curve, with coefficient of variation (CV) <10% taken as a valid result.

Supplementary table 6. 1 Clinical data for responders versus non responders

		With response (n=8)		Without a response (n=20)	
Outcome measure		**Week 0 (Habitual diet)**	**Week 8 (4-SURE diet)**	**Week 0 (Habitual diet)**	**Week 8 (4-SURE diet)**
Total Mayo score[a]		7 (4, 10)	3 (0, 7) [b]	6 (5, 8)	5 (5, 7)[b]
Mayo endoscopic sub score, n	0 1 2 3	0 1 5 2	2 2 4 0	0 1 15 4	0 6 8 6
GSRS, (13-91)	Overall global score[a]	30 (20, 46)	16 (14, 50)[b]	35 (27, 47)	31 (21, 35)[b]
IBD-Control 8, (0-16)		8 (6, 10)	10 (7, 14)[b]	7 (5, 9)	10 (9, 11)[b]
FRQoL, (0-145)		75 (53, 97)	86 (60, 112)	66 (58, 74)	76 (68, 85)[b]
Energy, kcal		2189 (1659, 2719)	1822 (1351, 2293)	2114 (1747, 2405)	1795 (1578, 2021)[b]
Protein, g	Total	102 (79, 125)	70 (55, 86)[b]	86 (71, 102)	73 (62, 85)
	Total sulphur protein	1.8 (1.2, 2.5)	1.4 (1, 1.9)	1.6 (1.2, 2)	1.5 (1.1, 1.9)
	Methionine	1.2 (0.8, 1.7)	0.9 (0.7, 1.3)	1.1 (0.8, 1.3)	1 (0.7, 1.3)
	Cysteine	0.6 (0.4, 0.8)	0.5 (0.3, 0.6)	0.5 (0.4, 0.7)	0.5 (0.4, 0.6)
Inorganic sulphur, mg		1216 (558, 1874)	1072 (374, 1769)	1385 (1049, 1721)	996 (804, 1188)

Carbohydrates, g	Resistant starch[a]	2.8 (0.7, 5.8)	14.4 (9.9, 15.7)[b]	2.5 (1.8, 2.7)	12.7 (8, 17)[b]
	Total Fibre	23 (18,29)	36 (27, 46)[b]	21 (17, 25)	34 (29, 39)[b]

Legend: *Post hoc analysis of those with a response (clinical and endoscopic response defined as reduction in total Mayo score ≥3) and those without a response following the 4-SURE diet. Results presented as mean (95% CI) unless otherwise specified and analysed using pairwise tests. False detection rates not applied to exploratory data. [a]Non parametric data analysed using Wilcoxon Signed Rank test and presented as median (95% CI) [b]p<0.05, unadjusted p value for pairwise comparison.*

Supplementary table 6. 2 Faecal characteristics of responders versus non responders

Faecal variable		Response (n=8)			Without a response (n=20)		
		Week 0 (Habitual diet)	Week 8 (4-SURE diet)	P value	Week 0 (Habitual diet)	Week 8 (4-SURE diet)	P value
Bowel frequency, times/day[a]		2 (1, 3)	2 (1, 3)	0.832	3 (2, 4)	3 (2, 4)	0.293
Faecal weight, g/day	Wet	203.3 (81.3, 325.3)	288.1 (140.5, 435.7)	0.074	224.5 (154.4, 294.7)	296.7 (217.7, 375.7)	0.017
	Faecal water content, %	81.3 (73.2, 89.5)	79.5 (72.2, 86.7)	0.375	81.6 (78.6, 84.7)	81.9 (79.5, 84.2)	0.782
Faecal pH		6.3 (6.1, 7)	6.7 (6.3, 7.2)	0.208[a]	6.6 (6.4, 6.9)	6.5 (6.2, 6.9)	0.332
SCFA concentration, µmol/g	Total	83 (49.4, 116.6)	91.6 (58.1, 125.1)	0.642	73.3 (58.2, 88.5)	87.6 (72.5, 102.9)	0.054
	Butyrate	16.5 (9.1, 24)	14 (7.8, 20.2)	0.554	14.6 (10.7, 18.5)	17.9 (14.1, 21.7)	0.043
	Acetate	51.1 (29.1, 73.1)	62.9 (37.1, 88.7)	0.374	44.5 (35.5, 53.4)	53.4 (44.1, 62.8)	0.037
	Propionate	13.6 (8.9, 18.4)	13.3 (9.4, 17.2)	0.875	13.1 (9.8, 16.4)	15.3 (10.2, 20.3)	0.282
	Valerate	1.3 (0.6, 2)	0.9 (0.5, 1.4)	0.123	1.1 (0.7, 1.6)	0.8 (0.5, 1.2)	0.133
	Caproate	0.4 (-0.2, 1)	0.4 (-0.4, 1.2)	0.980	0.1 (-0.1, 0.2)	0.2 (-0.1, 0.4)	0.218
Proportion of total SCFA, %	Butyrate	19.7 (16.2, 23.1)	15.1 (11.3, 18.9)	0.021	19.1 (16.5, 21.6)	20.6 (17.9, 23.3)	0.136
	Propionate	16.9 (14.2, 19.6)	15.3 (11.7, 18.9)	0.301	18 (15.5, 20.6)	17.1 (13.6, 20.6)	0.329
	Acetate	61.4 (56.7, 66.1)	67.9 (62.5, 73.3)	0.003	61.2 (58.8, 63.6)	61.1 (58.3, 63.9)	0.932
	Total	3.5 (2.5, 4.5)	3 (2.1, 3.9)	0.342	3.3 (2.2, 4.4)	2.6 (1.7, 3.5)	0.076
	Isobutyrate	1.6 (1.2, 2.1)	1.5 (1.1, 1.8)	0.449	1.6 (1.2, 2.1)	1.3 (0.9, 1.8)	0.164

BCFA concentration, µmol/g	Isovalerate	1.9 (1.2, 2.5)	1.5 (1, 2.1)	0.291	1.6 (1, 2.3)	1.3 (0.8, 1.7)	0.054
	BCFA:SCFA, %	4.89 (3.2, 6.6)	4.04 (1.9, 6.2)	0.524	4.9 (3.3, 6.5)	3.4 (2.1, 4.5)	0.001
Ammonia concentration, µmol/g		30.8 (15.7, 45.8)	19.8 (12.5, 27)	0.089	25 (19, 31)	22.1 (16, 28.4)	0.327
SCFA output, mmol/day	Total[a]	13.9 (4, 25.3)	21.3 (15.8, 34.1)	0.123	12.2 (1.2, 22.2)	22.9 (10.9, 39)	0.002
	Butyrate[a]	2.7 (0.8, 4.8)	3.1 (2.1, 5.8)	0.208	2 (1.1, 4.7)	4.8 (1.7, 7.2)	0.001
	Acetate[a]	8.5 (2.5, 16)	13.8 (9.8, 22.4)	0.093	7.9 (3.8, 13.8)	13.5 (7.1, 23.8)	0.005
	Propionate[a]	2.4 (0.6, 5.1)	3.2 (2, 6.6)	0.123	2.1 (1.2, 4.5)	3.3 (1.4, 6.3)	0.019
	Valerate[a]	0.2 (0.03, 0.3)	0.3 (0.06, 0.4)	0.575	0.1 (0, 0.4)	0.1 (0.01, 0.2)	0.852
	Caproate[a]	0 (0, 0.05)	0.002 (0, 0.009)	0.500	0 (0, 0.006)	0 (0, 0.002)	0.972
BCFA output, mmol/day	Total[a]	0.7 (0.3, 0.8)	0.6 (0.5, 1.1)	0.484	0.5 (0.2, 0.9)	0.5 (0.3, 0.7)	0.627
	Isobutyrate[a]	0.3 (0.1, 0.4)	0.3 (0.2, 0.6)	0.401	0.3 (0.1, 0.5)	0.3 (0.2, 0.4)	0.654
	Isovalerate	0.3 (0.1, 0.5)	0.3 (0.3, 0.5)	0.575	0.2 (0.1, 0.5)	0.2 (0.1, 0.4)	0.709
Ammonia output, mmol/day[a]		4.9 (2.5, 6.9)	4.9 (2.9, 8.5)	1.000	3.8 (2.3, 9.5)	4.9 (3, 7.9)	0.709

Legend: *Post hoc analysis of the faecal indices measured in those with a response (clinical and endoscopic response defined as reduction in total Mayo score ≥3) and those without a response following the 4-SURE diet. Results presented as mean (95% CI) unless otherwise specified and analysed using pairwise tests. False detection rates not applied to exploratory data. All data presented as mean 95% CI except where [a]= median (IQR) and Wilcoxon signed-rank test used*

CHAPTER 6 REFERENCES

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CHAPTER 7

Application of diet-augmented microbial therapy in ulcerative colitis

Published in *BMJ Case reports*

July 2020

&

Published in *Journal Gastroenterology Hepatology Open*

August 2021

CHAPTER 7: Application of diet-augmented microbial therapy in ulcerative colitis

Background

In ***chapter 6*** the Four strategies to SUlphide-REduction diet (4-SURE diet) signalled a therapeutic potential for mild-moderate ulcerative colitis (UC) through modulating carbohydrate and protein fermentation processes in the colon. The nutritionally adequate, whole-food diet therapy was well tolerated and adhered to, and improved food-related quality of life (FRQoL), even in those who clinically respond. Therefore, beyond therapeutic efficacy, this dietary strategy demonstrated the feasibility of achieving adequate intakes of dietary fibre without exacerbating gastrointestinal symptoms in active disease and was successful at liberalising the diets of individuals with UC.

Faecal microbiota therapy (FMT) has emerged as a potential microbial-based therapy in UC.[1] It is unknown whether dietary substrate has a key role in augmenting FMT however given dietary substrate directly influences microbial diversity and abundance in healthy individuals, it is plausible habitual diet could influence the engraftment and efficacy of FMT.[2, 3] Furthermore, a sulphide-reducing diet signalling efficacy in UC has the potential to augment and sustain FMT treatment response.

In a two-part case series, FMT with 4-SURE diet therapy was used as salvage therapy for severe and refractory UC to determine whether diet could assist in achieving sustained remission and avoidance of surgical colectomy. Both cases were observed for remission induction and treatment response, including adherence to diet and influence over FRQoL.

Case study 7A: Statement of authorship

Title of Paper	Faecal microbiota transplantation (FMT) with dietary therapy for acute severe ulcerative colitis
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Costello SP*, **Day A***, Yao CK, Bryant RV. Faecal microbiota transplantation (FMT) with dietary therapy for acute severe ulcerative colitis. BMJ Case Reports 2020;13:e233135 *joint first authors

Principal Author

Name of Principal Author (Candidate)	Alice S Day		
Contribution to the Paper	Contributed to study design, study coordinator, data collection, dietary analysis, data interpretation, writing of manuscript.		
Overall percentage (%)	70%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	26.5.21

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

x. the candidate's stated contribution to the publication is accurate (as detailed above);

xi. permission is granted for the candidate in include the publication in the thesis; and

xii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Study design, data collection, data interpretation, writing of manuscript, acted as corresponding author and joint-first author.		
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Contribution to the Paper	Analysis and interpretation of dietary data. Critical revision of manuscript		
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Contribution to the Paper	Study design. Interpreted data. Critical revision of manuscript.		
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[Manuscript 5] Faecal microbiota transplantation (FMT) with dietary therapy for acute severe ulcerative colitis

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ASD, RVB, SPC contributed to the study concept and design. RVB and SPC provided study supervision. ASD, RVB, SPC, KT and KM contributed to the acquisition of data. All authors contributed to data analysis. All authors contributed to the interpretation of the data. ASD and RVB drafted the manuscript. All authors provided critical revision of the manuscript for important intellectual content. All authors approved the final version of the article, including the authorship list.

Author declarations of personal interest

SPC has received advisory, speaking fees or research support from Ferring, Falk, Microbiotica, Janssen. SPC owns shares in BiomeBank. ASD has served as a speaker for Emerge Health and AbbVie (fees paid to employer for research support). CKY has received research funding from Atmo Biosciences, Ferring Pharmaceuticals, Danone and Yakult Australia. Her Department financially benefits from the sales of a digital application, booklets and on-line courses on the FODMAP diet. RVB has served as a speaker, a consultant and an advisory board member for (all fees paid to employer for research support), and has received research funding fromAbbVie, Ferring, Janssen, Shire, Takeda, Emerge Health. RVB owns shares in BiomeBank.

Summary

A 19-year-old man presented with acute severe ulcerative colitis. He was taking azathioprine (therapeutic metabolites) and sulphasalazine as well as infliximab with a therapeutic drug level. On day 3 of hydrocortisone therapy, he met day Oxford criteria with >8 bloody stools per day and was given FMT and subsequently commenced on dietary therapy combining several strategies –(1) increased intake of fermentable fibres, (2) reduced intake of overall and sulphur-containing protein, and (3) restriction of sulphate and sulphite food additives. At week 8 assessment, he was in clinical and endoscopic remission and remained in clinical and endoscopic remission at 12 months.

7.1 Background

Up to a quarter of patients with UC will develop acute severe colitis (ASC) during their disease course, a potentially life-threatening condition.[4] Intravenous corticosteroids are the mainstay of therapy however, approximately 30-40% of patients progress to second-line (salvage) therapy with infliximab or cyclosporin.[5] Despite salvage therapy, long-term colectomy rates remain high (>50% at three years) and new therapeutic options are required.[6]

7.2 Case presentation

A 19 year-old male carpenter presented to our hospital with ASC. He had a history of UC diagnosed six months prior, with poor disease control and four admissions to hospital with colitis requiring intravenous steroid therapy since diagnosis. At diagnosis he had been commenced on azathioprine 150mg daily and sulphasalazine 1500mg BD. At his last presentation 10 weeks prior, he was also

commenced on infliximab induction therapy with a partial response to therapy with a reduction from 10 bloody bowel motions per day to 4 non-bloody motions daily. He had completed three doses of induction therapy with infliximab (5mg/kg) with the last dose 4 weeks prior to this presentation.

On admission, he reported eight bloody bowel motions per day with associated abdominal pain. On examination, he had mild generalised abdominal tenderness without guarding, pulse rate 114 bpm, temperature 37.6 ºC, blood pressure 135/78 mmHg. He was anaemic with a Hb of 131 g/L (135-175g/L), his albumin was 40g/dL (34-48), CRP was 4. Stool testing was negative for parasites, bacterial and viral pathogens and C. Difficile toxin on nucleic acid amplification testing. He met Truelove and Witt's criteria for ASC (≥6 bloody stools per day and two of pulse >90 bpm, Temp >37.5, Hb ≤10g/dL, ESR >30). His thiopurine metabolites levels were therapeutic (6-TGN 400, 6-MMP 2907) and infliximab levels supra-therapeutic (14.4mg/L; range 3-7). Flexible sigmoidoscopy three days prior to admission had demonstrated moderately-severe colitis (***Figure 7.1***) with histopathology and immunohistochemistry demonstrating no evidence of cytomegalovirus infection.

Despite receiving intravenous hydrocortisone 100mg QID for three days, his stool frequency and bleeding failed to improve (nine stools per day) and he became more anaemic Hb 120g/L (135-175 g/L). Infliximab levels were 14.4 mg/L (trough range 3-7 mg/L). The patient met day 3 oxford criteria for ASC (>8 stools per day) and was offered and declined colectomy and was therefore offered donor FMT with a dietary prescription as salvage therapy. The consent for FMT detailed the experimental nature of FMT in this setting and the greater evidence for surgical colectomy

Severe confluent colitis (endoscopic Mayo -3) to the descending colon was noted at colonoscopy on day 4 of admission. FMT was delivered to the cecum and repeat FMT was given via enema on days three and seven following colonoscopy as per the Adelaide protocol.[1] The FMT had been sourced from a single anonymous stool donor three months prior at a stool bank. 50g of donor stool had been processed under anaerobic conditions with 130mls of normal saline and 20mls of glycerol to produce a 200ml suspension and then frozen at -80°C, prior to thawing on the morning of FMT delivery.

Dietary therapy was commenced immediately after initial FMT. The dietary prescription consisted of a whole diet approach that was (1) high in fermentable fibres, (2) reduced in overall and sulphur-containing protein, (3) restricted in sulphate and sulphite food additives, and (4) was nutritionally replete. Dietary education with comprehensive meal plans and recipes were provided at week 0, 4 and 8. Azathioprine 150mg daily and infliximab (5mg/kg 8 weekly) therapy were continued during the 12 months follow up period. Sulfasalazine was ceased by the patient 2 months after receiving FMT therapy.

7.3 Outcome and follow up

The patient improved rapidly following the FMT and dietary therapy; stool frequency reduced to 2-3 motions per day without blood after 2 days. At week 4 and 8, the patient was opening his bowels every second day without blood. At week 4, flexible sigmoidoscopy demonstrated Mayo-1 colitis and at week 8 there was endoscopic remission (Mayo-0) (***Figure 7.2***) and histological remission (absence of neutrophilic infiltrate). Dietary tolerability and compliance over the 8-week period was assessed to be excellent and he remained in clinical and endoscopic remission (Mayo-0) (***Figure 7.3***) 12 months following FMT (faecal calprotectin 4 µg/g).

7.4 Discussion

Although the efficacy of FMT is established for remission induction of mild to moderate UC,[7, 8] FMT is not yet used routinely to treat UC in clinical practice and is not currently included in clinical practice guidelines.[9] This is due to a number of factors including the relatively recent emergence of induction of remission data, a lack of data demonstrating maintenance of remission with FMT, as well as legislative restriction, a lack of funding and poor availability of screened stool from stool banks in many jurisdictions.[8, 10]

There have been reports of FMT inducing remission in patients with severe UC[11-13] however to our knowledge, this is the first case report of FMT as salvage therapy for ASC meeting Oxford criteria in a patient already receiving infliximab with therapeutic levels. This demonstrated the potential of FMT to alter the severe physiological changes present in ASC refractory to standard therapies. FMT likely acts via different mechanisms[1] to current immunologically targeted therapies and thus may offer an adjunctive or alternative salvage therapy in the case of failure of hydrocortisone or infliximab. In this case the infliximab dose was not increased because the infliximab level was high (14.4mg/L) cyclosporin was not added as a therapy because there is a significant risk of infective complications with sequential or combination therapy.[14, 15]

The prompt and durable efficacy of FMT observed in this case may have been augmented by diet prescription. An excellent clinical and histological response of four patients with active UC to a low sulphur diet was first reported in 1998.[16] There is progressively more evidence emerging to indicate dietary therapy alone may influence disease activity in UC.[17] There is also evidence that metabolites originating from activities of the colonic microbiota, both beneficial and toxic, can contribute significantly to epithelial defects documented in UC. Specifically, excessive exposure of the colonic epithelium to toxic hydrogen sulphide gas, a by-product of dietary protein and sulphur metabolism, produces biochemical lesions in the epithelium, mimicking those described in UC.[18] On the other hand, there is also evidence that the fermentation of resistant starch and other prebiotic fibres by colonic bacteria is critical for enterocyte function and colonic health.[19] The delivery of these nutrients

to the colon is dictated by dietary intake and their metabolism is largely controlled by the colonic microbiota. Thus, it is likely that FMT and dietary therapy work synergistically. The mechanism by which FMT induces remission in UC is not known however in a recent randomised controlled trial of FMT for induction of remission of UC, lamina propria mononuclear cell populations correlated with disease severity (Mayo score) but were not correlated with donor FMT.[1] This suggests that FMT may be inducing remission via a mechanism other than direct modulation of the mucosal lamina propria mononuclear cell populations. It is possible that alteration of the metabolic capacity of the microbiome plays a role in FMT induced mucosal healing in UC. It is also possible that dietary therapy may augment this process by changing substrate availability and therefore, the types of metabolic activities. Further trials are warranted to explore whether FMT may have a place in the therapeutic armamentarium in ASC and whether diet has a role in augmenting and sustaining the efficacy of FMT.

Patient's perspective

"The faecal transplant and diet treatment was the last resort and it has paid off in a big way for me. Before the FMT and diet I was on infliximab, azathioprine and sulfasalazine and I was in a bad way. Within 2 doses of the FMT I felt a lot better and I have not had any problems since. It really sorted everything out for me. This was the turning factor for me. The FMT was not difficult or painful, I would do it a hundred times again for this result. The diet took more effort but I have been able to stick to the diet pretty well. I tried to follow the diet closely to help the FMT work."

Learning points/take home messages

- Acute severe ulcerative colitis is assessed using Truelove and Witt's criteria and patients meeting these criteria should be commenced on intravenous hydrocortisone
- Patients who do not respond to intravenous hydrocortisone by day 3 should be offered rescue therapy with either Inflixmab or cyclosporin and assessed for surgical colectomy in case of failure of medical therapy
- There is evidence that FMT can induce remission in UC and further study is required before this therapy should be routinely offered to those patients failing infliximab or cyclosporin rescue therapy
- There is emerging evidence that dietary therapy may influence UC disease course however more research is required

Intellectual property rights

Figures

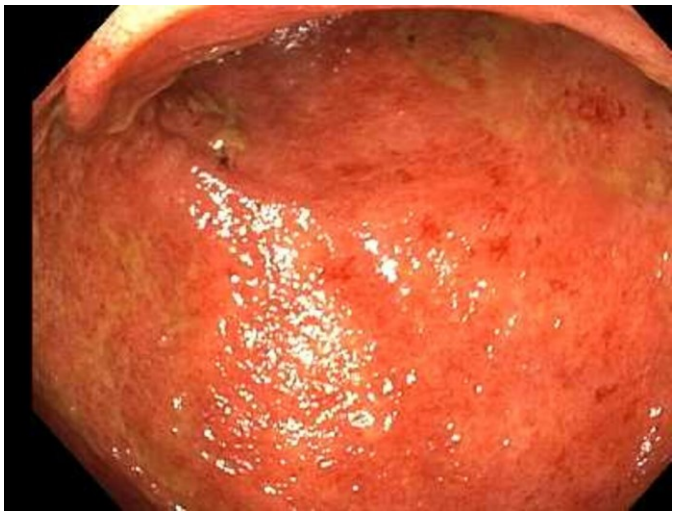

Figure 7. 1 Sigmoid colon at week 0 prior to post faecal microbiota transplantation and dietary therapy

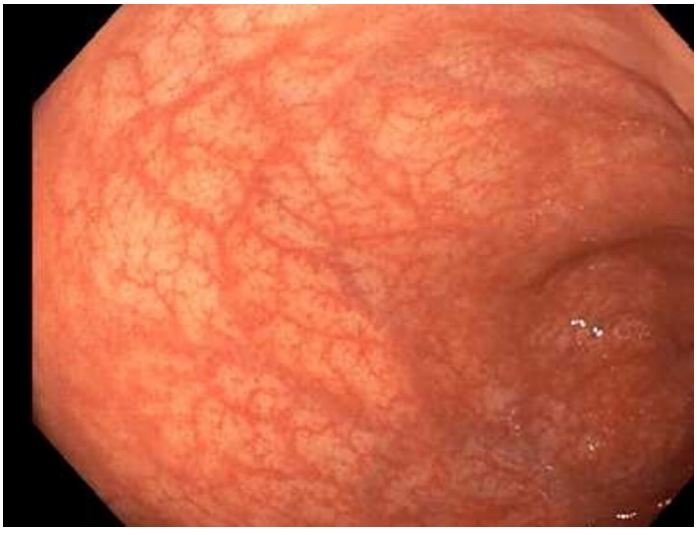

Figure 7. 2 Sigmoid colon at week 8 post faecal microbiota transplantation and dietary therapy

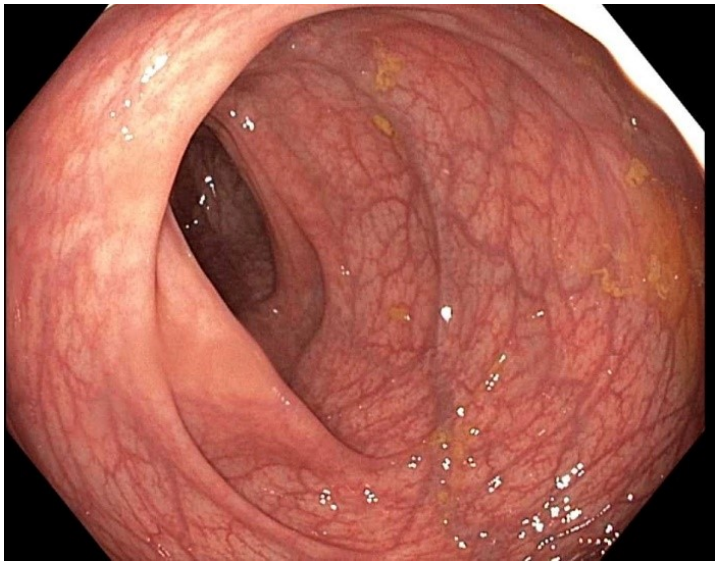

Figure 7. 3 Sigmoid colon at 12 months post faecal microbiota transplantation and dietary therapy

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Case study 7B: Statement of authorship

Title of Paper	Faecal microbiota transplantation augmented by a sulphide-reducing diet for refractory ulcerative colitis: a case report with functional metagenomic analysis
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Bryant, R.V., Day, A.S., McGrath, K.C., Telfer, K., Yao, C.K. and Costello, S.P. (2021), Fecal microbiota transplantation augmented by a sulfide-reducing diet for refractory ulcerative colitis: A case report with functional metagenomic analysis. JGH Open, 5: 1099-1102. https://doi.org/10.1002/jgh3.12623 *joint first authors

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Name of Principal Author (Candidate)	Alice S Day		
Contribution to the Paper	Contributed to study design, study coordinator, data collection, dietary analysis, data interpretation, writing of manuscript, corresponding author, joint first author*.		
Overall percentage (%)	70%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Study design. Interpreted data. Critical revision of manuscript.		
Signature		Date	21.10.21

[Manuscript 6] Faecal microbiota transplantation augmented by a sulphide-reducing diet for refractory ulcerative colitis: a case report with functional metagenomic analysis

Short tittle: Combined microbial manipulation in UC

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Acknowledgements

The authors would like to acknowledge the generous assistance of The Queen Elizabeth Hospital Inflammatory Bowel Disease Nurses, Sangwoo Han and Serena Martin. The authors would also like to acknowledge both Microba and BiomeBank for funding of metagenomic analysis and provision of stool for FMT respectively.

Author contributions

ASD, RVB, SPC contributed to the study concept and design. RVB and SPC provided study supervision. ASD, RVB, SPC, KT and KM contributed to the acquisition of data. All authors contributed to data analysis. All authors contributed to the interpretation of the data. ASD and RVB drafted the manuscript. All authors provided critical revision of the manuscript for important intellectual content. All authors approved the final version of the article, including the authorship list.

Author declarations of conflicts of interest

RVB has served as a speaker, a consultant and an advisory board member for (all fees paid to employer for research support), and has received research funding from AbbVie, Ferring, Janssen, Shire, Takeda, Emerge Health. RVB owns shares in BiomeBank. ASD has served as a speaker for Emerge Health and AbbVie (fees paid to employer for research support). KCM is an employee of Microba Life Sciences, who contributed the metagenomics analysis used in this study in-kind. KT has no conflicts to declare. CKY has received research funding from Atmo Biosciences, Ferring Pharmaceuticals, Danone and Yakult Australia. Her Department financially benefits from the sales of a digital application, booklets and on-line courses on the FODMAP diet. SPC has received advisory, speaking fees or research support from Ferring, Falk, Microbiotica, Janssen. SPC owns shares in BiomeBank.

Funding sources. None to declare.

Data availability statement. The data underlying this article are available in the article and in its online supplementary material.

Ethics approval. Granted (Central Adelaide Local Health Network HREC/18/CALHN/646).

Patient consent. Written informed consent was gained from the patient.

Abstract

FMT is effective for induction of remission in UC. Diet has potential to augment the efficacy and durability of FMT by encouraging engraftment of transplanted microorganisms. A trial of FMT combined with a defined diet was undertaken as salvage therapy for a 71-year-old woman with active steroid-refractory extensive UC. A multidimensional sulphide-reducing diet (4-SURE diet) was commenced followed by single donor FMT administered by colonoscopy and then enemas over 7 days. Dietary adherence, clinical evaluation and stool samples for metagenomic profiling were undertaken at weeks 0, 4, 8 and 24. Colonoscopy was performed 8-weeks post-FMT. Shotgun metagenomic profiling of the donor faecal suspension was also performed. A rapid clinical response to FMT and 4-SURE diet was observed with normalisation of stool frequency (≤2 motions/d) and resolution of rectal bleeding within 2 weeks. Dietary adherence was excellent. Colonoscopy at week 8 revealed no evidence of active colitis (Mayo endoscopic sub-score 0) with histology showing no evidence of acute or chronic lamina propria inflammatory cell infiltrate. Sustained clinical and endoscopic remission out to 24 weeks was observed. Metagenomic sequencing confirmed sustained engraftment of beneficial donor microbiota with increased alpha-diversity and capacity for short chain fatty acid production, including *Faecalibacterium prausnitzii* and *Eubacterium hallii*. This case report supports the rationale of prescribed diet therapy to support engraftment of donor microbiota following FMT for UC. Further large trials with a diet-arm control group are needed to evaluate FMT augmented by a defined diet in UC.

Keywords: Refractory ulcerative colitis; faecal microbiota transplantation; diet; metagenomics

7.5 Introduction

UC is a lifelong relapsing and remitting inflammatory disease of rising global prevalence.[1] The gut microbiota contribute to the pathogenesis of UC, however current therapies for UC are 'immunocentric', solely targeting the immune response to the gut microbiota without altering the luminal environment. FMT involves transferring gut microbiota from a healthy individual to another with disease to restore diversity and function. Early data shows FMT can be used for induction of remission in UC with rates of clinical and endoscopic remission comparable to available biologic therapies.[2]

Fermentable dietary substrate has a key role in shaping the composition and function of the gut microbiota, including modulation of potentially harmful microbial metabolites such as hydrogen sulphide (H_2S). Colonic fermentation of excess animal protein increases production of H_2S, whereas

fermentation of dietary fibres suppress and attenuate H_2S production via the gut microbiota preferentially fermenting complex carbohydrate over protein sources that would otherwise produce H_2S.[3, 4] Emerging observational data suggest modulation of fermentable fibres, total protein and sulphur proteins, and sulphated food additives, strategies central to the 4-SURE diet (FOUR strategies to Sulphide-REduction), are efficacious in inducing clinical and endoscopic response in UC.[5] Moreover, a single case report used combined FMT and 4-SURE diet as therapy and reported induction and maintenance of clinical and endoscopic remission out to 12 months.[6]

It is biologically plausible that a specific diet may augment the efficacy and durability of FMT by providing a favourable luminal milieu, encouraging engraftment of transplanted microorganisms and restoring luminal homeostasis.

7.6 Case report

A 71 year old woman with steroid-refractory extensive UC underwent microbial manipulation with FMT and 4-SURE diet, resulting in sustained clinical and endoscopic remission out to 24 weeks. Metagenomic sequencing confirmed sustained engraftment of beneficial donor microbiota.

Diagnosis

She was diagnosed with left-sided UC at age 54 years. Her disease was initially responsive to sulfasalazine therapy however over subsequent years she developed steroid-dependent disease complicated by osteopenia. Six months prior to FMT she was hospitalized for severe *Campylobacter jejuni* gastroenteritis. Thereafter, her disease became steroid-refractory, with persistent bloody diarrhoea (>6 bloody motions/d). Colonoscopy four months following hospitalisation revealed severe extensive colitis characterised as Mayo endoscopic sub-score 3. Biopsies confirmed moderately active chronic colitis without features of cytomegalovirus infection and both biopsies and serial stool cultures excluded persistent bacterial infection.

Escalation to immunomodulator or biologic therapy was precluded on account of concurrent medical comorbidities and patient reticence. Given salvage colectomy was the next most appropriate step in management, a trial of FMT combined with 4-SURE diet was undertaken. Usual therapy with sulfasalazine was continued. Ethics approval was granted (Central Adelaide Local Health Network HREC/18/CALHN/646) and written informed consent gained from the patient.

Single donor FMT was prepared and administered as per a previously described protocol.[6] Following a polyethylene glycol bowel preparation, 200ml of thawed faecal suspension was instilled into the patient's caecum via colonoscopy. Two further 100ml aliquots of the same faecal suspension were administered by enema over the following 7 days.

Prior to FMT, habitual diet was assessed using a 7-day weighed food diary. A research dietitian provided individualised 4-SURE dietary advice with a 1-week set meal plan and recipes to be followed for 8 weeks.[5] The 4-SURE diet was commenced first, followed by FMT. Adherence was assessed at weeks 4, 8 and 24 using a 3-day weighed food diary and self-reported dietary adherence checklists (≥76-100% always adherent).[5]

Stool samples were collected prior to FMT (week 0), and at weeks 4, 8 and 24 for metagenomic profiling and calprotectin. Clinical evaluation and blood testing including C-reactive protein were also undertaken at these time-points. Colonoscopy was performed 8-weeks post-FMT. Shotgun metagenomic profiling of the donor faecal suspension was performed as per established methods at Microba Life Sciences.

7.7 Outcome

Clinical

The patient reported a rapid clinical response to FMT and 4-SURE diet, with normalisation of stool frequency (≤2 motions/d) and resolution of rectal bleeding within 2 weeks. Corticosteroid taper and cessation was achieved within 6 weeks. She remained in steroid-free clinical remission for 24 weeks following FMT and 4-SURE diet. Concordant with clinical improvement, biomarkers of inflammation normalised by 8 weeks following FMT (***Figure 7.4***). Colonoscopy at week 8 revealed no evidence of active colitis (Mayo endoscopic sub-score 0) with histology showing no evidence of acute or chronic lamina propria inflammatory cell infiltrate (***Figure 7.4***). Durable remission and persistent normalisation of inflammatory biomarkers was evident 24 weeks post-FMT and diet therapy (***Figure 7.4***).

Diet

The 4-SURE diet was well tolerated with excellent self-reported adherence sustained to 24 weeks. This included maintaining a protein intake of 1.0-1.2g/kg (75-90g/d), increasing fermentable fibres to 25-30g/d, and avoidance of specified food additives. Reduction of sulphur amino acids was not achieved. Food-related quality of life score improved from 61 to 116 (poorer 29, greater 145).

Functional microbiome analysis

A rapid change in the patient's microbiota was observed following FMT, with a shift toward the donor's microbiota profile (***Supplementary material 7.1).*** Overall, the patient's microbiota remained stable in terms of most abundant organisms out to 24 weeks post-FMT, illustrating stable engraftment of the donor's microbiota profile. Moreover, an increase in alpha-diversity was observed over the follow-up period associated with the 4-SURE diet, with a steady increase in the patient's Shannon Diversity Index from 2.86 prior to FMT treatment, to 2.83 at 4 weeks, 3.19 at 8 weeks, and then 3.38 at 24 weeks, approximating the donor's Shannon Diversity Index of 3.32 at the time of stool donation.

At a species level, it was possible to categorise changes in the microbiota post-FMT to better conceptualise shifts in the ecosystem (***Supplementary material 7.1 and 7.2***). Engrafted species (Group C) were those not detectable in the patient at baseline and engrafted following FMT. These organisms may be drivers of the therapeutic effect of FMT or benefactors of the therapy. This included avid producers of short chain fatty acids (SCFA's) such as *Faecalibacterium prausnitzii* and *Eubacterium hallii*. Suppressed species (Group D) were those present in the patient at baseline but contracted or became undetectable following FMT. Some of these organisms may be drivers of luminal inflammation or benefactors of an oxygen-rich inflamed microenvironment, including species with toxigenic potential such as enterotoxigenic-positive strains of *Bacterioides fragilis*.

The metabolic potential of organisms based on functional genes was extrapolated from metagenomic data. An increase in the relative abundance of organisms with capacity to biosynthesise SCFA's was observed in the patient following FMT, sustained over 24 weeks (***Supplementary material 7.2***). Concurrently, loss of capacity for both *Bacteroides fragilis* toxin production and histamine production was evident. Sulphate-reducing capacity was diminished over the 24-week study period, consistent with preferential carbohydrate fermentation and suppression of protein fermentation.

7.8 Discussion

This is the first report demonstrating durable efficacy and sustained remission associated with microbial engraftment of induction FMT augmented by a diet designed to modulate colonic fermentation and sulphide metabolism in a patient with refractory UC. Mechanistic insights provided by functional microbiome analysis illustrate an exciting synergistic combined approach to microbial manipulation in UC.

Higher rates of FMT efficacy are thought to be related to a greater biodiversity and abundance of microbes as presumed with pooled donor FMT compared to autologous FMT.[7] Oxygen-sensitive viable anaerobes such as *Faecalibacterium prausnitzi* are also more likely to be preserved through anaerobic preparation.[7] As dietary substrate also directly influences microbial biodiversity and abundance, it is possible the diet of FMT recipients could affect engraftment and efficacy of FMT. The 4-SURE diet is hypothesised to facilitate donor organism engraftment and microbial diversity and modulate excess H_2S production at the colonic-luminal interface by reducing availability of dietary protein for reduction by sulphate-reducing bacteria and concurrently increasing the variety of slow and readily fermentable carbohydrates for degradation by SCFA-producing organisms.[5] This 'switch' to preferential carbohydrate fermentation increases the bioavailability of SCFAs as an energy source for colonocytes.[8] The sustained increase in SCFA-producing organisms and sulphate-reducing capacity observed is plausibly related to bioavailability of 4-SURE dietary substrate and suppression of protein fermentation and yields insights of the possible mechanisms of efficacy of diet and FMT in UC.

Beyond a single pilot study, longevity of efficacy of FMT following an induction regimen is limited. Sood *et al* reported significantly higher rates of endoscopic and histological remission using 8-weekly FMT via colonoscopy following a rigorous multi-session FMT induction, with no difference in steroid-free remission between FMT and placebo groups at 48 weeks.[6, 9] Only one other FMT study in UC has provided functional metagenomic data, similarly showing an increase in alpha-diversity following FMT in those who achieved remission, as well as enrichment in SCFA-producing organisms including *Eubacterium hallii*.[10] Interestingly, in contrast to the findings of this case report, *Bacterioides fragilis* was associated with a favourable donor microbial profile. However, *Bacterioides fragilis* has also been described as a part of a UC microbial signature and enterotoxigenic *Bacteroides fragilis* strains are associated with UC flares.

Collectively, the possibility of microbial manipulation using FMT and a defined diet to achieve durable remission in UC holds promise and warrants further study in high quality randomised-controlled trials using a control diet-arm.

Figures

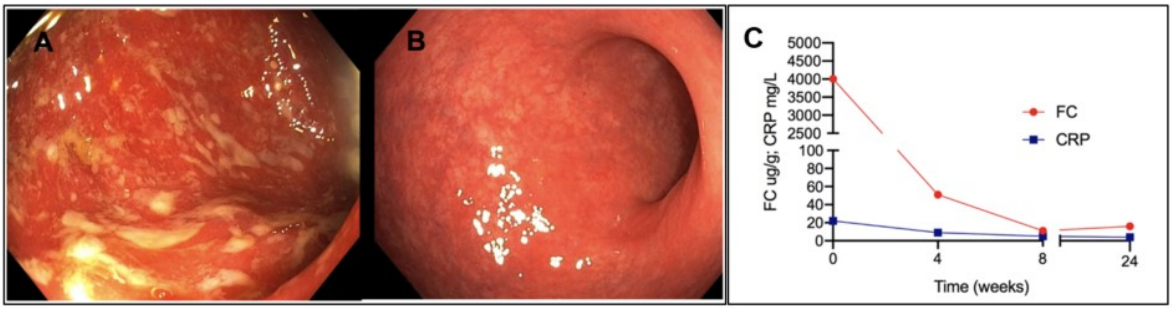
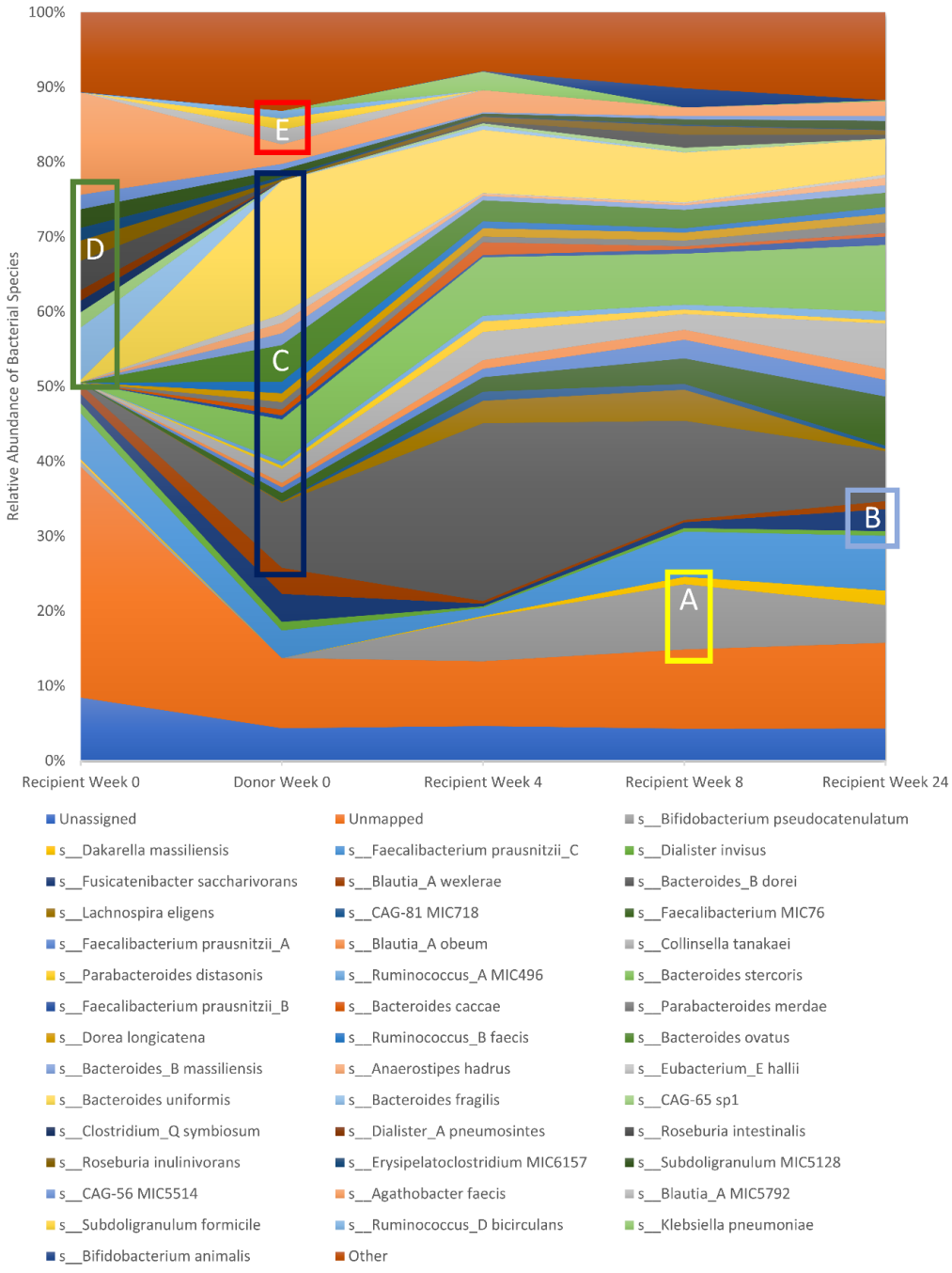


Figure 7. 4 Endoscopic response to FMT and diet.

Legend: *A). Week 0 (day of FMT and diet) showing ulceration, loss of vascular pattern, and erythema (endoscopic Mayo 3). B). Week 8 post FMT and diet showing normalization of colonic mucosal appearances with no visible evidence of inflammation (Mayo 0).* ***C.*** *Graph of faecal calprotectin (FC) and C - reactive protein (CRP) over time course from commencement of FMT and dietary therapy (week 0) until week 24*

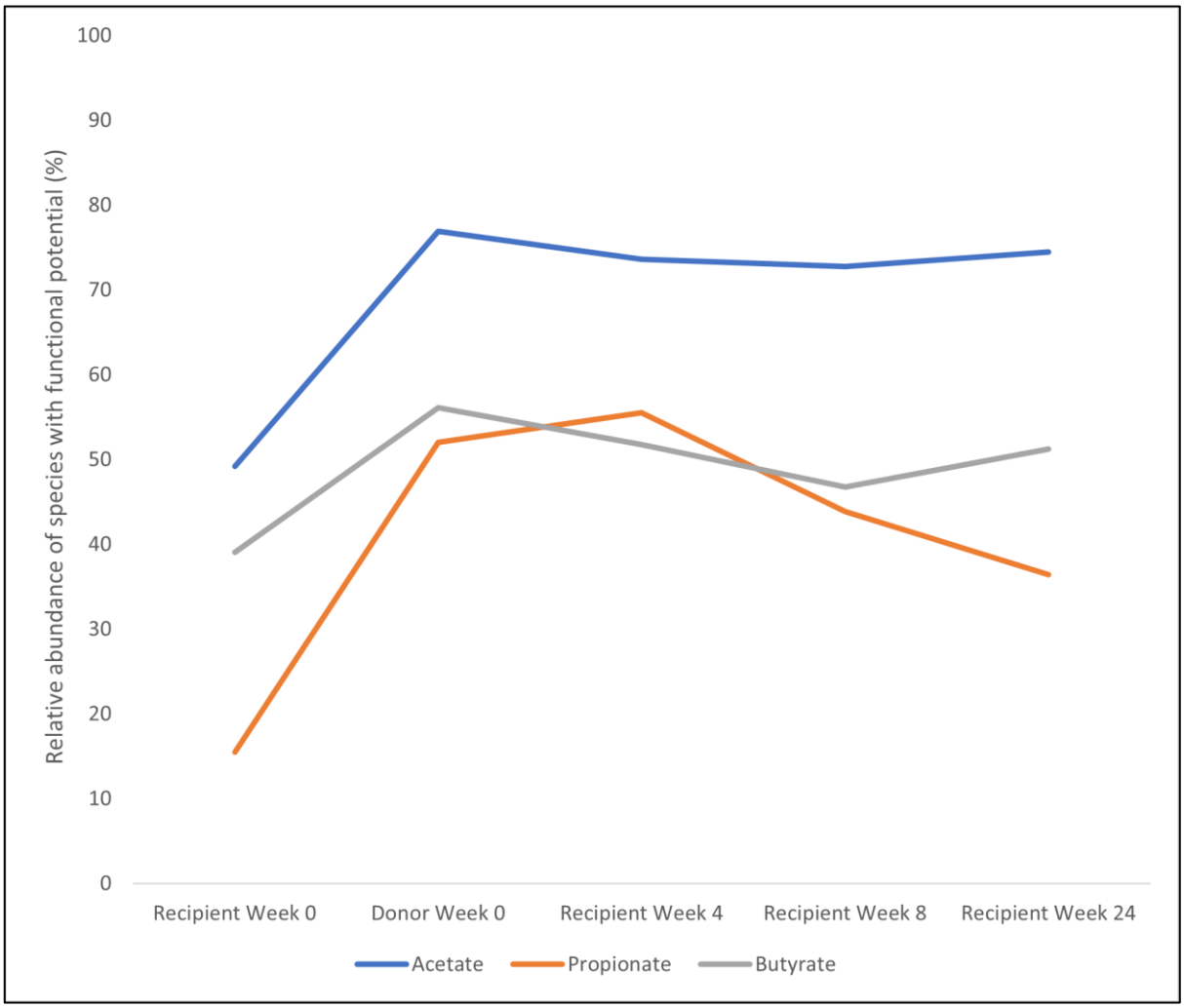
Supplementary figures



Supplementary figure 7. 1 Relative abundance of gut microbiota in recipient as compared to donor following FMT.

Legend: *Autologous growth (Group A) species were those present in the recipient at low levels prior to FMT, which bloomed following FMT despite not being detectable in the donor. Co-abundant species (Group B) were those present in both the donor and the recipient with minimal change in abundance following FMT. Engrafted species (Group C) were those that were not detectable in the recipient at baseline and engraft following FMT. Suppressed species (Group D) were those present in the recipient*

at baseline but contracted or became undetectable following FMT. Incompatible species (Group E) were those species present in the donor which did not engraft in the recipient, and hence are unlikely to be involved in the remission of UC.



Supplementary figure 7. 2 Relative abundance of organisms with functional capacity to biosynthesize short chain fatty acids over 6 months in recipient as compared to donor following FMT.

Supplementary tables

Supplementary table 7. 1 Relative abundance (%) of species in stool samples from FMT Donor and Recipient

Genome Taxonomy Database Taxon	Recipient Week 0	Donor Week 0	Recipient Week 4	Recipient Week 8	Recipient Week 24
Unassigned	8.43	4.34	4.65	4.28	4.30
Unmapped	30.86	9.36	8.64	10.60	11.45
s__Bifidobacterium pseudocatenulatum	0.63	0.00	5.87	8.71	5.06
s__Dakarella massiliensis	0.35	0.00	0.19	1.00	1.93
s__Faecalibacterium prausnitzii_C	6.14	3.70	1.07	6.03	7.32
s__Dialister invisus	1.36	1.15	0.21	0.49	0.63
s__Fusicatenibacter saccharivorans	1.21	3.75	0.37	0.78	2.92
s__Blautia_A wexlerae	1.30	3.49	0.36	0.28	1.09
s__Bacteroides_B dorei	0.19	8.66	23.75	13.27	6.67
s__Lachnospira eligens	0.00	0.15	3.00	4.13	0.28
s__CAG-81 MIC718	0.00	0.07	1.19	0.77	0.45
s__Faecalibacterium MIC76	0.04	1.12	1.94	3.41	6.55
s__Faecalibacterium prausnitzii_A	0.00	0.75	1.11	2.50	2.21
s__Blautia_A obeum	0.00	0.58	1.18	1.35	1.49
s__Collinsella tanakaei	0.00	1.88	3.76	2.11	6.05
s__Parabacteroides distasonis	0.00	0.42	1.43	0.59	0.42
s__Ruminococcus_A MIC496	0.00	0.56	0.72	0.66	1.18
s__Bacteroides stercoris	0.00	5.63	7.84	6.81	8.90
s__Faecalibacterium prausnitzii_B	0.00	0.55	0.25	0.56	1.14
s__Bacteroides caccae	0.00	0.76	1.74	0.42	0.44
s__Parabacteroides merdae	0.00	1.02	0.75	0.79	1.47
s__Dorea longicatena	0.00	1.18	1.11	1.06	1.12
s__Ruminococcus_B faecis	0.00	1.54	0.94	0.56	0.91
s__Bacteroides ovatus	0.07	4.90	2.80	2.45	1.91
s__Bacteroides_B massiliensis	0.00	1.55	0.60	0.62	1.01
s__Anaerostipes hadrus	0.00	1.42	0.25	0.25	1.01
s__Eubacterium_E hallii	0.00	1.14	0.11	0.16	0.42
s__Bacteroides uniformis	0.31	17.83	8.45	6.64	4.71
s__Bacteroides fragilis	6.97	0.00	0.53	0.07	0.00
s__CAG-65 sp1	2.06	0.00	0.33	0.59	0.09
s__Clostridium_Q symbiosum	1.55	0.00	0.03	0.00	0.00

s__Dialister_A pneumosintes	1.41	0.00	0.00	0.00	0.00
s__Roseburia intestinalis	3.92	0.00	0.21	1.72	0.46
s__Roseburia inulinivorans	2.70	0.23	0.62	1.17	0.66
s__Erysipelatoclostridium MIC6157	1.71	0.31	0.10	0.19	0.06
s__Subdoligranulum MIC5128	2.48	0.96	0.35	0.72	1.18
s__CAG-56 MIC5514	1.93	0.78	0.16	0.41	0.64
s__Agathobacter faecis	13.68	2.59	2.97	1.16	1.96
s__Blautia_A MIC5792	0.00	1.97	0.00	0.00	0.00
s__Subdoligranulum formicile	0.00	1.49	0.00	0.00	0.00
s__Ruminococcus_D bicirculans	0.00	1.03	0.00	0.00	0.00
s__Klebsiella pneumoniae	0.00	0.00	2.48	0.00	0.14
s__Bifidobacterium animalis	0.05	0.00	0.07	2.57	0.00
Other	10.65	13.17	7.86	10.14	11.75

Supplementary table 7. 2 Relative abundance of species with metabolic functions in Donor and Recipient stool samples out to 24 weeks

Metabolic function	Recipient Week 0	Donor Week 0	Recipient Week 4	Recipient Week 8	Recipient Week 24
B. fragilis toxin_production	3.06	0	0.28	0	0
Trimethylamine_consumption	0	0	0	0	0
Vitamin K_production	0	0	2.39	0	0
Tyramine_production	0	0	0	0	0
Histamine_production	7.51	0	0.83	0	0.17
3-indolepropionic acid (IPA)_production	2.38	1.05	1.31	1.03	1.42
Hydrogen sulphide_production	4.22	3.43	4.9	1.64	2.56
Oxalate_consumption	14.49	13.95	13.99	26.31	28.57
Ammonia (urease)_production	7	7.76	2.86	2.73	2.36
Trimethylamine_production	1.47	1.86	3.91	2.1	5.93
Butyrate_production	39.07	56.14	51.74	46.78	51.23
Biotin (B7)_production	37.57	54.41	52.02	38.51	32.52
Riboflavin (B2)_production	36.23	56.12	54.46	45.87	46.67
Lactate_production	44.3	68.77	70.61	63.47	61.64
Formate_production	46.26	72.31	71.13	68.42	68.68
Acetate_production	49.19	76.95	73.61	72.79	74.5
Cobalamin (B12)_production	39.73	63.11	58.63	53.04	59.92
Folate (B9)_production	41.03	65.87	69.63	60.45	55.75
Branched chain amino acids_production	46.92	75.84	73.14	73.16	74.85
Beta-glucuronidase_production	13.05	32.52	18.57	27.94	29.56
GABA_consumption	0.5	1.59	2.79	0.58	0.68
Propionate_production	15.48	52.06	55.51	43.86	36.45
Succinate_production	9.63	41.6	51.23	43.9	39.56
Lipopolysaccharide_production	7.27	32.44	37.89	24.27	20.71
GABA_production	7.51	34.91	37.43	24.7	22.31

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CHAPTER 8

Thesis discussion

CHAPTER 8: Thesis discussion

8.1 Thesis summary

The body of research presented in this thesis highlights the important multi-dimensional role of diet in patient-centred care for people with inflammatory bowel disease (IBD). A complex dietary belief system exists among people with IBD which appears to dichotomise food as either problematic or beneficial. A high prevalence of self-reported food avoidance and dietary restriction exists which could explain the inadequate habitual fibre intakes of people with IBD. Food-related quality of life (FRQoL) is impaired in people with IBD, lowered by restrictive eating behaviours and presence of active disease. Those who have a greater symptom burden or experience psychological distress also have poorer FRQoL, yet IBD-related surgery may lead to positive food-related outcomes.

The novel multi-dimensional Four strategies to a SUlphide-REduction (4-SURE) diet, a whole food diet strategy with sound mechanistic rationale, was well tolerated by patients with mild-moderately active ulcerative colitis (UC). This therapy also signalled clinical, endoscopic and biomarker efficacy and successfully modulated certain markers of carbohydrate and protein fermentation. Concurrently, the 4-SURE diet also addressed prevalent food-related concerns for patients with UC, including providing simple individualised dietary guidance, liberalising restrictive dietary behaviour, increasing habitual fibre intake without exacerbating gastrointestinal symptoms and improving FRQoL. Moreover, insights into using a diet such as the 4-SURE diet to support engraftment of donor microbiota and augment a sustained efficacy of faecal microbiota transplantation (FMT) in refractory UC were observed. The key outcomes of this thesis are summarised in ***Figure 8.1*****.**

8.2 The added value of identifying the relationship between diet and disease control

Collectively, the studies within this thesis highlight important yet neglected areas of IBD care and identify areas that diet can provide added value, including as a possible therapy for UC. The study findings signal the potential for a shift in conventional IBD treatment paradigms towards a model that not only optimises control of active disease but improves quality of life (QoL) and positively reframes the relationship between diet and IBD.

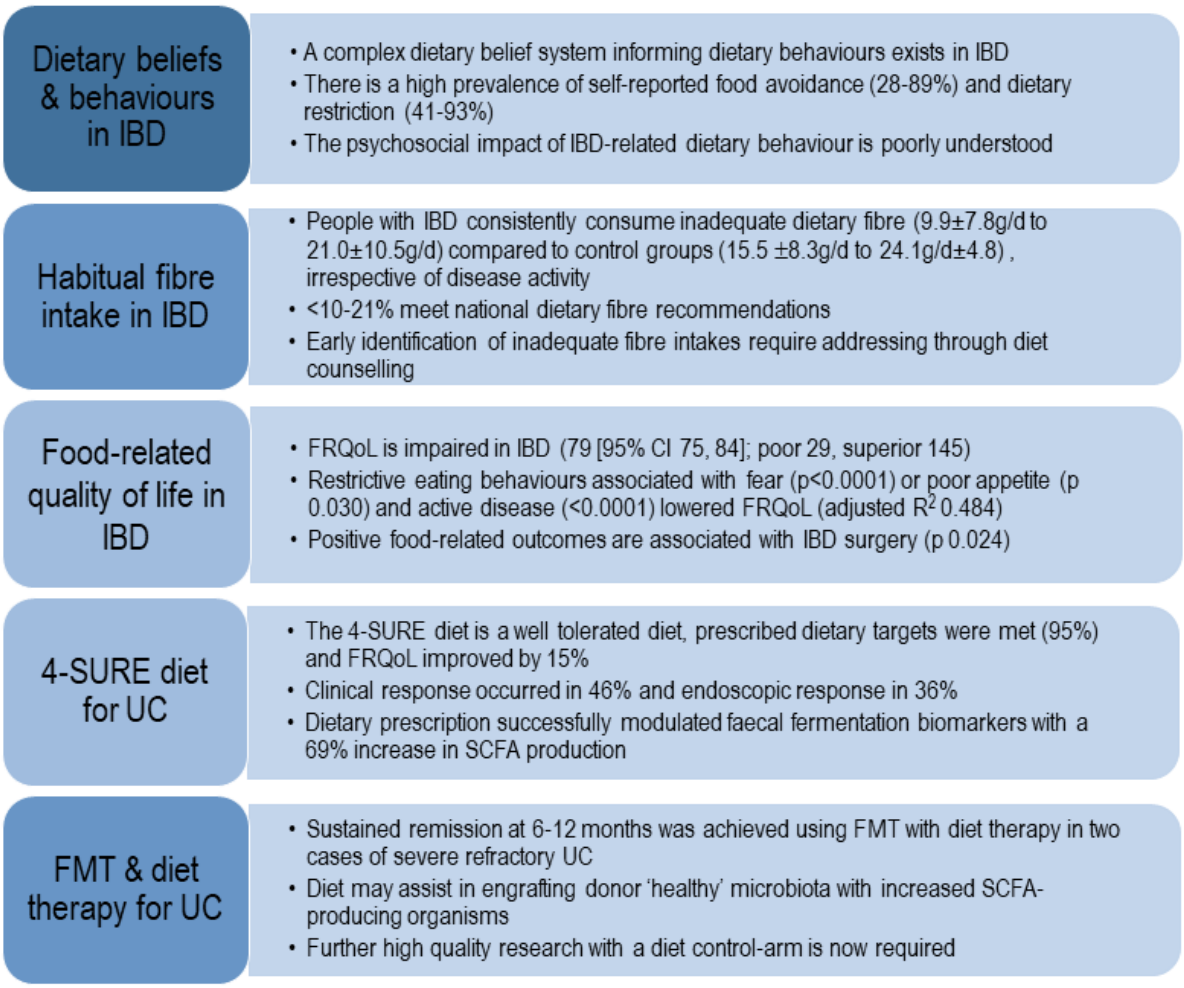

Figure 8.1 Summary of thesis outcomes

A high prevalence of self-reported food avoidance and restrictive eating behaviour exists in people with IBD

The scoping review presented in ***chapter 3*** draws attention to the fractured relationship with food that many people with IBD experience. Although not all food avoidance behaviour is perceived to have a negative effect, the findings of this review indicate that food is more commonly dichotomised as problematic than beneficial. This perception is plausibly due to misinformed dietary beliefs, stemming from inadequate access to a specialist IBD dietitian who can individualise dietary education. The findings in ***chapter 5*** show 60% of patients with IBD use the internet as their primary source of dietary information and only one third of these patients have seen a dietitian to guide food choice during their disease course. Moreover, the presence of gastrointestinal symptoms may be driving food avoidances. Symptom burden in quiescent disease can often be lowered through individualised dietary counselling.[1] Misinformed dietary beliefs and food avoidance behaviours may contribute to the risk of avoidable nutrition-related complications through an inadequate dietary intake.[2, 3] These findings

highlight dietary education and management is a neglected area of IBD care. They also evidence that there are inconsistencies between service modelling and evidence-based recommendations for dietetic and multidisciplinary IBD care and what is actually received by patients.[4, 5]

The moderate FRQoL of people with IBD presented in ***chapter 5*** adds validity to the high prevalence of self-reported restrictive eating behaviour identified in this scoping review (***chapter 3***). However, the interpretation of these behaviours are limited by the heterogeneity between studies. This includes the dietary terminology used to describe beliefs and behaviours and the instruments used to measure dietary behaviour. Existing instruments to directly measure dietary behaviour independent of QoL are either unvalidated for IBD or at risk of bias particularly when designed for evaluating disordered eating traits and behaviours.[6, 7] Nonetheless, the existence of this poor relationship with food is also confirmed by other studies that measure FRQoL in IBD, including the studies presented in ***chapter 5 and 6***.[8, 9]

Habitual dietary fibre intakes are inadequate in IBD, irrespective of disease activity

The prevalence of restrictive dietary behaviours reported in ***chapter 3*** presents a possible explanation for the inadequate habitual fibres intakes of people with IBD presented in ***chapter 4***. These inadequate fibre intakes are independent of disease activity and lower than healthy control (HC) populations. There is significant heterogeneity not only in the study designs and dietary assessment tools used to measure total habitual fibre intake, but also in how fibre was defined, categorised for assessment including whether fibre sub-types were measured, geographical location and cultural influence on dietary patterns and fibre intakes. Moreover, a universal definition of fibre is not used within respective national dietary guidelines.[10] Food composition tables from different countries do not always calculate fibre sub-types including non-starch polysaccharides (NSP), resistant starches (RS), or other fermentable fibres such as oligosaccharides. For example, in the United Kingdom total dietary fibre is calculated as NSP (soluble + insoluble fibre) whereas in Australia food composition tables include RS data.[11] This is the key reason for discrepancies between food composition databases and also reporting of fibre data, adding to the complexity of both measuring fibres and interpreting the clinical implications of an inadequate fibre intake in disease.

This review was unable to determine which sub-types of fibres were inadequate as only four studies measured different fibre sub-types such as soluble and insoluble fibre fractions. Conclusions could not be drawn from the nine studies that examined the total fibre contributions from each core group to daily intakes although vegetables and wholegrains were equally restricted. Moreover, there are very little data informing the dose (and types) of fibre to be manipulated for a desired therapeutic effect in the colon. For example, in health, consumption of 15-20g/d of RS has been proposed for optimal bowel health.[12, 13]

Nonetheless, these findings of inadequate total habitual fibre intake are clinically important as fibre may have a pathogenic role in sustaining periods of remission in CD and downgrading inflammation in UC. [14, 15] These thesis findings identify an important area for dietary counselling by a specialised dietitian who is best placed to deliver complex diet education and to address any dietary misconceptions that could lead to unnecessary fibre avoidance.[16] This includes provision of advice on manipulating fibre to manage gastrointestinal symptoms or overt inflammation in the settings of active and quiescent disease.[10, 17] As shown in ***chapter 6***, higher intakes of fibre >30g/d are well tolerated in active UC despite a perception fibre exacerbates symptoms, therefore a dietitian can assist with navigating food-anxiety around fibre optimisation to a tolerable level. As scientific knowledge of the physiochemical characteristics and functionalities of fibre evolves, a deeper understanding of the habitual intakes of total fibre and fibre sub-types will be important if manipulation of different fibre sub-types are to be explored as co-administered therapy or modulated within novel IBD diet therapies.[10, 18]

FRQoL is impaired in IBD, lowered by restrictive eating behaviour and active disease

The relationship between restrictive eating behaviour driven by fear of gastrointestinal consequences and poor appetite, disease activity and FRQoL is a novel finding in this thesis. The cross-sectional study presented in ***chapter 5*** also confirms dietary restrictions are often liberalised after surgery or with ostomies, illustrating some of the broader benefits of surgical intervention to QoL.[19, 20] Although this study was not powered to detect a difference between CD and UC, the observation that individuals with UC have poorer FRQoL than CD is worthy of further exploration. This is also supported by the poor FRQoL sum scores of patients with UC prior to starting the 4-SURE diet presented in ***chapter 6***. A large proportion of diet research and provision of dietary counselling in a clinical setting is directed toward CD with more people with CD having received dietary support from a dietitian, however, symptom burden in UC may be responsive to dietary modification.[21, 22] While nutrition-related complications such as malnutrition and vitamins deficiencies tend to be greater in CD, these do not necessarily confer a daily symptom burden that drives dietary change in comparison to the functional symptom burden and psychological distress observed in both active and quiescent UC.[22, 23] Therefore, UC may be an under represented group being referred for dietetic support. Another significant but unexpected finding in this thesis was the improvement in FRQoL after dietary education, irrespective of an improvement in disease activity observed in the study in ***chapter 6***. This suggests that the provision of dietary support is influential over multiple domains of FRQoL and illustrates the importance of people with IBD having access to individualised dietary advice from a specialised dietitian.

Collectively, these data add to the current FRQoL evidence base and increases an awareness that QoL is affected by the interaction between diet and disease, during active and quiescent phases. The negative correlation between psychological distress and FRQoL sum scores offers an explanation for why FRQoL may be impaired irrespective of disease activity. Quiescent disease is not necessarily associated with relaxing dietary restrictions, possibly because some restrictions are perpetuated by food-related anxiety.[22] While irritable bowel syndrome symptom severity scores were not measured in this study, the presence of concurrent functional gut symptoms may also have lowered FRQoL irrespective of disease activity.[9]

The 4-SURE diet is tolerable, modulates colonic fermentation and has therapeutic potential for mild to moderately active UC

As part of the steps to minimise conflicting dietary misinformation surrounding the management of UC and its subsequent impact on FRQoL, this thesis has contributed to the evidence base for a diet therapy. The open label pilot dietary advice study presented in ***chapter 6*** is the first step toward determining whether a sulphide-reducing diet (4-SURE diet) is an effective therapy for UC.

The 4-SURE diet has a defined mechanistic rationale supported by a body of observational and experimental data.[24-28] It is designed for long-term use and is based on a simple whole-foods approach to eating, wholly unrestrictive in nature beyond swapping between preservative-free product alternatives. Furthermore, the 4-SURE diet was very well tolerated and challenged any patient belief that a high intake of dietary fibre would exacerbate symptoms of active disease. Total fibre intakes were optimised above dietary recommendations of 30g/d with concurrent daily targets for RS and NSP fibres. Mean total fibre intakes increased by 12.9g/d to 34.4g/d and RS intakes from whole foods increased by 9.8g/d to 12.6g/d and were well tolerated with a concurrent 24% reduction in the most troublesome gastrointestinal symptoms at baseline. This is in contrast to reports of higher intakes of supplemental RS in non-gastrointestinal disease increasing gastrointestinal symptoms.[29] Beyond this, there has been very little evaluation of tolerability of increasing dietary RS from whole foods in functional or inflammatory bowel disease. Accurate NSP food composition data was unattainable therefore the interpretation of this fibre sub-type was limited beyond increases in stool weight.[30]

There were several strengths in the design of the study as a feasibility study. The methodological rigour used included gold standard objective markers of disease activity at regular intervals to assess the therapeutic efficacy of the diet, as well as established methods of monitoring dietary adherence.[17, 31] Directly measuring real time colonic production of hydrogen sulphide gas (H_2S) is impractical, therefore surrogate markers of colonic fermentation were used despite their known limitations.[27] *In vivo*, short chain fatty acids (SCFA) are rapidly absorbed in the colon. Faecal concentrations of these compounds will therefore be a function of production, detoxification and absorption and more reflective

of microbial activities in the rectum rather than the distal colon.[32, 33] However, until more direct approaches are available, faecal SCFA remains the best available markers for measuring protein and carbohydrate fermentation.[32] There may also be room for incorporation of plasma SCFA to assess whether carbohydrates occurred, although generally most of the SCFA detected in blood is acetate. While a direct association between changes in SCFA, branched chain fatty acids (BCFA) and ammonia output and H_2S suppression cannot be drawn from these results, these surrogate markers of carbohydrate fermentation were able to be modulated as hypothesised, which signals that dietary attenuation of H_2S in UC possible.

While signals of therapeutic efficacy were observed in the presented pilot study, the 4-SURE dietary prescription of daily carbohydrate and protein intakes required to suppress protein fermentation requires further review. Firstly, existing food composition databases used to develop the dietary prescription and assess dietary intake are inadequate. Comprehensive databases are needed to accurately measure the sulphur amino acid content of common Australian foods. Furthermore, accurate NSP and RS data requires consolidation. Methods of assessment of RS are highly diverse and account for discrepancies between published food composition tables. Moreover, RS data needs extending beyond the limited number of foods analysed in Australian and American reports.[12, 34]

Secondly, existing dietary guidelines propose protein recommendations of 1.2-1.5g/kg/d for active CD and UC.[35] It is possible that such broad-brush recommendations are inappropriate given the data informing these recommendations is derived from general consensus statements and data from paediatric studies of active CD and the generalised metabolic effect of injury on skeletal muscle rather than any UC data.[35] Therefore, 1.2g/kg/d may be too high for mild-moderately active UC, in which inflammation is confined only to the colonic mucosa. The protein prescription of 1.2g/kg/d adopted in the presented pilot study may also explain why a significant reduction in sulphur proteins and output of protein fermentation biomarkers (ammonia and BCFA:SCFA) were not achieved. In keeping with this hypothesis, by post-hoc analysis a greater reduction in protein intake was associated with overall therapeutic response to the 4-SURE diet. For future studies, it is possible that a greater reduction in protein targets could be achieved without nutritional compromise.

Lastly, the prospect of liberalising all fermentable oligo, di-, monosaccharide and polyols (FODMAP) within limits of individualised tolerance requires review. Such an approach could be beneficial to increasing consumption of a wider variety of other fermentable carbohydrates and thereby inadvertently lowering protein intake. It may well be that liberalisation of FODMAP intake under dietitian supervision may not increase gastrointestinal symptom burden as much as initially thought.

A final qualitative observation of implementing the 4-SURE diet was the baseline food anxiety reported by many patients relating to increasing wholegrains and fruit. Beyond exacerbation of gastrointestinal

symptoms, weight gain was the primary reservation cited during baseline dietary education. Many participants reported being fearful of weight gain by eating more fibre-rich grains, cereals and fruits due to the perceived metabolic effects of the carbohydrate content. In fact, one participant dropped out prior to starting the 4-SURE diet for this reason. However, mean energy intakes actually reduced by 302kcal/d (15%) and total carbohydrate intake remained stable during the 8-week intervention. This data is most likely explained by participants swapping low fibre carbohydrates for high fibre alternatives. Many high fibre foods also have a higher protein content, though low in sulphur amino acids. Both total fibre and protein can induce earlier and sustained satiety and assist with maintaining a lower calorie intake and weight.[36, 37] These findings also add to the evidence presented in ***chapter 3*** that dietary misinformation can lead to unnecessary food avoidance behaviours, including restriction of fibre-rich wholegrains and fruit due to fear of weight gain.

Diet signals the potential to augment and sustain the efficacy of FMT in refractory UC

The use of diet to engraft FMT is novel. It is logical that a dietary strategy, designed to encourage microbial enrichment and to downgrade inflammation in UC, could also augment donor FMT engraftment in UC. This combined approach could plausibly lead to a more durable FMT-induced remission in UC. Emerging data also suggests it is possible diet alone may have a greater treatment efficacy.[38] However, the optimal diet for donors and recipients is yet to be examined in FMT trials and data on sustained efficacy in FMT is scarce.[38-40] The two-part case series presented in ***chapter 7*** shows colectomy was avoided in both cases and sustained remission beyond 24-52 weeks was achieved with a combined FMT and dietary therapy approach. The 4-SURE diet was well adhered to with marked increases in fibre including achieving RS and NSP targets and a reduction in protein intake. This could explain the sustained increase in SCFA-producing organisms and the decreases in sulphide-producing capacity. Whilst limited to case reports, the functional metagenomic data presented yields insights of the possible mechanistic action of FMT and diet in UC, which warrants further exploration in a controlled combination FMT and diet study.

8.3 Implications for clinical practice

Together, the body of research presented in this thesis illuminate the possibility of a patient-centred treatment paradigm that uses diet to optimise existing IBD therapies and to improve QoL (***Figure 8.2***). This proposed model aligns with patient values and key priorities for IBD care.[41] Recommendations for clinical practice generated from this body of research are outlined below.

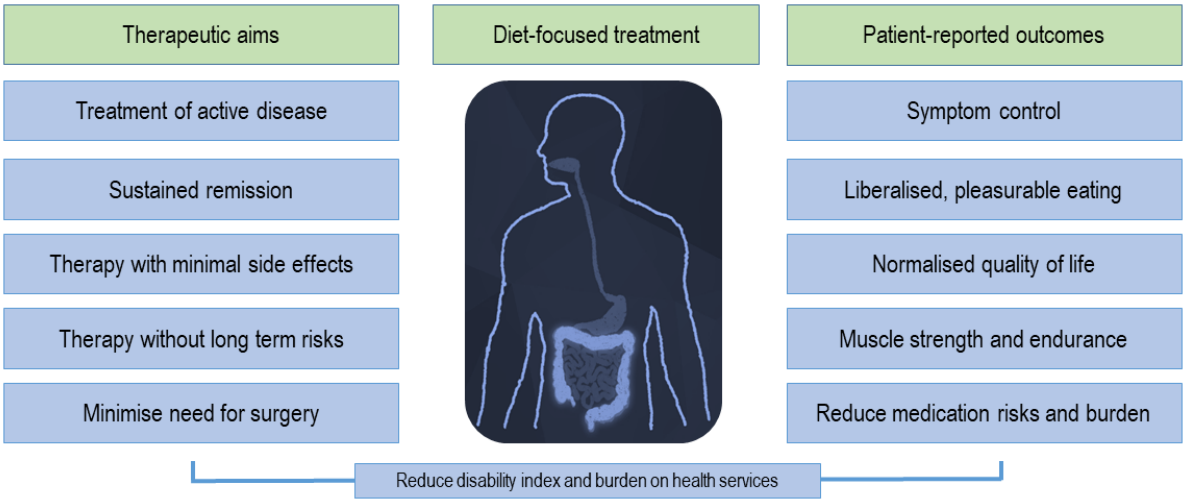

Figure 8.2 Towards a patient-centred, diet-focused treatment paradigm for inflammatory bowel disease

Individualised dietary education should be provided soon after diagnosis to inform dietary beliefs and behaviour and optimise FRQoL

Dietary counselling should be routinely integrated into IBD care as a preventative practice for optimising nutritional status and FRQoL. Provision of generic dietary education that is not tailored to the individual may be insufficient to correct dietary misinformation.[21] Complex dietary advice requires the delivery of consistent, evidence based information with appropriate dietary support, otherwise it is unlikely to improve dietary behaviour, nutritional status or FRQoL.[16] The timing of dietary education is important. All patients should have access to dietary education after diagnosis and it should be individualised to disease phenotype, disease activity and location, symptom severity, and current nutritional status. Furthermore, advice must be clear and simple to follow. An IBD specialist dietitian is well placed to provide this support within a multidisciplinary IBD team and greater emphasis by health services into resourcing this service for patients is required as access to IBD dietitians is limited.[4, 42]

Screening for food-related anxiety and restrictive dietary behaviours should be part of routine care

IBD services should routinely screen for malnutrition and restrictive dietary behaviour that omits one or more core food groups providing essential nutrients including protein, iron, calcium and fibre.[7, 43] Disease severity is a predictor of restrictive dietary behaviours and poorer FRQoL (***chapter 3 and 5***), therefore, moderate to severe IBD patients should have access to a dietitian during a flare or in the setting of complex disease to minimise any ineffective dietary restrictions. Furthermore, nutritional status and associated food-related challenges are likely to fluctuate throughout disease course given the chronic relapsing and remitting nature of IBD and rates of surgical resections, therefore patients may intermittently require access to dietary support with a change in disease status or after surgery to

guide food choice and minimise the risk of nutrition and hydration-related complications.[3, 43, 44] At these time points in disease course, screening for changes in nutritional status and dietary behaviour would ensure potentially harmful dietary behaviours are identified and addressed earlier.

Dietary counselling should aim to optimise habitual fibre intakes in both quiescent and active disease

Confusion exists between health professionals over how and when to modify fibre intake.[16] This is most likely because fibre advice has evolved over the past few decades from low residue or low fibre diets for symptom management during active phases of disease, toward a more in-depth understanding of the functional importance of different fibre sub-types in gastrointestinal health, including modification of oligosaccharides to manage symptoms in quiescent disease.[10, 17, 45] Avoidance of dietary fibre beyond stricturing disease is common in IBD and may be detrimental to overall health and IBD outcomes.[14, 15] An experienced dietitian can translate current evidence regarding optimising either total fibre or sub-types of fibre appropriate for different stages of disease course.[14, 15]

Individualised dietary counselling can improve FRQoL

Dietary counselling and support was demonstrated to improve FRQoL (***chapter 6***), irrespective of overall response to diet therapy. This demonstrates one of the many benefits of individualised dietary advice for people with IBD delivered by a specialised dietitian. Fear-driven restrictive eating behaviour was identified as a predictor of poorer FRQoL (***chapter 5***) however positively reframing diet to encourage liberalisation of restricted fibrous foods improved FRQoL. The FRQoL-29 instrument may be a useful tool for evaluating the appropriateness of a dietary intervention for patients or the effectiveness of dietary counselling after dietetic consultations whereby a decrease in FRQoL may indicate a change in dietary approach is required.

Dietary advice for UC and for those receiving FMT

Dietary advice to correct misinformation, minimise restrictive eating behaviour and to optimise the overall quality of diet should be provided to people with UC, even in the absence of a defined diet therapy. While UC may not directly interfere with digestion and micronutrient absorption to the same extent as CD, inflammation in the colon influences gastrointestinal symptom burden and there are signals FRQoL may be poorer in UC than CD (***chapter 5, chapter 6***) and this is an area that can be addressed in clinical practice through greater awareness of the impact UC has on dietary intake, irrespective of severity of inflammation.[8, 22, 23] The studies within this thesis illuminate the complex relationship people with IBD have with food and demonstrate in ***chapter 6*** these can be resolved through simple, individualised dietary advice that aligns with healthy eating principles.[46] Optimisation of habitual diet should also be a consideration in any UC recipient receiving FMT. Whilst there is limited

data on the optimal diet to engraft donor FMT, at a minimum, broad healthy eating principles can be recommended as these focus on optimising fibre-rich foods for general health. The data presented in ***chapter 7*** indicate a potential benefit of optimising fermentable fibres and lowering protein load to potentiate the durable efficacy of FMT in UC.[46] There is now emerging data to suggest diet may even be superior to FMT in treating refractory UC which highlights an important research gap to be addressed.[38]

Recruitment into diet trials should be a priority for IBD services

Recruitment into well designed diet trials should be a priority for IBD clinical services. People with IBD already modify their diets and want further dietary information (***chapter 3***) therefore are plausibly a motivated group. Trialling diet therapy is not associated with the same risks of infection and malignancy that plague immunosuppressive therapy trials and structured dietary guidance has been shown to improve FRQoL (***chapter 6***) irrespective of clinical response.

8.3 Future research directions

The body of research presented in this thesis highlights future directions for diet research in IBD and proposes how conventional models of IBD care could adopt simple strategies to shift toward a more patient-centred, diet-focused treatment paradigm.

Develop and validate a dietary behaviour tool specific for chronic digestive diseases

The development of an instrument specific to identifying positive and negative dietary behaviours associated with chronic gastrointestinal disease is essential. Such a tool would eliminate the heterogeneity of diet terminology used to describe dietary behaviour and allow assessment of potentially harmful dietary behaviours in IBD, which are prevalent and could be addressed through dietary counselling. Such a tool could also identify inclusive, positive dietary behaviours that are used to prevent avoidable nutrition-related complications. Clinicians and patients would better understand the relationship between dietary behaviour and disease without labelling as eating disorders. Moreover, it could be used to identify those who would benefit from additional dietary support and those whom would not require a dietetic referral. A working group of IBD specialist dietitians and psychologists would be well placed to develop and validate such an instrument to determine its responsiveness, reliability and inter-observer variability. This instrument could also be used to standardise further research in this area.

Integrate FRQoL as an outcome measure into dietary research

The influence of diet on disability indices and QoL has been poorly explored in IBD with existing instruments failing to include questions relating to diet.[47, 48] The FRQoL tool may help to bridge this gap in both clinical and research settings, measuring the effectiveness of dietary counselling and

appropriateness of diet therapy in IBD. The responsivity of the FRQoL tool at different time points, including in response to changes in disease activity, now needs to be established within a larger, representative cohort with a control group. It would also be useful to concurrently examine what people are eating to determine whether dietary perception align with dietary behaviour or whether food-related anxiety has a greater impact on FRQoL than food intake per se. Furthermore, the FRQoL tool should be included in all dietary intervention studies for IBD as a measure of the capacity of diet therapies to improve FRQoL in the short and long term.

Advance research into the physicochemical properties and physiological effects of fibres

Modulation of, or supplementation with, dietary fibres have therapeutic potential for IBD. However, before therapeutic effects can be accurately interpreted, the physicochemical effects of fibre sub-types and fibre definitions must be universally accepted.[10] Only then can the functionality of fibres for optimal gastrointestinal health be clearly understood. Food compositional tables require to accurately measure and analyse intakes of fibre sub-types. Well-designed trials are needed to evaluate the physiological effects of fibres and how fibres interact with a healthy gut microbiota. Further research into modulating fibres to increase microbial diversity and abundance in IBD is also required, including how this could influence the microbial signature of CD or UC.[49]

Trial the 4-SURE diet in a high quality, randomised controlled trial

The next step in testing a sulphide-reducing diet as therapy for UC should be in a high quality randomised-controlled trial (RCT). This may be in the form of a blinded, randomised-controlled feeding study or a blinded, randomised placebo-controlled sham dietary advice study to test this hypothesis against rigorous methodology. Both trial designs have their strengths and weaknesses. Feeding studies may increase dietary adherence through provision of food items and meals. However, adherence may be substantially reduced in the 'real-world' if alternative meals are consumed without guidance of how to follow and apply the dietary principles. Blinded dietary advice trials are considered gold-standard as have this 'real-world' application. Participants shop and cook meals in line with dietary prescription. Conversely, dietary adherence may be limited without provision of food items and extensive dietary counselling.[50] Prior to an RCT, the feasibility and tolerability of both intervention and placebo diets must be trialled to ensure both diets will be adhered to.[50, 51] Moreover, food composition tables require updating with renewed Australian data on sulphur amino acids, fibre sub-types and food additives to guide dietary prescription.

Furthermore, strategies to reduce risk of bias along with state of the art techniques to measure the mechanistic action of the 4-SURE diet are required. Blinded, centralised reading of endoscopy as an objective marker of change in disease activity is required in a high-quality trial design. Faecal sampling and practical, accurate biomarkers of colonic fermentation are required. This includes measuring

colonic production of H_2S, nitric oxide and other volatile compounds in patients with UC and healthy controls in real-time using gas profiling technology, precision in measuring luminal SCFA production and utilisation in the colon and measuring changes in microbial composition and function using metagenomic sequencing and bioinformatics on faecal and mucosal samples. This would provide a deeper understanding of the interaction between dietary substrate and functionality of the colonic microbiota at the colonic-luminal interface. [52-54]

Integrate adjunctive diet therapy with a habitual diet control arm into future FMT trials

It would be novel to design a high quality FMT trial with a diet-arm to investigate whether optimising diet can augment the durability and efficacy of FMT in UC. As a first step, further exploration into the habitual diets of FMT donors and recipients may be performed, comparing responders and non-responders to provide insight into the potential role of diet in FMT. Habitual diet should be optimised for both donor and recipients. Specifically, the role of modulating colonic fermentation of dietary fibres and protein should be addressed in an FMT-diet prescription.

8.4 Thesis conclusion

Diet is a topic of great significance to people with IBD and is influential over many important aspects of living with IBD. Individualised dietary education from a specialised dietitian can treat many of the food-related challenges people with IBD experience and improve QoL. The future of diet as therapy to treat overt inflammation for UC is promising, however the process of developing a diet therapy must progress sequentially and with methodological rigour. Developing diet therapy is arguably more challenging in the trial phase than trialling pharmacological therapy due to availability of food composition data and the unique challenges of blinding and administering diet therapy. A diet therapy must be tolerable, nutritionally adequate and be supported by a defined mechanistic rationale. The possibility of a sulphide-reducing diet as therapy for mild-moderate UC and to augment FMT is novel and exciting and the studies in this thesis signal a therapeutic potential that warrants further investigation in a high quality trial.

In the interim, whilst research into diet as therapy for both CD and UC progresses, the body of work presented in this thesis illuminates other benefits of adopting a patient-centred, diet-focused treatment paradigm for IBD. Dietary counselling by an experienced dietitian within a multidisciplinary team can be proactively integrated into conventional treatment models to improve the overall quality of habitual diets and minimise food-related anxiety and unnecessary restrictive eating behaviours. These factors are important to reduce avoidable nutrition-related complications of IBD, reducing symptom burden and importantly, improving FRQoL.

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APPENDIX

APPENDIX 1: Food and quality of life in IBD questionnaire

PART 1: 79-item patient administered questionnaire

The Central Adelaide Local Health Network Inflammatory Bowel Disease Service would like to understand more about your views on how your health, eating and lifestyle can be affected by living with Inflammatory Bowel Disease.

We will ask a series of questions about your IBD in relation to diet, eating habits and mental well-being. This survey should take 10-15 minutes to complete. It is recommended you answer each question with the first answer that comes to mind as this is often most reflective of your thoughts.

This information will remain confidential and used for research and service development purposes only. Your choice to participate will not affect your IBD care or treatment plans in any way.

1. Please state your full name

Click or tap here to enter text.

2. Please record your date of birth (DD/MM/YYYY)

Click or tap here to enter text.

3. Which hospital currently provides your IBD care?

☐ Royal Adelaide Hospital IBD Service

☐ The Queen Elizabeth Hospital IBD Service

4. Do you feel confident in choosing what you should be eating for your IBD?

☐Yes

☐No

☐Unsure

5. Where do you access dietary information for your IBD? (tick as many as applicable)

☐ GP

☐ Gastroenterologist

☐ IBD Nurse

☐ Dietitian

☐ Surgeon

☐ Naturopath

☐ Family and friends

☐ Internet

☐ Support groups

☐ Other (please specify)

6. Have you seen a dietitian for IBD dietary advice?

☐ Yes

☐ No

☐ Unsure

7. What has been the most helpful type of dietary information for your IBD?

Click or tap here to enter text.

8. What dietary information would you still like to receive?

Click or tap here to enter text.

9. This question refers to your disease activity. There is a short questionnaire about current symptoms you are experiencing relating to your Crohn's Disease.

10. Do you believe that your IBD has been well controlled in the past 2 weeks?

☐ Yes

☐ No

☐ Unsure

11. Do you believe that your current treatment is useful in controlling your IBD?

☐ Yes

☐ No

☐ Unsure

☐ Please also tick this box if you are not on any treatment

The next 7 questions refer to your IBD over the past 2 weeks.

In the past 2 weeks:

12. Did you miss any planned activities because of IBD (ie school, work, social event)?

☐ Yes

☐ No

☐ Unsure

13. Did you wake up at night because of symptoms of IBD?

☐ Yes

☐ No

☐ Unsure

14. Have your bowel symptoms been getting worse, getting better, no change?

☐ Better

☐ No worse

☐ Worse

15. Did you often feel lacking in energy (fatigued)? *(by often, we mean more than half the time)*

☐ Yes

☐ No

☐ Unsure

16. Did you feel anxious or depressed because of your IBD?

☐ Yes

☐ No

☐ Unsure

17. Did you think you needed a change to your treatment?

☐ Yes

☐ No

☐ Unsure

18. Did you suffer from significant pain or discomfort?

☐ Yes

☐ No

☐ Unsure

The next 29 questions refer to the past two weeks and will ask you to agree or disagree whether your IBD has affected your eating.

In the past two weeks:

19. I have regretted eating or drinking something which has made my IBD symptoms worse

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

20. My enjoyment of a particular food or drink has been affected by the knowledge that it might trigger my IBD symptoms

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

21. My IBD has meant that I have had to leave the table while I am eating to go to the toilet

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

22. I have not been able to predict how long it will take for my body to respond to something I have had

to eat or drink due to my IBD

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

23. Certain foods have triggered symptoms of my IBD

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

24. My IBD has meant that I have been nervous that if I eat something I will need to go to the toilet straight away

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

25. I have avoided having certain food and drink I know does not agree with my IBD

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

26. I have felt relaxed about what I can eat and drink despite my IBD

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

27. I have felt in control of what I eat and drink despite my IBD

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

28. I struggled to eat the way that is best for my IBD because of other commitments during the day

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

29. I have been frustrated about not knowing how food and drink will react with my IBD

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

30. I have had to concentrate on what I have been eating and drinking because of my IBD

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

31. I have been worried that if I eat I will get symptoms of my IBD

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

32. I have felt the way that I eat and drink for my IBD has affected my day to day life

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

33. The way I have had to eat for my IBD has restricted my lifestyle

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

34. I have had to concentrate on what food I buy because of my IBD

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

35. It has been on my mind how my IBD will be affected by what I eat and drink

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

36. My IBD has prevented me from getting full pleasure from the food and drink I have had

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

37. I have felt that I need to know what is in the food I am eating due to my IBD

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

38. I have felt that I have had to be careful about when I have eaten because of my IBD

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

39. I have had to be more aware of what I am eating due to my IBD

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

40. I have missed being able to eat or drink whatever I want because of my IBD

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

41. I have felt that I would like to be able to eat and drink like everyone else

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

42. I have been happy to eat and drink around people I do not know despite my IBD

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

43. I have felt that I have been eating and drinking normally despite my IBD

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

44. I have found it hard not knowing if a certain food will trigger my IBD symptoms

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

45. My IBD has meant I have had to make an effort to get all the nutrients my body needs

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

46. I have felt that I have not known how my IBD will react to food or drink

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

47. My IBD has meant that I have had to work hard to fit my eating habits in around my activities during the day

☐ Strongly agree

☐ Agree

☐ Neither agree nor disagree

☐ Disagree

☐ Strongly disagree

The next 9 questions will ask you to disagree or agree with statements that describe your relationship with eating and food.

48. I am a picky eater

☐ Strongly disagree

☐ Disagree

☐ Slightly disagree

☐ Slightly agree

☐ Agree

☐ Strongly agree

49. I dislike most of the foods that other people eat

☐ Strongly disagree

☐ Disagree

☐ Slightly disagree

☐ Slightly agree

☐ Agree

☐ Strongly agree

50. The list of foods I like and will eat is shorter than the list of foods I won't eat

☐ Strongly disagree

☐ Disagree

☐ Slightly disagree

☐ Slightly agree

☐ Agree

☐ Strongly agree

51. I am not very interested in eating; I seem to have a smaller appetite that other people

☐ Strongly disagree

☐ Disagree

☐ Slightly disagree

☐ Slightly agree

☐ Agree

☐ Strongly agree

52. I have to push myself to eat regular meals throughout the day, or to eat large enough volumes at meals

☐ Strongly disagree

☐ Disagree

☐ Slightly disagree

☐ Slightly agree

☐ Agree

☐ Strongly agree

53. Even when I am eating a food I really like, it is hard for me to eat a large volume at meals

☐ Strongly disagree

☐ Disagree

☐ Slightly disagree

☐ Slightly agree

☐ Agree

☐ Strongly agree

54. I avoid or put off eating because I am afraid that other foods will cause GI discomfort, choking or vomiting

☐ Strongly disagree

☐ Disagree

☐ Slightly disagree

☐ Slightly agree

☐ Agree

☐ Strongly agree

55. I restrict myself to certain foods because I am afraid that other foods will cause GI discomfort, choking or vomiting

☐ Strongly disagree

☐ Disagree

☐ Slightly disagree

☐ Slightly agree

☐ Agree

☐ Strongly agree

56. I eat small portions because I am afraid of GI discomfort, choking or vomiting

☐ Strongly disagree

☐ Disagree

☐ Slightly disagree

☐ Slightly agree

☐ Agree

☐ Strongly agree

The next 21 questions will ask you about your mental well-being over the past one week.

Over the past week:

57. I found it hard to wind down

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

58. I was aware of dryness of my mouth

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

59. I experienced breathing difficulty

(e.g. excessively rapid breathing, breathlessness in the absence of physical exertion)

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

60. I couldn't seem to experience any positive feeling at all

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

61. I found it difficult to work up the initiative to do things

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

62. I experienced trembling *(e.g. in the hands)*

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

63. I tended to over-react to situations

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

64. I felt that I was using a lot of nervous energy

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

65. I was worried about situations in which I might panic and make a fool of myself

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

66. I felt that I had nothing to look forward to

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

67. I found myself getting agitated

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

68. I felt down-hearted and blue

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

69. I found it difficult to relax

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

70. I was intolerant of anything that kept me from getting on with what I was doing

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

71. I felt I was close to panic

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

72. I was unable to become enthusiastic about anything

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

73. I felt I wasn't worth much as a person

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

74. I was aware of the action of my heart in the absence of physical exertion

(e.g. sense of heart rate increase, heart missing a beat)

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

75. I felt I was rather touchy

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

76. I felt scared without any good reason

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

77. I felt that life was meaningless

☐ Did not apply to me at all

☐ Applied to me to some degree, or some of the time

☐ Applied to me to a considerable degree or a good part of time

☐ Applied to me very much or most of the time

Could you please record the following information:

Height (cm)

Current weight (kg) Click or tap here to enter text.

Have you ever smoked? ☐ Yes ☐ No

If yes, are you a current smoker? ☐ Yes ☐ No

If you would like to be contacted regarding the EAT-UC dietary intervention study for Ulcerative Colitis or to participate in a future study exploring opinions on how food and eating is affected by IBD, please complete the following contact information.

Name Click or tap here to enter text.

Email Address Click or tap here to enter text.

Phone Number Click or tap here to enter text.

Thank you for taking the time to complete our questionnaire. If you have any other comments you would like to make, please feel free to do so.

Part 2: Clinician administered Harvey Bradshaw Index Instrument for Crohn's Disease

Variable	Question	Description	Score
General well-being	How have you been feeling?	☐ Very well ☐ Slightly below par ☐ Poor ☐ Very poor ☐ Terrible	0 1 2 3 4
Abdominal pain	Have you been experiencing any abdominal pain?	☐ None ☐ Mild ☐ Moderate ☐ Severe	0 1 2 3
Abdominal mass	*(Clinician to complete physical assessment)*	☐ None ☐ Dubious ☐ Definite ☐ Definite and tender	0 1 2 3
Liquid stools	How many liquid stools per day do you pass?	How many per day?_____	(1 per occurrence)
Complications	Do you experience any of the following complications of Crohn's disease?	☐ Arthralgia (painful joints)	
		☐ Uveitis *(painful eye inflammation)*	
		☐ Erythema nodosum *(painful skin inflammation, usually on shins)*	
		☐ Apothous ulcer	
		☐ Pyoderma gangenosum	

		(wounds / ulcers usually on legs)	(1 per item)
		☐ Anal fissure	
		☐ New fistula	
		☐ Abscess	
Total			

PART 2: Clinician administered Simple Clinical Colitis Activity Index for Ulcerative Colitis

Descriptor	Description	Tick	Score
Bowel frequency (day)	0-3	☐	0
	4-6	☐	1
	7-9	☐	2
	>9	☐	3
Bowel frequency (night)	0	☐	0
	1-3	☐	1
	4-6	☐	2
Urgency of defecation	None	☐	0
	Hurry	☐	1
	Immediately (toilet nearby)	☐	2
	Incontinence	☐	3
Blood in stool	None	☐	0
	Trace	☐	1
	Occasionally frank (<50% of defecation)	☐	2
	Usually frank (>50% of defecation)	☐	3
General well being	very well	☐	0
	slightly below par	☐	1
	poor	☐	2
	very poor	☐	3

	terrible	☐	4
Extra colonic features	Arthritis (joint pain)	☐ Yes ☐ No	1 0
	Uveitis (painful eye inflammation)	☐ Yes ☐ No	1 0
	Erythema nodosum (painful skin inflammation)	☐ Yes ☐ No	1 0
	Pyoderma gangenosum (wounds / ulcers)	☐ Yes ☐ No	1 0
Total		Of 19	

Reference: Walmsley RS, Ayres RCS, Pounder RE, Allan RN. A simple clinical colitis activity index. Gut 1998;43:29–32.

APPENDIX 2: 4-SURE diet materials

Appendix 2.1 4-SURE Dietary prescription

FOOD ITEM	SERVE	SUGGESTION
Firm banana	Minimum x 1	1 medium firm banana on cereal / as a snack / in a smoothie
Wholegrains	Minimum 3 serves high in resistant starch	1 cup Freedom Foods Wholegrain cereal flakes, fruit-free 2 x slices Bohdis Rye, Burgen Rye 2 x slices Pumpernickel bread, preservative-free 1 x Barley wrap 1 cup couscous 4 wheat crackers 1 cup barley porridge
Potato products	Minimum 1 serve (or can include an extra grain serve instead)	1 cup gnocchi 1 cup potato salad (preservative free dressing) 1 x small jacket potato 2 x hash browns (preservative free)
Legumes	Minimum 1 cup	1 cup baked beans (without meat) 1 cup lentil bolognese sauce 1 cup (125g) tin 4-bean mix 1 cup chickpea salad
Rice Bran / Psyllium	1 tablespoon	Sprinkle into breakfast, dinner or into a smoothie
Meat / fish / chicken / pork / eggs	Limit to 100-150g per day (dependent on source of protein)	Halve your meat intake Include meat for lunch OR dinner (NOT both unless choosing small serves for both meals)
Sulphur, sulphites E220-228	Avoid	Alternate names to be aware of: Sulphur dioxide, hydrosulphites, bisulphites, metabisulphites E code numbers 220-228
Nitrates E249-252	Avoid	Alternate names to be aware of: Sodium nitrate/nitrite, potassium nitrate/nitrite or E code numbers 249-252
Carrageenan E407	Avoid	Alternate names to be aware of: Vegetable gum (407), carrageenan gum, stabiliser (407) E code number 407

Appendix 2.2 4-SURE 7-day set meal plan

Day 1-3 adaptation phase

This 1-week meal plan must be followed as it has been designed to allow for gradual increases in resistant starch and fermentable fibres. This gradual upgrade will assist in minimising any bloating or abdominal symptoms that may occur when fibre is increased too rapidly.

Where a recipe is provided, you will see the symbol 

Adaptation phase *Gradual upgrade of resistant starch and fermentable fibres*			
	Monday **Day 1**	**Tuesday** **Day 2**	**Wednesday** **Day 3**
Breakfast	Hi Fibre cereal flakes (>1C) *[Choose brand from list]* Green tipped banana, Milk Psyllium 1 tsp	2 slices Burgen rye toast *[or choose other brand from list]* ≥½ cup baked beans	Barley & banana porridge ½ cup berries 
Snack	Tub of yoghurt	Tub of yoghurt	Banana bread 
Lunch	Pasta salad 	Leftovers: black bean beef stir fry with rice noodles	Minestrone soup with Hi fibre toast 
Snack	Ryvita's Hummous  *Or purchase preservative free hummous to use during week 1*	Banana & psyllium smoothie 	Ryvita's Hummous 
Dinner	Black bean beef stir fry with rice noodles 	Chilli con carne with red kidney beans and corn chips 	Barley & chicken risotto with green beans 
Snack	Orange or mandarin *(Or choose fruit from list)*	Orange or mandarin *(Or choose fruit from list)*	Tub of yoghurt

If you miss a snack, include it with the next meal or in the evening.

Appendix 2.3 4-SURE 7-day set meal plan

Day 4-7 transition phase

Transition phase *Stable intake of resistant starch and fermentable fibres*				
	Thursday **Day 4**	**Friday** **Day 5**	**Saturday** **Day 6**	**Sunday** **Day 7**
Breakfast	1-2 slices Burgen rye bread with peanut butter, banana and maple syrup *Can substitute almond butter and golden syrup*	Hi Fibre cereal flakes (>1C) *[Choose from list]* 2 tbs barley flakes ½ C berries Milk	Shakshuka eggs 1-2 slice Burgen rye bread *Or Baked beans on Rye toast*	Overnight Barley porridge with roasted rhubarb *Or Hi Fibre cereal* *Green tipped banana* *Milk*
Snack	Tub of yoghurt 1 tsp psyllium	Tub of yoghurt	Banana & psyllium smoothie	Tub of yoghurt
Lunch	Ryvita (4 slices) with tinned tuna, tomato and avocado	Baked jacket potato with 4 bean salad	Grain bowl *Or use leftover couscous salad*	Warmed freekeh salad
Snack	Roasted chickpeas	Banana bread	Ryvita crackers with Hummous	Sweet biscuits *Or use leftover banana bread*
Dinner	Mediterranean couscous with grilled salmon	Red kidney bean & lamb tagine *Or use leftovers from chilli con carne meal*	Lentil & potato burgers with yoghurt & mixed salad leaf	Grilled white fish with white bean & potato mash & green beans
Snack	*Choose fruit from list*	*Choose fruit from list*	*Choose fruit from list*	*Choose fruit from list*

From Day 4, any lunch meal can be substituted with leftovers from lunch and dinner meals can be substituted with leftovers from dinner meals. Remember to limit animal protein to one meal per day e.g. do not use dinner leftovers for lunch and then have a second meal containing meat in the evening as this will have too much sulphur protein for one day.

Appendix 2.4 Participant questionnaires

Demographic Questionnaire

Surname	
First Name	
Date of Birth	
Gender	Ethnicity
Address	
Mobile	Email
Gastroenterologist Name / Address / Phone	

Past Medical Hx			
IBD Hx Date Dx		Last scope: Disease location: Last faecal calpro:	
Past Surgical Hx			
Medications			
Are you currently	Taking steroids	☐ Yes	☐ No
	Taking laxatives	☐ Yes	☐ No
	Taking fibre supplement	☐ Yes	☐ No
	Taking probiotic	☐ Yes	☐ No
	Taking antidiarrheal	☐ Yes	☐ No
Hospitalisations			
Social hx			
Other Smoking status	current / never / ex-smoker		

Inclusion criteria

Must meet all inclusion criteria to be eligible for the study

Aged 18 or older		☐ Yes	☐ No
Disease activity			
Mild-moderate	Mayo score 3-10	☐ Yes	☐ No
Ulcerative Colitis	(with a Mayo endoscopic sub score ≥ 1)	☐ Yes	☐ No
Therapy			
On stable therapy	No therapy (4 weeks)	☐ Yes	☐ No
	Oral and/or topical 5-ASA (4 weeks)	☐ Yes	☐ No
	Immunomodulators (8 weeks)	☐ Yes	☐ No
	Biologics (12 weeks)	☐ Yes	☐ No
Diet	Habitually consume sulphur proteins	☐ Yes	☐ No

Exclusion criteria

If any of the following criteria are met, patients are ineligible and excluded from the study

Disease	Crohn's disease	☐ Yes	☐ No
	Crohn's colitis	☐ Yes	☐ No
Disease activity			
Quiescent UC	Mayo score < 2	☐ Yes	☐ No
	Mayo endoscopic sub score 0	☐ Yes	☐ No
Severely active UC	Mayo score > 10	☐ Yes	☐ No
	Mayo endoscopic sub score 3	☐ Yes	☐ No
	Evidence of systemic toxicity (tachycardia, fever, CRP > 40, Haemoglobin <110g/l)	☐ Yes	☐ No
Other conditions / issues	Pregnant or breastfeeding	☐ Yes	☐ No
	Significant medical, cognitive, psychiatric comorbidities	☐ Yes	☐ No
	Prior colonic surgery	☐ Yes	☐ No
	Tapering corticosteroid therapy	☐ Yes	☐ No
	Active infection	☐ Yes	☐ No
	Antibiotic therapy	☐ Yes	☐ No
	Antiplatelet / anticoagulant therapy	☐ Yes	☐ No
	Vegan	☐ Yes	☐ No
	Unable to provide informed consent	☐ Yes	☐ No

Simple Clinical Colitis Activity Index (Week 0,4,8)

Complete retrospectively using information from cross sectional questionnaire.

Descriptor	**Description**	**Score**
Bowel frequency (day)	0-3	0
	4-6	1
	7-9	2
	>9	3
Bowel frequency (night)	0	0
	1-3	1
	4-6	2
Urgency of defecation	None	0
	Hurry	1
	Immediately (toilet nearby)	2
	Incontinence	3
Blood in stool	None	0
	Trace	1
	Occasionally frank (<50% of defecation)	2
	Usually frank (>50% of defecation)	3
General well being	very well	0
	slightly below par	1
	poor	2
	very poor	3
	terrible	4
Extra colonic features	1 per manifestation:	
	Arthritis	1
	Uveitis (eye)	1
	Erythema nodosum (skin)	1
	Pyoderma gangenosum (ulcers)	1

Total		/19

Higher score indicates a higher severity of disease

Reference: Walmsley RS, Ayres RCS, Pounder RE, Allan RN. A simple clinical colitis activity index. Gut 1998;43:29–32.

Partial Mayo score (weeks 0, 4, 8)

Criteria	Please tick where applicable	Score
Stool frequency		
"Normal" number of stools when disease is inactive	☐	= 0
1-2 stools/day more than normal	☐	= 1
3-4 stools/day more than normal	☐	= 2
5 or more stools/day more than normal	☐	= 3
Rectal bleeding		
None	☐	= 0
Streaks of blood with stool less than half the time	☐	= 1
Obvious blood with stool most of the time	☐	= 2
Passing blood alone (at least 50% of bowel motions accompanied by visible blood and at least one bowel motion with blood alone)	☐	= 3
Physician rating of disease activity*		
Normal	☐	= 0
Mild disease	☐	= 1
Moderate disease	☐	= 2
Severe disease	☐	= 3
Total Partial Mayo Score (out of 9)		

*The physician's global assessment acknowledges the three other criteria, the patient's daily record of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

Score interpretation: Clinical remission – score of 1 or less[2]

Reference: Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. N Engl J Med 1987;317:1625-1629.

Mayo Endoscopic sub-score (Week 0,8)

Disease Activity	Endoscopic features ('descriptors')	Score	Tick which is applicable
Normal or inactive	None	= 0	☐
Mild	Erythema, decreased vascular pattern, mild friability	= 1	☐
Moderate	Marked erythema, absent vascular pattern, friability, erosions	= 2	☐
Severe	Spontaneous bleeding, ulceration	= 3	☐
	Partial Mayo Total Mayo	= =	

Reference: Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic therapy for mildly to moderately active ulcerative colitis. A randomized study. BMJ 1987;317(26):1625-9.

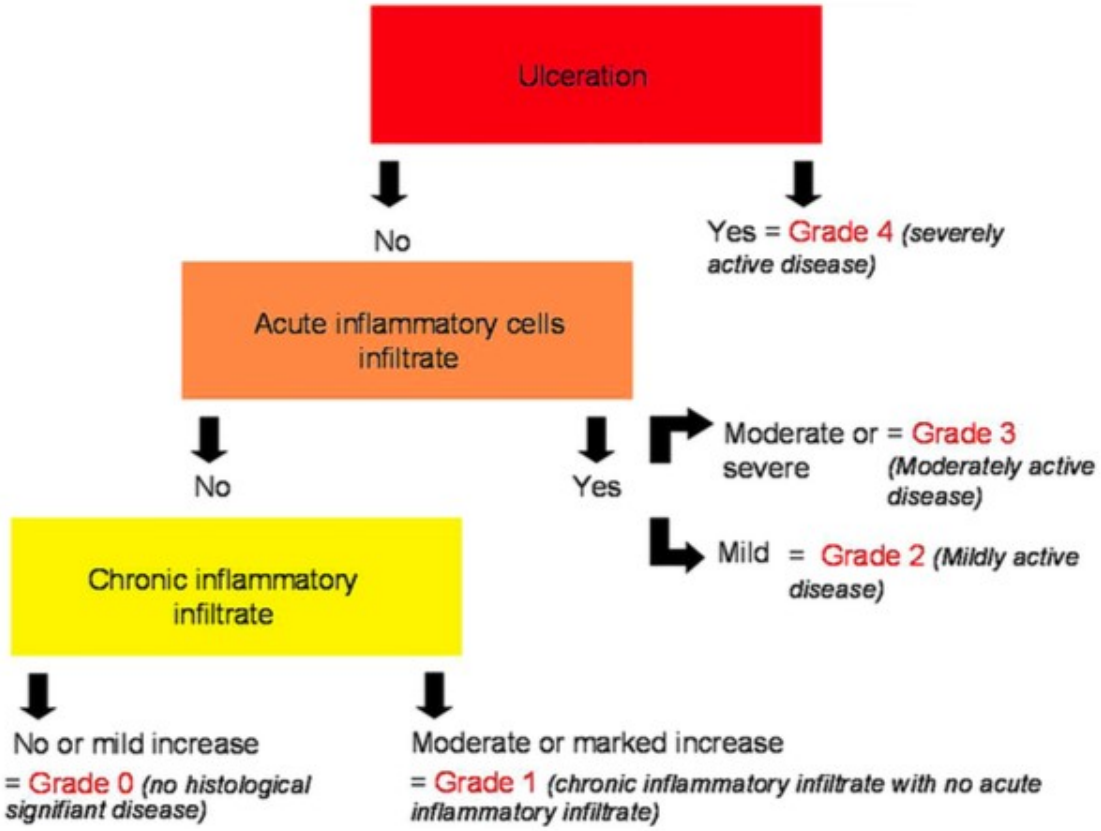
Ulcerative Colitis Endoscopic Index of Severity (UCEIS) (Week 0,8)

Score the most severe lesions in real time

Descriptor	Likert Scale anchor points	Definition	Score
Vascular pattern	Normal	Normal vascular pattern with arborisation of capillaries clearly defined, or with blurring or patchy loss of capillary margins	= 0
	Patchy obliteration	Patchy obliteration of vascular pattern	= 1
	Obliterated	Complete obliteration of vascular pattern	= 2
Bleeding	None	No visible blood	= 0
	Mucosal	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away	= 1
	Luminal mild	Some free liquid blood in the lumen	= 2
	Luminal moderate or severe	Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intra-luminal blood, or visible oozing from a hemorrhagic mucosa	= 3
Erosions & Ulcers	None	Normal mucosa, no visible erosions or ulcers	= 0
	Erosions	Tiny (≤5mm) defects in the mucosa, of a white or yellow color with a flat edge	= 1
	Superficial ulcer	Larger (>5mm) defects in the mucosa, which are discrete fibrin-covered ulcers when compared to erosions, but remain superficial	= 2
	Deep ulcer	Deeper excavated defects in the mucosa, with a slightly raised edge	= 3
Higher score indicates greater disease severity		Total	/8

Reference: Travis SPL, Schnell D, Krzeski P, et al. Reliability and initial validation of the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Gastroenterology 2013; 145:987-95.

Histological assessment: Nancy Histological Index (Week 0, 8)



Baseline grade: _____

Reference: Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, Bastien C, Cahn V, Cadiot G, et al. Development and validation of the Nancy histological index for UC. Gut. 2017 Jan;66(1):43-9. DOI: 10.1136/gutjnl-2015-310187.

Gastrointestinal Symptom Rating Scale (Week 0,4,8)

During the past week, have you been bothered by:

Abdominal pain?

1	2	3	4	5	6	7
No discomfort at all	Minor discomfort	Mild discomfort	Moderate discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort

Pain or discomfort in your abdomen, relieved by a bowel action?

1	2	3	4	5	6	7
No discomfort at all	Minor discomfort	Mild discomfort	Moderate discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort

A feeling of bloating?

1	2	3	4	5	6	7
No discomfort at all	Minor discomfort	Mild discomfort	Moderate discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort

Passing gas?

1	2	3	4	5	6	7
No discomfort at all	Minor discomfort	Mild discomfort	Moderate discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort

Constipation (problems emptying the bowel)?

1	2	3	4	5	6	7
No discomfort at all	Minor discomfort	Mild discomfort	Moderate discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort

Diarrhoea (frequent bowel movements)?

1	2	3	4	5	6	7
No discomfort at all	Minor discomfort	Mild discomfort	Moderate discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort

Loose bowel movements?

1	2	3	4	5	6	7
No discomfort at all	Minor discomfort	Mild discomfort	Moderate discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort

During the past week, have you been bothered by:

Hard stools?

1	2	3	4	5	6	7
No discomfort at all	Minor discomfort	Mild discomfort	Moderate discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort

An urgent need to have a bowel movement (need to go to the toilet urgently to empty the bowel)?

1	2	3	4	5	6	7
No discomfort at all	Minor discomfort	Mild discomfort	Moderate discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort

A feeling that your bowel was not completely emptied after having a bowel movement?

1	2	3	4	5	6	7
No discomfort at all	Minor discomfort	Mild discomfort	Moderate discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort

Feeling full shortly after you have started a meal?

1	2	3	4	5	6	7
No discomfort at all	Minor discomfort	Mild discomfort	Moderate discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort

Feeling full even long after you have stopped eating?

1	2	3	4	5	6	7
No discomfort at all	Minor discomfort	Mild discomfort	Moderate discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort

Visible swelling or your abdomen?

1	2	3	4	5	6	7
No discomfort at all	Minor discomfort	Mild discomfort	Moderate discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort

Reference: K WI, S F, J HC, H JR, F LG, A ME, et al. An Irritable Bowel Syndrome-Specific Symptom Questionnaire: Development and Validation. Scandinavian Journal of Gastroenterology. 2003 2003/01/01;38(9):947-54. DOI: 10.1080/00365520310004209.

IBD Control-8 (Week 0,4,8)

	Tick applicable box	Score
Do you believe that:		
Your IBD has been well controlled in the past 2 weeks	☐ Yes ☐ No ☐ Unsure	= 2 = 0 = 1
Your current treatment is useful in controlling your IBD?	☐ Yes ☐ No ☐ Unsure	= 0 = 2 = 1
Tick box if not taking any therapy / nil treatment	☐	*(= 1)*
Over the past 2 weeks have your bowel symptoms been getting worse, getting better, no change?	☐ Better ☐ No worse ☐ Worse	= 2 = 1 = 0
In the past 2 weeks, did you:		
Miss any planned activities because of IBD (ie school, work, social event)	☐ Yes ☐ No ☐ Unsure	= 0 = 2 = 1
Wake up at night because of symptoms of IBD	☐ Yes ☐ No ☐ Unsure	= 0 = 2 = 1
Suffer from significant pain or discomfort	☐ Yes ☐ No ☐ Unsure	= 0 = 2 = 1
Often feel lacking in energy (fatigued) (often = > 50%)	☐ Yes ☐ No ☐ Unsure	= 0 = 2 = 1

Feel anxious or depressed because of your IBD	☐ Yes ☐ No ☐ Unsure	= 0 = 2 = 1
Think you needed a change to your treatment?	☐ Yes ☐ No ☐ Unsure	= 0 = 2 = 1
Total		16

Higher score = better IBD control.

If patient not on medication, then they will need to tick a box and that gets a score of 1. Adding this transition question may be useful and has been recommended however it is not part of score. It is a standalone indicator of direction of control over last 2 weeks.

Reference: Bodger K, Ormerod C, Shackcloth D, Harrison M, Collaborative IBDC. Development and validation of a rapid, generic measure of disease control from the patient's perspective: the IBD-control questionnaire. Gut. 2014 Jul;63(7):1092-102. DOI: 10.1136/gutjnl-2013-305600.

MaInutrition Universal Screening Tool (Week 0)

Questions	Tick which is applicable	Score
Current weight (kg)		
Height (cm)		
BMI kg/m^2	☐ > 30 ☐ >20 ☐ 18.5 -20 ☐ <18.5	= 0 = 0 = 1 = 2
Weight 3-6 months ago (kg)		
Unintential weight loss over 3-6 months (%)	☐ <5% ☐ 5-10% ☐ >10	 = 0 = 1 = 2
Patient is acutely ill and there has been or is likely to be no nutritoinal intake for > 5 days	☐ Yes ☐ No	= 2 = 0
Total		

High nutrition risk = ≥2

Moderate nutrition risk = 1

Low nutrition risk = 0

Reference: BAPEN 2003

Patient-generated subjective global assessment (Week 0)

Weight			**Score**
1a	Current weight (kg)		
	Weight 1 month ago (kg)	>10% 5-9.9% 3-4.9% 2-2.9% 0-1.9%	= 4 = 3 = 2 = 1 = 0
	OR if 1 month data unavailable Weight 6 months ago (kg)	>20% 10-19.9% 6-9.9% 2-5.9% 0-1.9%	= 4 = 3 = 2 = 1 = 0
1b	During the past 2 weeks has your weight	Decreased Not changed Increased	= 1 = 0 = 0
Add score 1a + 1b =			
Food Intake			
	In the **<u>past month</u>** would you rate your food intake (compared to you normal food intake) as:	☐ unchanged ☐ more than usual ☐ less than usual	= 0 = 0 = 1
	If you are taking **<u>less than usual</u>** are you know now taking:	☐ normal food but less than normal in amount ☐ little solid food ☐ only liquids ☐ only nutritional supplements ☐ very little of anything ☐ only tube feeds or only nutrition by vein (TPN)	= 1 = 2 = 3 = 3 = 4 = 0

Use highest score only =			
Symptoms			
	In the past 2 weeks have you had any of the following problems which have kept you from eating:	☐ No problems eating	= 0
		☐ No appetite, did not feel like eating	= 3
		☐ Nausea	= 1
		☐ Vomiting	= 3
		☐ Constipation	= 1
		☐ Diarrhoea	= 3
		☐ Mouth sores	= 2
		☐ Things taste funny or have no taste	= 1
		☐ Smells bother me	= 1
		☐ Problems swallowing	= 1
		☐ Feels full quickly	= 2
		☐ Dry mouth	= 1
		☐ Pain, where? _____	= 3
		☐ Other e.g. depression, money or dental problems (1) _____	= 1
Total (additive) =			

4. Activities and Function			**Score**
	Over the **past month** would you describe your activity level as:	☐ Normal, no limitations ☐ Somewhat limited ☐ Little activity	
	If **somewhat limited** would you describe it as:	☐ Not my normal self, but able to be up and about with fairly normal activities for **more than half** the day	= 1 = 2

		☐ Or not feeling up to most things, but in bed or sit in a chair for **less than h**alf the day	
	If **little activity C** would you describe it as:	☐ Pretty much bedridden, rarely out of bed, or do you do little activity and spend **most of the day** in bed or sitting in a chair	= 3
Use highest score only =			
5. Diagnoses and Disease			
5a.	Do you have any of the following medical conditions:	☐ Cancer ☐ AIDS ☐ Presence of pressure (decubitus) ulcer, open wound, or fistula ☐ Pulmonary or cardiac cachexia ☐ Presence of trauma	= 1 = 1 = 1 = 1 = 1 = 1
5b.	Are you greater than 65	☐ **Yes** ☐ **No**	= 1 = 0
Additive score =			
6. Metabolic Demand			
6a.	**Do you currently have a fever?**	☐ **A**. No ☐ **B**. Yes	= 0 = 1
	If yes, what is your temperature	☐ > 37.2 but < 38.2 ☐ ≥ 38.2 but < 38.9 ☐ ≥ 38.9	= 1 = 2 = 3
	If yes, how long have you had the fever for?	☐ < 72 hours ☐ 72 hours ☐ > 72 hours	= 1 = 2 = 3

<table>
<tr>
<td>6b.</td>
<td>Are you currently taking steroids?
<table>
<tr><th colspan="2">Steroid Equivalents</th></tr>
<tr><td>No steroids</td><td>No Steroid medications</td></tr>
<tr><td>Low Dose Steroids
10mg Prednisone equivalents</td><td>10mg Prednisolone
50mg Cortisone
40mg hydrocortisone
8mg methylprednisolone
1.5mg dexamethasone</td></tr>
<tr><td>Moderate Dose Steroids
20mg Prednisone equivalents</td><td>20mg Prednisolone
100mg Cortisone
80mg hydrocortisone
16mg methylprednisolone
3mg dexamethasone</td></tr>
<tr><td>High Dose Steroids
30mg Prednisone equivalents</td><td>30mg Prednisolone
150mg Cortisone
120mg hydrocortisone
24mg methylprednisolone
4.5mg dexamethasone</td></tr>
</table>
</td>
<td>☐ no steroids
☐ low dose (< 10mg prednisone equivalents/day)
☐ moderate dose (> 10mg & ≤ 30mg prednisone equivalents/day)
☐ high dose (> 30mg prednisone equivalents/day)

Add scores</td>
<td>= 0
= 1
= 2
= 3</td>
</tr>
</table>

Physical Examination

Assess each parameter and determine deficit ratings for muscle, fat and fluid (not additive).

Determine overall deficit rating using the following weighting: muscle status group > fat stores group > fluid status group

Deficit ratings for body stores		**Nil**	**Mild**	**Moderate**	**Severe**
Muscle status	Temples (temporalis muscle)	0	1+	2+	3+
	Clavicles (pectoralis & deltoids)	0	1+	2+	3+
	Shoulders (deltoids)	0	1+	2+	3+
	Interosseous muscles	0	1+	2+	3+
	Scapula (latissimus dorsi, trapezius, deltoids)	0	1+	2+	3+
	Thigh (quadriceps)	0	1+	2+	3+
	Calf (gastrocnemius)	0	1+	2+	3+
	Overall muscle stores rating	**0**	**1+**	**2+**	**3+**
Fat stores	Orbital fat pads	0	1+	2+	3+
	Triceps skin fold	0	1+	2+	3+
	Fat overlying lower ribs	0	1+	2+	3+
	Overall fat stores rating	**0**	**1+**	**2+**	**3+**
Fluid stores	Ankle oedema	0	1+	2+	3+
	Sacral oedema	0	1+	2+	3+
	Ascites	0	1+	2+	3+
	Overall fluid status rating	**0**	**1+**	**2+**	**3+**
Total degree of deficit rating (circle)		**0**	**1+**	**2+**	**3+**

Global assessment of nutritional status

Category	**Stage A** **Well Nourished**	**Stage B** **Moderately malnourished or Suspected malnutrition**	**Stage C** **Severely malnourished**
Weight	No recent weight loss or Recent non-fluid wt gain	~5% wt loss within 1 month (or 10% in 6 months. No weight stabilisation or wt gain	>5% wt loss within 1 month (or >10% in 6 months). No weight stabilisation or wt gain
Nutrient Intake	No deficit or sig. recent improvement	Definite decrease in intake	Severe deficit in intake
Nutrition Impact Symptoms	None or Sig. recent improvement allowing adequate intake	Presence of nutrition impact symptoms (Box 3 of PG-SGA)	Presence of nutrition impact symptoms (Box 3 of PG-SGA)
Functioning	No deficit or sig. recent improvement	Moderate functional deficit or recent deterioration	Severe functional deficit or recent significant deterioration
Physical Exam	No deficit or chronic deficit but with recent clinical improvement	Evidence of mild to moderate loss of SQ fat &/or muscle mass &/or muscle tone on palpation	Obvious signs of malnutrition (eg. Severe loss of SQ tissues, possible oedema)
Predominant global score	☐	☐	☐

Sum of box 1- 4 = _____+ Box 5 _____ + Box 6 _____ + Box 7 _____ =

Reference: Ottery F. Patient-Generated Subjective Global Assessment. . In: Polisena M, editor. The Clinical Guide to Oncology. Chicargo: American Dietetic Association; 2000. p. 12.

Grip Strength (Week 0,4,8)

	Left 1	Left 2	Left 3	Left average	Right 1	Right 2	Right 3	R average
Week 0								
Week 4								
Week 8								

FRQoL-29 (Week 0,8)

FOOD-RELATED QUALITY OF LIFE (FR-QoL-29)

KING'S College LONDON

In the past **TWO WEEKS**

	Tick which box is applicable	Score
I have regretted eating and drinking things which have made my IBD symptoms worse	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
My enjoyment of a particular food or drink has been affected by the knowledge that it might trigger my IBD symptoms	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
My IBD has meant that I have had to leave the table while I am eating to go to the toilet	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
I have not been able to predict how long it will take for my body to respond to something I have had to eat or drink due to my IBD	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
Certain foods have triggered symptoms of my IBD	☐ Strongly agree	= 1

	☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 2 = 3 = 4 = 5
My IBD has meant that I have been nervous that if I eat something I will need to go to the toilet straight away	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
I have avoided having certain food and drink I know does not agree with my IBD	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
I have felt relaxed about what I can eat and drink despite my IBD	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 5 = 4 = 3 = 2 = 1

I have felt in control of what I eat and drink despite my IBD	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 5 = 4 = 3 = 2 = 1
I struggled to eat the way that is best for my IBD because of other commitments during the day	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree	= 1 = 2 = 3

	☐ Disagree ☐ Strongly disagree	= 4 = 5
I have been frustrated about not knowing how food and drink will react with my IBD	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
I have had to concentrate on what I have been eating and drinking because of my IBD	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
I have been worried that if I eat I will get symptoms of my IBD	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
I have felt the way that I eat and drink for my IBD has affected my day to day life	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
The way I have had to eat for my IBD has restricted my lifestyle	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
I have had to concentrate on what food I buy because of my IBD	☐ Strongly agree	= 1

	☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 2 = 3 = 4 = 5
It has been on my mind how my IBD will be affected by what I eat and drink	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5

My IBD has prevented me from getting full pleasure from the food and drink I have had	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
I have felt that I need to know what is in the food I am eating due to my IBD	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
I have felt that I have had to be careful about when I have eaten because of my IBD	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
I have had to be more aware of what I am eating due to my IBD	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree	= 1 = 2 = 3

	☐ Disagree ☐ Strongly disagree	= 4 = 5
I have missed being able to eat or drink whatever I want because of my IBD	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
I have felt that I would like to be able to eat and drink like everyone else	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
I have been happy to eat and drink around people I do not know despite my IBD	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 5 = 4 = 3 = 2 = 1
I have felt that I have been eating and drinking normally despite my IBD	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 5 = 4 = 3 = 2 = 1
I have found it hard not knowing if a certain food will trigger my IBD symptoms	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
My IBD has meant I have had to make an effort to get all the nutrients my body needs	☐ Strongly agree	= 1

	☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 2 = 3 = 4 = 5
I have felt that I have not known how my IBD will react to food or drink	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5
My IBD has meant that I have had to work hard to fit my eating habits in around my activities during the day	☐ Strongly agree ☐ Agree ☐ Neither agree nor disagree ☐ Disagree ☐ Strongly disagree	= 1 = 2 = 3 = 4 = 5

Questions 8,9,24,25 have had their scores reveresed for scoring.

Reference: Hughes LD, King L, Morgan M, Ayis S, Direkze N, Lomer MC, et al. Food-related Quality of Life in Inflammatory Bowel Disease: Development and Validation of a Questionnaire. J Crohns Colitis. 2016 Feb;10(2):194-201. DOI: 10.1093/ecco-jcc/jjv192.

Clinical review (Week 4,8)

Recent illness			
Recent antibiotic use			
Any change in medications			
Are you currently	Taking laxatives	□ Yes	□ No
	Taking antidiarrheal	□Yes	□ No
	Taking probiotic	□ Yes	□ No
Hospitalisations			
Other			

4-SURE Diet Tolerability scales (Week 4, 8)

Please score your opinion of the 4-SURE diet by drawing a vertical line where you rate your opinion

1. How do you rate your knowledge of how to follow the 4-SURE diet?

Measured Score: (mm)

2. How do you rate the ease of purchasing food items for the 4-SURE diet?

Measured Score: (mm)

3. How would you rate the ease of preparing meals for the 4-SURE diet?

Measured Score: (mm)

4. How would you rate the overall ease of following the 4-SURE diet?

Measured Score: (mm)

5. How do you rate the overall tolerability of following the 4-SURE diet?

Measured Score: (mm)

Note: VAS (100mm scale), participant to mark on line then measure line with ruler to calculate score 0-100.

4-SURE Dietary adherence checklist (Weeks 2-8)

Week ending (date):

Circle the number of days in the past week you consumed the following amounts of foods

4-SURE Food item	Number of days in the week
Minimum of x 1 Banana with green tinge to skin	0 1 2 3 4 5 6 7
Minimum of 1 cup Legumes / beans	0 1 2 3 4 5 6 7
Minimum ½ – 1 cup Potato (cooked, reheated)	0 1 2 3 4 5 6 7
Minimum 3 serves of recommended high RS wholegrains Such as hi fibre bread, couscous, barley, millet	0 1 2 3 4 5 6 7
Minimum of 1 tspn Psyllium husk	0 1 2 3 4 5 6 7
Minimum of 1 tbs Barley Flakes	0 1 2 3 4 5 6 7
150g or less of unprocessed meat / fish / chicken / pork / eggs (free from nitrates, preservatives)	0 1 2 3 4 5 6 7

Did you consume any foods containing the following:

Food additive	Yes / No	If yes, how many days did you consume these food additives
Sulphate / sulphite		0 1 2 3 4 5 6 7
Carrageenan		0 1 2 3 4 5 6 7
Nitrates / nitrites		0 1 2 3 4 5 6 7

Appendix 2.5 Example weighed food diary

Name _____Eg *John Smith*_____

Date ___*4*___/_____*8*___/_____*09*__ **Day of week** ____*Tuesday*____

Description of food/drink	**Weight served (g)**	**Leftovers (g)**	**Amount eaten (g)**
Nippy's Unsweetened Orange Juice (Pulp-free)	*200*	*0*	*200*
Sanitarium Weet-Bix (Original)	*30*	*0*	*30*
Pura Light Start Milk	*150*	*0*	*150*
Granny Smith Apple, unpeeled	*180*	*50*	*130*
Meatballs in pasta sauce (for spaghetti) – see recipe	*80*	*0*	*80*
San Remo Spaghetti, regular (cooked)	*120*	*0*	*120*
Helgas Soy & Linseed Bread	*85*	*0*	*85*
Tetley English Breakfast (1 tea bag) + water	*120*	*0*	*120*
Pura Light Start Milk (in tea)	*30*	*0*	*30*
Sugar, White	*1 tsp*	*0*	*1 tsp*
Caffe Latte (Cibo), 1 regular	*~250*	*0*	*~250*

Recipe name: *Meatballs in pasta sauce*	**Number of serves:** *4*
Ingredients	**Amount**
Dolmio Smooth Bolognaise Sauce, Classic Tomato	*1 jar, 550g*
Woolworths Heart Smart Minced Beef (makes 16 meatballs)	*450g*
Mushrooms	*48g*
Brown Onion	*168g*
Canola Oil	*2 tsp*

Method of preparation:

Brown meatballs and onion with canola oil till cooked through.

Add mushrooms and simmer in Dolmio pasta sauce.