EFFECTS OF EXTRA VIRGIN OLIVE OIL ON ULCERATIVE COLITIS

Kenneth Daniel

Sydney School of Health Sciences

Faculty of Medicine and Health

The University of Sydney

8th August 2025

A thesis submitted to the Faculty of Medicine and Health at the University of Sydney to fulfil the requirements of the degree Doctor of Philosophy

ACKNOWLEDGEMENT OF COUNTRY

I would like to begin by acknowledging the traditional custodians of the lands on which this manuscript and activities relating to its creation was conducted, the lands of the Gadigal people of the Eora nation and the Dharug people of the Eora nation.

I pay my respects to the people, the culture, and the Elders past and present, and extend my gratitude for their custodianship on the place I now call home. Sovereignty has never been ceded. It always was and always will be, Aboriginal land.

ABSTRACT

Inflammatory bowel disease (IBD) is a chronic, lifelong, and complex condition that affects approximately 6.8 million people worldwide. Its global prevalence is rising, with Australia ranking among the countries with the highest incidence rates. It comprises of several conditions characterised by inflammation of the gastrointestinal tract. Ulcerative Colitis is one of the most common manifestations and presents in the form of inflammation along the colonic mucosa beginning in the rectum and spreading proximally. Symptoms include both gastrointestinal dysfunction and extraintestinal manifestations which can occur in a relapsing remitting fashion. Comorbidities is high in this population, and medications can have severe side effects. As such, there is significant interest in exploring complementary approaches to treatment which are safe and effective.

Evidence points towards the potential of diet influencing disease outcomes, either through impacting risk of developing IBD or for management of the condition. The Mediterranean diet has been identified as one approach which is associated with a range of positive health outcomes in chronic conditions including IBD. Unfortunately, several attributes of the diet such as high fibre intakes may be challenging to adopt due to concerns relating to food tolerance and IBD complications. Separately, the contribution of individual components of the diet towards overall health outcomes remains unclear due to limited evidence. As such, the aim of this thesis was to address the gap in the evidence and examine the effects of a single food dietary intervention on IBD with a focus on ulcerative colitis (UC). To address this aim, we utilised a broad range of evidence-based approaches and scientific methodologies throughout the six chapters of this thesis, including a study protocol, cross-sectional study, systematic literature review, and randomised controlled trial.

Overall, the broad range of outcomes examined in this thesis highlights several gaps in the evidence on dietary approaches in IBD, with few human trials. Furthermore, we identified a significant level of impairment and lack of support in individuals living with IBD highlighting unmet needs for comprehensive, evidence-based support strategies. Through this manuscript, we hope to build the case for robustly designed studies examining dietary composition and its broader impact towards health outcomes, as well as broader changes to behaviour and eating pattern.

STUDENT DECLARATION

This is to certify that the content of this thesis is my own work. This thesis has not been submitted for any other degree or purpose.

I certify that the intellectual content of this thesis is the product of my own work, and that all assistance received in preparing this thesis and all sources have been acknowledged.

Kenneth Daniel

08 August 2025

SUPERVISOR'S STATEMENT

This is to certify that the thesis titled **Effects of Extra Virgin Olive Oil on Ulcerative Colitis** submitted by Kenneth Daniel in fulfilment of the requirements for the degree of Doctor of Philosophy is in a form ready for examination.

Professor Maria Fiatarone Singh

Faculty of Medicine and Health

The University of Sydney

08 August 2025

Acknowledgements

I have been privileged to be supported by many friends, family, colleagues, mentors, and loved ones. I am and will be eternally grateful for your compassion, selfless love and encouragement throughout my journey. You have all contributed to what I am and where I am today.

First and foremost, I give thanks to God for His mercy and enduring love. My great teacher and counsel, my rock and salvation. Your teachings inspire me to be a better person daily.

To my primary supervisor, Professor Maria Fiatarone Singh; it is an extraordinary privilege to be under the mentorship of such an inspiring woman. Your fierce dedication to your craft paired with your remarkable empathy and genuine care for others is something that will continue to inspire me throughout my career. You have not only exemplified what it means to be an accomplished scholar but also demonstrated what it truly means to be a compassionate leader. I am deeply grateful for the invaluable lessons, encouragement, and support you have provided, which continue to guide and inspire me both professionally and personally.

To my associate supervisor, Professor Luis Vitteta; I will never forget the kindness you've extended to us during our first meeting. Your passion and excitement for research was a truly amazing thing to witness. And despite the challenges we faced throughout these projects, you've continued to be a great source of positivity, and for that I am deeply grateful.

To my late associate supervisor, Vale Professor Hellen O'Connor; I wish I had more time to spend with you during this journey. I will never forget your humour in one of the lectures you taught us during my master's degree, or your mentorship when I first taught for one of your classes. In our short interaction you have taught me what it truly means to be a teacher, and a leader with an enduring legacy.

To my senior colleague, Dr Daniel Hackett; your work has been instrumental in the development of all these studies on inflammatory bowel disease. Despite the challenges we faced as an investigating team, I am glad to say that we pulled through.

To Associate Professor Janelle Gifford; I am truly blessed to have gotten to know you. Although we don't have a formal mentoring relationship, I will never forget the many opportunities that you have given me and for taking me under your wing. Your belief in me is what has led me to excel beyond my means. You are an amazing teacher, mentor, friend, and for that I am forever grateful.

To the MFS team past and present, Guy, Yareni, Isabel, Ewan, Yorgi, Skip, Nidhi, Matt, and many others; I am humbled to be in the company of such brilliant minds. The collegiality that you all have extended will forever be in my mind. Thank you all for your encouragements through the highs and lows of this academic journey, and the laughs along the way.

To my church family, past and present. Hey guys I'm finally done! For now…. Thank you all for the company, the laughs, the encouragement. I am grateful to be sharing this journey with all of you and to be surrounded by such good company.

To Stef, John, Jordan and Noah; thank you for making my life more colourful. The joy that you give me is immeasurable, and I am privileged to call you all family.

To mom and dad, Ongkie and Jennie; thank you for affording me this life that I have. And I am sorry for the times that I fell short of your expectations. Although neither of you may fully understand the things that I do or have been doing in the past several years, I know that you are

fully supportive and proud of me anyway. My works are and will always continue to be the fruits of your sacrifice and love.

To mami Lisye; thank you for your love and care over my family. And thank you for accepting me as one of your own. I am blessed to be able to call you family.

To my amazing wife, Intan. I dedicate this work to you. Thank you for always being there for me and putting up with my mistakes and difficult moments. Your love and support throughout this journey are truly what made this all possible. Thank you for believing in me and the future that we have together. Now that we've closed one chapter of our lives, I look forward to starting the next one with you. I love you.

To everyone who has either participated or expressed interest in the XIBD, COLONiC, and PREBIOTIC studies, thank you. I am in awe of the amazing things that you all do in spite of everything. It is my firm belief that one day in this lifetime we will find breakthroughs for the treatment of Inflammatory Bowel Disease, and it will be all because of the dedication, perseverance, and compassion of amazing human beings just like yourselves.

I'd like to thank Jacqui Plozza and Cobram Estate Pty Ltd. for supplying the Extra Virgin Olive Oil used in the COLONiC randomised controlled trial (Chapter 5).

This research was supported by an Australian Government Research Training Program (RTP) Scholarship.

AUTHORSHIP ATTRIBUTION STATEMENT

Chapter 4 of this thesis has been published as **"Effects of olives and their constituents on the expression of ulcerative colitis: a systematic review of randomised controlled trials".**

I designed the study, conducted and managed the study data, and was responsible for critical appraisal of the content and drafting the manuscript. I am the corresponding author for the published material.

Kenneth Daniel, 04 March 2025

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Professor Maria Fiatarone A Singh, 04 March 2025

PUBLICATIONS

Chapter 4 of this thesis has been published as:

Daniel, K., Vitetta, L., & Fiatarone Singh, M. A. (2022). Effects of olives and their constituents on the expression of ulcerative colitis: a systematic review of randomised controlled trials. The British journal of nutrition, 127(8), 1153-l I 71. https://doi.org/ I 0.1017/S0007 I1452l001999

A copy of this manuscript can be found in Appendix 7. As the first author of this manuscript, 1 was responsible for the study design, data collection and data extraction, drafting and editing of the final manuscript with contributions from my co-authors.

Kenneth Daniel,

28 February 2025

LIST OF ABBREVIATIONS

1RM	-	1 repetition maximum
12D/12N	-	12-hour daylight and 12-hour night cycles
16S rRNA	-	16S ribosomal RNA
AIN	-	American Institute of Nutrition
ALM	-	appendicular lean mass
ASM	-	appendicular skeletal mass
ASMI	-	appendicular skeletal mass index
BMC	-	bone mineral content
BMD	-	bone mineral density
CD	-	Crohn's disease
CDAI	-	Crohn's disease activity index
CRP	-	C-reactive protein
DAI	-	Disease Activity Index
DXA	-	Dual x-ray absorptiometry
DSS	-	Dextran sulfate sodium
ECG	-	electrocardiogram
ECCO	-	European Crohn's and Colitis Organisation
ES	-	effect size

kEDTA	-	potassium ethylenediaminetetraacetic acid
EVOO	-	extra virgin olive oil
Hty-Ac	-	Hydroxytyrosol acetate
IBD	-	inflammatory bowel disease
IC	-	indeterminate colitis
IL1	-	interleukin 1
IL6	-	interleukin 6
IL10	-	interleukin 10
IL12	-	interleukin 12
LOO	-	light olive oil
LPS	-	lipopolysaccharide
MCID	-	minimal clinically important difference
NaCl	-	Sodium chloride
NS	-	not significant
NR	-	not reported
OO	-	olive oil
OOC	-	out of calibration
PAL	-	physical activity level
PCOS	-	polycystic ovarian syndrome
PRN	-	pro re nata, “as needed”

QoL	-	quality of life
RCT	-	randomised controlled trial
RPE	-	rate of perceived exertion
RPM	-	rotations per minute
rRNA	-	ribosomal ribonucleic acid
SD	-	standard deviation
SEM	-	standard error of the mean
SM	-	skeletal mass
TNBS	-	2,4,6-trinitrobenzene sulfonic acid.
TNF-α	-	tumour necrosis factor
UC	-	ulcerative colitis

TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION

1.1. Inflammatory Bowel Disease History and Classification

Inflammatory Bowel Disease (IBD) refers to a group of complex, chronic conditions characterised by inflammation along the gastrointestinal tract, with symptoms occurring in a remitting and relapsing manner. Although exact dates are unclear, the earliest reports of the condition likely date back to medieval Greece with descriptions of "violent ulcerations" and "uncontrolled diarrhoea" in the Plague of Athens between 431-404 BC. [1-3] The term ulcerative colitis (UC) was first reported in 1859; [4] however, it wasn't until 1909 that the term became part of standard medical vocabulary following several published cases of non-infectious, severe and persistent diarrhoea. [5] Formal descriptions of Crohn's disease (CD) would soon follow, with the first published case reported in 1913 in the British Medical Journal. [6]

Since its first description, significant advances have been made in understanding IBD, it's causes, and treatment strategies to manage the condition. Currently, much of IBD classification is unchanged. ulcerative colitis and Crohn's disease remain the primary classification of IBD, despite the broad spectrum of disease presentation described in the literature. [7] Ulcerative colitis is broadly characterised by chronic inflammation along the colonic mucosa, mainly affecting the rectum and variably extending to other parts of the colon in a progressive fashion. [8] By contrast, CD may occur throughout the length and thickness of the gastrointestinal tract in a discontinuous, patchy, and segmental manner, most commonly in the terminal ileum and proximal colon. [9] Overlapping pathologies occur in 10-15% of IBD cases and are referred to as indeterminate colitis (IC), a term at times used interchangeably with inflammatory bowel disease unclassified (IBDU), with a proportion of patients reclassified into either UC or CD following more definite diagnosis. [10-12]

Globally, an estimated 6.8 million cases of IBD were recorded in 2017, which was a significant increase from 3.7 million in 1990. [13] Australia ranks among one of the countries with the highest prevalence of IBD, with an estimated 179,420 cases reported in 2025, resulting in a combined cost of $7.8 billion AUD to the economy.[14] Greater prevalence has previously been described in Caucasian and Jewish cohorts, however an increasing number of cases reported in Black, Asian and Hispanic populations have been reported globally. [15, 16] Disease onset may occur at any stage of life, however epidemiological data suggests IBD is predominantly diagnosed in individuals under the age of 40, whilst 10-15% of cases are identified after the age of 60. [17-19]

Evidence suggests deregulation of host immunity in genetically susceptible individuals combined with environmental and lifestyle factors is a major contributor to IBD pathogenesis. Family history is the primary risk factor for developing IBD, with up to 28% of patients reporting a first degree relative with either UC or CD. [20-22]. Early research resulted in the identification of genes such as NOD2, which is associated with increased susceptibility to developing CD, [23-25] however results were less conclusive in UC. With the development of genome-wide association studies (GWAS), there have been advancements in the identification of IBD-specific loci both for CD and UC. To date, 163 IBD-specific genes have been identified through GWAS, with some overlap between UC and CD. [26] More than 29 genes/loci associated with increased susceptibility to UC have been identified. [27-29] However, research is ongoing to determine how these genes may vary between populations. [30]

Beyond genetics and family history, an increasing body of evidence suggests the impact of environmental and lifestyle factors on the development and progression of IBD. Studies on

migrant families from countries with a lower prevalence of IBD have shown comparable risk of developing the condition, similar to populations of the destination country. [31-33] Observations of higher IBD prevalence in "developed" nations have led to the association among several environmental exposures, lifestyle factors and risk of developing IBD, including air pollutants,[34] smoking,[35, 36] antibiotics,[36-38] pathogens,[36, 39] consumption of "ultra processed foods" (NOVA classification 4),[40, 41] and history of appendectomy.[42-44] It should be noted that despite the growing body of evidence, the literature is highly heterogeneous and there remain inherent challenges in isolating specific environmental and lifestyle triggers for IBD.[45]

1.2. Inflammatory Bowel Disease Symptoms and Comorbidities

Gastrointestinal symptoms including abdominal pain, diarrhoea, constipation, urgency and rectal bleeding are common features in IBD, [46] with some variability between individuals. Disruption relating to the large intestine such as diarrhoea, anaemia, and rectal bleeding appear to be more common in UC, while bowel thickening, bowel pain, and mouth ulcers are more commonly associated with CD. [7] Presentation in IC may share similar features to both UC and CD, with overlapping symptoms. [47, 48] Occurrence of these symptoms tend to occur in a relapsing-remitting fashion, with alternating periods of active disease (flares) and remission, which complicates long-term disease management and significantly impacts quality of life. [49] Furthermore, even during remission, persistent symptoms and discomfort are frequently reported, [50-52] leading to ongoing impairments in daily functioning and wellbeing.

Digestive issues related to IBD symptoms can lead to reduced oral intakes and malnutrition, leading to further decline or complications. Prevalence of malnutrition in IBD ranges between 16-85% depending on disease severity, [53-57] while unintended weight loss, [58-60] iron deficiency

anaemia, [61-64] reduced bone mineral density (BMD), [65-68] and sarcopenia [69-72] are frequently reported. Likewise, fatigue is highly prevalent in IBD with up to 76% of patients reporting it as a comorbidity, [73-77] and sleep impairments have been reported in 50% of patients. [78-82].

Beyond the gut, IBD is associated with a range of chronic conditions. Increased risk of non-alcoholic fatty liver disease (NAFLD), [83] diabetes, [84-86] cardiovascular disease, [87-90] arthritis, [86, 91-93] skin lesions, [94-96] asthma, [97, 98] and allergies [99, 100] have been described in literature, likely as a consequence of systemic inflammation and disease complications. This significant level of burden in combination with the uncertainty of managing the condition likely contributes towards the high rates of psychological impairments such as depression and anxiety reported in this cohort, [49, 101-104] thus highlighting the need for comprehensive, multimodal support strategies.

1.3. Treatment and Medication

Inflammatory Bowel Disease frequently requires long-term medical therapy. Treatment goals are to induce and maintain remission, manage active symptoms, and prevent disease progression, as well as prevent and treat complications. [105] A range of therapeutic approaches are available to achieve this goal, and treatment strategies may evolve following initial diagnosis depending on disease distribution, progression, severity, the presence/absence of complications, medical response and tolerance.

Medication in IBD can largely be classified into five categories: aminosalicylates (e.g., mesalazine, sulfasalazine, 4-aminosalicylic acid), corticosteroids (e.g., prednisone,

budesonide, hydrocortisone), immunomodulators (e.g., azathioprine, 6-mercaptopurine, cyclosporine, methotrexate), biologics and biosimilars (e.g., adalimulab, infliximab, golimulab), and janus kinase (JAK) inhibitors (tofacitinib), [105] which may be prescribed individually or as combination therapy. Traditionally, medical therapy follows a stepwise approach, with aminosalicylates generally prescribed for mild-to-moderate disease or for maintenance therapy rather than more advanced therapies such as immunomodulators and biologics. However, recent studies indicate early initiation of advanced and combination therapies may modify disease progression and thus improve long-term patient outcomes. [106] Medication regimens and administration pathways vary, and may include oral medications, intravenous applications, enemas or suppositories. Antibiotics, antidiarrhoeals, prebiotics, probiotics, postbiotics and synbiotics may also be incorporated as part of ongoing therapy. [107] Considering the wide range of options and treatment modalities, and the need to manage both IBD and associated comorbidities, it is therefore unsurprising that polypharmacy has been described in 18-50% of IBD patients. [108-110]

Despite the success of pharmacological approaches, there are several barriers which may preclude patients from achieving their treatment goals. Non-response to medical therapy has been reported in 10-40% of patients living with IBD, [111] while up to 50% of patients report a loss of response after the first 12 months of treatment, [112] requiring more advanced therapies. Similarly, loss of tolerance to ongoing medical therapy has been observed in 30% of patients resulting in voluntary discontinuation. [113-115]

Medication side effects vary depending on treatment type and duration and may range from mild symptoms to more severe complications. Although usually associated with more

advanced therapies, side effects have been described in all IBD medications. [116-118] These include gastrointestinal symptoms such as diarrhoea, abdominal pain, nausea, and vomiting, [119] opportunistic infections, [120, 121] respiratory issues such as pneumonitis and dyspnoea, [122, 123], dermatological complications including psoriasis and skin lesions, [124, 125] haematological complications such as low white blood cell counts and anaemia, [125] nutritional deficiencies, [126, 127] low bone mineral density, [128] renal complications, [129] toxic hepatitis, [130] and pancreatitis. [131]

Concerns around developing these complications may contribute to the high rates of non-adherence in IBD, with observational studies reporting up to 72% of patients were not following prescribed therapy. [132-135] Voluntary non-adherence to treatment which includes deliberate changes to medication dosage and skipping medications ranges from 7-35%, [136-138] while involuntary non-adherence (physician-prescribed withdrawal of medications) ranges from 32-81%. [137-139] Beyond concerns relating to medication side effects, inconvenience relating to multiple medications or multiple daily doses, time restrictions, the need for medication during quiescent disease, forgetfulness, cost, access to medication, and/or psychological distress are commonly cited barriers. [134, 139-141] Unfortunately, regardless of the reason, medication non-adherence is associated with worsening health outcomes in IBD. Findings from a retrospective study in the United Kingdom found patients with UC foregoing maintenance therapy were at an increased risk of colorectal cancer compared to their adherent peers ($p < 0.001$). [142] Medication non-adherence is also associated with an increased risk of relapse, increased disease severity, increased risk of complications, and IBD-associated disability, ultimately resulting in a greater need for hospitalisation and surgery. [143-146]

Surgical measures for IBD are usually considered following non-response to medical therapy, particularly in severe disease, substantial damage to the gastrointestinal tract, or the presence of complications such as toxic megacolon, perforation, excessive bleeding, abdominal abscesses, bowel obstruction, or cancers. [147, 148] Although removal of the gastrointestinal tract affected by IBD may improve outcomes (or in the case of UC, sometimes viewed as a "curative" option), surgery does not address the underlying impairments to the immune system or non-gastrointestinal pathology in IBD, and post-surgical complications are common. [148-150] A retrospective cohort of 140,540 IBD patients estimated 10-30% of patients with UC and 50-80% of patients with CD require surgery over their lifetime.[151] Surgery rates are declining with the development of new therapies, [152] however concerns related to undergoing surgery consistently rate amongst the top issues for patients living with IBD.[153-155]

1.4. Diet as a Therapy for IBD

Alongside medical therapy, best practice recommendations highlight the need to incorporate adjunctive support strategies through multidisciplinary care teams to address the various comorbidities associated with IBD. Within an Australian context, care teams may be comprised of a combination of dietetics, psychological support services, IBD nurse specialists and other specialists with an interest in gastroenterology.[156] Despite gradual improvements in the current healthcare system, variable access to such services has been demonstrated in past benchmarking activities with insufficient funding and staffing, and few public hospitals having dedicated IBD services staffed by multidisciplinary teams. [157, 158]

Similarly, attitudes towards supportive strategies may present barriers to accessing care. Diet has historically been largely ignored in IBD management, with differing opinions of its value

between specialists and patients with IBD, [159] potentially attributable to significant heterogeneity in the evidence at the time. However, in the past decade an increasing body of evidence highlights the importance of integrating diet therapy into existing models of care for the management of IBD and optimisation of patient outcomes. Strategies may include malnutrition screening, exclusive enteral nutrition (EEN) as induction therapy in paediatric CD patients, diets which replicate EEN, elimination diets for the management of gastrointestinal symptoms, prevention of strictures, pre-surgical and post-surgery nutrition, supplements and the management of disordered eating prevalent in this cohort.[160-162] Access to dietitians experienced with IBD management is critical, considering the complexities associated with IBD and the need to individualise diet therapy. However, few public health IBD services have access to a dietitian[157] and referral rates for IBD management are often low.[158]

Despite the lack of access to evidence based and experienced clinicians, individuals living with IBD will often incorporate dietary modifications as part of broader adoption of non-pharmacological approaches to support their health and wellbeing. Cross sectional studies indicate that more than 60% of patients believe that diet plays an important role in the course of their illness, [163-166] and more than 50% report modifying their diet since initial diagnosis to manage symptoms. [164, 167] Strategies may include adherence to specialised diets, consumption of herbal and/or botanical dietary supplements, vitamins, mineral, and probiotics. [168, 169] Unfortunately, the substantial interest in dietary interventions and variability of strategies adopted significantly outweighs the ability of researchers and clinicians to establish evidence-based recommendations, in part due to challenges associated with recruiting participants, cost associated with performing clinical trials, and difficulty in isolating specific environmental or lifestyle elements. [45, 170, 171]

Epidemiological data and observational studies provide some insights on the relationship between diet and IBD, particularly for major food groups. Higher prevalence of IBD in industrialised nations parallels changes to local dietary patterns towards a more "westernised diet", defined as an eating pattern with high intakes of red meat, saturated fat, and processed foods such as refined grains and sugar sweetened beverages, while being low in fibre-rich foods such as vegetables, fruits and wholegrains. [172] This observation isn't particularly unique to IBD, with "westernised diets" being implicated with the global rise of non-communicable diseases including obesity, cardiovascular disease, type 2 diabetes, and cancer. [173] Although the reason for this observation remains to be determined, it is plausible that the association between this dietary pattern and IBD may be influenced by its nutritional composition and its potential effects on gut health and inflammation. For example, high intakes of red meat are associated with elevated serum levels of high-sensitivity C-Reactive Protein (hs-CRP), [174-176] which is associated with inflammation in the gut and are elevated during active disease in IBD. Large prospective cohort studies have similarly reported increased risk of UC when comparing lower and higher quartiles of meat (53.1 ± 36.3 vs 154.8 ± 67.8 g/day) and red meat intake (19.9 ± 19.7 vs 68. 5 ± 44.5 g/day), however no clear association has been observed for CD.[177] Unfortunately, findings from both systematic literature reviews and meta-analysis suggest significant heterogeneity in published studies and low levels of certainty,[178, 179] warranting further investigations.

Positive associations have also been reported between high intakes of refined carbohydrate and IBD risk in meta-analyses. [180, 181] Disruptions to the gut barrier and intestinal permeability facilitated by high sugar intakes have been proposed as drivers for heightened inflammatory responses, [182, 183] with implications for a wide range of chronic conditions. [184] By contrast, consumption of high fibre foods such as wholegrains, fruits, and vegetables appears to be

protective. [185-187] Interestingly, findings from the European Prospective Investigation into Cancer and Nutrition – IBD study (EPIC-IBD) cohort indicated increased risk associated with high consumption of sugar and soft drinks were only significant in participants with lower vegetable intakes, [188] suggesting that interactions between nutrients rather than individual components could play a key role in predicting disease risk.

Therefore, it is also possible that the relationship observed between red meat consumption and IBD could in part be ascribed to its fat content and composition. Saturated fat has been shown to stimulate inflammatory gene expression through Toll-like receptor 4 (TLR4) signalling, while oleic acid appears to attenuate this response in cell cultures. [189] In humans, elevated hs-CRP has been previously reported with increased saturated fat intake, however it's impact on other inflammatory markers has been inconclusive. [190, 191] Systematic reviews have not consistently reported links between fatty acids and IBD risk factors, however, and the heterogeneity of studies investigating these relationships to date highlights the need for more robust studies in this space. [192, 193]

1.5. The Gut Microbiome and IBD

Many of the risk factors associated with foods and nutrients in IBD suggest a potential link to the gut microbiome as an explanatory factor in these relationships. Broadly defined as a collection of microorganisms native to a specific environment, the microbiome has been the focus of extensive research, particularly in its relationship with human health and disease. The human gastrointestinal tract is home to approximately 10^{14} microorganisms that form a symbiotic relationship with their host through co-evolution. [194-196] Primarily located on the mucosal surface, the gut microbiome contributes to a range of important functions.

Fermentation of dietary fibre facilitated by commensal bacteria in the gut (organisms benefiting from this close ecological relationship to their host) results in the production of short chain fatty acids such as butyrate, acetate, and propionate which are substrates for colonocytes and contribute to the maintenance of intestinal barrier function, regulation of mucosal immunity, inflammation, and oxidative stress. [197, 198] Collectively, the gut microbiome also plays a key role in maintaining host immunity by inhibiting growth of pathogenic strains through competition or bactericidal activity. [199]

Generally, a healthy gut microbiome is defined by a high bacterial diversity comprised of many different species, high microbial richness, a relatively stable composition of commensal organisms, and low abundance of pathogenic strains. The composition of the microbiome varies between individuals, with further alterations occurring in response to health, lifestyle and environmental factors, however its ability to maintain a relatively stable distribution over time is an important aspect of a healthy gut. [200] Consequently, disruptions in gut microbiome composition (dysbiosis) have been linked to a variety of chronic conditions, while modulating the gut microbiome has emerged as a promising therapeutic target for disease management and intervention.

Dysbiosis is associated with IBD, as evidenced by reduced bacterial diversity and richness compared to healthy controls, [201] and may be associated with altered host immunity. The reason for this difference is not clear, as perturbations to the microbiome could be attributed to both systemic inflammation inherent to IBD, and interventions such as medications and food and activity restrictions. Results from microbiome targeting therapies have varied, with probiotics such as VSL#3 showing promising outcomes in UC, with limited evidence for its use in CD.

[202] Likewise, the use of faecal microbial transplantation (FMT) in UC has shown promising results in clinical trials, however efficacy remains variable, and long-term data on its sustainability is limited. [203] Interestingly, a recent randomised controlled trial (RCT) reported superior clinical outcomes and sustained remission in patients receiving a combined FMT and anti-inflammatory diet intervention compared to FMT alone in patients with mild to moderate UC, [204] highlighting the need to consider diet in a range of IBD management strategies.

1.6. Diets in the Management of IBD

Several consensus statements have highlighted the need to consider dietary approaches in IBD management, and the need for more studies to better understand how food might interact with IBD. [205-208] Unfortunately, there is limited understanding of the underlying mechanisms for food-related sensitivities in IBD, as well as effective and safe nutrition interventions to manage these symptoms. In combination with the unpredictability of symptoms regardless of disease states, [209-211] high prevalence of comorbidities, [212-214] and variable response to therapy, [215-218] there are significant challenges associated with implementing comprehensive IBD-specific diet in this cohort. As such, current guidelines for the role of diet in IBD have generally taken a pragmatic approach due to insufficient evidence to recommend specific dietary changes. [127, 160, 219, 220].

By contrast, as highlighted in published literature, patients living with IBD tend to ascribe a high importance to the role of diet in managing their condition and continue to seek comprehensive guidelines to help improve or manage their condition. [163-166, 221] This unmet expectation is further complicated by low rates of referral for dietetic support in this cohort, [222, 223] and limited access to specialist services. [157, 224] Several studies also highlight a disconnect

between patient expectations and recommendations provided by their healthcare provider, which is likely related to gaps in the evidence. [221, 225] As such, patients are reliant on trial and error, anecdotal evidence, and alternative sources such as social media. [226, 227]

1.6.1. Enteral Nutrition Mimicking Diets

A broad range of diets have been proposed for the management of IBD. Some of these approaches are disease-specific to accommodate specific needs of patients with CD and UC, while other diets apply a broad approach for IBD management. For example, the use of enteral nutrition (EN) for the treatment of CD has been extensively studied in the past few decades resulting in the emergence of diets such as the Crohn's disease exclusion diet (CDED). The diet involves restriction for wheat, dairy, soy, processed foods and red meat with or without EN, and has resulted in remission rates above 80% for both children and adult patients with CD. [228-230] Further research has resulted in the development of diets designed to mimic exclusive enteral nutrition (EEN) using ordinary foods, such as CD-TREAT. [231] By comparison, the inclusion of EN as an adjunctive therapy in UC has been shown to only moderately improve albumin and prealbumin levels in severe flares [232] and acute severe ulcerative colitis (ASUC). [233, 234] An uncontrolled trial investigating the novel ulcerative colitis Exclusion Diet (UCED) reported potential benefits in a small sample of paediatric patients, however, research is limited. [235]

1.6.2. Elimination Diets

Elimination diets are frequently used for the management of functional gastrointestinal disorders, which share some symptomatic overlap with IBD. As such, several of these diets have been examined for the management of symptoms and to induce remission. The Low-

FODMAP diet which involves restriction of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) [236] is one commonly-adopted diet shown to be effective in managing irritable bowel syndrome (IBS)-like symptoms in both CD and UC. [237-239] The diet involves a 2-6 week elimination of low FODMAP foods followed by a reintroduction phase for 8-12 weeks where patients slowly introduce individual food items to assess for tolerance. [236] Due to considerable advice required during the elimination and reintroduction phases, dietitian-led support is vital to prevent nutritional deficiencies, optimise adherence and long-term sustainability. [240] Thus, although low FODMAP diets have been shown to be effective for the management of symptoms in IBD, [241] difficulty with clinical implementation, oversight, and adherence should be acknowledged.

Similar patterns can be observed with other elimination-style diets including the Specific Carbohydrate Diet™ (SCD™) which was conceptualised in the 1920s to manage coeliac disease. The SCD™ classifies foods into 'legal' (red meat, poultry, eggs, non-starchy vegetables, fruit) and illegal' categories (grain, legumes, tuberous vegetables, sugar, lactose, most packaged foods) aimed at selectively promoting the growth of commensal bacteria. [242] The proposed mechanisms of the diet lack consistency with established scientific principles, [243] and evidence for its use in IBD has largely come from uncontrolled studies [244-246] However, recent randomised controlled trials (RCTs) suggest some potential as an adjunctive therapy. [247, 248]

The Anti-inflammatory Diet for Inflammatory Bowel Disease (IBD-AID) is a derivative of the SCD™ which restricts most grains and cereals (except oats), milk, soft cheeses, refined sugar and processed foods while promoting fermented foods such as kimchi, sauerkraut, and yogurt

(probiotics) and fibre-rich options such as leafy vegetables and fruit (prebiotics). [249] Avoidance of trigger foods, particularly complex carbohydrates, may also contribute towards the adoption of more restrictive diets such as the carnivore diet or ketogenic diet. Longitudinal studies have reported an increased risk of flares in UC with higher red meat intake [250] and in CD with lower intakes of fibre [251], both of which are characteristics of these diets. While clinical trials remain limited beyond animal studies, [252-254] case reports suggest that a small number of IBD patients maintain remission and quality of life on these dietary approaches, warranting further investigation. [255]

1.6.3. Traditional Dietary Patterns

On the opposite end of the spectrum from the various elimination diets mentioned above, the Mediterranean diet, which emphasises extra virgin olive oil (EVOO), fibre-rich foods (whole grains, vegetables, fruits, legumes, nuts), and moderate consumption of fish, meat, and dairy, has gained interest for its potential to modulate the intestinal microbiome, alleviate functional gut disorders, and reduce inflammatory markers. [256, 257] Small RCTs have shown that the Mediterranean diet supports remission maintenance and improves faecal calprotectin, short-chain fatty acid production, and gut microbiome composition in UC [258], while promoting symptomatic relief and quality of life in CD. [248] Similar findings have also been reported in studies exploring the role of plant-base diets in IBD, [259-261] however to our knowledge no RCTs have been conducted in this space. Cross-sectional studies of patients with IBD have found low intakes of wholegrains, vegetables and fruit amongst individuals with both CD and UC [262, 263], suggesting that dietetic support may be necessary based on individual tolerance and preference. It is important to note that although all these diets have been trialled in IBD, heterogeneity of study design, small participant numbers and variable end points limit the generalisability of these findings, with robustly designed human trials needed. Therefore, the identification of

clear nutritional guidelines and effective therapeutic diets remains one of the top research priorities in IBD. [207, 208, 264, 265]

1.6.4. Limitations of Prescribed Diets

Adherence to dietary prescriptions can often be challenging due to complex diet regiments involving different phases, restriction of staple foods, requirement to buy specialised ingredients and associated costs involved, as well as extensive preparation requirements. [240, 266, 267] Further complicating this issue, variable response to dietary intervention in IBD likely mirrors loss of response to medical therapy, which is well-documented in IBD. [115, 268, 269] For example, a RCT evaluating a 6-week low FODMAP diet in 89 IBD patients reported greater efficacy in those with quiescent disease compared to those with mild-to-moderate disease states. [241] Nonresponse rates of 15-30% have been observed in RCTs examining the CDED in both paediatric and adult patients with CD. [228-230, 270] Although several variables might be considered, including duration of the intervention and individual factors, the determinants contributing to this variation remain unclear, and further investigations are warranted.

Likewise, there is an uncertainty about the effect of modifying components of a prescribed diet regimen, in addition to the variability of definitions used to described predefined diets in literature. [271] Modifications to existing diets introduce additional complexity in evaluating the effects of dietary interventions in IBD, considering few studies examine the role of specific nutrient composition on the efficacy of a diet. Given that individuals living with IBD who frequently modify dietary prescriptions based on tolerance, severity of symptoms, personal preferences, and beliefs, [272] it is critical to understand how these adaptations might influence overall diet quality.

1.7. A Case for Disease Specific Investigations

Differing disease presentation, treatment modalities, tolerance and approaches to the management of IBD have been described in existing literature, warranting a targeted approach to treatment. Nutritional strategies and priorities may vary between populations, such as the use of low fibre diets and EN in CD. [273, 274] Likewise, several differences in risk factors have been identified when examining the relationship between diet and risk of developing IBD, such as the association between red meat intake and UC which was not observed in CD. [177] Although the application of broad recommendations is reasonable considering the difficulties faced with dietary adherence in IBD, [272] unique responses between IBD classifications should be considered when determining efficacy.

Importantly, a substantial body of evidence on diet approaches in CD have been identified in this review, while targeted dietary strategies in UC appear to be less common. Dietary and other research has more often focused on CD rather than UC, perhaps due to perceptions of greater risk of clinical complications in CD relative to UC. However, evidence indicates comparable levels of burden between both CD and UC, highlighting the potential for unmet treatment needs in UC. [275] As such, this thesis argues for an exploration of a single IBD presentation (UC) which can then be expanded into other disease sub-types if warranted.

1.8. The Rationale for Extra Virgin Olive Oil

The initial proposal for this project was to consider a Mediterranean diet intervention in patients living with IBD, considering the growing evidence for its impact in improving health outcomes and attenuating inflammation in chronic conditions relevant to IBD. [276] Some of the protective

effects ascribed to the diet appear to be related to higher intakes of oleic acid due to consumption of extra virgin olive oil as part of habitual intake. [277, 278] Although composition will vary based on variety of olives and growing conditions, oleic acid forms 55-83% of the total fatty acid methyl esters found in extra virgin olive oil. [279] Higher intakes of oleic acid are likely to influence the proportion of omega-6 polyunsaturated fatty acids in the diet which is associated with the aetiology of UC, [280] while lower intakes of omega-6 polyunsaturated fatty acids long-term have been associated with reduced risk of UC. [281] Furthermore, olive oil polyphenols attenuate inflammatory response in intestinal cells, [282] which may partially explain the anti-inflammatory potential of the Mediterranean diet pattern.

Few studies have aimed to investigate the effects of dietary fat manipulation beyond comprehensive dietary prescriptions in IBD referred to earlier. Previous investigations cite significant barriers to adherence to the Mediterranean diet pattern, [262] therefore the use of a single component as part of the broader diet may present an opportunity to trial a simpler, single food intervention and evaluate its effects on health outcomes in UC. This simpler approach may allow for greater translation to practice, as well as help to define the underlying mechanism of some of the beneficial effects of the Mediterranean diet pattern in other conditions.

At the time of writing no rigorous human trials had examined the effects of extra virgin olive oil interventions on UC or CD. However, findings from animal models of IBD have been promising, as will be presented in the systematic review within this thesis. [283, 284] We proposed the investigation of this targeted dietary approach based on these pre-clinical data, but also due to the consideration that single food interventions offer greater flexibility compared to comprehensive dietary prescription, thus potentially improving adherence in clinical cohorts

with IBD. Therefore, the purpose of the RCT within this thesis was to investigate the effects of a single food intervention using extra virgin olive oil on the clinical presentation, diet, and quality of life of individuals living with UC. Based on the existing evidence, we hypothesised that an EVOO dietary intervention would improve the clinical presentation of UC.

1.9. Thesis Structure and Chapter Breakdown

To address these aims, the thesis is organised into six chapters, focusing on the effects of dietary fat manipulation using extra virgin olive oil as the primary intervention in ulcerative colitis:

Chapter 1: Introduction and Rationale

This chapter provides an overview of the thesis and outlines the rationale behind the study. It presents an overview of current evidence exploring dietary approaches in IBD and presents a rationale for a focused intervention particularly for UC. Within this chapter we highlight gaps in existing literature and some practical challenges faced in adopting dietary interventions in this cohort.

Chapter 2: Methodology of the Cross-Sectional Study and Randomised Controlled Trial

This chapter details the methods of two studies examined in this thesis. The first study is a cross-sectional study exploring the health status, lifestyle habits and perceptions of individuals with IBD with the aim of examining differences between individuals living with UC and CD. The second part of this chapter describes the protocol for a randomised controlled trial examining a novel dietary intervention using extra virgin olive oil in participants living with UC.

Chapter 3: Baseline Characteristics and Observations

This chapter presents findings from the cross-sectional study, describing characteristics of individuals living with UC and CD. The purpose of this chapter is to examine potential differences in health status, dietary choices, physical activity participation, quality of life, sleep quality, fatigue, and past experiences with dietary interventions between these two cohorts. The aim of this chapter is to evaluate differences and similarities experienced by individuals living with IBD which may be used to inform future support strategies in each population

Chapter 4: Systematic Review of Olive-Based Interventions in Ulcerative Colitis

This chapter is a systematic review of the literature published in the *British Journal of Nutrition* in 2021 entitled: "Effects of olives and their constituents on the expression of ulcerative colitis: a systematic review of randomised controlled trials" The aim of this manuscript was to summarise the current evidence on olive-based interventions in ulcerative colitis from randomised controlled trials.

Chapter 5: Pilot Randomised Controlled Trial

Due to recruitment challenges for the COLONIC study, this chapter presents results from a pilot RCT involving three participants with UC, two of whom completed the trial. The 4-week dietary intervention using extra virgin olive oil was evaluated for its effects on disease outcomes, dietary intake, food-related quality of life, health-related quality of life, fatigue, and sleep quality. This was then followed by a 4-week washout period where we examined residual effects after conclusion of the intervention.

Chapter 6: Summary and Discussion

This chapter summarises the key findings from all previous chapters. Within this chapter we discuss the practical implications of the studies in this manuscript, and future directions of single-ingredient dietary modifications for individuals living with IBD. In this chapter we also highlight some of the strengths and limitations of this manuscript and propose future research opportunities in this space.

The body of research within this thesis addresses some of the key research gaps in our understanding between the role of diet, particularly dietary composition, and its potential impact on health outcomes in ulcerative colitis. Furthermore, we provide a case for the further examinations of single food interventions as part of habitual diet to influence broader change to eating patterns.

1.10. References

1 Connor WR. *Thucydides*. Princeton University Press; 1984.

2 Lim ML, Wallace MR. Infectious diarrhea in history. *Infectious Disease Clinics of North America*. 2004;18(2):261-274.

3 Mulder DJ, Noble AJ, Justinich CJ, Duffin JM. A tale of two diseases: The history of inflammatory bowel disease. *Journal of Crohn's and Colitis*. 2014;8(5):341-348.

4 Wilks S. Morbid appearances in the intestine of Miss Bankes. *Med Times Gazette*. 1859;2(2):264-265.

5 White H. A Discussion on "Ulcerative Colitis." Introductroy Address. *Proceedings of the Royal Society of Medicine*. 1909;2(Med Sect):79.

6 Dalziel T. Chronic interstitial enteritis. *The British Medical Journal*. 1913:1068-1070.

7 Chang S, Shen B. Chapter 2 - Classification and Reclassification of Inflammatory Bowel Diseases: From Clinical Perspective. In: Shen B, ed. *Interventional Inflammatory Bowel Disease: Endoscopic Management and Treatment of Complications*. Academic Press; 2018:17-34.

8 Magro F, Gionchetti P, Eliakim R, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *Journal of Crohn's and Colitis*. 2017;11(6):649-670.

9 Dolinger M, Torres J, Vermeire S. Crohn's disease. *The Lancet*. 2024;403(10432):1177-1191.

10 Sairenji T, Collins KL, Evans DV. An Update on Inflammatory Bowel Disease. *Prim Care*. Review. 2017;44(4):673-692.

11 Tontini GE, Vecchi M, Pastorelli L, Neurath MF, Neumann H. Differential diagnosis in inflammatory bowel disease colitis: state of the art and future perspectives. *World journal of gastroenterology*. 2015;21(1):21-46.

12 Rinawi F, Assa A, Eliakim R, et al. The natural history of pediatric-onset IBD-unclassified and prediction of Crohn's disease reclassification: a 27-year study. *Scandinavian Journal of Gastroenterology*. 2017;52(5):558-563.

13 Alatab S, Sepanlou SG, Ikuta K, et al. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Gastroenterology & Hepatology*. 2020;5(1):17-30.

14 Insight Economics. State of the Nation in Inflammatory Bowel Disease in Australia, Final Report 2025, report prepared for Crohn's & Colitis Australia. 2025

15 Shi HY, Levy AN, Trivedi HD, Chan FKL, Ng SC, Ananthakrishnan AN. Ethnicity Influences Phenotype and Outcomes in Inflammatory Bowel Disease: A Systematic Review and

Meta-analysis of Population-based Studies. *Clinical Gastroenterology and Hepatology*. 2018;16(2):190-197.e111.

16 Misra R, Faiz O, Munkholm P, Burisch J, Arebi N. Epidemiology of inflammatory bowel disease in racial and ethnic migrant groups. *World journal of gastroenterology*. 2018;24(3):424-437.

17 Ruel J, Ruane D, Mehandru S, Gower-Rousseau C, Colombel J-F. IBD across the age spectrum—is it the same disease? *Nat Rev Gastroenterol Hepatol*. 2014;11(2):88-98.

18 Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology*. 2011;140(6):1785-1794.

19 Molodecky NA, Soon IS, Rabi DM, et al. Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases With Time, Based on Systematic Review. *Gastroenterology*. 2012;142(1):46-54.e42.

20 Ek WE, D'Amato M, Halfvarson J. The history of genetics in inflammatory bowel disease. *Annals of gastroenterology*. 2014;27(4):294-303.

21 Santos MPC, Gomes C, Torres J. Familial and ethnic risk in inflammatory bowel disease. *Annals of gastroenterology*. 2018;31(1):14-23.

22 Nunes T, Fiorino G, Danese S, Sans M. Familial aggregation in inflammatory bowel disease: is it genes or environment? *World journal of gastroenterology*. 2011;17(22):2715-2722.

23 Sidiq T, Yoshihama S, Downs I, Kobayashi KS. Nod2: A Critical Regulator of Ileal Microbiota and Crohn's Disease. *Front Immunol*. 2016;7:367.

24 Ogura Y, Bonen DK, Inohara N, et al. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. *Nature*. 2001;411(6837):603-606.

25 Hugot JP, Chamaillard M, Zouali H, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature*. 2001;411(6837):599-603.

26 Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature*. 2012;491(7422):119-124.

27 Anderson CA, Boucher G, Lees CW, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. *Nat Genet*. 2011;43(3):246-252.

28 Thompson AI, Lees CW. Genetics of ulcerative colitis. *Inflammatory Bowel Diseases*. 2011;17(3):831-848.

29 McGovern DPB, Gardet A, Törkvist L, et al. Genome-wide association identifies multiple ulcerative colitis susceptibility loci. *Nature Genetics*. 2010;42(4):332-337.

30 Juyal G, Negi S, Sood A, et al. Genome-wide association scan in north Indians reveals three novel HLA-independent risk loci for ulcerative colitis. *Gut*. 2015;64(4):571-579.

31 Carr I, Mayberry JF. The effects of migration on ulcerative colitis: a three-year prospective study among Europeans and first- and second-generation South Asians in Leicester (1991–1994). *American Journal Of Gastroenterology*. Original Contribution. 1999;94:2918.

32 Probert CS, Jayanthi V, Pinder D, Wicks AC, Mayberry JF. Epidemiological study of ulcerative proctocolitis in Indian migrants and the indigenous population of Leicestershire. *Gut*. 1992;33(5):687-693.
33 Ko Y, Butcher R, Leong RW. Epidemiological studies of migration and environmental risk factors in the inflammatory bowel diseases. *World journal of gastroenterology*. 2014;20(5):1238-1247.
34 Olstrup H, Mohamed HAS, Honoré J, et al. Air pollution exposure and inflammatory bowel disease: a systematic literature review of epidemiological and mechanistic studies. *Frontiers in Environmental Health*. Review. 2024;Volume 3 - 2024.
35 Piovani D, Pansieri C, Kotha SRR, et al. Ethnic Differences in the Smoking-related Risk of Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *Journal of Crohn's and Colitis*. 2021;15(10):1658-1678.
36 Agrawal M, Sabino J, Frias-Gomes C, et al. Early life exposures and the risk of inflammatory bowel disease: Systematic review and meta-analyses. *eClinicalMedicine*. 2021;36.
37 Duan R, Zhang C, Li G, Li J, Duan L. Antibiotic Exposure and Risk of New-Onset Inflammatory Bowel Disease: A Systematic Review and Dose-Response Meta-Analysis. *Clinical Gastroenterology and Hepatology*. 2025;23(1):45-58.e15.
38 Dar SH, Maniya MT, Merza N, et al. The association of antibiotic exposure with new-onset inflammatory bowel disease: A systematic review and meta-analysis. *Clinics and Research in Hepatology and Gastroenterology*. 2023;47(6):102129.
39 Axelrad JE, Cadwell KH, Colombel J-F, Shah SC. The role of gastrointestinal pathogens in inflammatory bowel disease: a systematic review. *Therapeutic Advances in Gastroenterology*. 2021;14:17562848211004493.
40 Monteiro CA, Cannon G, Moubarac JC, Levy RB, Louzada MLC, Jaime PC. The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. *Public Health Nutr*. 2018;21(1):5-17.
41 Narula N, Chang NH, Mohammad D, et al. Food Processing and Risk of Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *Clinical Gastroenterology and Hepatology*. 2023;21(10):2483-2495.e2481.
42 Kaplan GG, Jackson T, Sands BE, Frisch M, Andersson RE, Korzenik J. The Risk of Developing Crohn's Disease After an Appendectomy: A Meta-Analysis. *Official journal of the American College of Gastroenterology | ACG*. 2008;103(11).
43 Chung W-S, Chung S, Hsu C-Y, Lin C-L. Risk of Inflammatory Bowel Disease Following Appendectomy in Adulthood. *Frontiers in Medicine*. Original Research. 2021;Volume 8 - 2021.
44 Uhe I, Gialamas E, Combescure C, et al. Is the risk of developing a Crohn’s disease increased after appendectomy? A systematic review of the literature and meta-analysis. *Digestive Surgery*.

45 Ho SM, Lewis JD, Mayer EA, et al. Challenges in IBD Research: Environmental Triggers. *Inflammatory Bowel Diseases*. Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Review. 2019;25(Suppl 2):S13-S23.

46 Halpin SJ, Ford AC. Prevalence of Symptoms Meeting Criteria for Irritable Bowel Syndrome in Inflammatory Bowel Disease: Systematic Review and Meta-Analysis. *Official journal of the American College of Gastroenterology | ACG*. 2012;107(10):1474-1482.

47 Yu YR, Rodriguez JR. Clinical presentation of Crohn's, ulcerative colitis, and indeterminate colitis: Symptoms, extraintestinal manifestations, and disease phenotypes. *Seminars in Pediatric Surgery*. 2017;26(6):349-355.

48 Perler BK, Ungaro R, Baird G, et al. Presenting symptoms in inflammatory bowel disease: descriptive analysis of a community-based inception cohort. *BMC Gastroenterology*. 2019;19(1):47.

49 Byron C, Cornally N, Burton A, Savage E. Challenges of living with and managing inflammatory bowel disease: A meta-synthesis of patients' experiences. *Journal of Clinical Nursing*. 2020;29(3-4):305-319.

50 Vivinus-Nébot M, Frin-Mathy G, Bzioueche H, et al. Functional bowel symptoms in quiescent inflammatory bowel diseases: role of epithelial barrier disruption and low-grade inflammation. *Gut*. 2014;63(5):744-752.

51 Farrokhyar F, Marshall JK, Easterbrook B, Irvine JE. Functional Gastrointestinal Disorders and Mood Disorders in Patients with Inactive Inflammatory Bowel Disease: Prevalence and Impact on Health. *Inflammatory Bowel Diseases*. 2006;12(1):38-46.

52 Baars JE, Nuij VJAA, Oldenburg B, Kuipers EJ, van der Woude CJ. Majority of Patients with Inflammatory Bowel Disease in Clinical Remission Have Mucosal Inflammation. *Inflammatory Bowel Diseases*. 2012;18(9):1634-1640.

53 Casanova MJ, Chaparro M, Molina B, et al. Prevalence of Malnutrition and Nutritional Characteristics of Patients With Inflammatory Bowel Disease. *Journal of Crohn's and Colitis*. 2017;11(12):1430-1439.

54 Gold SL, Rabinowitz LG, Manning L, et al. High Prevalence of Malnutrition and Micronutrient Deficiencies in Patients With Inflammatory Bowel Disease Early in Disease Course. *Inflamm Bowel Dis*. 2023;29(3):423-429.

55 Liu J, Ge X, Ouyang C, et al. Prevalence of Malnutrition, Its Risk Factors, and the Use of Nutrition Support in Patients with Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. 2022;28(Supplement_2):S59-S66.

56 Pulley J, Todd A, Flatley C, Begun J. Malnutrition and quality of life among adult inflammatory bowel disease patients. *JGH Open*. 2020;4(3):454-460.

57 Gassull MA, Cabré E. Nutrition in inflammatory bowel disease. *Current Opinion in Clinical Nutrition & Metabolic Care*. 2001;4(6).

58 Kaazan P, Tan Z, Maiyani P, et al. Weight and BMI Patterns in a Biologicals-Treated IBD Cohort. *Digestive Diseases and Sciences*. 2022;67(12):5628-5636.

59 Harper JW, Sinanan MN, Zisman TL. Increased Body Mass Index Is Associated with Earlier Time to Loss of Response to Infliximab in Patients with Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. 2013;19(10):2118-2124.

60 Campo M, Hjelle H, Granlund AVB, Sandvik AK, Ness-Jensen E. The relationship between weight change and inflammatory bowel disease. A population-based cohort study, the HUNT study. *Scand J Gastroenterol*. 2024;59(7):830-834.

61 Dignass AU, Gasche C, Bettenworth D, et al. European Consensus on the Diagnosis and Management of Iron Deficiency and Anaemia in Inflammatory Bowel Diseases. *Journal of Crohn's and Colitis*. 2015;9(3):211-222.

62 Wilson A, Reyes E, Ofman J. Prevalence and outcomes of anemia in inflammatory bowel disease: a systematic review of the literature. *The American Journal of Medicine*. 2004;116(7, Supplement 1):44-49.

63 Eriksson C, Henriksson I, Brus O, et al. Incidence, prevalence and clinical outcome of anaemia in inflammatory bowel disease: a population-based cohort study. *Alimentary Pharmacology & Therapeutics*. 2018;48(6):638-645.

64 Kaitha S, Bashir M, Ali T. Iron deficiency anemia in inflammatory bowel disease. *World J Gastrointest Pathophysiol*. 2015;6(3):62-72.

65 Ali T, Lam D, Bronze MS, Humphrey MB. Osteoporosis in inflammatory bowel disease. *Am J Med*. 2009;122(7):599-604.

66 Kärnsund S, Lo B, Bendtsen F, Holm J, Burisch J. Systematic review of the prevalence and development of osteoporosis or low bone mineral density and its risk factors in patients with inflammatory bowel disease. *World J Gastroenterol*. 2020;26(35):5362-5374.

67 Bernstein CN, Leslie WD. Osteoporosis and inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*. 2004;19(9):941-952.

68 Andreassen H, Rungby J, Dahlerup JF, Mosekilde L. Inflammatory Bowel Disease and Osteoporosis. *Scandinavian Journal of Gastroenterology*. 1997;32(12):1247-1255.

69 Dhaliwal A, Quinlan JI, Overthrow K, et al. Sarcopenia in Inflammatory Bowel Disease: A Narrative Overview. *Nutrients*. 2021;13(2).

70 Fatani H, Olaru A, Stevenson R, et al. Systematic review of sarcopenia in inflammatory bowel disease. *Clinical Nutrition*. 2023;42(8):1276-1291.

71 Ryan E, McNicholas D, Creavin B, Kelly ME, Walsh T, Beddy D. Sarcopenia and Inflammatory Bowel Disease: A Systematic Review. *Inflammatory Bowel Diseases*. 2019;25(1):67-73.

72 Bourikas LA, Papadakis KA. Musculoskeletal Manifestations of Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. 2009;15(12):1915-1924.
73 Borren NZ, van der Woude CJ, Ananthakrishnan AN. Fatigue in IBD: epidemiology, pathophysiology and management. *Nature Reviews Gastroenterology & Hepatology*. 2019;16(4):247-259.
74 D'Silva A, Fox DE, Nasser Y, et al. Prevalence and Risk Factors for Fatigue in Adults With Inflammatory Bowel Disease: A Systematic Review With Meta-Analysis. *Clin Gastroenterol Hepatol*. 2022;20(5):995-1009.e1007.
75 Farrell D, Artom M, Czuber-Dochan W, Jelsness-Jørgensen LP, Norton C, Savage E. Interventions for fatigue in inflammatory bowel disease. *Cochrane Database Syst Rev*. 2020;4(4):Cd012005.
76 Haß U, Herpich C, Norman K. Anti-Inflammatory Diets and Fatigue. *Nutrients*. 2019;11(10):2315.
77 Van Langenberg DR, Gibson PR. Systematic review: fatigue in inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*. 2010;32(2):131-143.
78 Marinelli C, Savarino EV, Marsilio I, et al. Sleep disturbance in Inflammatory Bowel Disease: prevalence and risk factors – A cross-sectional study. *Scientific Reports*. 2020;10(1):507.
79 Ananthakrishnan AN, Long MD, Martin CF, Sandler RS, Kappelman MD. Sleep Disturbance and Risk of Active Disease in Patients With Crohn's Disease and Ulcerative Colitis. *Clinical Gastroenterology and Hepatology*. 2013;11(8):965-971.
80 Ali T, Orr WC. Sleep Disturbances and Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. 2014;20(11):1986-1995.
81 Ranjbaran Z, Keefer L, Farhadi A, Stepanski E, Sedghi S, Keshavarzian A. Impact of sleep disturbances in inflammatory bowel disease. *Journal of Gastroenterology and Hepatology*. 2007;22(11):1748-1753.
82 Graff LA, Vincent N, Walker JR, et al. A population-based study of fatigue and sleep difficulties in inflammatory bowel disease. *Inflammatory Bowel Diseases*. 2011;17(9):1882-1889.
83 Zou Z-Y, Shen B, Fan J-G. Systematic Review With Meta-analysis: Epidemiology of Nonalcoholic Fatty Liver Disease in Patients With Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. 2019;25(11):1764-1772.
84 Shen Z, Zhang M, Liu Y, et al. Prevalence of metabolic syndrome in patients with inflammatory bowel disease: a systematic review and meta-analysis. *BMJ Open*. 2024;14(3):e074659.
85 Jess T, Jensen BW, Andersson M, Villumsen M, Allin KH. Inflammatory Bowel Diseases Increase Risk of Type 2 Diabetes in a Nationwide Cohort Study. *Clinical Gastroenterology and Hepatology*. 2020;18(4):881-888.e881.

86 Kappelman MD, Galanko JA, Porter CQ, Sandler RS. Association of paediatric inflammatory bowel disease with other immune-mediated diseases. *Archives of Disease in Childhood*. 2011;96(11):1042-1046.

87 Andersen NN, Jess T. Risk of cardiovascular disease in inflammatory bowel disease. *World J Gastrointest Pathophysiol*. 2014;5(3):359-365.

88 Nevulis MG, Baker C, Lebovics E, Frishman WH. Overview of Link Between Inflammatory Bowel Disease and Cardiovascular Disease. *Cardiology in Review*. 2018;26(6).

89 Chen B, Collen LV, Mowat C, et al. Inflammatory Bowel Disease and Cardiovascular Diseases. *The American Journal of Medicine*. 2022;135(12):1453-1460.

90 Yarur AJ, Deshpande AR, Pechman DM, Tamariz L, Abreu MT, Sussman DA. Inflammatory Bowel Disease Is Associated With an Increased Incidence of Cardiovascular Events. *Official journal of the American College of Gastroenterology | ACG*. 2011;106(4).

91 Palm Ø, Moum B, Jahnsen J, Gran JT. The prevalence and incidence of peripheral arthritis in patients with inflammatory bowel disease, a prospective population-based study (the IBSEN study). *Rheumatology*. 2001;40(11):1256-1261.

92 Song K, Satsangi J, Coates LC. Arthritis complicating inflammatory bowel disease— the future is now. *The Lancet Rheumatology*. 2024;6(11):e805-e810.

93 Yüksel İ, Ataseven H, Başar Ö, et al. Peripheral Arthritis in the Course of Inflammatory Bowel Diseases. *Digestive Diseases and Sciences*. 2011;56(1):183-187.

94 Greuter T, Navarini A, Vavricka SR. Skin Manifestations of Inflammatory Bowel Disease. *Clinical Reviews in Allergy & Immunology*. 2017;53(3):413-427.

95 Tavarela Veloso F. Skin complications associated with inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*. 2004;20(s4):50-53.

96 Huang BL, Chandra S, Shih DQ. Skin manifestations of inflammatory bowel disease. *Front Physiol*. 2012;3:13.

97 Kuenzig ME, Bishay K, Leigh R, Kaplan GG, Benchimol EI. Co-occurrence of Asthma and the Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis. *Clin Transl Gastroenterol*. 2018;9(9):188.

98 Kisiel MA, Sedvall M, Malinovschi A, et al. Inflammatory bowel disease and asthma. Results from the RHINE study. *Respir Med*. 2023;216:107307.

99 Rossi CM, Lenti MV, Merli S, Santacroce G, Di Sabatino A. Allergic manifestations in autoimmune gastrointestinal disorders. *Autoimmunity Reviews*. 2022;21(1):102958.

100 Engkilde K, Menné T, Duus Johansen J. Inflammatory bowel disease in relation to contact allergy: A patient-based study. *Scandinavian Journal of Gastroenterology*. 2007;42(5):572-576.

101 Black J, Sweeney L, Yuan Y, Singh H, Norton C, Czuber-Dochan W. Systematic review: the role of psychological stress in inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*. 2022;56(8):1235-1249.

102 Chan W, Shim HH, Lim MS, et al. Symptoms of anxiety and depression are independently associated with inflammatory bowel disease-related disability. *Digestive and Liver Disease*. 2017;49(12):1314-1319.
103 Mawdsley JE, Rampton DS. The role of psychological stress in inflammatory bowel disease. *Neuroimmunomodulation*. 2006;13(5-6):327-336.
104 Sajadinejad MS, Asgari K, Molavi H, Kalantari M, Adibi P. Psychological Issues in Inflammatory Bowel Disease: An Overview. *Gastroenterology Research and Practice*. 2012;2012(1):106502.
105 Cai Z, Wang S, Li J. Treatment of Inflammatory Bowel Disease: A Comprehensive Review. *Frontiers in Medicine*. Review. 2021;8.
106 Thomas A, Lodhia N. Advanced Therapy for Inflammatory Bowel Disease: A Guide for the Primary Care Physician. *The Journal of the American Board of Family Medicine*. 2014;27(3):411-420.
107 Bernstein CN. Treatment of IBD: Where We Are and Where We Are Going. *Official journal of the American College of Gastroenterology | ACG*. 2015;110(1).
108 Mesonero F, Fernández C, Sánchez-Rodríguez E, et al. Polypharmacy in Patients With Inflammatory Bowel Disease: Prevalence and Outcomes in a Single-center Series. *Journal of Clinical Gastroenterology*. 2022;56(3).
109 Cross RK, Wilson KT, Binion DG. Polypharmacy and Crohn's disease. *Alimentary Pharmacology & Therapeutics*. 2005;21(10):1211-1216.
110 Wang J, Nakamura TI, Tuskey AG, Behm BW. Polypharmacy is a risk factor for disease flare in adult patients with ulcerative colitis: a retrospective cohort study. *ir*. 2019;17(4):496-503.
111 Ben-Horin S, Kopylov U, Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. *Autoimmun Rev*. 2014;13(1):24-30.
112 Papamichael K, Cheifetz AS. Therapeutic drug monitoring in inflammatory bowel disease: for every patient and every drug? *Current Opinion in Gastroenterology*. 2019;35(4).
113 Goodman TA, Polisson RP. Methotrexate: adverse reactions and major toxicities. *Rheumatic Disease Clinics of North America*. 1994;20(2):513-528.
114 Wahed M, Louis-Auguste J, Baxter L, et al. Efficacy of methotrexate in Crohn's disease and ulcerative colitis patients unresponsive or intolerant to azathioprine/mercaptopurine. *Alimentary pharmacology & therapeutics*. 2009;30(6):614-620.
115 Papamichael K, Rivals-Lerebours O, Billiet T, et al. Long-Term Outcome of Patients with Ulcerative Colitis and Primary Non-response to Infliximab. *Journal of Crohn's and Colitis*. 2016;10(9):1015-1023.
116 McLean LP, Cross RK. Adverse events in IBD: to stop or continue immune suppressant and biologic treatment. *Expert Rev Gastroenterol Hepatol*. 2014;8(3):223-240.

117 D'Haens G. Risks and benefits of biologic therapy for inflammatory bowel diseases. *Gut*. 2007;56(5):725-732.

118 Beaugerie L, Rahier J-F, Kirchgesner J. Predicting, Preventing, and Managing Treatment-Related Complications in Patients With Inflammatory Bowel Diseases. *Clinical Gastroenterology and Hepatology*. 2020;18(6):1324-1335.e1322.

119 Rogler G. Gastrointestinal and liver adverse effects of drugs used for treating IBD. *Best Practice & Research Clinical Gastroenterology*. 2010;24(2):157-165.

120 Toruner M, Loftus Jr EV, Harmsen WS, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology*. 2008;134(4):929-936.

121 Marehbian J, Arrighi MH, Hass S, Tian H, Sandborn WJ. Adverse events associated with common therapy regimens for moderate-to-severe Crohn's disease. *Official journal of the American College of Gastroenterology| ACG*. 2009;104(10):2524-2533.

122 Margagnoni G, Papi V, Aratari A, Triolo L, Papi C. Methotrexate-induced pneumonitis in a patient with Crohn's disease. *J Crohns Colitis*. 2010;4(2):211-214.

123 Imokawa S, Colby TV, Leslie KO, Helmers RA. Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. *Eur Respir J*. 2000;15(2):373-381.

124 Eligius Hellström A, Färkkilä M, Kolho K-L. Infliximab-induced skin manifestations in patients with inflammatory bowel disease. *Scandinavian Journal of Gastroenterology*. 2016;51(5):563-571.

125 Shivaji UN, Sharratt CL, Thomas T, et al. Review article: managing the adverse events caused by anti-TNF therapy in inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*. 2019;49(6):664-680.

126 Swinson CM, Perry J, Lumb M, Levi AJ. Role of sulphasalazine in the aetiology of folate deficiency in ulcerative colitis. *Gut*. 1981;22(6):456-461.

127 Miele E, Shamir R, Aloi M, et al. Nutrition in Pediatric Inflammatory Bowel Disease. *Journal of Pediatric Gastroenterology and Nutrition*. 2018;66(4):687-708.

128 Bernstein CN, Seeger LL, Sayre JW, Anton PA, Artinian L, Shanahan F. Decreased bone density in inflammatory bowel disease is related to corticosteroid use and not disease diagnosis. *Journal of Bone and Mineral Research*. 1995;10(2):250-256.

129 Oikonomou K, Kapsoritakis A, Eleftheriadis T, Stefanidis I, Potamianos S. Renal manifestations and complications of inflammatory bowel disease. *Inflammatory Bowel Diseases*. 2011;17(4):1034-1045.

130 Koller T, Galambosova M, Filakovska S, et al. Drug-induced liver injury in inflammatory bowel disease: 1-year prospective observational study. *World J Gastroenterol*. 2017;23(22):4102-4111.

131 Antonini F, Pezzilli R, Angelelli L, Macarri G. Pancreatic disorders in inflammatory bowel disease. *World J Gastrointest Pathophysiol*. 2016;7(3):276-282.

132 Hawthorne AB, Rubin G, Ghosh S. Review article: medication non-adherence in ulcerative colitis – strategies to improve adherence with mesalazine and other maintenance therapies. *Alimentary Pharmacology & Therapeutics*. 2008;27(12):1157-1166.

133 Kane SV, Cohen RD, Aikens JE, Hanauer SB. Prevalence of nonadherence with maintenance mesalamine in quiescent ulcerative colitis. *Am J Gastroenterol*. 2001;96(10):2929-2933.

134 Shale MJ, Riley SA. Studies of compliance with delayed-release mesalazine therapy in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2003;18(2):191-198.

135 Jackson CA, Clatworthy J, Robinson A, Horne R. Factors Associated With Non-Adherence to Oral Medication for Inflammatory Bowel Disease: A Systematic Review. *Official journal of the American College of Gastroenterology | ACG*. 2010;105(3).

136 San Román AL, Bermejo F, Carrera E, Pérez-Abad M, Boixeda D. Adherence to treatment in inflammatory bowel disease. *Rev Esp Enferm Dig*. 2005;97(4):249-257.

137 Cerveny P, Bortlik M, Vlcek J, Kubena A, Lukás M. Non-adherence to treatment in inflammatory bowel disease in Czech Republic☆. *Journal of Crohn's and Colitis*. 2007;1(2):77-81.

138 Bernal I, Domènech E, Garcia-Planella E, et al. Medication-Taking Behavior in a Cohort of Patients with Inflammatory Bowel Disease. *Digestive Diseases and Sciences*. 2006;51(12):2165-2169.

139 Sewitch MJ, Abrahamowicz M, Barkun A, et al. Patient nonadherence to medication in inflammatory bowel disease. *Am J Gastroenterol*. 2003;98(7):1535-1544.

140 Kane SV. Systematic review: adherence issues in the treatment of ulcerative colitis. *Alimentary Pharmacology & Therapeutics*. 2006;23(5):577-585.

141 Kane S, Huo D, Aikens J, Hanauer S. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. *Am J Med*. 2003;114(1):39-43.

142 Moody GA, Jayanthi V, Probert CS, Mac Kay H, Mayberry JF. Long-term therapy with sulphasalazine protects against colorectal cancer in ulcerative colitis: a retrospective study of colorectal cancer risk and compliance with treatment in Leicestershire. *Eur J Gastroenterol Hepatol*. 1996;8(12):1179-1183.

143 Chan W, Chen A, Tiao D, Selinger C, Leong R. Medication adherence in inflammatory bowel disease. *Intest Res*. 2017;15(4):434-445.

144 Perry J, Chen A, Kariyawasam V, et al. Medication non-adherence in inflammatory bowel diseases is associated with disability. *Intest Res*. 2018;16(4):571-578.

145 Aluzaite K, Braund R, Seeley L, Amiesimaka OI, Schultz M. Adherence to Inflammatory Bowel Disease Medications in Southern New Zealand. *Crohn's & Colitis 360*. 2021;3(3):otab056.

146 Tae CH, Jung S-A, Moon HS, et al. Importance of patients' knowledge of their prescribed medication in improving treatment adherence in inflammatory bowel disease. *Journal of clinical gastroenterology*. 2016;50(2):157-162.

147 Sica GS, Biancone L. Surgery for inflammatory bowel disease in the era of laparoscopy. *World J Gastroenterol*. 2013;19(16):2445-2448.

148 Hwang JM, Varma MG. Surgery for inflammatory bowel disease. *World J Gastroenterol*. 2008;14(17):2678-2690.

149 Peyrin-Biroulet L, Germain A, Patel AS, Lindsay JO. Systematic review: outcomes and post-operative complications following colectomy for ulcerative colitis. *Alimentary Pharmacology & Therapeutics*. 2016;44(8):807-816.

150 Targownik LE, Singh H, Nugent Z, Bernstein CN. The Epidemiology of Colectomy in Ulcerative Colitis: Results From a Population-Based Cohort. *Official journal of the American College of Gastroenterology | ACG*. 2012;107(8).

151 Khoudari G, Mansoor E, Click B, et al. Rates of Intestinal Resection and Colectomy in Inflammatory Bowel Disease Patients After Initiation of Biologics: A Cohort Study. *Clin Gastroenterol Hepatol*. 2022;20(5):e974-e983.

152 Lowe SC, Sauk JS, Limketkai BN, Kwaan MR. Declining Rates of Surgery for Inflammatory Bowel Disease in the Era of Biologic Therapy. *Journal of Gastrointestinal Surgery*. 2021;25(1):211-219.

153 Moser G, Tillinger W, Sachs G, et al. Disease-related worries and concerns: a study on out-patients with inflammatory bowel disease. *European Journal of Gastroenterology & Hepatology*. 1995;7(9).

154 Casati J, Toner BB, De Rooy EC, Drossman DA, Maunder RG. Concerns of Patients with Inflammatory Bowel Disease. *Digestive Diseases and Sciences*. 2000;45(1):26-31.

155 Spinelli A, Carvello M, Adamina M, et al. Patients' perceptions of surgery for inflammatory bowel disease. *Colorectal Disease*. 2021;23(10):2690-2698.

156 Crohn's & Colitis Australia. Australian IBD Standards: Standards of healthcare for people with inflammatory bowel disease in Australia Inflammatory Bowel Disease Quality of Care Program: Crohn's & Colitis Australia, 2016

157 Massuger W, Moore GTC, Andrews JM, et al. Crohn's & Colitis Australia inflammatory bowel disease audit: measuring the quality of care in Australia. *Intern Med J*. 2019;49(7):859-866.

158 Mikocka-Walus A, Massuger W, Knowles SR, et al. Quality of care in inflammatory bowel disease: actual health service experiences fall short of the standards. *Internal Medicine Journal*. 2020;50(10):1216-1225.

159 Holt DQ, Strauss BJ, Moore GT. Patients with inflammatory bowel disease and their treating clinicians have different views regarding diet. *J Hum Nutr Diet*. 2017;30(1):66-72.

160 Bischoff SC, Escher J, Hébuterne X, et al. ESPEN practical guideline: Clinical Nutrition in inflammatory bowel disease. *Clinical Nutrition*. 2020;39(3):632-653.

161 Fitzpatrick JA, Melton SL, Yao CK, Gibson PR, Halmos EP. Dietary management of adults with IBD - the emerging role of dietary therapy. *Nat Rev Gastroenterol Hepatol*. 2022;19(10):652-669.

162 Gerasimidis K, Godny L, Sigall-Boneh R, Svolos V, Wall C, Halmos E. Current recommendations on the role of diet in the aetiology and management of IBD. *Frontline Gastroenterology*. 2022;13(2):160-167.

163 Kamp KJ, Pennings B, Javelli D, Wyatt G, Given B. Dietary patterns, beliefs and behaviours among individuals with inflammatory bowel disease: a cross-sectional study. *J Hum Nutr Diet*. 2021;34(2):257-264.

164 Verdina M, Seibold F, Grandmaison G, et al. Survey of dietary beliefs and habits of inflammatory bowel disease patients. *Clinical Nutrition ESPEN*. 2023;57:624-629.

165 Crooks B, McLaughlin J, Limdi J. Dietary beliefs and recommendations in inflammatory bowel disease: a national survey of healthcare professionals in the UK. *Frontline Gastroenterol*. 2022;13(1):25-31.

166 Godala M, Gaszyńska E, Durko Ł, Małecka-Wojciesko E. Dietary Behaviors and Beliefs in Patients with Inflammatory Bowel Disease. *J Clin Med*. 2023;12(10).

167 de Vries Jeanne HM, Dijkhuizen M, Tap P, Witteman Ben JM. Patient's Dietary Beliefs and Behaviours in Inflammatory Bowel Disease. *Digestive Diseases*. 2018;37(2):131-139.

168 Lindberg A, Fossum B, Karlen P, Oxelmark L. Experiences of complementary and alternative medicine in patients with inflammatory bowel disease – a qualitative study. *BMC Complementary and Alternative Medicine*. 2014;14(1):407.

169 Lin SC, Cheifetz AS. The Use of Complementary and Alternative Medicine in Patients With Inflammatory Bowel Disease. *Gastroenterol Hepatol (N Y)*. 2018;14(7):415-425.

170 Ananthakrishnan AN, Kwon J, Raffals L, et al. Variation in Treatment of Patients With Inflammatory Bowel Diseases at Major Referral Centers in the United States. *Clinical Gastroenterology and Hepatology*. 2015;13(6):1197-1200.

171 Sawczenko A, Lynn R, Sandhu BK. Variations in initial assessment and management of inflammatory bowel disease across Great Britain and Ireland. *Archives of Disease in Childhood*. 2003;88(11):990-994.

172 Rizzello F, Spisni E, Giovanardi E, et al. Implications of the Westernized Diet in the Onset and Progression of IBD. *Nutrients*. 2019;11(5):1033.

173 Adolph TE, Tilg H. Western diets and chronic diseases. *Nature Medicine*. 2024;30(8):2133-2147.

174 van Woudenbergh GJ, Kuijsten A, Tigcheler B, et al. Meat consumption and its association with C-reactive protein and incident type 2 diabetes: the Rotterdam Study. *Diabetes Care*. 2012;35(7):1499-1505.

175 Papier K, Hartman L, Tong TYN, Key TJ, Knuppel A. Higher Meat Intake Is Associated with Higher Inflammatory Markers, Mostly Due to Adiposity: Results from UK Biobank. *J Nutr*. 2022;152(1):183-189.
176 Ley SH, Sun Q, Willett WC, et al. Associations between red meat intake and biomarkers of inflammation and glucose metabolism in women. *The American Journal of Clinical Nutrition*. 2014;99(2):352-360.
177 Dong C, Chan SSM, Jantchou P, et al. Meat Intake Is Associated with a Higher Risk of Ulcerative Colitis in a Large European Prospective Cohort Study. *J Crohns Colitis*. 2022;16(8):1187-1196.
178 Talebi S, Zeraattalab-Motlagh S, Rahimlou M, et al. The Association between Total Protein, Animal Protein, and Animal Protein Sources with Risk of Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis of Cohort Studies. *Advances in Nutrition*. 2023;14(4):752-761.
179 Ge J, Han TJ, Liu J, et al. Meat intake and risk of inflammatory bowel disease: A meta-analysis. *Turk J Gastroenterol*. 2015;26(6):492-497.
180 Fu T, Chen H, Chen X, et al. Sugar-sweetened beverages, artificially sweetened beverages and natural juices and risk of inflammatory bowel disease: a cohort study of 121,490 participants. *Alimentary Pharmacology & Therapeutics*. 2022;56(6):1018-1029.
181 Khademi Z, Milajerdi A, Larijani B, Esmaillzadeh A. Dietary Intake of Total Carbohydrates, Sugar and Sugar-Sweetened Beverages, and Risk of Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. *Front Nutr*. 2021;8:707795.
182 Bischoff SC, Kaden-Volynets V, Filipe Rosa L, Guseva D, Seethaler B. Regulation of the gut barrier by carbohydrates from diet – Underlying mechanisms and possible clinical implications. *International Journal of Medical Microbiology*. 2021;311(4):151499.
183 Damms-Machado A, Louis S, Schnitzer A, et al. Gut permeability is related to body weight, fatty liver disease, and insulin resistance in obese individuals undergoing weight reduction. *The American journal of clinical nutrition*. 2017;105(1):127-135.
184 Vrakas S, Mountzouris KC, Michalopoulos G, et al. Intestinal Bacteria Composition and Translocation of Bacteria in Inflammatory Bowel Disease. *PLoS One*. 2017;12(1):e0170034.
185 Milajerdi A, Ebrahimi-Daryani N, Dieleman LA, Larijani B, Esmaillzadeh A. Association of Dietary Fiber, Fruit, and Vegetable Consumption with Risk of Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *Advances in Nutrition*. 2021;12(3):735-743.
186 Liu X, Wu Y, Li F, Zhang D. Dietary fiber intake reduces risk of inflammatory bowel disease: result from a meta-analysis. *Nutrition Research*. 2015;35(9):753-758.
187 Li F, Liu X, Wang W, Zhang D. Consumption of vegetables and fruit and the risk of inflammatory bowel disease: a meta-analysis. *European Journal of Gastroenterology & Hepatology*. 2015;27(6).

188 Racine A, Carbonnel F, Chan SS, et al. Dietary Patterns and Risk of Inflammatory Bowel Disease in Europe: Results from the EPIC Study. *Inflamm Bowel Dis*. 2016;22(2):345-354.
189 Lee JY, Sohn KH, Rhee SH, Hwang D. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. *Journal of Biological Chemistry*. 2001;276(20):16683-16689.
190 Santos S, Oliveira A, Lopes C. Systematic review of saturated fatty acids on inflammation and circulating levels of adipokines. *Nutrition Research*. 2013;33(9):687-695.
191 Fernández-Real J-M, Broch M, Vendrell J, Ricart W. Insulin Resistance, Inflammation, and Serum Fatty Acid Composition. *Diabetes Care*. 2003;26(5):1362-1368.
192 Hou JK, Abraham B, El-Serag H. Dietary Intake and Risk of Developing Inflammatory Bowel Disease: A Systematic Review of the Literature. *Official journal of the American College of Gastroenterology | ACG*. 2011;106(4).
193 Wang F, Lin X, Zhao Q, Li J. Fat intake and risk of ulcerative colitis: Systematic review and dose–response meta-analysis of epidemiological studies. *Journal of Gastroenterology and Hepatology*. 2017;32(1):19-27.
194 Gill SR, Pop M, DeBoy RT, et al. Metagenomic analysis of the human distal gut microbiome. *science*. 2006;312(5778):1355-1359.
195 Postler TS, Ghosh S. Understanding the holobiont: how microbial metabolites affect human health and shape the immune system. *Cell metabolism*. 2017;26(1):110-130.
196 Ley RE, Lozupone CA, Hamady M, Knight R, Gordon JI. Worlds within worlds: evolution of the vertebrate gut microbiota. *Nature Reviews Microbiology*. 2008;6(10):776-788.
197 Tan JK, Macia L, Mackay CR. Dietary fiber and SCFAs in the regulation of mucosal immunity. *Journal of Allergy and Clinical Immunology*. 2023;151(2):361-370.
198 Liu P, Wang Y, Yang G, et al. The role of short-chain fatty acids in intestinal barrier function, inflammation, oxidative stress, and colonic carcinogenesis. *Pharmacological Research*. 2021;165:105420.
199 Pickard JM, Zeng MY, Caruso R, Núñez G. Gut microbiota: Role in pathogen colonization, immune responses, and inflammatory disease. *Immunol Rev*. 2017;279(1):70-89.
200 Van Hul M, Cani PD, Petitfils C, De Vos WM, Tilg H, El-Omar EM. What defines a healthy gut microbiome? *Gut*. 2024;73(11):1893-1908.
201 Glassner KL, Abraham BP, Quigley EMM. The microbiome and inflammatory bowel disease. *J Allergy Clin Immunol*. 2020;145(1):16-27.
202 Derwa Y, Gracie DJ, Hamlin PJ, Ford AC. Systematic review with meta-analysis: the efficacy of probiotics in inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*. 2017;46(4):389-400.

203 Colman RJ, Rubin DT. Fecal microbiota transplantation as therapy for inflammatory bowel disease: A systematic review and meta-analysis. *Journal of Crohn's and Colitis*. 2014;8(12):1569-1581.

204 Kedia S, Virmani S, K Vuyyuru S, et al. Faecal microbiota transplantation with anti-inflammatory diet (FMT-AID) followed by anti-inflammatory diet alone is effective in inducing and maintaining remission over 1 year in mild to moderate ulcerative colitis: a randomised controlled trial. *Gut*. 2022;71(12):2401-2413.

205 Lomer MCE, Wilson B, Wall CL. British Dietetic Association consensus guidelines on the nutritional assessment and dietary management of patients with inflammatory bowel disease. *Journal of Human Nutrition and Dietetics*. 2023;36(1):336-377.

206 Casellas F, Guinard Vicens D, García-López S, et al. Consensus document on the management preferences of patients with ulcerative colitis: points to consider and recommendations. *European Journal of Gastroenterology & Hepatology*. 2020;32(12).

207 Hart AL, Lomer M, Verjee A, et al. What Are the Top 10 Research Questions in the Treatment of Inflammatory Bowel Disease? A Priority Setting Partnership with the James Lind Alliance. *Journal of Crohn's and Colitis*. 2017;11(2):204-211.

208 Sigall-Boneh R, Levine A, Lomer M, et al. Research Gaps in Diet and Nutrition in Inflammatory Bowel Disease. A Topical Review by D-ECCO Working Group [Dietitians of ECCO]. *Journal of Crohn's and Colitis*. 2017;11(12):1407-1419.

209 Fairbrass KM, Costantino SJ, Gracie DJ, Ford AC. Prevalence of irritable bowel syndrome-type symptoms in patients with inflammatory bowel disease in remission: a systematic review and meta-analysis. *The Lancet Gastroenterology & Hepatology*. 2020;5(12):1053-1062.

210 Teruel C, Garrido E, Mesonero F. Diagnosis and management of functional symptoms in inflammatory bowel disease in remission. *World J Gastrointest Pharmacol Ther*. 2016;7(1):78-90.

211 Minderhoud IM, Oldenburg B, Wismeijer JA, Van Berge Henegouwen GP, Smout AJPM. IBS-Like Symptoms in Patients with Inflammatory Bowel Disease in Remission; Relationships with Quality of Life and Coping Behavior. *Digestive Diseases and Sciences*. 2004;49(3):469-474.

212 Vadstrup K, Alulis S, Borsi A, et al. Extraintestinal Manifestations and Other Comorbidities in Ulcerative Colitis and Crohn Disease: A Danish Nationwide Registry Study 2003–2016. *Crohn's & Colitis 360*. 2020;2(3):otaa070.

213 Bernstein CN, Nugent Z, Shaffer S, Singh H, Marrie RA. Comorbidity before and after a diagnosis of inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*. 2021;54(5):637-651.

214 Argollo M, Gilardi D, Peyrin-Biroulet C, Chabot J-F, Peyrin-Biroulet L, Danese S. Comorbidities in inflammatory bowel disease: a call for action. *The Lancet Gastroenterology & Hepatology*. 2019;4(8):643-654.

215 Bjerrum JT, Wang YL, Seidelin JB, Nielsen OH. IBD metabonomics predicts phenotype, disease course, and treatment response. *eBioMedicine*. 2021;71.
216 Ferrante M, Vermeire S, Katsanos KH, et al. Predictors of early response to infliximab in patients with ulcerative colitis. *Inflammatory Bowel Diseases*. 2007;13(2):123-128.
217 Parsi MA, Achkar JP, Richardson S, et al. Predictors of response to infliximab in patients with Crohn's disease. *Gastroenterology*. 2002;123(3):707-713.
218 Dubinsky MC, Mei L, Friedman M, et al. Genome wide association (GWA) predictors of anti-TNFα therapeutic responsiveness in pediatric inflammatory bowel disease. *Inflammatory Bowel Diseases*. 2010;16(8):1357-1366.
219 Levine A, Rhodes JM, Lindsay JO, et al. Dietary Guidance From the International Organization for the Study of Inflammatory Bowel Diseases. *Clin Gastroenterol Hepatol*. 2020;18(6):1381-1392.
220 Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*. 2019;68(Suppl 3):s1-s106.
221 Wong S, Walker JR, Carr R, et al. The Information Needs and Preferences of Persons with Longstanding Inflammatory Bowel Disease. *Canadian Journal of Gastroenterology and Hepatology*. 2012;26(8):735386.
222 Baldwin C, McGough C, Norman AR, Frost GS, Cunningham DC, Andreyev HJN. Failure of dietetic referral in patients with gastrointestinal cancer and weight loss. *European Journal of Cancer*. 2006;42(15):2504-2509.
223 Gout BS, Barker LA, Crowe TC. Malnutrition identification, diagnosis and dietetic referrals: Are we doing a good enough job? *Nutrition & Dietetics*. 2009;66(4):206-211.
224 Czuber-Dochan W, Morgan M, Hughes LD, Lomer MCE, Lindsay JO, Whelan K. Perceptions and psychosocial impact of food, nutrition, eating and drinking in people with inflammatory bowel disease: a qualitative investigation of food-related quality of life. *Journal of Human Nutrition and Dietetics*. 2020;33(1):115-127.
225 Bernstein KI, Promislow S, Carr R, Rawsthorne P, Walker JR, Bernstein CN. Information needs and preferences of recently diagnosed patients with inflammatory bowel disease. *Inflammatory Bowel Diseases*. 2011;17(2):590-598.
226 Reich J, Guo L, Groshek J, et al. Social Media Use and Preferences in Patients With Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. 2019;25(3):587-591.
227 Miglioretto C, Beck E, Lambert K. A scoping review of the dietary information needs of people with inflammatory bowel disease. *Nutrition & Dietetics*. 2024;81(1):79-93.
228 Pasta A, Formisano E, Calabrese F, et al. The use of the Crohn's disease exclusion diet (CDED) in adults with Crohn's disease: A randomized controlled trial. *European Journal of Clinical Investigation*. 2025;n/a(n/a):e14389.

229 Sigall-Boneh R, Pfeffer-Gik T, Segal I, Zangen T, Boaz M, Levine A. Partial Enteral Nutrition with a Crohn's Disease Exclusion Diet Is Effective for Induction of Remission in Children and Young Adults with Crohn's Disease. *Inflammatory Bowel Diseases*. 2014;20(8):1353-1360.
230 Sigall Boneh R, Van Limbergen J, Wine E, et al. Dietary Therapies Induce Rapid Response and Remission in Pediatric Patients With Active Crohn's Disease. *Clinical Gastroenterology and Hepatology*. 2021;19(4):752-759.
231 Svolos V, Hansen R, Nichols B, et al. Treatment of Active Crohn's Disease With an Ordinary Food-based Diet That Replicates Exclusive Enteral Nutrition. *Gastroenterology*. 2019;156(5):1354-1367.e1356.
232 Klaassen J, Zapata R, Mella JG, et al. Enteral nutrition in severe ulcerative colitis. Digestive tolerance and nutritional efficiency. *Rev Med Chil*. 1998;126(8):899-904.
233 Sahu P, Kedia S, Vuyyuru SK, et al. Randomised clinical trial: exclusive enteral nutrition versus standard of care for acute severe ulcerative colitis. *Alimentary Pharmacology & Therapeutics*. 2021;53(5):568-576.
234 González-Huix F, Fernández-Bañares F, Esteve-Comas M, et al. Enteral versus parenteral nutrition as adjunct therapy in acute ulcerative colitis. *Am J Gastroenterol*. 1993;88(2):227-232.
235 Sarbagili-Shabat C, Albenberg L, Van Limbergen J, et al. A Novel UC Exclusion Diet and Antibiotics for Treatment of Mild to Moderate Pediatric Ulcerative Colitis: A Prospective Open-Label Pilot Study. *Nutrients*. 2021;13(11):3736.
236 Gibson PR, Shepherd SJ. Evidence-based dietary management of functional gastrointestinal symptoms: The FODMAP approach. *Journal of Gastroenterology and Hepatology*. 2010;25(2):252-258.
237 Gearry RB, Irving PM, Barrett JS, Nathan DM, Shepherd SJ, Gibson PR. Reduction of dietary poorly absorbed short-chain carbohydrates (FODMAPs) improves abdominal symptoms in patients with inflammatory bowel disease-a pilot study. *J Crohns Colitis*. 2009;3(1):8-14.
238 Prince AC, Myers CE, Joyce T, Irving P, Lomer M, Whelan K. Fermentable Carbohydrate Restriction (Low FODMAP Diet) in Clinical Practice Improves Functional Gastrointestinal Symptoms in Patients with Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. 2016;22(5):1129-1136.
239 Maagaard L, Ankersen DV, Végh Z, et al. Follow-up of patients with functional bowel symptoms treated with a low FODMAP diet. *World J Gastroenterol*. 2016;22(15):4009-4019.
240 Tuck CJ, Reed DE, Muir JG, Vanner SJ. Implementation of the low FODMAP diet in functional gastrointestinal symptoms: A real-world experience. *Neurogastroenterology & Motility*. 2020;32(1):e13730.
241 Pedersen N, Ankersen DV, Felding M, et al. Low-FODMAP diet reduces irritable bowel symptoms in patients with inflammatory bowel disease. *World J Gastroenterol*. 2017;23(18):3356-3366.

242 Gottschall E. *Breaking the vicious cycle: intestinal health through diet*. Kirkton, Ont.: Kirkton Press; 1994.
243 Sanders ME, Merenstein DJ, Reid G, Gibson GR, Rastall RA. Probiotics and prebiotics in intestinal health and disease: from biology to the clinic. *Nat Rev Gastroenterol Hepatol*. 2019;16(10):605-616.
244 Suskind DL, Cohen SA, Brittnacher MJ, et al. Clinical and Fecal Microbial Changes With Diet Therapy in Active Inflammatory Bowel Disease. *J Clin Gastroenterol*. 2018;52(2):155-163.
245 Cohen SA, Gold BD, Oliva S, et al. Clinical and mucosal improvement with specific carbohydrate diet in pediatric Crohn disease. *Journal of pediatric gastroenterology and nutrition*. 2014;59(4):516-521.
246 Obih C, Wahbeh G, Lee D, et al. Specific carbohydrate diet for pediatric inflammatory bowel disease in clinical practice within an academic IBD center. *Nutrition*. 2016;32(4):418-425.
247 Suskind DL, Lee D, Kim YM, et al. The Specific Carbohydrate Diet and Diet Modification as Induction Therapy for Pediatric Crohn's Disease: A Randomized Diet Controlled Trial. *Nutrients*. 2020;12(12).
248 Lewis JD, Sandler RS, Brotherton C, et al. A Randomized Trial Comparing the Specific Carbohydrate Diet to a Mediterranean Diet in Adults With Crohn's Disease. *Gastroenterology*. 2021;161(3):837-852.e839.
249 Olendzki BC, Silverstein TD, Persuitte GM, Ma Y, Baldwin KR, Cave D. An anti-inflammatory diet as treatment for inflammatory bowel disease: a case series report. *Nutr J*. 2014;13:5.
250 Zinger A, Barnes EL, Weisbein L, Kappelman M, Micic D. High Red Meat Consumption is Associated With Greater Risk of Ulcerative Colitis Flare. *Official journal of the American College of Gastroenterology | ACG*. 2023;118(12S).
251 Brotherton CS, Martin CA, Long MD, Kappelman MD, Sandler RS. Avoidance of Fiber Is Associated With Greater Risk of Crohn's Disease Flare in a 6-Month Period. *Clinical Gastroenterology and Hepatology*. 2016;14(8):1130-1136.
252 Hadžić K, Gregor A, Kofler B, Pignitter M, Duszka K. The beneficial impact of ketogenic diets on chemically-induced colitis in mice depends on the diet's lipid composition. *The Journal of Nutritional Biochemistry*. 2024;134:109736.
253 Li S, Zhuge A, Wang K, et al. Ketogenic diet aggravates colitis, impairs intestinal barrier and alters gut microbiota and metabolism in DSS-induced mice. *Food Funct*. 2021;12(20):10210-10225.
254 Kong C, Yan X, Liu Y, et al. Ketogenic diet alleviates colitis by reduction of colonic group 3 innate lymphoid cells through altering gut microbiome. *Signal Transduction and Targeted Therapy*. 2021;6(1):154.
255 Norwitz NG, Soto-Mota A. Case report: Carnivore-ketogenic diet for the treatment of inflammatory bowel disease: a case series of 10 patients. *Front Nutr*. 2024;11:1467475.

256 Serra-Majem L, Roman B, Estruch R. Scientific Evidence of Interventions Using the Mediterranean Diet: a Systematic Review. *Nutrition Reviews*. 2006;64(suppl_1):S27-S47.
257 Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: A systematic review and meta-analysis of intervention trials. *Nutrition, Metabolism and Cardiovascular Diseases*. 2014;24(9):929-939.
258 Haskey N, Estaki M, Ye J, et al. A Mediterranean Diet Pattern Improves Intestinal Inflammation Concomitant with Reshaping of the Bacteriome in Ulcerative Colitis: A Randomised Controlled Trial. *Journal of Crohn's and Colitis*. 2023;17(10):1569-1578.
259 Chiba M, Abe T, Tsuda H, et al. Lifestyle-related disease in Crohn's disease: relapse prevention by a semi-vegetarian diet. *World J Gastroenterol*. 2010;16(20):2484-2495.
260 Chiba M, Nakane K, Tsuji T, et al. Relapse Prevention by Plant-Based Diet Incorporated into Induction Therapy for Ulcerative Colitis: A Single-Group Trial. *Perm J*. 2019;23.
261 Schreiner P, Yilmaz B, Rossel J-B, et al. Vegetarian or gluten-free diets in patients with inflammatory bowel disease are associated with lower psychological well-being and a different gut microbiota, but no beneficial effects on the course of the disease. *United European Gastroenterology Journal*. 2019;7(6):767-781.
262 Vrdoljak J, Vilović M, Živković PM, et al. Mediterranean Diet Adherence and Dietary Attitudes in Patients with Inflammatory Bowel Disease. *Nutrients*. 2020;12(11).
263 Marsh A, Radford-Smith G, Banks M, Lord A, Chachay V. Dietary intake of patients with inflammatory bowel disease aligns poorly with traditional Mediterranean diet principles. *Nutrition & Dietetics*. 2022;79(2):229-237.
264 Lomer MC, Hart AL, Verjee A, Daly A, Solomon J, McLaughlin J. What are the dietary treatment research priorities for inflammatory bowel disease? A short report based on a priority setting partnership with the James Lind Alliance. *Journal of Human Nutrition and Dietetics*. 2017;30(6):709-713.
265 Geldof J, LeBlanc J-F, Lucaciu L, Segal J, Lees CW, Hart A. Are we addressing the top 10 research priorities in IBD? *Frontline Gastroenterology*. 2021;12(7):564-569.
266 Horne R, Parham R, Driscoll R, Robinson A. Patients' Attitudes to Medicines and Adherence to Maintenance Treatment in Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. 2009;15(6):837-844.
267 Wang R, Hirano I, Doerfler B, Zalewski A, Gonsalves N, Taft T. Assessing Adherence and Barriers to Long-Term Elimination Diet Therapy in Adults with Eosinophilic Esophagitis. *Digestive Diseases and Sciences*. 2018;63(7):1756-1762.
268 Gibble TH, Naegeli AN, Grabner M, et al. Identification of inadequate responders to advanced therapy among commercially-insured adult patients with Crohn’s disease and ulcerative colitis in the United States. *BMC Gastroenterology*. 2023;23(1):63.

269 Marsal J, Barreiro-de Acosta M, Blumenstein I, Cappello M, Bazin T, Sebastian S. Management of Non-response and Loss of Response to Anti-tumor Necrosis Factor Therapy in Inflammatory Bowel Disease. *Front Med (Lausanne)*. 2022;9:897936.

270 Correia I, Oliveira PA, Antunes ML, Raimundo MdG, Moreira AC. Is There Evidence of Crohn's Disease Exclusion Diet (CDED) in Remission of Active Disease in Children and Adults? A Systematic Review. *Nutrients*. 2024;16(7):987.

271 Abdelhamid A, Jennings A, Hayhoe RPG, Awuzudike VE, Welch AA. High variability of food and nutrient intake exists across the Mediterranean Dietary Pattern—A systematic review. *Food Science & Nutrition*. 2020;8(9):4907-4918.

272 Hou JK, Lee D, Lewis J. Diet and Inflammatory Bowel Disease: Review of Patient-Targeted Recommendations. *Clinical Gastroenterology and Hepatology*. 2014;12(10):1592-1600.

273 Hu D, Ren J, Wang G, et al. Exclusive Enteral Nutritional Therapy Can Relieve Inflammatory Bowel Stricture in Crohn's Disease. *Journal of Clinical Gastroenterology*. 2014;48(9).

274 Cox SR, Clarke H, O'Keeffe M, et al. Nutrient, Fibre, and FODMAP Intakes and Food-related Quality of Life in Patients with Inflammatory Bowel Disease, and Their Relationship with Gastrointestinal Symptoms of Differing Aetiologies. *Journal of Crohn's and Colitis*. 2021;15(12):2041-2053.

275 Le Berre C, Ananthakrishnan AN, Danese S, Singh S, Peyrin-Biroulet L. Ulcerative Colitis and Crohn's Disease Have Similar Burden and Goals for Treatment. *Clinical Gastroenterology and Hepatology*. 2020;18(1):14-23.

276 Haskey N, Gibson DL. An Examination of Diet for the Maintenance of Remission in Inflammatory Bowel Disease. *Nutrients*. 2017;9(3):259.

277 de Silva PS, Luben R, Shrestha SS, Welch A, Khaw K-T, Hart A. 100 Dietary Oleic Acid Protects Against the Development of Ulcerative Colitis–A UK Prospective Cohort Study Using Data From Food Diaries. *Gastroenterology*. 2010;138(5):S-18.

278 Shores DR, Binion DG, Freeman BA, Baker PR. New insights into the role of fatty acids in the pathogenesis and resolution of inflammatory bowel disease. *Inflamm Bowel Dis*. 2011;17(10):2192-2204.

279 Boskou D, Blekas G, Tsimidou M. 4 - Olive Oil Composition. In: Boskou D, ed. *Olive Oil (Second Edition)*. AOCS Press; 2006:41-72.

280 Tjonneland A, Overvad K, Bergmann MM, et al. Linoleic acid, a dietary n-6 polyunsaturated fatty acid, and the aetiology of ulcerative colitis: a nested case-control study within a European prospective cohort study. *Gut*. 2009;58(12):1606-1611.

281 Ananthakrishnan AN, Khalili H, Konijeti GG, et al. Long-term intake of dietary fat and risk of ulcerative colitis and Crohn's disease. *Gut*. 2014;63(5):776.

282 Serra G, Incani A, Serreli G, et al. Olive oil polyphenols reduce oxysterols -induced redox imbalance and pro-inflammatory response in intestinal cells. *Redox Biology*. 2018;17:348-354.

283 Sánchez-Fidalgo S, Cárdeno A, Sánchez-Hidalgo M, Aparicio-Soto M, de la Lastra CA. Dietary extra virgin olive oil polyphenols supplementation modulates DSS-induced chronic colitis in mice. *J Nutr Biochem*. 2013;24(7):1401-1413.

284 Sánchez-Fidalgo S, Cárdeno A, Sánchez-Hidalgo M, et al. Dietary unsaponifiable fraction from extra virgin olive oil supplementation attenuates acute ulcerative colitis in mice. *Eur J Pharm Sci*. 2013;48(3):572-581.

CHAPTER 2: PROTOCOL FOR A CROSS-SECTIONAL STUDY IN INFLAMMATORY BOWEL DISEASE AND A RANDOMISED CONTROLLED TRIAL IN ULCERATIVE COLITIS

Authors: Kenneth Daniel [1], Luis Vitetta [2], Helen O'Connor[1], Daniel Hackett [1], Maria A. Fiatarone Singh [1,2]

[1]Sydney School of Health Sciences, Faculty of Medicine & Health, The University of Sydney, Lidcombe, NSW, Australia

[2]Sydney Medical School, The University of Sydney, Sydney 2000, Australia; Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife, Boston, MA, USA

[1] Deceased 13 January 2020

2.1. Abstract

Background: Inflammatory Bowel Disease (IBD) is a group of chronic conditions characterised by both intestinal and systemic inflammation manifesting in transient symptoms which impact quality of life. Crohn's disease (CD) and ulcerative colitis (UC) are the most common presentations. Although some overlap exists between the two conditions, management strategies such as dietary approaches can often be quite distinct. Currently there is limited consensus on the role of diet as a therapeutic approach, and as such experimentation with both validated and unvalidated strategies are frequently reported in both cohorts. To address this unmet need, understanding patient perspectives and past experiences with dietary strategies is vital for the development of targeted and sustainable strategies.

Separately, animal studies have suggested that extra virgin olive oil may play a role in attenuating disease activity particularly in UC. Few human studies however have been attempted. Likewise, few studies have explored the role of individual foods, and their impact towards broader dietary behaviours, diet quality and health outcomes. A single food intervention in UC therefore presents a unique opportunity to explore these relationships, offering insights into the development of other simple and effective strategies that may support patient health outcomes.

Aims and objectives: The aims of this manuscript is to examine the impact of a single food intervention using extra virgin olive oil on health outcomes in UC. Two concurrent studies have been developed for this purpose and described within this chapter: 1) a cross-sectional study to examine current dietary habits in participants with IBD (XIBD), and 2) a randomised

controlled trial examining the role of olive-based interventions in individuals living with UC in comparison to generally healthy populations (COLONiC)

Design: The XIBD is a cross-sectional study describing the health status, quality of life, physical activity and fitness, dietary habits, food choice, body composition, inflammatory markers and gut microbiome profiles of individuals living with IBD.

The COLONiC Study is a randomised controlled trial using a parallel arm design. The intervention group participants were instructed to replace all their cooking oils and fats with EVOO over 4 weeks, followed by a 4-week washout period of usual diet. Participants in the control group were asked to maintain their usual dietary habits for the study duration.

Participants: For XIBD, we recruited participants with a diagnosis of IBD who were either in remission or had mild to moderate disease (Partial Mayo Score 0-6 for UC, Crohn's Disease Activity Index ≤ 450 for CD). Participants were recruited from the Greater Sydney region and were eligible with the following criteria: aged between 18-75 years at study commencement, had English language proficiency, had no pre-existing conditions precluding them from the study assessments, and could attend two in person assessments.

For the COLONiC Study**,** two groups of participants were recruited: individuals living with UC and generally healthy populations. A total of 44 participants were required for this study: 22 for each population group. Participants were recruited from the Greater Sydney region and were eligible with the following criteria: aged between 18-75 years at study commencement,

stable medications in the preceding 4-weeks, not currently using EVOO or other olive based products less than 4 days a week and ability to commit to the study protocol. A formal diagnosis in the preceding 3 months and remission to moderate disease (Partial Mayo Score between 0-6) was also required for UC cohorts.

Measurement: Assessment outcomes for both studies include participant demographics and medical histories, anthropometry (height, weight, BMI, body composition, appendicular skeletal muscle mass, bone mineral density), inflammatory markers in blood and stool samples, gut microbiome profile through 16S rRNA sequencing of stool samples, food intake through a 3-day weighted food diary, self-reported dietary behaviours and experiences with nutrition support, physical fitness, self-reported physical activity participation, food related quality of life, health related quality of life, fatigue and sleep quality.

Specific to the COLONiC study, primary outcomes were UC disease activity as per Partial Mayo Score and gut microbiome outcomes at baseline, 4 weeks and 8 weeks. Secondary outcomes included body weight changes, inflammatory markers in stool and blood, food intake through a 3-day weighted food diary, self-reported dietary behaviours, self-reported physical activity participation, food related quality of life, health related quality of life measures, and adverse events at baseline, 4 weeks and 8 weeks.

Discussion: Recruitment for both the XIBD and COLONiC Study has concluded as of December 2021. Publication of manuscripts and revisions are ongoing at the time of writing. Study outcomes will provide insights on the current lifestyle intervention opportunities present in IBD, and the role of dietary fats on symptomatic measurements in UC.

2.2. Introduction

Inflammatory Bowel Disease (IBD) refers to a group of idiopathic conditions characterized by chronic gastrointestinal inflammation and dysregulated immune response. It is broadly classified as two major phenotypes, ulcerative colitis (UC) and Crohn's disease (CD). Symptoms vary depending on disease type and severity and may include both intestinal and extra intestinal manifestations such as diarrhoea, abdominal pain, rectal bleeding, fatigue and malnutrition. Predominantly diagnosed in people under the age of 40, IBD is lifelong, and support strategies may evolve over time to match disease progression, symptoms, and comorbidities. [1-3] Significant advancements in IBD care have been achieved in recent years. However, complicated medication regimens, prolonged treatment durations, medication side effects, drug interactions, suboptimal response to treatment, and unmet patient expectations pose challenges for adherence and treatment success. [4-6] As such, non-pharmacological approaches are often viewed as an attractive option for IBD management and symptom control. [7-9]

Many IBD patients believe foods can cause relapse or worsening symptoms. Consequently, up to 68% report specific dietary behaviours or food restrictions, with some variance between UC and CD cohorts. [10, 11] At the time of writing, there is no single diet which is widely advocated for the management of IBD, and the quality of evidence in literature has been variable. [12-15] Generally, adherence to dietary prescription can often be challenging due to complex regiments involving multiple phases, restriction of staple foods, requirement to buy specialised ingredients and associated cost involved, as well as extensive preparation requirements. [16-18] This is further complicated in IBD due to the relapsing-remitting nature of symptoms,

prevalence of food intolerances, and potential variability in therapeutic response between individuals, [19-21] which negatively influences long term sustainability of these interventions.

Modifications to dietary prescription may be attempted based on individual tolerance, personal preference, and beliefs through experimentation or trial and error, [22-27] however, the effects of these adjustments remain unclear. Few studies have explored the role of different foods as part of a broader pre-defined prescription and their impact on published health outcomes, which is further complicated by arbitrary definitions of different dietary patterns. For example, several variations of the Mediterranean diet have been previously described in literature, [28, 29] which complicates the translation of findings into evidence-based dietary guidelines. The contributions of individual food groups and ingredients on the efficacy of the diet are similarly not well understood. [30] For individuals living with IBD, this presents a particular challenge, as dietary modifications and restrictions frequently reported in this population may unintentionally compromise the overall nutritional quality and balance of the diet. This gap in the literature was also recognized by the Dietitians of the European Crohn's and Colitis Organisation (D-ECCO) working group, which highlighted the importance of identifying individual dietary components and their mechanistic effects on IBD symptoms and disease progression as a key area of interest. [31] As such, robust investigations of individual food components are warranted

Although a broad range of experiments have been attempted using single-ingredient or single nutrient interventions such as fish oil, [32] green tea polyphenols, [33] curcumin [34] and probiotics, [35-37] most studies prioritise supplements over a 'food-first' approach. While this may be practical in randomised controlled trials (RCTs) where a placebo might be incorporated, it

limits our understanding of how these components interact within the broader context of dietary patterns. [38] Many supplements also differ significantly from their natural food sources due to their highly concentrated levels of active compounds, raising concerns about toxicity, [39, 40] contamination during the manufacturing process, [41] and their comparability to dietary intake and real-world applicability. Finally, adverse interactions between supplements and IBD medications, [42, 43] alongside the additional burden of incorporating supplements into already complex medication regimens [16, 44] may pose challenges to the feasibility and safety of this approach.

In other lines of research, the Mediterranean diet pattern is increasingly recognized as a lifestyle strategy associated with positive health outcomes. Mediterranean diet adherence as part of a healthy lifestyle is associated with reduced risk of non-communicable diseases including cardiovascular disease, [30, 45] type 2 diabetes, [46] and Alzheimer's disease. [47] A small but growing body of evidence similarly suggest reduced risk of gastrointestinal diseases, [48] various cancers, [49, 50] and auto-immune conditions [51, 52] in populations adopting the diet.

Amongst various components of the traditional Mediterranean diet, the use of extra virgin olive oil (EVOO) has been credited as a significant contributor for the healthful effects of the diet. [30] Consumption of EVOO and its polyphenols have been associated with improvements to cardiovascular health and metabolic outcomes similar to effects of the Mediterranean diet. [53, 54] Emerging evidence suggests these benefits may also extend to inflammatory diseases such as IBD, predominantly through mediation of inflammation and modulation of the gut microbiome. [52, 55] Compared to other fats and oils, EVOO contains a substantial concentration of biological active compounds such as α-tocopherol, oleocanthal, hydroxytyrosol, tyrosol and

oleuropein. [56, 57] Consumption of these polyphenols have been associated with a reduction of inflammatory markers and subsequent improvements to disease outcomes in IBD. [45, 58-61] Furthermore, the use of EVOO as a major source of dietary fat would displace other fatty acids which are associated with risk of developing IBD and worsening symptoms in active disease. [62-65] Finally, evidence from basic animal studies have demonstrated the potential for EVOO and olive polyphenols to influence intestinal microbiome by facilitating the growth of commensal bacteria species and increase short chain fatty acid production. [66-70]

Unfortunately, few experimental trials have explored the relationship between EVOO consumption and IBD outcomes in human cohorts. Animal studies have demonstrated protection against experimental colitis in animals supplemented with EVOO and/or its polyphenols, evident through milder disease scores, symptoms, and normalised colon histology. [71, 72] By contrast, human trials have primarily consisted of observational, [73, 74] prospective cohort studies, [62, 75, 76] and whole dietary prescriptions where EVOO forms part of the intervention. [77, 78]

Interestingly, both prospective cohort studies and RCTs suggest the impact of dietary fat manipulation may favour UC over CD. [74, 79] More recently, a randomised cross-over study in a UC cohort identified attenuation of gastrointestinal symptoms and inflammatory markers in participants supplemented with EVOO which was not evident in participants consuming canola oil. [80] With consideration to the gaps in current evidence for food-based strategies in IBD, promising evidence from basic animal studies and emerging human trials in UC, as well as the substantial effects of EVOO cited in the literature, further investigations on dietary fat manipulations in IBD cohorts are warranted.

2.3. Aims and Objectives

The primary aim of this manuscript is to fill the gap in evidence by exploring the effects of single food dietary interventions using EVOO and investigate the effects on health outcomes in UC. To achieve the aims of this manuscript, we designed two studies that will be fully described in this chapter.

1. A cross-sectional study comparing the lifestyles habits, food beliefs, nutrition support, food related quality of life, health related quality of life, sleep quality, fatigue, and physical activity participation of individuals living with CD and UC (XIBD). We hypothesised that differences between individuals with Crohn's disease (CD) and ulcerative colitis (UC) may be reflected in habitual dietary intake, food-related quality of life, and dietary attitudes and beliefs. Understanding these differences could provide insights into tailored and effective nutrition support strategies for individuals living with CD and UC

2. A randomised controlled trial exploring the effect of dietary fat manipulation using EVOO on health outcomes in UC and generally healthy individuals (COLONiC). The secondary aim of this project is to identify whether there are any sustained clinical outcomes after return to usual care. We hypothesize that EVOO consumption would improve disease activity in individuals with mild to moderate disease activity and health related quality of life outcomes. These microbiome mediated changes will likely diminish following cessation of the intervention during the 4-week wash-out period.

2.4. Methods

2.4.1. The XIBD Study

2.4.1.1. XIBD Study Design

The relationship between physical fitness, quality of life and disease activity in people with Inflammatory Bowel Disease (XIBD) was a cross-sectional study examining the health status, body composition, physical activity participation, dietary habits, food choices, and quality of life of individuals living with IBD. Assessments were completed over 2 separate visits, with 7-14 days between visits. During the study period, participants were asked to maintain usual care. Participants completed all assessments in at the University of Sydney, Faculty of Health Sciences, Cumberland Campus, NSW, Australia. Recruitment of prospective participants commenced on the 06th of June 2018 and concluded on the 14th of December 2021. Written consent was obtained, and the ethics application was approved by the University of Sydney Human Ethics Committee (Protocol no. 2018/734).

2.4.1.2. XIBD Participants and Eligibility

2.4.1.2.1. Eligibility criteria

Prospective participants living with IBD were eligible if they had a confirmed diagnosis of either Ulcerative Colitis (UC) or Crohn's Disease (CD) more than 3 months prior to enrolment in addition to confirmation from their specialist. Participants had to be between the ages of 18 and 75 years at the time of recruitment, had English language proficiency, and could attend the two in-person assessments at the University of Sydney Faculty of Medicine & Health. Participants with UC were eligible if they scored 0-6 out of 9 (remission to moderate disease)

on the Partial Mayo Score [81] during the first in-person screening with the study physician (M.A.F.S.), or had confirmation of remission to moderate disease from their specialist. Participants with Crohn's Disease (CD) were eligible if they scored ≤ 450 (remission to moderate disease) on the Crohn's Disease Activity Index (CDAI) [82] during the first in-person screening with the study physician, or had confirmation of remission to moderate disease from their specialist. Haematocrit blood results were sought from participants with CD to complete the CDAI following the first in-person screening (Assessment 1).

2.4.1.2.2. Waitlist or requiring further evaluation

Inclusion of participants with Inflammatory Bowel Disease Unclassified (IBDU) and/or Indeterminate Colitis (IC) was considered on a case-by-case basis assuming all other eligibility criteria was fulfilled. Participants with severe disease, defined by a Partial Mayo Score above 6 out of 9 for UC, [81] a CDAI >450 for CD, [82] or as indicated by their managing specialist, were placed on a 12-week waiting list pending the management of their active disease.

Participants under medical supervision for the management of unstable disease, in the process of modifying any medication (including tapering), consuming antibiotic or anti-tuberculosis treatment during the study period or preceding 4 weeks, planning to travel, and/or currently enrolled in another clinical trial in which concurrent participation was deemed inappropriate, were also placed on a 12-week wait list and re-invited to participate at conclusion of the waiting period.

2.4.1.2.3. Exclusion criteria

Participants who were pregnant or planning for pregnancy, had comorbid chronic conditions that precluded study assessments, or those reporting any absolute contraindications to exercise testing as defined by the American College of Sports Medicine [83] were excluded from this study.

2.4.1.3. XIBD Recruitment Strategy

Participant recruitment, communications and database management was shared equally between two investigators (K.D. and D.H). Prospective participants living with IBD were sought through online advertising through Crohn's and Colitis Australia (CCA), Australian IBD support networks, the University of Sydney Volunteer for Research Study Webpage, social media posts, and study flyers distributed to both private and public hospitals within greater Sydney. Participants who expressed interest from other projects running concurrently with this study; COLONiC: Consequences of OLive Oil replacemenNt on ulcerative Colitis (University of Sydney Human Ethics Committee Protocol no. 2018/981) and PRE-BIOTIC: Progressive Resistance Exercise- BIOTa and Inflammation in Crohn's & colitis (University of Sydney Human Ethics Committee Protocol no. 2018/029) were also included in this study, subject to meeting the eligibility criteria.

2.4.1.4. XIBD Screening

Following initial expression of interest, prospective participants were provided with an electronic copy of the Participant Information Sheet (PIS) to provide information of the study details. Participants who consented following provision of the forms were invited to complete

a telephone screen by study investigators K.D. and D.H. prior to the two in-person assessments at the Faculty of Health Sciences, Cumberland Campus clinic. Once verbal consent was provided and documented on the telephone screening form, the 60-minute call involved collection of basic demographic information, contact details, and medical history. Following completion of the telephone screen, telephone screening forms were reviewed by the study physician to determine the participants eligibility prior to scheduling the first in-person assessment at the University of Sydney clinic. Participants were then informed of their eligibility to enrol into the study.

Participants eligible as determined by the telephone screen were appointed a schedule comprising of two days, with a 7–14 days between assessments. Information on assessment procedures which include a schedule of the two assessment days and study location. Participants were also asked to submit a signed permission slip addressed to their nominated healthcare provider to allow release of relevant medical information and inform of the participant's intent to participate in this study.

At the start of the first in-person assessment, a review of the study information was completed, and a physical copy of the PIS was provided. Informed consent was then requested prior to commencing the session. For participants who were deemed ineligible for the study at any time point during the screening process, consent was requested to obtain and retain contact details in the event that their situation changed over time.

2.4.1.5. XIBD Outcome Measures

Evaluation of outcome measures in this study was completed over two separate days, with 7-14 days in between assessments. An electronic copy of validated questionnaires used in this study were created and stored within a secure online database hosted on the University of Sydney's REDCap platform only accessible to the study investigators. A schedule outlining of type and sequence of assessments for these two dates are outlined in *Figure 2.1*.

2.4.1.5.1. Participant Characteristics and Medical History

Participant characteristics were collected from completion of a questionnaire administered in the form of a semi-structured interview with study investigators (K.D. and D.H.). Collected information include age, sex, cultural identity, place of birth, migration history, marital status, caregiving responsibilities, accommodations, highest level of education attained, work, study, and volunteer activities, income status, past hospital admission in the preceding 12 months, smoking status, alcohol consumption, and recent travel in the preceding 6 months.

Examination of medical history was completed through a physician screen with the study physician comprising of past medical history, family history including history of IBD and other gastrointestinal conditions, evaluation of disease severity during assessment through the Partial Mayo Score for UC and CDAI for CD, review of medical history, medications, and records provided by participant's nominated healthcare provider, cardiopulmonary and vascular assessment (blood pressure, resting heart rate, varicosities, venous stasis changes, oedema), abdominal examination (tenderness, organomegaly, distension, abnormal bowel sounds, presence of abdominal or inguinal hernias), mood, affect, speech, gait and joint assessments to assess contraindications for cardiopulmonary exercise test and muscle strength. Findings from the physician assessment was discussed with the investigating team, with any required modifications documented.

2.4.1.5.2. Quality of Life, Fatigue, and Sleep Quality

Self-reported quality of life outcomes were assessed through the Inflammatory Bowel Disease Questionnaire (IBDQ-32) examining disease specific quality of life,[84] the Food-related Quality of Life Questionnaire (FRQoL-29) [85] examining the relationship between food and symptoms of patients living with IBD, and the Patient Health Questionnaire (PHQ-9)[86] and Hospital and Anxiety Depression Index (HADS) [87] to screen for anxiety and depressive symptoms. Examination of fatigue through the Inflammatory Bowel Disease Fatigue scale (IBD-F) [88] and sleep quality through the Pittsburgh Sleep Quality Index (PSQI) [89] as also included as part of this sequence.

The IBDQ-32 [84] is a 32-item questionnaire which examines 4 domains which includes bowel symptoms, systemic symptoms, emotional function, and social function. Each item was assigned a 7-point Likert scale in the preceding 2 weeks, with 1 representing worst function and 7 representing best function. Higher domain and total scores indicate better health related quality of life; with a maximum score of 70 for bowel symptoms, 35 for systemic symptoms, 84 for emotional function, 35 for social function, and 224 for the total score (range 32 – 224). A total score ≥ 170 points have been estimated to reflect remission, while meaningful responses in literature range between 16 to 32 points of the total score. [90, 91]

The FRQoL-29 [85] is a 29-item self-reported questionnaire comprising of a 5-point Likert scale examining the psychosocial aspect of food and beverage consumption in IBD in the previous 2 weeks. Higher scores reflect better food related quality of life for each item and the total calculated score (range 29 to 145). No formal cut-offs nor minimal clinically important

difference have been established, however scores ≤ 90 have been used to suggest impairments of food related quality of life. [92]

The PHQ-9, [86] which was originally derived from the full PHQ, [93] is a self-reported 9-item questionnaire assessing for depressive symptoms in the past 2 weeks. Score range from 0 to 27, with each item scoring between 0 (not at all) to 3 (nearly every day), with greater scores indicating more severe depressive symptoms. Major depression is diagnosed if 5 or more items from the 9-item questionnaire were present at least "more than half the days" (score ≥2) in the past 2 weeks and the includes depressive mood (question b, "Feeling down, depressed, or hopeless"). For severity, score of <5 is suggestive of minimal depression, between 5-9 suggestive of mild depression, between 10-14 suggestive of moderate depression, 15-19 suggestive of moderate-severe depression, and >19 severe depression. [86] A widely accepted minimal clinically important difference have yet to be defined for this tool, however score changes between 2.59 – 4.78 have been suggested to be significant in clinical populations. [94-96]

The HADS [87] is a self-reported 14-item questionnaire composed of a 4-point Likert scale (range 0 to 3 for each item) assessing for anxiety and depressive symptoms in the past week. It is divided into two subscales: the HADS-A for anxiety and HADS-D for depression, both comprising of 7 questions with a total score of 21. For both depression and anxiety subscales, higher scores are suggestive of worse symptoms, with a cut-off of >8 defined as "possible" cases, while >11 defined as "probable" cases. No minimal clinically important difference in IBD have been defined, however a change score between 1-2 points for each subscale have

been determined to be clinically significant in cardiovascular [97] and cardiopulmonary settings. [98]

The IBD-F [88] examines and monitors for the presence, severity, frequency, and duration of fatigue in the previous 2 weeks. The tool is divided into 3 sections: level and duration of fatigue (Section 1, 5 questions), impact on daily activities (Section 2, 30 questions), and other factors relating to fatigue (Section 3, 5 question). Items in Section 1 and Section 2 comprise of a 5-point Likert scale from 0 (no fatigue) to 4 (severe fatigue), with higher scores representing worse symptoms. Scoring of the tool is derived from the sum score of Section 1 and Section 2 with a maximum score of 140, while Section 3 is used to describe circumstances which are associated with fatigue. Suggested cut-offs between 7.5 [99] and 11 [100] for Section 1 to distinguish significant and non-significant fatigue, however there were limited consistency between the settings and populations represented across these studies which limits their generalisability. Likewise, clearly defined minimal clinically important difference for this tool is lacking. [101]

The PSQI [89] examines sleep quality in the past 1 month. The self-reported questionnaire is comprised of 19 items used to generate scores across 7 sleep-related components including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. Each component is scored between 0 and 3, with a global calculated score of 21 for all 7 components. Greater scores are suggestive of greater sleep impairments, with a cut-off of ≥ 5 indicative of poor sleep quality. No widely accepted minimal clinically important difference has been established for this tool, however a change between 3 – 5.5 points has been reported to be significant in rotator cuff repair [102] and insomnia patients. [103]

The FRQoL-29 was administered by the study dietitian (K.D.) All remaining quality-of-life assessments were administered by a single assessor (either K.D. or D.H.) nominated for a participant for the study duration who verbally prompted the questions for each tool. Participants were also presented with the questions on the computer screen to assist with administration of the questionnaires. All questionnaires were completed prior to physical fitness assessments (cardiopulmonary exercise testing and muscle strength assessment) to reduce the likelihood of acute affective changes following physical activity [104, 105]. Breaks were offered between each questionnaire to minimise participant distress. Questionnaires that could not be administered during Assessment 1 due to fatigue or participant's time constraints were documented and moved to Assessment 2. Questionnaires administered during Assessment 2 were completed prior to the repeated muscle strength assessment. All calculations and interpretations of the health-related quality of life questionnaires were completed by a single assessor (K.D.). Participants were not informed of the results or scores from each questionnaire until the end of their participation in the study.

2.4.1.5.3. Fitness testing

Clearance from the study physician was required prior to commencement of the exercise testing, with modifications to the protocol implemented if appropriate for safety purposes. Participants were instructed to wear light articles of clothing and sports or comfortable walking shoes for the assessment. The exercise testing protocol included cardiopulmonary exercise tests and muscle strength, which was supervised by an accredited exercise physiologist (D.H.) for the study duration.

I Cardiopulmonary Exercise Test

Peak aerobic capacity (VO2 peak), exercise electrocardiogram (ECG), and cardiovascular performance during exercise was assessed via a graded treadmill test under supervision of the study physician. Calibration was completed prior to commencement of the test, and a habitual gait speed was measured through a timed 2-meter walk measured in duplicate. This information was then used to calculate walking speed on the treadmill (Q-Stress System, Quinton, Bothwell, WA, U.S.A.).

Participants were fitted with three sets of equipment; a 12-lead ECG, blood pressure monitor (SunTech Tango Blood Pressure Monitor, SunTech Medical, Morrisville, NC, U.S.A), exercise preVent® Mask (Pat. #6718982, Taiwan) and accompanying preVent® flow sensor. Placement of ECG electrodes on the torso was completed in accordance with standard procedures. [106] Blood pressure, heart rate, ECG, and oxygen consumption (VO2) was monitored both at rest prior to assessment and during exercise using the Medical Graphics' Ultima™ PFX Series (St. Paul, Minnesota, U.S.A) and accompanying BreezeSuite Software (Version 6.2a).

The protocol comprised of 19 1-minute stages divided over 2 phases with increasing difficulty at each stage. Stage 1 to 13 began at 0% incline, increasing 2% each minute up to 24% at stage 13 while maintaining the calculated walking speed. This was followed by stages 14-19 where incline was maintained, however walking speed was increased at a rate of 0.5 km/h at each stage. Exertion was measured using the classical Borg 6-20 RPE scale (BORG-RPE) [107] at the end of each stage, and participants were asked to signal if they were able to continue with the protocol. At completion of the test, a 1-minute active recovery period at 0% incline and 1.4 km/h speed was implemented followed by a seated cool down period while the participant

continued to be monitored for any adverse events. The test was terminated in the event participants requested to discontinue for any reason (pain, fatigue), cardiovascular abnormalities (hypertension >250 mm Hg systolic; >120 mm Hg diastolic, ST elevations above resting level, symptoms of angina), loss of coordination, mental confusion, and other adverse reactions as determined by the physician. Any adverse events occurring during the test were documented, with follow-up organised as appropriate to review the participant's suitability to continue with the study.

II Muscle Strength

Muscle strength was assessed through supervised 1-repetition maximum (1RM) tests done twice over a 7–14-day period, first during Assessment 1 and repeated at Assessment 2. A demonstration of the task was provided by the accredited exercise physiologist in addition to verbal instructions prior to commencing each assessment. Peak power was measured during Assessment 1 following the first 1 RM test. Testing was conducted using Keiser (https://www.keiser.com) pneumatic resistance training machines and included bilateral leg press, bilateral leg extension, bilateral triceps extension, and chest press in no particular order. For the power testing, participants were asked to push loads from 20% to 100% of the previously determined 1RM one time only as fast as possible, with power, velocity and load recorded at each repetition. Peak concentric power was recorded from the repetition with the highest Watts achieved during the test on each machine. Verbal encouragement to elicit maximal performance was provided for the duration of the muscle strength assessment. Modifications or the removal of any of the muscle strength assessment following recommendations by the study physician were documented.

2.4.1.5.4. Habitual physical activity and sleep

Habitual physical activity levels and sleep was assessed with an Axivity monitor (Axivity MEMS AX3 3-axis accelerometer, Axivity, Newcastle upon Tyne, United Kingdom) and self-reported physical activity and sleep logs completed over a 7-day period (Appendix 1). The device was fitted in the middle of participant's lumbar spine, centred between the L3 and L4 vertebrae using a waterproof silicone adhesive (OPSITE™ FlexiFix 10cm×10m roll transparent, Smith & Nephew, Watford, United Kingdom) by the study dietitian (K.D.) for all participants.

Participants were provided with an instruction sheet to complete the self-reported physical activity and sleep logs, a diagram showing placement location of the Axivity monitor, and spare silicone adhesives. In the event of the device detaching, participants were asked to document time of the event and re-attachment using the new adhesive.

Participants were instructed to wear the device for a 7-day period and maintain all habitual physical activity during the monitoring period. Participants were required to refrain from long periods (defined as >30 minutes) of water immersion including baths, swimming, or exposure to extreme conditions such as saunas and steam rooms which are likely to compromise device functionality. Participants reporting these activities who agreed to the conditions of wearing the Axivity monitor were asked to document these changes in their habitual physical activity logs. Participants refusing to wear the Axivity monitor, those unable to modify their participation in activities contraindicated with wearing the device, and those reporting a history of allergic reaction to medical tapes were excluded from wearing the Axivity monitor and only provided with the habitual physical activity and sleep logs to complete over a 7-day period.

Participants reporting discomfort and adverse reactions to the Axivity monitor and/or adhesives were instructed to remove the device and record the time and date of removal on their logs. Following completion of the 7-day recording period, participants were asked to remove the Axivity monitor on the 8th day and present both the device and completed logs to study investigators during Assessment 2.

An open-source movement analysis software (OMGUI V43, https://github.com/openmovementproject/openmovement) was used to configure and extract data from the Axivity monitors. Sampling frequency was set to 100Hz, range was set to ± 8g, mounting site was set to the lower back and recording time was set to commence at 12:00 AM following completion of Assessment 1 alongside completion of habitual physical activity and sleep logs. Raw data exports from all returned Axivity monitors were kept in a university-maintained research folder only accessible by the study investigators for future analysis. Habitual physical activity logs comprised of intentional physical activity or exercise, duration of the activity, and a self-reported Borg category-ratio 10 scale (BORG-CR10). [107] Sleep components include waking time, time out of the bed, daytime sleeping, time participants attempt to go to sleep, time the Axivity monitor has fallen off or was removed for any reason, and medications.

2.4.1.5.5. Diet

Dietary outcomes include energy and macronutrient estimates through a 3-day weighted food diary, dietary attitudes, and experiences with diet and nutrition support was examined through a semi structured interview with the study dietitian (K.D.).

I Estimated Energy and Macronutrient Intake

Recording of food intakes through the 3-day weighed food diary was designed to run concurrently with completion of the self-reported habitual physical activity and sleep diaries (2.4.1.5.4). Participants were instructed to nominate 2 weekdays and 1 weekend within a 7-day period between Assessment 1 and Assessment 2 to record all foods and beverages consumed as part of usual intake. One of the nominated recording days was required to be within 24 hours prior to the stool sampling date (2.4.1.5.7) to account for potential impact of food on microbiome richness, diversity, and inflammatory markers. Otherwise, no other restrictions were placed on the sequence of the food recording dates.

Food records were collected through 1 of 2 methods: a paper-based food diary (Appendix 2) or an app-based electronic food diary containing a database for Australian foods (Easy Diet Diary, Xyris Software Pty Ltd, Brisbane, Australia). Participants completing a paper-based diary were provided with a sample template on how to use the paper forms. Participants electing to use the electronic food diary were instructed to download the app on their smart mobile devices and provided an instruction booklet upon completion of Assessment 1. Participants were instructed to prioritise weighted amounts using digital kitchen scales rather than volumetric measures (teacups, tablespoons, measuring cups and measuring jugs) or estimates to record food quantities. A digital kitchen scale (5kg/1g Electronic Weight Balance Scale, FineLife, China) was provided assist with this task. If unable to weight their meals (e.g., while dining out), participants were instructed to take a photo of their meal and record their estimates using utensils available to them during the meal for review during Assessment 2. All completed food diaries were reviewed by both the study dietitian (K.D.) and participants to confirm the type of foods and quantities recorded using a dietitian assisted food records checklist (Appendix 3).

Completed electronic and paper-based food diaries were analysed with FoodWorks 10 Professional (Xyris Software Pty Ltd, Brisbane, Australia). Electronic diaries were exported in the form of FoodWorks interchange file (FWEDD) to import into FoodWorks 10 Professional, and paper- based diaries were manually entered by the research dietitian. In the event that foods were not available in the FoodWorks database, a proxy food substitute was used, with the actual recorded food logged on the comment section of the database. The selection of proxy foods to substitute unavailable entries was as follows: using the same branded item with a different flavour, using a generic food item matching the food's description, and if neither was viable, adding a new food item in using the nutrition information panel published in the manufacturer's website. Both raw food diary exports and analysed records were retained in the FoodWorks database as separate files for each participant. Individual analysed records were saved into a project specific database. Averages of the 3-day weighted food diary was selected to represent average energy and macronutrient intakes.

Estimation of basal metabolic rate (BMR) for each participant was calculated using sex- and age- specific Schofield equations [108] based on measured weight (in kg). This was then multiplied by sex-specific physical activity level (PAL) selected based on self-reported habitual physical activity matched against published definitions for sedentary, light, moderate, and vigorous activity [108-110] to calculate estimated energy requirements (EER).

II Dietary Attitudes

Dietary attitudes were assessed using a subjective Food Choice Questionnaire (FCQ) [111] which was administered verbally through an interview with the study dietitian (K.D.). The tool,

consisting of 36 statements, examines motivations for food choice and is categorized into nine domains: mood, convenience, sensory appeal, natural content, price, weight control, familiarity and ethics. Participants rated each statement using a 4-point Likert scale, where higher scores indicated a greater perceived importance for each item.

III Experiences with Diet and Nutrition Support

Experiences with diets and dietary patterns were assessed through a general diet questionnaire developed for this study comprising of; 1) personal nutrition goals, 2) shopping and cooking habits, 3) diagnosed and suspected food-related allergies and/or intolerances, 4) past and current experiences with dietary strategies for the management of IBD, and 5) past experiences with nutrition advice (Appendix 4).

2.4.1.5.6. Body Composition

Anthropometry outcomes included naked weight, standing height, BMI, body composition, and total body, hip, and spine bone mineral density. All body composition measures were completed while fasting after in-person consent was granted during Assessment 2.

Anthropometry assessments were completed by a single assessor trained in ISAK level 1 anthropometry techniques (K.D.), with assessment time and dates recorded for each task. Participants were instructed to remove all articles of clothing except undergarments and wear a clinic gown of a known weight which was measured prior to the commencement of the assessment in triplicate. Average values of the 3 measurements were used to report gown weight.

I Standing Height, Naked Weight, and BMI

Standing height were measured with a wall-mounted Holtain stadiometer (Holtain Ltd, Crymmych Pembs. UK). Participants were instructed to remove all footwear, socks, and hair ties, with the heel and buttocks placed against the stadiometer and head positioned at Frankfort plane during measurement. Measurements were repeated in triplicate, and participants were instructed to step away from the stadiometer prior to repeat measures. Recording of height results were done while measures were read at the investigator's eye level to minimize the potential for parallax error.

Naked weight was measured using electronic scales (AND HW (100 kg)) in triplicate, with the gown weight subtracted from the weight measured. For each measure participants were instructed to step on the scales and face forward, stand relaxed and maintain even weight between both feet. Measurements were taken once the scale values are stable, at which point participants were asked to step off the scales and repeat the assessment an additional 2 times.

For both standing height and naked weight, a 1% deviation threshold was established between the 3 measurements. Any values exceeding this limit required repeat assessment. The mean values of triplicate measurements for both height and weight were reported. Body Mass Index (BMI) was calculated by dividing weight (in kg) over height (in metres) squared using these mean values.

II Body Composition and Bone Mineral Density

Body composition and total body, hip, spine bone mineral density was assessed using a Lunar Prodigy Dual-energy X-ray Absorptiometry (DXA) Scanner and encore software (GE Medical Systems Lunar, Madison, Wisconsin). Operation and calibration of the DXA was performed by a single trained assessor who has attained the Australian New Zealand Bone Mineral Society (ANZBMS) clinical densitometry course and current radiation user license issued by the New South Wales Environmental Protection Agency (NSW EPA). Daily calibration was performed prior to assessment of a participant and achieved using a quality a calibration block for quality assurance, and an enclosed spine phantom of a known composition for quality control in line with best practice recommendations. [112, 113] Scans indicating repeat "out of calibration" (OOC) values resulted in suspension of DXA scans pending further evaluations of the instrument by technicians.

Participants were required to present to clinic while fasted (8 hours prior to the scan), present in an euhydrated state, and refrain from both alcohol consumption (due to likely impacts on hydration status) and exercise (due to impacts on hydration status and glycogen stores) 8 hours prior to presenting in clinic. Sips of water and consumption of time critical medications were excepted and documented. Participants were asked to change into a clinic gown of a known weight, remove any metal items including jewellery, hair ties, clips, and underwire bra, and asked to empty their bladder. History of surgical repairs, metal implants, back pain or known fractures, and any deviation from protocols were recorded in the DXA data collection sheet. (Appendix 5)

Prior to the scan, participant information was entered into the encore software including study code, date of birth, sex, height and weight (anthropometric measurements done prior), and ethnicity. Participants were then positioned supine within the border of the DXA bed, head positioned 3cm below the top horizontal line, body centred along the centre line the bed, head positioned in the Frankfort plane, and clear separation of limbs. Legs are internally rotated and affixed using a positioning strap, while arms are abducted to ensure sufficient clearance from the torso while remaining within the borders of the DXA bed. Once positioned, participants were instructed to remain still and refrain from talking for the duration of the scan (approximately 5-6 minutes). Scan mode (Thick, Standard, Thin) and any deviations from the protocol for all scans were recorded on the DXA record form.

Examination of participants too tall to fit within the length of the DXA bed (>195 cm) for the whole-body scan used the 'total body less head' (TBLH) where participants were positioned and centred on the bed as previously described, however head placement was shifted up to ensure that feet were placed within the scanning bed. [113] Participants not fitting the width of the bed (≥60 cm) or those unable to sufficiently separate their limbs for the whole-body scan completed two partial right and left scans, where participants were scanned twice, and both half images were combined for analysis.

Anteroposterior spine (AP spine) was examined while participants were centred on the DXA bed in supine position, arms alongside the body and palms facing down. To flatten the lower back and show separation of the vertebrae, participant's legs were elevated using a foam support block with 3 different heights allowing for their thighs to be positioned at a 90° angle relative to the bed surface, while the DXA technician examined the participant's lower back

for any gaps. The DXA scanning arm was levelled with the participant's iliac crest and centred between the width of the bed. Once the scan commenced, scanning images were examined by the DXA technician for quality assurance. Errors resulting from incorrect positioning or insufficient participant preparation resulted in readjustment and repeat scans.

Imaging of the bilateral femur comprised of individual scans for the right and left hip. Participants remained supine and centred along the DXA with hips internally rotated and parallel with the scanning bed. A foot brace was used as a positioning aid to hold each leg's position in place during the scan. Participants unable to achieve sufficient internal rotation due to hip arthritis or femoral necks were positioned to the best of their ability and documented in the DXA form. Participants with a hip replacement were not scanned on the affected side. Hip scans were examined for clear separation of the greater trochanter, femoral neck, and part of the ischium, femoral shaft perpendicular to the lower border of the scanned image, and minimised lesser trochanter.

Analysis of DXA scans were completed on the encore software and comprised of the following; 1) combining partial right and left scans for whole body scans and defining regions of interest (ROI) for segmental assessment of body composition, 2) identification of correct markers and ROI positioning in AP spine scans, 3) ROI positioning in bilateral femur scans, 4) verification of tissue types (bone, soft tissue, artefacts) and 5) removal of artefacts.

Appendicular lean mass (ALM) was calculated by the addition of left and right arm lean mass and left and right leg lean mass from the whole-body scan. Total skeletal mass (Total SM) uses previously published prediction equations, where: $Total\ SM: 1.12 \times ALM - 0.63.$ [114] Ams

skeletal muscle mass (Arm SM) and legs skeletal muscle mass (Leg SM) were estimated using previously published prediction equations, where; $Arm\ SM: 0.58 \times (arm\ left\ lean + arm\ right\ lean) + 0.15$ and $Leg\ SM: 0.78 \times (leg\ left\ lean + leg\ right\ lean) - 1.07$. [114] Appendicular skeletal muscle (ASM) was the sum of both Arm SM and Leg SM. Appendicular skeletal muscle index (ASMI) was calculated by dividing ASM by height (in metres) squared. To determine low muscle mass in this cohort, ASMI was compared against the updated European Working Group on Sarcopenia in Older People (EWGSOP2, version 2019) definitions using ASMI cutoff values of <7.0 kg/m^2 for men and <5.5 kg/m^2 for women. [115] Cut-off values used a European population reference group [116] and was determined based on -2 standard deviations (SD) below healthy young adult means. Bone mineral density (BMD) results of the AP spine and bilateral femur in this study were compared against a population matched reference database of young healthy adult norms of a predominantly Caucasian population aged ≥20 years. A Normal BMD was defined as a T-score ≥ - 1.0 SD from the reference population, T-score between -1.0 and -2.4 SD was defined as Osteopenia, and T-score ≤ 2.5 defined as Osteoporosis. [117]

2.4.1.5.7. Inflammatory Markers

Inflammatory markers were assessed through fasting blood samples and stool samples collected during Assessment 2.

I Blood Markers of Inflammation

Fasting blood samples were collected by research staff trained in venepuncture under sterile conditions. Prior to collection, participants were queried on medical histories pertinent to the collection which included any history of blood-borne diseases, blood clotting issues, bleeding

disorders, consumption of blood thinning medications, and adverse events related to venepuncture and blood collection. The study physician was consulted for any new histories identified which potentially precluded participants from blood sampling, and the procedure was excluded from the battery of assessments if necessary.

Blood sampling was performed by investigators trained in venepuncture (K.D. and M.A.F.S.), completed while participants were lying down to avoid light headedness or fainting during the procedure. For the blood sampling procedure, 4 Vacuette® tubes were used for collection comprising of 2 x 9 mL CAT serum clot activator tubes (red top) and 2 x 9 mL K3 EDTA tubes (lavender top). The correct order of draw commencing with red top tubes followed by lavender top tubes was completed to minimise the risk of cross contamination with potassium ethylenediaminetetraacetic acid EDTA (kEDTA).[118] Filled blood tubes were gently inverted to ensure adequate mixing with the additives and allowed to sit in room temperature for 30 minutes prior to processing. If blood samples were not immediately processed, tubes were stored in a refrigerator set at 4°C. All blood samples were processed within 6 hours of collection.

Blood processing was completed in a Physical Containment Level 2 (PC2) laboratory at the University of Sydney Faculty of Medicine & Health under sterile conditions. Bloods were first centrifuged at 2000 rpm at 4°C for 15 minutes. The supernatant solution was then divided under a fume hood into sterilised and labelled 1.5 mL micro tubes (Eppendorf Safe-Lock tubes; total 8 aliquots; 0.5 mL per tube); for red top tubes and lavender top tubes (EDTA). Once sealed, blood aliquots were batched and stored in a -80°C freezer until processing to quantify blood

lipopolysaccharide (LPS), C-reactive Protein (CRP), tumour necrosis factor alpha (TNF–α) and Interleukin–1 beta (IL–1β), 6 (IL – 6), 10 (IL–10), and 12 (IL–12).

Plasma LPS was quantified using chromogenic limulus amebocyte lysate (LAL) assay commercial kits (Pierce™ chromogenic endotoxin quant kit, A39553, Thermo Fisher, Sydney, NSW, Australia).[119] Plasma samples aliquots from EDTA tubes were diluted 50-fold in endotoxin free water. Alongside pre-prepared endotoxin standard stock solution and blanks (endotoxin-free water), 50 µL samples were dispensed in 96-well plates maintained at 37°C in triplicate. Reconstituted Amebocyte Lysate reagent (50 µL) was then added to each well, mixed, and incubated at 37°C for 25 minutes. Pre-warmed chromogenic substrate solution (100 µL) was then added into each well, and the plate incubated for another 6 minutes. Upon completion of the incubation period, 50 µL of 25% acetic acid was added to each well to stop the reaction. Optical density was measured at 405 nm after completion of the assay using a 96-well plate reader. Concentrations between 0 and 10 ng/mL have been described as being clinically relevant, [120] however due to significant variability in reported baseline values in healthy subjects [121-123] a cut-off was not selected.

Serum samples were used to quantify CRP using commercially available h Human C-Reactive Protein ELISA Kit (RAB0096, Sigma-Aldrich, St Louis, Missouri, United States)[124] following manufacturer's instructions. Briefly, all prepared reagents, diluents, and frozen samples were brought to room temperature (20°C) prior to use. Serum samples were diluted 20,000-fold using prepared diluents prior to the assay. Alongside prepared protein standards and blanks, 100 µL samples were dispensed in 96-well plates duplicate and incubated at 25°C for 2.5 hours. Three reagents (biotin antibody, Streptavidin solution, TMB One-Step Substrate Reagent) were

then added sequentially in 100 µL dose to each well while temperature was maintained at 25°C for the duration of the experiment. Upon completion of the incubation period, 50 µL of a Stop Solution was added to each well. Optical density was measured at 450 nm immediately after completion of the assay using a 96-well plate reader. Intra-assay coefficient was set at 10%, with samples exceeding this value repeated. Serum CRP concentration below 5 mg/L were considered within reference intervals for healthy subjects. [125, 126]

Cytokine concentrations of TNF–α, IL–1β, IL – 6, IL–10, and IL–12 was quantified in plasma EDTA using commercially available assay kits (MILLIPLEX® Human Cytokine/Chemokine/Growth Factor Panel A Magnetic Bead Panel, HCYTA-60K, Milipore, Minneapolis, United States) according to manufacturer's instructions.[127] Samples for LPS, CRP and plasma cytokines were assessed in duplicate, and any sample with an intra-assay coefficient greater than 10% was repeated. Results were compared against reported serum concentrations in healthy subjects from previous publications; 28 – 38 ρg/m for TNF–α,[128] <5 ρg/ml for IL–1β,[129] <14 ρg/ml for IL–6,[128, 130] <17 ρg/ml for IL–10,[128, 131, 132] and 20 – 56 ρg/ml for IL–12.[119, 128, 133]

II Faecal Calprotectin and Gut Microbiome Analysis

Stool samples were collected by participants at the end of a 3-day weighted food diary and 7-day activity log from the first bowel motion of the day in a fasted state. A collection kit was provided which included a 70 mL specimen container with a scoop lid (Techno Plas, P5744F), an absorbent pad (Livingstone International, 8-Ply, 56 x 40cm), powder-free latex gloves (Lincon, AS/NZ Standard, Polymer Coated), a copy of the Bristol Stool Chart, [134] a collection checklist (Appendix 6), and a plastic biological specimen bag for transportation.

During sample collection, participants were instructed to line their toilet with the absorbent pad to prevent contact with the toilet bowl and water. Once the sample was produced, participants needed to collect enough to fill half of the specimen container using the scoop lid, fill out details on the stool collection checklist and place in the specimen bag provided. Participants were instructed to store samples in the deepest part of their home fridge until transport to the clinic. In the event that the samples could not be transported to the university clinic within 72 hours of production, collection was organised by the research team. Samples were transported in an insulated container filled with dry ice to ensure that the samples remained cool during transport. Limited data currently exist outlining the impact of transport and processing variables on gut microbiome analysis, [135, 136] however precautions outlined in this study were to ensure that these variables were controlled. Accompanying the stool samples were the collection checklist, a 7-day physical activity and sleep logs (2.4.1.5.4), as well as a 3-day food diary (2.4.1.5.5) which included a record of foods consumed 24 hours prior to specimen production.

Stool specimens were processed by the study dietitian (K.D.) in a Physical Containment Level 2 (PC2) laboratory at the University of Sydney Faculty of Medicine & Health under sterile conditions, which involved manual homogenization using a UV-sterilised plastic stirring rod in a fume hood. Once well mixed, samples were divided into 5 × 1gram aliquots (Sarstedt 101 x 16.55 faecal tubes, SARSTEDT, Nümbrecht, Germany) and labelled with the participant study code, sample processing date, and tube number. All samples were batched by study code and stored in a -80-degree Celsius freezer until processing for 16S rRNA sequencing using Ion GeneStudio™ S5 sequencing system (Thermo Fisher, Sydney, NSW, Australia) and quantification of faecal calprotectin by an external laboratory. Reference ranges of 75-150 µg/g

for faecal calprotectin concentration based on previous publications [137, 138] was selected to determine patients with quiescent disease.

2.4.1.5.8. Tracking and Adverse Events

Reporting of adverse events between Assessment 1 and Assessment 2 whether or not it was deemed to be related to the study was examined either in-person, through phone calls or e-mail correspondence for the duration of study participation. Participants were requested to report all changes to medication or supplement regimen, visits to a healthcare professional, new diagnosis, acute illnesses, physical activity and new symptoms between assessments.

2.4.1.6. XIBD Statistical analysis

Statistical analysis was performed by the study dietitian (K.D.). Descriptive statistics using means, standard deviations (SD), medians, ranges and frequencies as appropriate to the data distribution were used to describe participant characteristics, medical history, habitual physical activity and diet. Categorical variables were reported as numbers (n) and percentages (%), representing the proportion of total responses within groups. Data analysis was completed using SPSS® Statistics version 28.0 (IBM®, Chicago, IL, USA). Unpaired t-tests were used to analyse differences in continuous variables between UC and CD as well as between sexes. Normality of data distribution was examined using the Shapiro-Wilk tests. Relationships between categorical variables of interest were evaluated using Pearsons's chi-squared tests. Confidence interval was set at 95% and p values of <0.05 were defined as statistically significant. One-way ANOVA was used to analyse differences in dietary intake and disease severity categories.

2.4.2. The COLONiC Study

2.4.2.1. COLONiC Study Design

The COLONiC Study was a randomised controlled trial using a parallel arm design adhering to CONSORT guidelines for clinical trials [139] with additional consideration for nutrition interventions. [140] The study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) with the registration number ACTRN12619000150145 in January 2019. Recruitment of prospective participants commenced on the 24th of April 2019 and concluded on the 14th of December 2021. Participants completed all assessments and follow ups at the University of Sydney, Faculty of Health Sciences, Cumberland Campus, NSW, Australia. Interventions were completed at each participant's residence, including completion of a symptom's diary and EVOO consumption log. Study design and randomisation into study arms for subjects are outlined in *Figure 2.2*. Written consent was obtained, and the ethics application was approved by the University of Sydney Human Ethics Committee on in March 2019 (Protocol no: 2018/981). Participants living with UC deemed ineligible for this study were invited to participate in the XIBD cross sectional study.

2.4.2.2. COLONiC Participants and Eligibility

Two groups of participants were recruited for this study; participants living with UC and generally healthy participants with no history of IBD (healthy controls). Separate participant information sheets for participants living with UC and healthy controls were provided.

2.4.2.2.1. Participant with UC eligibility criteria

Participants with UC comprised of both men and women aged between 18 and 75 with a confirmed diagnosis of UC more than 3 months prior to commencing the study. Participants were included if they were currently either in remission or with active mild-to-moderate disease as defined by a Partial Mayo Score [81] between 0-6. The full Mayo Score which includes an endoscopy rating was considered, however could not be included due to funding limitations. Stable medication in the preceding 4 weeks was required to minimise the likelihood of altered disease outcomes unrelated to the intervention. Furthermore, all prospective participants were required to attend the in-person clinic assessment to be eligible for the study.

2.4.2.2.2. Participant with UC exclusion criteria

Exclusion criteria for individuals with UC included the following: 1) other forms of IBD such as CD, IBDU or IC, 2) prior or concomitant faecal microbial transplant, 3) gastrointestinal resection with the exception of appendectomy, 4) evidence of any terminal or rapidly progressing disease which precluded the participant from assessments, 5) coexistence of serious autoimmune disease such as rheumatoid arthritis or systemic sclerosis, 6) regular consumption (more than 3 days a week) of olive-based product(s) in any form (including olive oil, pickles, tapenade, spreads, and supplements) as determined by the diet history and medication list, and 7) special dietary requirements precluding the intervention.

2.4.2.2.3. Healthy controls eligibility criteria

The healthy control group was comprised of both men and women aged between 18 and 75 with no history of chronic disease or comorbidities. Eligibility criteria for this cohort included: 1) body mass index (BMI) between 18.5 and 30 kg/m^2, 2) ability to attend the in-person clinic

assessment and 3) no prior chronic conditions or comorbidities. Age- and sex- matched participants were initially considered as part of the eligibility criteria for healthy controls, however was abandoned due to the broad range of variables likely to influence gut microbiome beyond these parameters, and inconsistent findings on sex and age specific variations in published literature during development of this study. [141-143]

2.4.2.2.4. Healthy controls exclusion criteria

Exclusion criteria for the healthy control cohort included the following: 1) prior or concomitant faecal microbial transplant, 2) gastrointestinal resection with the exception of appendectomy, 3) evidence of any terminal or rapidly progressing disease which precluded the participant from assessments, 4) formal diagnosis or suspected chronic condition, metabolic disease, and/or autoimmune condition such as type 2 diabetes, irritable bowel syndrome (IBS), coeliac disease, arthritis, 5) regular consumption of olive-based product(s) in any form (including olive oil, pickles, tapenade, spreads, and supplements) as determined by the diet history and medication list, and 6) special dietary requirements precluding the intervention.

2.4.2.2.5. Wait list or requiring further evaluation

Prospective participants for both cohorts were placed on hold with the following: 1) current adjustments to medications and/or supplementation in the preceding 4 weeks, 2) antibiotic consumption for any reason in the past 4 weeks, 3) probiotic supplements or biological/monoclonal antibody agents during the study period or in the preceding 12 weeks, 4) planned major surgery within the first 3 months after randomisation, 5) pregnancy or planning pregnancy within the first 3 months after randomisation, 6) participation in another clinical trial where concurrent participation was deemed inappropriate, and 7) temporary

dietary adjustments for which participation was deemed inappropriate, and 8) current exercise participation at an elite competitive level.

2.4.2.3. COLONiC Recruitment Strategy

Recruitment strategy for both cohorts was achieved through Crohn's & Colitis Australia's website and IBD support networks newsletters, non-government organisations, University of Sydney research website, private and public clinics, and social media focusing on the Greater Sydney region. Inclusion of potentially eligible participants in New South Wales and interstate was considered on a case-by-case basis under the condition that participants were able to attend in-person assessment sessions. Participant recruitment, telephone screening, communications, database management was performed by one investigator (K.D.).

2.4.2.4. COLONiC Screening

2.4.2.4.1. Telephone Screening

Potentially eligible participants underwent a two-stage screening process which included a telephone screen and two in-person assessments at the University of Sydney clinic. The telephone screen consisted of a 60-minute telephone call with a research staff to assess a participant's eligibility, collect basic demographic information, contact details and medical history. Verbal consent was requested prior to commencing the screening procedures.

2.4.2.4.2. Investigator Review

Once completed, the telephone screening form was reviewed by the primary investigator to assess a participant's eligibility prior to scheduling the in-person assessments. Participants were informed of their eligibility or if they were placed on hold for further medical information or ongoing investigation(s). For participants who were deemed eligible for the in-person assessment, an appointment was organised over the phone and an information package containing a brief schedule of the two assessment days and study location was provided. A letter addressed to the participant's nominated healthcare professional was also sent with a signed permission slip by the participant to allow release of relevant medical information and inform of the participant's intent in participating in the study. Upon arrival for the first in person assessment, participants were provided information about the study and a hard copy of the Participant Information Sheet. Informed consent was then requested prior to commencing the session. For participants who were deemed ineligible for the study at any time point during the screening process, consent was requested to obtain and retain contact details in the event that their situation changed over time.

2.4.2.4.3. Physician Review

As part of the in-person assessment, a structured interview comprising a physical examination, review of clinical history, current medication, and examination of IBD severity was performed by the study physician (M.A.F.S) prior to commencement of the exercise testing. Activities which comprised the in-person physical and health screen is as previously described in this chapter (2.4.1.5.1)

2.4.2.5. COLONiC Randomisation

Concealed randomisation in variable blocks of 4-8 was prepared by an independent researcher not otherwise involved with the study. Stratification was based on a former diagnosis of Ulcerative Colitis (yes, no) and sex (male, female). Randomisation sequence was generated using the website Randomization.com (http://randomization.com) [144] and logged into an online COLONIC database hosted on the University of Sydney's REDCap platform managed by the lead investigator (K.D.). Once logged into the database, the sequence itself was inaccessible by any study investigator attached with the study and functioned as an automatic allocation generator for prospective participants. Randomisation was done at the end of the baseline assessment, and allocation confirmed with the staff member who generated the sequence. Participants were informed of their allocation in person at the end of baseline assessments and provided with study-related materials based on their allocated arm.

2.4.2.6. COLONiC Study Blinding

Participants were not blinded to the allocation due to the nature of the intervention. A placebo oil was considered, however determined to be inappropriate due to the changes it might induce in a participants' diets if the oil used was different from their usual oil. Similarly, providing an oil that participants were currently using at home was previously considered, however a variety of fats are used depending on the type of foods prepared, and substitution with a single oil product would alter participants' behaviour. Furthermore, the characteristics of the intervention oil (colour, smell, taste) may have allowed participants to identify their allocation if a sham oil was provided. Thus, blinding of participants to their intervention arm was determined to be not possible.

We considered the use of a metabolic unit rather than free-living dietary interventions for blinding to account for heterogeneity between participants diets which may influence outcome measures, however this was abandoned due to funding constraints and the impact on usual dietary habits. Likewise, the use of encapsulated oils was considered in this study however volume restrictions would have limited the quantity of EVOO that could be consumed daily to match usual fat intake. Furthermore, the use of either a metabolic unit or capsules to deliver the intervention would preclude the ability of participants to incorporate the intervention into their diet according to their habits.

2.4.2.7. COLONiC Study Arm and Intervention

Participants in both study groups were randomised into one of two study arms at the end of baseline assessments: an olive oil intervention arm and a usual care arm. The study intervention comprised of Australian EVOO (Cobram Estate Pty Ltd, Classic Flavour, Southbank, Australia) with a labelled harvest date of 2019 and best before date of December 2020. Following randomisation, participants in the intervention group received 24 x 200 mL bottles of the intervention product to be used in place of their usual cooking oils and added fats (butter, margarine, and spreads) over a 4-week period. Smaller bottle sizes were selected for this study for ease of use, quantification of consumed amounts, and to minimise the degradation of sensory and phenolic qualities of the product. [145]

The intervention commenced at completion of all baseline assessments (Assessment 2), and participants were asked to record consumption of the intervention oil using a calendar provided by the research team. At the end of the 4-week active intervention period, participants were

invited for a mid-point assessment followed by a 4-week “wash out” period where participants resumed consumption of their usual fats and oils. Participants in the intervention group were asked to maintain all other aspects of their diet and exercise patterns. At the end of the study, all used and unused bottles were collected by the research team for quantification. By contrast, no interventions were in place for participants in the usual care arm. Instead, this cohort was asked to maintain all lifestyle patterns including diet and exercise habits for 8 weeks after randomization.

Both groups received a paper-based symptom diary to record any changes to bowel habits, gastrointestinal symptoms or general health for the duration of the study. Participants in the intervention group were also asked to record the dates that the intervention oil was consumed. The study dietitian (K.D.) completed weekly status checks by telephone for both study groups including questions regarding any new diagnosis or adverse events, changes to treatment, symptoms, or lifestyle occurring independently from this study, and for participants in the intervention group: consumption of EVOO in the preceding week. In-person assessments replicating baseline measures were repeated at 4 weeks and 8 weeks post randomisation, comprising of questionnaires, collection of fasting blood samples and stool samples, as well as completion of a 3-day food diary.

2.4.2.8. COLONiC Outcome Measures

Outcome measures selected and assessment procedures for the COLONiC study were consistent with the XIBD study unless otherwise described in each section below. A separate

REDCap database separate from the XIBD study was created to host electronic copies of validated questionnaires used in this study.

2.4.2.8.1. Primary Outcomes

Blinded primary outcomes were comprised of disease activity though a Partial Mayo Score [81] for participants living with UC, and gut microbiome profile through 16S rRNA sequencing of stool samples collected at baseline, 4 weeks, and at 8 weeks for all participants. The Partial Mayo Score is a widely-used tool to assess disease severity in IBD through stool frequency, rectal bleeding, and physician global assessment scores. The tool excludes endoscopic sub-scores in the full Mayo score, and despite limited validation of the tool it performs well against other non-invasive indices to measure clinical response. [146, 147] The Partial Mayo Score was administered at baseline, 4 weeks and 8 weeks by the study physician blinded to intervention group during the in-person assessment.

Gut microbiome outcomes through blinded 16S rRNA sequencing was included to identify potential links between commensal bacteria, diet and health status. Distinctions between UC and healthy controls with a reduction of microbial richness, evenness, and diversity associated with disease severity and treatment response have previously been described. [148-150] However, the impact of olive-based interventions on these outcomes have yet to be investigated. Descriptions of the stool sampling procedure and analysis are outlined in previous parts of this chapter (2.4.1.5.7). Stool sampling was repeated 3 times: at baseline, 4-weeks post randomisation, and at the end of study participation.

2.4.2.8.2. Secondary Outcomes

I Participant Characteristics and Medical History

Methods for examining participant demographics and medical history were as described in previous parts of this chapter (2.4.1.5.1) and completed at baseline.

II Quality of Life, Fatigue and Sleep Quality

Self-reported quality of life outcomes was examined as previously described in this chapter (2.4.1.5.2) repeated at baseline, 4 weeks and 8 weeks. Inflammatory bowel disease specific questionnaires (IBDQ-32, IBD-F) were not administered to participants in the healthy control group.

III Physical Fitness, Physical Activity Patterns and Sleep Patterns

Evaluation of habitual physical activity and physical fitness was as previously described in this chapter (2.4.1.5.3 and 2.4.1.5.4). Cardiopulmonary exercise test was completed once at baseline. Muscle strength assessments and habitual physical activity through fitting of an Axivity MEMS AX3 3-axis accelerometer, Axivity and completion of physical activity and sleep logs were repeated at baseline, 4 weeks and 8 weeks.

IV Diet

Dietary outcomes through the completion of weighed 3-day food diaries and the FCQ was repeated at baseline, 4 weeks, and 8 weeks for all participants. Participant's experience with diet and nutrition support was examined once at baseline. Procedure for collecting and analysing dietary data were as described in previous sections of this chapter (2.4.1.5.5).

To minimise alterations to gut microbiome profile and inflammatory markers due to acute dietary changes, [151] participants were instructed to replicate their dietary pattern from the 24 hours preceding baseline blood and stool sampling (day 3 of the 3-day weighted food diary) at 4 weeks and 8 weeks. Participants in the intervention group were instructed to replicate this diet with the inclusion of EVOO at the end of their intervention period (4 weeks). To facilitate compliance with this task, a copy of the reported food intake and quantities for this day was provided to participants at 4 weeks and 8 weeks.

V Body Composition

Anthropometry outcomes including weight, height, BMI, body composition, and total body, hip and spine bone mineral density followed procedures described in previous parts of this chapter (2.4.1.5.6). Weight measures were repeated at baseline, 4 weeks and 8 weeks. Weight history in the preceding 6 months prior to study participation for all participants and weight changes since initial diagnosis of UC for participants with UC was also documented at baseline.

Standing height, body composition and total body, hip, spine bone mineral density was assessed only at baseline. Repeated measurements were deemed inappropriate due to the short timeframe between follow-up assessments, with differences observed within the study period likely reflecting measurement error rather than “true” change. [113]

.

VI Inflammatory Markers

Assessment of inflammatory markers collected through blood samples and stool samples adhered to procedures described previously within this chapter (2.4.1.5.7) for all participants. Samples were collected over 3 separate timepoints (baseline, 4 weeks, and 8 weeks). All samples were batched by study code and collection timepoint for storage.

VII Tracking and Adverse Events

Weekly health status checks and reporting of adverse events whether or not deemed related to the study were assessed either by telephone or in-person for the duration of study participation. Participants were requested to report all changes to medication or supplement regimen, visits to a healthcare professional, new diagnosis, acute illnesses, physical activity and new symptoms. Any gastrointestinal discomfort or metabolic abnormality were considered as a potential adverse event and recorded. Weekly case conferences were held to discuss all active study participants in terms of adherence to the study protocol, changes to health status, new symptoms, adverse events, diet, and behaviour changes relevant to study participation. For participants in the intervention group, olive oil consumption was captured in the symptoms calendar provided.

2.4.2.9. COLONiC Power Calculation

Sample size calculation for the primary outcome (Partial Mayo Score) was estimated using the statistical power analysis program G*Power 3.1. [152] At the time of writing, few papers had investigated the effects of fat-based interventions on active UC. Two papers were selected for sample size calculation; a cross-over study evaluating the effects of EVOO and canola oil

interventions on high sensitivity C-reactive protein (hs-CRP) in UC, [80] and a 6 week uncontrolled dietary intervention examining outcomes in both CD (Harvey Bradshaw Index) and UC (Partial Mayo Score). [153] Pre and post outcomes (*mean ± standard deviation*) were used to estimate Hedges' bias corrected effect size (Table 2.1).

Calculated effect size from these studies were 1.132 for hs-CRP outcomes [80] and 1.25 for a 2-point reduction of partial Mayo Scores in UC, [153] with alpha 0.05 and beta 0.2, providing 80% power. With consideration to the primary outcome of the COLONiC Study, the paper reporting the partial Mayo Score was initially selected to estimate participant sample size. However, due to the experimental design of the two studies and inclusion of an uncontrolled study, a conservative approach for sample size estimation using the secondary outcome of hs-CRP was used. As such, the larger sample of 14 participants per study arm was selected for this study.

An attrition rate of 16 - 17.5 % was reported between both studies and selecting the higher attrition rate of 17.5% we aimed to recruit 17 participants in each study arm. We also aimed to recruit an equal number of participants without a history of IBD to act as healthy controls due to the limited evidence investigating the effects of EVOO consumption and gut microbiome and inflammatory outcomes in apparently healthy individuals. In total, we estimated a sample size of 68 participants comprised of 34 individuals with UC and 34 individuals as healthy controls were required for this study.

2.4.2.10. COLONiC Statistical analysis

Intention-to-treat analysis regardless of dropout or study adherence is the primary analytic strategy. Primary and secondary continuous outcomes were analysed via linear repeated measures mixed models for testing of Group × Time interaction, with covariate adjustment over baseline and 4 weeks to characterise the intervention effects. In addition, outcomes at 5-8 weeks will identify and characterise any residual effects of the intervention during the washout phase. Covariates selected *a priori* based on the literature include age, sex, macronutrient intake, energy intake, and habitual physical activity level; other potential confounders identified at baseline may be added as required. A mediation analysis was conducted via the PROCESS macro for SPSS version 2.13.2 to determine the indirect effect of dietary change on objective and subjective outcomes mediated by hypothesised beneficial alterations in the gut microbiota, while accounting for any potentially direct effects of EVOO.

2.4.2.11. Acknowledgements for the COLONiC study

EVOO used in this study was provided in kind by Cobram Estate Pty Ltd. Cobram Estate have not been involved in any aspect of the trial including study design, data collection, reporting of results nor dissemination.

2.4.3. Outcomes not Examined in this Manuscript

Habitual physical activity and sleep as assessed by the Axivity MEMS AX3 3-axis accelerometer for both studies, examination of intestinal microbiome through 16S rRNA sequencing of faecal samples and inflammatory markers through fasting plasma and serum samples collected for the XIBD study (Chapter 3), and at baseline, 4 weeks and 8 weeks for

the COLONiC study (Chapter 5) could not be completed due to funding limitations. Data from AX3 3-axis accelerometers are kept in a secure University maintained server, while stool, blood serum and plasma samples have been retained at -80 degrees Celsius which provides some stability for long-term storage,[154, 155] and will be analysed when funding permits.

Evaluation of faecal microbiome, inflammatory markers, and habitual activity data from the AX3 3-axis accelerometers would have provided additional insights when combined with self-reported outcomes examined in this study. Comparisons between subjective ratings of disease activity from the Partial Mayo Score with serum levels of inflammatory markers, faecal biomarkers would have been of significant interest in the XIBD cross-sectional study to describe burden of illness and disease severity beyond symptomatic presentation. Furthermore, examining the responses (or lack thereof) following the dietary intervention would have provided valuable human data on the effects of EVOO consumption on inflammatory markers and faecal biomarkers of IBD, considering the limited human data available.[156] Funding constraints related to biomarker discovery and assessments have been previously described as a challenge in IBD research,[157] which unfortunately was reflected in this study.

Results from fitness testing (cardiopulmonary exercise test and muscle strength assessments), were part of a separate study (PRE-BIOTIC: Progressive Resistance Exercise- BIOTa and Inflammation in Crohn's & colitis, University of Sydney Human Ethics Committee Protocol no. 2018/029) and not presented here as it falls beyond the scope of this manuscript.

2.5. Discussion

Within this chapter we have described in an extensive evaluation of individuals living with IBD and generally healthy populations. A range of assessments tools were included in both studies considering the variability of lived experience and heterogeneous strategies implemented by individuals impacting disease presentation and the quality of life.[158, 159] The implications of the study design selected however meant that both projects required significant time commitment by participants to enrol into the study, which may limit participant recruitment. It should also be acknowledged that the study procedures are resource intensive, particularly for the COLONiC RCT which is a known limitation in IBD research.[158] Furthermore, the authors acknowledge that challenges inherent to select a well-defined study population is a potential limiting factor in generalising the study outcomes to a broader population,[160] despite the quality of evidence presented by such projects. As such, the inclusion a cross-sectional study (the XIBD Study) provided an avenue to more broadly define individuals living with IBD participating in the study, which could be then compared against participants enrolled in the COLONiC RCT. Analysis of the XIBD Study would also allow for a comprehensive evaluation of lifestyle habits of individuals living with IBD in the Greater Sydney region and surrounding areas. Similarly, findings from the COLONiC study will provide a novel insight on the interplay between small changes to diet and its impact on broader dietary patterns and quality of life. Analysis of intestinal microbiome and inflammatory markers would provide additional insights of the changes observed and will be analysed subject to the availability of funding.

2.6. References

1 Conrad K, Roggenbuck D, Laass MW. Diagnosis and classification of ulcerative colitis. *Autoimmun Rev*. 2014;13(4):463-466.

2 da Silva BC, Lyra AC, Rocha R, Santana GO. Epidemiology, demographic characteristics and prognostic predictors of ulcerative colitis. *World Journal of Gastroenterology : WJG*. 2014;20(28):9458-9467.

3 Carter MJ, Lobo AJ, Travis SPL. Guidelines for the management of inflammatory bowel disease in adults. *Gut*. 10.1136/gut.2004.043372. 2004;53(suppl 5):v1.

4 Cross RK, Lapshin O, Finkelstein J. Patient Subjective Assessment of Drug Side Effects in Inflammatory Bowel Disease. *Journal of Clinical Gastroenterology*. 2008;42(3).

5 Selinger CP, Robinson A, Leong RW. Clinical impact and drivers of non-adherence to maintenance medication for inflammatory bowel disease. *Expert Opinion on Drug Safety*. 2011;10(6):863-870.

6 Lakatos PL. Prevalence, predictors, and clinical consequences of medical adherence in IBD: how to improve it? *World journal of gastroenterology*. 2009;15(34):4234-4239.

7 Duff W, Haskey N, Potter G, Alcorn J, Hunter P, Fowler S. Non-pharmacological therapies for inflammatory bowel disease: Recommendations for self-care and physician guidance. *World journal of gastroenterology*. 2018;24(28):3055-3070.

8 Hilsden RJ, Verhoef MJ, Best A, Pocobelli G. Complementary and alternative medicine use by Canadian patients with inflammatory bowel disease: results from a national survey. *Am J Gastroenterol*. 2003;98(7):1563-1568.

9 Rawsthorne P, Shanahan F, Cronin NC, et al. An international survey of the use and attitudes regarding alternative medicine by patients with inflammatory bowel disease. *The American Journal of Gastroenterology*. 1999;94(5):1298-1303.

10 Zallot C, Quilliot D, Chevaux JB, et al. Dietary beliefs and behavior among inflammatory bowel disease patients. *Inflammatory Bowel Diseases*. 2013;19(1):66-72.

11 Holt DQ, Strauss BJ, Moore GT. Patients with inflammatory bowel disease and their treating clinicians have different views regarding diet. *Journal of Human Nutrition & Dietetics*. 2017;30(1):66-72.

12 Weber AT, Shah ND, Sauk J, Limketkai BN. Popular Diet Trends for Inflammatory Bowel Diseases: Claims and Evidence. *Curr Treat Options Gastroenterol*. 2019;17(4):564-576.

13 Limketkai BN, Godoy-Brewer G, Parian AM, et al. Dietary Interventions for the Treatment of Inflammatory Bowel Diseases: An Updated Systematic Review and Meta-analysis. *Clinical Gastroenterology and Hepatology*. 2023;21(10):2508-2525.e2510.

14 Comeche JM, Gutierrez-Hervás A, Tuells J, Altavilla C, Caballero P. Predefined Diets in Patients with Inflammatory Bowel Disease: Systematic Review and Meta-Analysis. Nutrients, Vol. 13, 2021

15 Knight-Sepulveda K, Kais S, Santaolalla R, Abreu MT. Diet and Inflammatory Bowel Disease. *Gastroenterol Hepatol (N Y)*. 2015;11(8):511-520.

16 Horne R, Parham R, Driscoll R, Robinson A. Patients' Attitudes to Medicines and Adherence to Maintenance Treatment in Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. 2009;15(6):837-844.

17 Wang R, Hirano I, Doerfler B, Zalewski A, Gonsalves N, Taft T. Assessing Adherence and Barriers to Long-Term Elimination Diet Therapy in Adults with Eosinophilic Esophagitis. *Digestive Diseases and Sciences*. 2018;63(7):1756-1762.

18 Tuck CJ, Reed DE, Muir JG, Vanner SJ. Implementation of the low FODMAP diet in functional gastrointestinal symptoms: A real-world experience. *Neurogastroenterology & Motility*. 2020;32(1):e13730.

19 Kaplan HC, Opipari-Arrigan L, Yang J, et al. Personalized Research on Diet in Ulcerative Colitis and Crohn's Disease: A Series of N-of-1 Diet Trials. *Official journal of the American College of Gastroenterology | ACG*. 2022;117(6):902-917.

20 Gibble TH, Naegeli AN, Grabner M, et al. Identification of inadequate responders to advanced therapy among commercially-insured adult patients with Crohn's disease and ulcerative colitis in the United States. *BMC Gastroenterology*. 2023;23(1):63.

21 Marsal J, Barreiro-de Acosta M, Blumenstein I, Cappello M, Bazin T, Sebastian S. Management of Non-response and Loss of Response to Anti-tumor Necrosis Factor Therapy in Inflammatory Bowel Disease. *Front Med (Lausanne)*. 2022;9:897936.

22 Tinsley A, Ehrlich OG, Hwang C, et al. Knowledge, Attitudes, and Beliefs Regarding the Role of Nutrition in IBD Among Patients and Providers. *Inflammatory Bowel Diseases*. 2016;22(10):2474-2481.

23 Czuber-Dochan W, Morgan M, Hughes LD, Lomer MCE, Lindsay JO, Whelan K. Perceptions and psychosocial impact of food, nutrition, eating and drinking in people with inflammatory bowel disease: a qualitative investigation of food-related quality of life. *Journal of Human Nutrition & Dietetics*. 2020;33(1):115-127.

24 Limdi JK, Aggarwal D, McLaughlin JT. Dietary Practices and Beliefs in Patients with Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. 2016;22(1):164-170.

25 Jamieson AE, Fletcher PC, Schneider MA. Seeking Control Through the Determination of Diet: A Qualitative Investigation of Women With Irritable Bowel Syndrome and Inflammatory Bowel Disease. *Clinical Nurse Specialist*. 2007;21(3).

26 Hou JK, Lee D, Lewis J. Diet and Inflammatory Bowel Disease: Review of Patient-Targeted Recommendations. *Clinical Gastroenterology and Hepatology*. 2014;12(10):1592-1600.

27 Cohen AB, Lee D, Long MD, et al. Dietary patterns and self-reported associations of diet with symptoms of inflammatory bowel disease. *Digestive Diseases & Sciences*. Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't. 2013;58(5):1322-1328.

28 Abdelhamid A, Jennings A, Hayhoe RPG, Awuzudike VE, Welch AA. High variability of food and nutrient intake exists across the Mediterranean Dietary Pattern—A systematic review. *Food Science & Nutrition*. 2020;8(9):4907-4918.

29 Radd-Vagenas S, Kouris-Blazos A, Singh MF, Flood VM. Evolution of Mediterranean diets and cuisine: Concepts and definitions. *Asia Pacific Journal of Clinical Nutrition*. Journal Article. 2017;26(5):749-763.

30 Grosso G, Marventano S, Yang J, et al. A comprehensive meta-analysis on evidence of Mediterranean diet and cardiovascular disease: Are individual components equal? *Critical Reviews in Food Science and Nutrition*. 2017;57(15):3218-3232.

31 Sigall-Boneh R, Levine A, Lomer M, et al. Research Gaps in Diet and Nutrition in Inflammatory Bowel Disease. A Topical Review by D-ECCO Working Group [Dietitians of ECCO]. *Journal of Crohn's and Colitis*. 2017;11(12):1407-1419.

32 Turner D, Shah PS, Steinhart AH, Zlotkin S, Griffiths AM. Maintenance of remission in inflammatory bowel disease using omega-3 fatty acids (fish oil): A systematic review and meta-analyses. *Inflammatory Bowel Diseases*. 2011;17(1):336-345.

33 Haghighatdoost F, Hariri M. The effect of green tea on inflammatory mediators: A systematic review and meta-analysis of randomized clinical trials. *Phytotherapy Research*. 2019;33(9):2274-2287.

34 Coelho MR, Romi MD, Ferreira DMTP, Zaltman C, Soares-Mota M. The Use of Curcumin as a Complementary Therapy in Ulcerative Colitis: A Systematic Review of Randomized Controlled Clinical Trials. *Nutrients*. 2020;12(8):2296.

35 Vakadaris G, Stefanis C, Giorgi E, et al. The Role of Probiotics in Inducing and Maintaining Remission in Crohn’s Disease and Ulcerative Colitis: A Systematic Review of the Literature. *Biomedicines*. 2023;11(2):494.

36 Jonkers D, Penders J, Masclee A, Pierik M. Probiotics in the Management of Inflammatory Bowel Disease. *Drugs*. 2012;72(6):803-823.

37 Derwa Y, Gracie DJ, Hamlin PJ, Ford AC. Systematic review with meta-analysis: the efficacy of probiotics in inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*. 2017;46(4):389-400.

38 Lichtenstein AH, Russell RM. Essential Nutrients: Food or Supplements?Where Should the Emphasis Be? *JAMA*. 2005;294(3):351-358.

39 MacFarquhar JK, Broussard DL, Melstrom P, et al. Acute Selenium Toxicity Associated With a Dietary Supplement. *Archives of Internal Medicine*. 2010;170(3):256-261.
40 Poniedziałek B, Niedzielski P, Kozak L, et al. Monitoring of essential and toxic elements in multi-ingredient food supplements produced in European Union. *Journal of Consumer Protection and Food Safety*. 2018;13(1):41-48.
41 Costa JG, Vidovic B, Saraiva N, et al. Contaminants: a dark side of food supplements? *Free Radical Research*. 2019;53(sup1):1113-1135.
42 Rahman H, Kim M, Leung G, Green JA, Katz S. Drug-Herb Interactions in the Elderly Patient with IBD: a Growing Concern. *Current Treatment Options in Gastroenterology*. 2017;15(4):618-636.
43 Lippert A, Renner B. Herb-Drug Interaction in Inflammatory Diseases: Review of Phytomedicine and Herbal Supplements. *J Clin Med*. 2022;11(6).
44 Linn AJ, van Dijk L, Smit EG, Jansen J, van Weert JCM. May you never forget what is worth remembering: The relation between recall of medical information and medication adherence in patients with inflammatory bowel disease. *Journal of Crohn's and Colitis*. 2013;7(11):e543-e550.
45 Schwingshackl L, Christoph M, Hoffmann G. Effects of Olive Oil on Markers of Inflammation and Endothelial Function-A Systematic Review and Meta-Analysis. *Nutrients*. 2015;7(9):7651-7675.
46 Schwingshackl L, Missbach B, König J, Hoffmann G. Adherence to a Mediterranean diet and risk of diabetes: a systematic review and meta-analysis. *Public Health Nutrition*. 2015;18(7):1292-1299.
47 Singh B, Parsaik AK, Mielke MM, et al. Association of Mediterranean Diet with Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and Meta-Analysis. *Journal of Alzheimer's Disease*. 2014;39:271-282.
48 Mitsou EK, Kakali A, Antonopoulou S, et al. Adherence to the Mediterranean diet is associated with the gut microbiota pattern and gastrointestinal characteristics in an adult population. *British Journal of Nutrition*. 2017;117(12):1645-1655.
49 Benetou V, Trichopoulou A, Orfanos P, et al. Conformity to traditional Mediterranean diet and cancer incidence: the Greek EPIC cohort. *British Journal of Cancer*. 2008;99(1):191-195.
50 Grosso G, Buscemi S, Galvano F, et al. Mediterranean diet and cancer: epidemiological evidence and mechanism of selected aspects. *BMC Surgery*. 2013;13(2):S14.
51 Forsyth C, Kouvari M, D'Cunha NM, et al. The effects of the Mediterranean diet on rheumatoid arthritis prevention and treatment: a systematic review of human prospective studies. *Rheumatology International*. 2018;38(5):737-747.
52 Casas R, Estruch R, Sacanella E. The protective effects of extra virgin olive oil on immune-mediated inflammatory responses. *Endocrine, Metabolic and Immune Disorders - Drug Targets*. Review. 2018;18(1):23-35.

53 George ES, Marshall S, Mayr HL, et al. The effect of high-polyphenol extra virgin olive oil on cardiovascular risk factors: A systematic review and meta-analysis. *Critical Reviews in Food Science and Nutrition*. 2019;59(17):2772-2795.
54 Marcelino G, Hiane PA, Freitas KdC, et al. Effects of Olive Oil and Its Minor Components on Cardiovascular Diseases, Inflammation, and Gut Microbiota. *Nutrients*. 2019;11(8):1826.
55 Santangelo C, Varì R, Scazzocchio B, et al. Anti-inflammatory activity of extra virgin olive oil polyphenols: Which role in the prevention and treatment of immune-mediated inflammatory diseases? *Endocrine, Metabolic and Immune Disorders - Drug Targets*. Review. 2018;18(1):36-50.
56 Carrasco-Pancorbo A, Cerretani L, Bendini A, Segura-Carretero A, Lercker G, Fernández-Gutiérrez A. Evaluation of the Influence of Thermal Oxidation on the Phenolic Composition and on the Antioxidant Activity of Extra-Virgin Olive Oils. *Journal of Agricultural and Food Chemistry*. 2007;55(12):4771-4780.
57 Tripoli E, Giammanco M, Tabacchi G, Di Majo D, Giammanco S, La Guardia M. The phenolic compounds of olive oil: structure, biological activity and beneficial effects on human health. *Nutrition Research Reviews*. 2005;18(1):98-112.
58 Urpi-Sarda M, Casas R, Chiva-Blanch G, et al. Virgin olive oil and nuts as key foods of the Mediterranean diet effects on inflammatory biomakers related to atherosclerosis. *Pharmacol Res*. 2012;65(6):577-583.
59 Fernandes J, Fialho M, Santos R, et al. Is olive oil good for you? A systematic review and meta-analysis on anti-inflammatory benefits from regular dietary intake. *Nutrition*. 2020;69:110559.
60 Bogani P, Galli C, Villa M, Visioli F. Postprandial anti-inflammatory and antioxidant effects of extra virgin olive oil. *Atherosclerosis*. 2007;190(1):181-186.
61 Sánchez-Fidalgo S, Cárdeno A, Sánchez-Hidalgo M, et al. Dietary unsaponifiable fraction from extra virgin olive oil supplementation attenuates acute ulcerative colitis in mice. *European Journal of Pharmaceutical Sciences*. Article. 2013;48(3):572-581.
62 Barnes EL, Nestor M, Onyewadume L, et al. High Dietary Intake of Specific Fatty Acids Increases Risk of Flares in Patients With Ulcerative Colitis in Remission During Treatment With Aminosalicylates. *Clinical Gastroenterology and Hepatology*. Article. 2017;15(9):1390-1396.e1391.
63 De Silva P, Luben R, Mc Taggart A, Khaw KT, Hart A. Dietary arachidonic acid and the aetiology of ulcerative colitis: Data from a UK prospective cohort study, using 7-day food diaries. *Gut*. Conference Abstract. 2011;1):A140.
64 Wiese DM, Horst SN, Brown CT, et al. Serum fatty acids are correlated with inflammatory cytokines in ulcerative colitis. *PLoS ONE*. Article. 2016;11(5).
65 Aggarwal D, Burns H, McLaughlin JT, Limdi JK. Dietary practices in patients with inflammatory bowel disease-food for thought. *Gut*. Conference Abstract. 2015;1):A232-A233.
66 Hidalgo M, Prieto I, Abriouel H, et al. Effect of virgin and refined olive oil consumption on gut microbiota. Comparison to butter. *Food Research International*. 2014;64:553-559.

67 Patterson E, O' Doherty RM, Murphy EF, et al. Impact of dietary fatty acids on metabolic activity and host intestinal microbiota composition in C57BL/6J mice. *British Journal of Nutrition*. 2014;111(11):1905-1917.

68 Martínez N, Prieto I, Hidalgo M, et al. Refined versus Extra Virgin Olive Oil High-Fat Diet Impact on Intestinal Microbiota of Mice and Its Relation to Different Physiological Variables. *Microorganisms*. 2019;7(2):61.

69 Gavahian M, Mousavi Khaneghah A, Lorenzo JM, et al. Health benefits of olive oil and its components: Impacts on gut microbiota antioxidant activities, and prevention of noncommunicable diseases. *Trends in food science & technology*. 2019;88:220-227.

70 Farràs M, Martinez-Gili L, Portune K, et al. Modulation of the Gut Microbiota by Olive Oil Phenolic Compounds: Implications for Lipid Metabolism, Immune System, and Obesity. *Nutrients*. 2020;12(8):2200.

71 Haskey N, Gibson DL. An examination of diet for the maintenance of remission in inflammatory bowel disease. *Nutrients*. Review. 2017;9(3).

72 De Silva PS, Luben R, Shrestha SS, Welch A, Khaw KT, Hart A. Dietary oleic acid protects against the development of ulcerative colitis - A UK prospective cohort study using data from food diaries. *Gastroenterology*. Conference Abstract. 2010;1):S18.

73 De Silva P, Lund EK, Chan S, Hart AR. Is diet involved in the etiology of ulcerative colitis and Crohn's disease? A review of the experimental and epidemiological literature. *Inflammatory Bowel Disease Monitor*. Review. 2011;12(1):14-22.

74 Ananthakrishnan AN, Khalili H, Konijeti GG, et al. Long-term intake of dietary fat and risk of ulcerative colitis and Crohn's disease. *Gut*. Article. 2014;63(5):776-784.

75 De Silva PSA, Luben R, Shrestha SS, Khaw KT, Hart AR. Dietary arachidonic and oleic acid intake in ulcerative colitis etiology: A prospective cohort study using 7-day food diaries. *European Journal of Gastroenterology and Hepatology*. Article. 2014;26(1):11-18.

76 Tjonneland A, Overvad, K., Bergmann, M.M., Nagel, G., Linseisen, J., Hallmans, G., Palmqvist, R., Sjodin, H., Hagglund, G., Berglund, G., Lindgren, S., Grip, O., Palli, D., Day, N.E., Khaw, K.T., Bingham, S., Riboli, E., Kennedy, H., Hart, A. Linoleic acid, a dietary n-6 polyunsaturated fatty acid, and the aetiology of ulcerative colitis: a nested case–control study within a European prospective cohort study. *Gut*. 2009;58(12):1606.

77 Marlow G, Ellett S, Ferguson IR, et al. Transcriptomics to study the effect of a Mediterranean-inspired diet on inflammation in Crohn's disease patients. *Human genomics*. 2013;7:24.

78 Chicco F, Magrì S, Cingolani A, et al. Multidimensional Impact of Mediterranean Diet on IBD Patients. *Inflammatory Bowel Diseases*. 2020.

79 Lorenz R, Weber PC, Szimnau P, Heldwein W, Strasser T, Loeschke K. Supplementation with n-3 fatty acids from fish oil in chronic inflammatory bowel disease - a randomized, placebo-

controlled, double-blind cross-over trial. *Journal of Internal Medicine, Supplement*. 1989;225(731):225-232.

80 Morvaridi M, Jafarirad S, Seyedian SS, Alavinejad P, Cheraghian B. The effects of extra virgin olive oil and canola oil on inflammatory markers and gastrointestinal symptoms in patients with ulcerative colitis. *Eur J Clin Nutr*. 2020.

81 Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis*. 2008;14(12):1660-1666.

82 Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology*. 1976;70(3):439-444.

83 Fletcher GF, Balady GJ, Amsterdam EA, et al. Exercise Standards for Testing and Training. *Circulation*. 2001;104(14):1694-1740.

84 Irvine EJ. Development and subsequent refinement of the inflammatory bowel disease questionnaire: a quality-of-life instrument for adult patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 1999;28(4):S23-27.

85 Hughes LD, King L, Morgan M, et al. Food-related Quality of Life in Inflammatory Bowel Disease: Development and Validation of a Questionnaire. *Journal of Crohn's and Colitis*. 2015;10(2):194-201.

86 Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. *Journal of General Internal Medicine*. 2001;16(9):606-613.

87 Bernstein CN, Zhang L, Lix LM, et al. The Validity and Reliability of Screening Measures for Depression and Anxiety Disorders in Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. 2018;24(9):1867-1875.

88 Czuber-Dochan W, Norton C, Bassett P, et al. Development and psychometric testing of inflammatory bowel disease fatigue (IBD-F) patient self-assessment scale. *Journal of Crohn's and Colitis*. 2014;8(11):1398-1406.

89 Keefer L, Stepanski EJ, Ranjbaran Z, Benson LM, Keshavarzian A. An initial report of sleep disturbance in inactive inflammatory bowel disease. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*. 2006;2(4):409-416.

90 Dubinsky M, Rice A, Yarlas A, et al. Systematic Literature Review: Ability of the IBDQ-32 to Detect Meaningful Change in Ulcerative Colitis Health Indicators. *Inflammatory Bowel Diseases*. 2023:izad282.

91 Irvine JE. Quality of life of patients with ulcerative colitis: Past, present, and future. *Inflammatory Bowel Diseases*. 2008;14(4):554-565.

92 Cox SR, Czuber-Dochan W, Wall CL, et al. Improving Food-Related Quality of Life in Inflammatory Bowel Disease through a Novel Web Resource: A Feasibility Randomised Controlled Trial. *Nutrients*. 2022;14(20):4292.

93 Spitzer RL, Kroenke K, Williams JB, Group PHQPCS, Group PHQPCS. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *Jama*. 1999;282(18):1737-1744.
94 Bauer-Staeb C, Kounali DZ, Welton NJ, et al. Effective dose 50 method as the minimal clinically important difference: Evidence from depression trials. *J Clin Epidemiol*. 2021;137:200-208.
95 Lynch CP, Cha EDK, Jenkins NW, et al. The Minimum Clinically Important Difference for Patient Health Questionnaire-9 in Minimally Invasive Transforaminal Interbody Fusion. *Spine (Phila Pa 1976)*. 2021;46(9):603-609.
96 Chyr LC, Sauers EG, Dy SM, Waldfogel JM. The Application of Minimal Clinically Important Differences in Palliative Research: Interpretation of Results of a Systematic Review. *J Pain Symptom Manage*. 2022;64(6):e363-e371.
97 Lemay KR, Tulloch HE, Pipe AL, Reed JL. Establishing the Minimal Clinically Important Difference for the Hospital Anxiety and Depression Scale in Patients With Cardiovascular Disease. *J Cardiopulm Rehabil Prev*. 2019;39(6):E6-e11.
98 Puhan MA, Frey M, Büchi S, Schünemann HJ. The minimal important difference of the hospital anxiety and depression scale in patients with chronic obstructive pulmonary disease. *Health and Quality of Life Outcomes*. 2008;6(1):46.
99 Varbobitis I, Kokkotis G, Gizis M, et al. The IBD-F patient self-assessment scale accurately depicts the level of fatigue and predicts a negative effect on the quality of life of patients with IBD in clinical remission. *Inflammatory Bowel Diseases*. 2021;27(6):826-835.
100 Lage AC, Oliveira CC, Batalha APDB, et al. The Inflammatory Bowel Disease-Fatigue Patient self-assessment scale: translation, cross-cultural adaptation and psychometric properties of the Brazilian version (IBD-F Brazil). *Arquivos de Gastroenterologia*. 2020;57:50-63.
101 Farrell D, Artom M, Czuber-Dochan W, Jelsness-Jørgensen LP, Norton C, Savage E. Interventions for fatigue in inflammatory bowel disease. *Cochrane Database Syst Rev*. 2020;4(4):Cd012005.
102 Longo UG, Berton A, De Salvatore S, et al. Minimal Clinically Important Difference and Patient Acceptable Symptom State for the Pittsburgh Sleep Quality Index in Patients Who Underwent Rotator Cuff Tear Repair. *Int J Environ Res Public Health*. 2021;18(16).
103 Qin Z, Zhu Y, Shi D-D, Chen R, Li S, Wu J. The gap between statistical and clinical significance: time to pay attention to clinical relevance in patient-reported outcome measures of insomnia. *BMC Medical Research Methodology*. 2024;24(1):177.
104 Dunton GF, Leventhal AM, Rothman AJ, Intille SS. Affective response during physical activity: Within-subject differences across phases of behavior change. *Health Psychol*. 2018;37(10):915-923.
105 Magnan RE, Kwan BM, Bryan AD. Effects of current physical activity on affective response to exercise: physical and social-cognitive mechanisms. *Psychol Health*. 2013;28(4):418-433.

106 Jevon P. Procedure for recording a standard 12-lead electrocardiogram. *British Journal of Nursing*. 2010;19(10):649-651.
107 Heath EM. Borg's Perceived Exertion and Pain Scales. *Medicine and science in sports and exercise*. 1998;30(9):1461.
108 Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr*. 1985;39 Suppl 1:5-41.
109 Human energy requirements : report of a joint FAO/WHO/UNU Expert Consultation, Rome 17-24 October 2001. Rome :: Food and Agriculture Organization of the United Nations, 2004
110 Trumbo P, Schlicker S, Yates AA, Poos M. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. *J Am Diet Assoc*. 2002;102(11):1621-1630.
111 Steptoe A, Pollard TM, Wardle J. Development of a measure of the motives underlying the selection of food: the food choice questionnaire. *Appetite*. 1995;25(3):267-284.
112 Hangartner TN, Warner S, Braillon P, Jankowski L, Shepherd J. The Official Positions of the International Society for Clinical Densitometry: Acquisition of Dual-Energy X-Ray Absorptiometry Body Composition and Considerations Regarding Analysis and Repeatability of Measures. *Journal of Clinical Densitometry*. 2013;16(4):520-536.
113 Slater G, Townsend N, Morabito A, et al. Technician Best Practice Protocols for DXA Assessment of Body Composition GE-Lunar. 2022.
114 McCarthy C, Tinsley GM, Bosy-Westphal A, et al. Total and regional appendicular skeletal muscle mass prediction from dual-energy X-ray absorptiometry body composition models. *Scientific Reports*. 2023;13(1):2590.
115 Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age and Ageing*. 2019;48(1):16-31.
116 Dodds RM, Syddall HE, Cooper R, et al. Grip strength across the life course: normative data from twelve British studies. *PLoS One*. 2014;9(12):e113637.
117 Henry MJ, Pasco JA, Pocock NA, Nicholson GC, Kotowicz MA. Reference ranges for bone densitometers adopted Australia-wide: Geelong osteoporosis study. *Australas Radiol*. 2004;48(4):473-475.
118 Dhingra N. *WHO Guidelines on Drawing Blood: Best Practices in Phlebotomy*. 2010.
119 Thermo Fisher Scientific. Pierce™ Chromogenic Endotoxin Quant Kit. 2018
120 Guo S, Al-Sadi R, Said HM, Ma TY. Lipopolysaccharide causes an increase in intestinal tight junction permeability in vitro and in vivo by inducing enterocyte membrane expression and localization of TLR-4 and CD14. *Am J Pathol*. 2013;182(2):375-387.
121 Opal SM, Scannon PJ, Vincent J-L, et al. Relationship between Plasma Levels of Lipopolysaccharide (LPS) and LPS-Binding Protein in Patients with Severe Sepsis and Septic Shock. *The Journal of Infectious Diseases*. 1999;180(5):1584-1589.

122 Ahola AJ, Lassenius MI, Forsblom C, Harjutsalo V, Lehto M, Groop P-H. Dietary patterns reflecting healthy food choices are associated with lower serum LPS activity. *Scientific Reports*. 2017;7(1):6511.
123 Erridge C, Attina T, Spickett CM, Webb DJ. A high-fat meal induces low-grade endotoxemia: evidence of a novel mechanism of postprandial inflammation. *Am J Clin Nutr*. 2007;86(5):1286-1292.
124 Sigma-Aldrich. Human CRP ELISA Kit. 2024
125 Koerbin G, Cavanaugh JA, Potter JM, et al. 'Aussie normals': an a priori study to develop clinical chemistry reference intervals in a healthy Australian population. *Pathology*. 2015;47(2):138-144.
126 Ridker PM. A Test in Context: High-Sensitivity C-Reactive Protein. *J Am Coll Cardiol*. 2016;67(6):712-723.
127 Millipore. MILLIPLEX® Human Cytokine/Chemokine/Growth Factor Panel A Magnetic Bead Panel. 2022
128 Liu C, Chu D, Kalantar-Zadeh K, George J, Young HA, Liu G. Cytokines: From Clinical Significance to Quantification. *Advanced Science*. 2021;8(15):2004433.
129 Di Iorio A, Ferrucci L, Sparvieri E, et al. Serum IL-1beta levels in health and disease: a population-based study. 'The InCHIANTI study'. *Cytokine*. 2003;22(6):198-205.
130 Said EA, Al-Reesi I, Al-Shizawi N, et al. Defining IL-6 levels in healthy individuals: A meta-analysis. *J Med Virol*. 2021;93(6):3915-3924.
131 Sarris AH, Kliche KO, Pethambaram P, et al. Interleukin-10 levels are often elevated in serum of adults with Hodgkin's disease and are associated with inferior failure-free survival. *Annals of Oncology*. 1999;10(4):433-440.
132 Cabral-Santos C, de Lima Junior EA, Fernandes IMdC, et al. Interleukin-10 responses from acute exercise in healthy subjects: A systematic review. *Journal of Cellular Physiology*. 2019;234(7):9956-9965.
133 Sarmin N, Roknuzzaman ASM, Mouree TZ, Islam MR, Al Mahmud Z. Evaluation of serum interleukin-12 and interleukin-4 as potential biomarkers for the diagnosis of major depressive disorder. *Scientific Reports*. 2024;14(1):1652.
134 Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997;32(9):920-924.
135 Gorzelak MA, Gill SK, Tasnim N, Ahmadi-Vand Z, Jay M, Gibson DL. Methods for Improving Human Gut Microbiome Data by Reducing Variability through Sample Processing and Storage of Stool. *PLOS ONE*. 2015;10(8):e0134802.
136 Wu W-K, Chen C-C, Panyod S, et al. Optimization of fecal sample processing for microbiome study — The journey from bathroom to bench. *Journal of the Formosan Medical Association*. 2019;118(2):545-555.

137 Stevens TW, Gecse K, Turner JR, de Hertogh G, Rubin DT, D'Haens GR. Diagnostic Accuracy of Fecal Calprotectin Concentration in Evaluating Therapeutic Outcomes of Patients With Ulcerative Colitis. *Clinical Gastroenterology and Hepatology*. 2021;19(11):2333-2342.
138 Costa F, Mumolo MG, Ceccarelli L, et al. Calprotectin is a stronger predictive marker of relapse in ulcerative colitis than in Crohn's disease. *Gut*. 2005;54(3):364-368.
139 Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *Trials*. 2010;11:32.
140 Welch RW, Antoine J-M, Berta J-L, et al. Guidelines for the design, conduct and reporting of human intervention studies to evaluate the health benefits of foods. *British Journal of Nutrition*. 2011;106(S2):S3-S15.
141 de la Cuesta-Zuluaga J, Kelley ST, Chen Y, et al. Age- and Sex-Dependent Patterns of Gut Microbial Diversity in Human Adults. *mSystems*. 2019;4(4).
142 Zhang X, Zhong H, Li Y, et al. Sex-and age-related trajectories of the adult human gut microbiota shared across populations of different ethnicities. *Nature Aging*. 2021;1(1):87-100.
143 Zhong H, Penders J, Shi Z, et al. Impact of early events and lifestyle on the gut microbiota and metabolic phenotypes in young school-age children. *Microbiome*. 2019;7(1):2.
144 Dallal GE. Randomization Plans: Randomizing subjects to a single treatment. Vol. 2019. Randomization.com, 2013
145 Stefanoudaki E, Williams M, Harwood J. Changes in virgin olive oil characteristics during different storage conditions. *European Journal of Lipid Science and Technology*. 2010;112(8):906-914.
146 Walsh AJ, Bryant RV, Travis SPL. Current best practice for disease activity assessment in IBD. *Nat Rev Gastroenterol Hepatol*. 2016;13(10):567-579.
147 Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflammatory bowel diseases*. 2008;14(12):1660-1666.
148 Michail S, Durbin M, Turner D, et al. Alterations in the gut microbiome of children with severe ulcerative colitis. *Inflammatory bowel diseases*. 2012;18(10):1799-1808.
149 Schirmer M, Denson L, Vlamakis H, et al. Compositional and Temporal Changes in the Gut Microbiome of Pediatric Ulcerative Colitis Patients Are Linked to Disease Course. *Cell host microbe*. 2018;24(4):600-610.e604.
150 Wills ES, Jonkers DMAE, Savelkoul PH, Masclee AA, Pierik MJ, Penders J. Fecal Microbial Composition of Ulcerative Colitis and Crohn's Disease Patients in Remission and Subsequent Exacerbation. *PLOS ONE*. 2014;9(3):e90981.
151 Leeming ER, Johnson AJ, Spector TD, Le Roy CI. Effect of Diet on the Gut Microbiota: Rethinking Intervention Duration. *Nutrients*. 2019;11(12):2862.

152 Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*. 2007;39(2):175-191.
153 Konijeti GG, Kim N, Lewis JD, et al. Efficacy of the Autoimmune Protocol Diet for Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't. 2017;23(11):2054-2060.
154 Kordulewska NK, Topa J, Tańska M, Cieślińska A, Fiedorowicz E, Jarmołowska B. Stability of interleukin-1β, -4, -6, -8, -10, -13, interferon-γ and tumor necrosis factor-α in human sera after repetitive freeze-thaw cycles and long storage. *Journal of Pharmaceutical and Biomedical Analysis*. 2021;196:113900.
155 Binnington B, Sakac D, Yi Q, et al. Stability of 40 cytokines/chemokines in chronically ill patients under different storage conditions. *Cytokine*. 2020;130:155057.
156 Daniel K, Vitetta L, Fiatarone Singh MA. Effects of olives and their constituents on the expression of ulcerative colitis: a systematic review of randomised controlled trials. *Br J Nutr*. 2022;127(8):1153-1171.
157 Syed S, Boland BS, Bourke LT, et al. Challenges in IBD Research 2024: Precision Medicine. *Inflammatory Bowel Diseases*. 2024;30(Supplement_2):S39-S54.
158 Salleron J, Danese S, D'Agay L, Peyrin-Biroulet L. Effectiveness Research in Inflammatory Bowel Disease: A Necessity and a Methodological Challenge. *Journal of Crohn's and Colitis*. 2016;10(9):1096-1102.
159 Piovani D, Pansieri C, Peyrin-Biroulet L, Danese S, Bonovas S. Confounding and bias in observational studies in inflammatory bowel disease: a meta-epidemiological study. *Alimentary Pharmacology & Therapeutics*. 2021;53(6):712-721.
160 Ha C, Ullman TA, Siegel CA, Kornbluth A. Patients Enrolled in Randomized Controlled Trials Do Not Represent the Inflammatory Bowel Disease Patient Population. *Clinical Gastroenterology and Hepatology*. 2012;10(9):1002-1007.

***Figure 2.1*. In-person Physical and Health Screen Schedule**

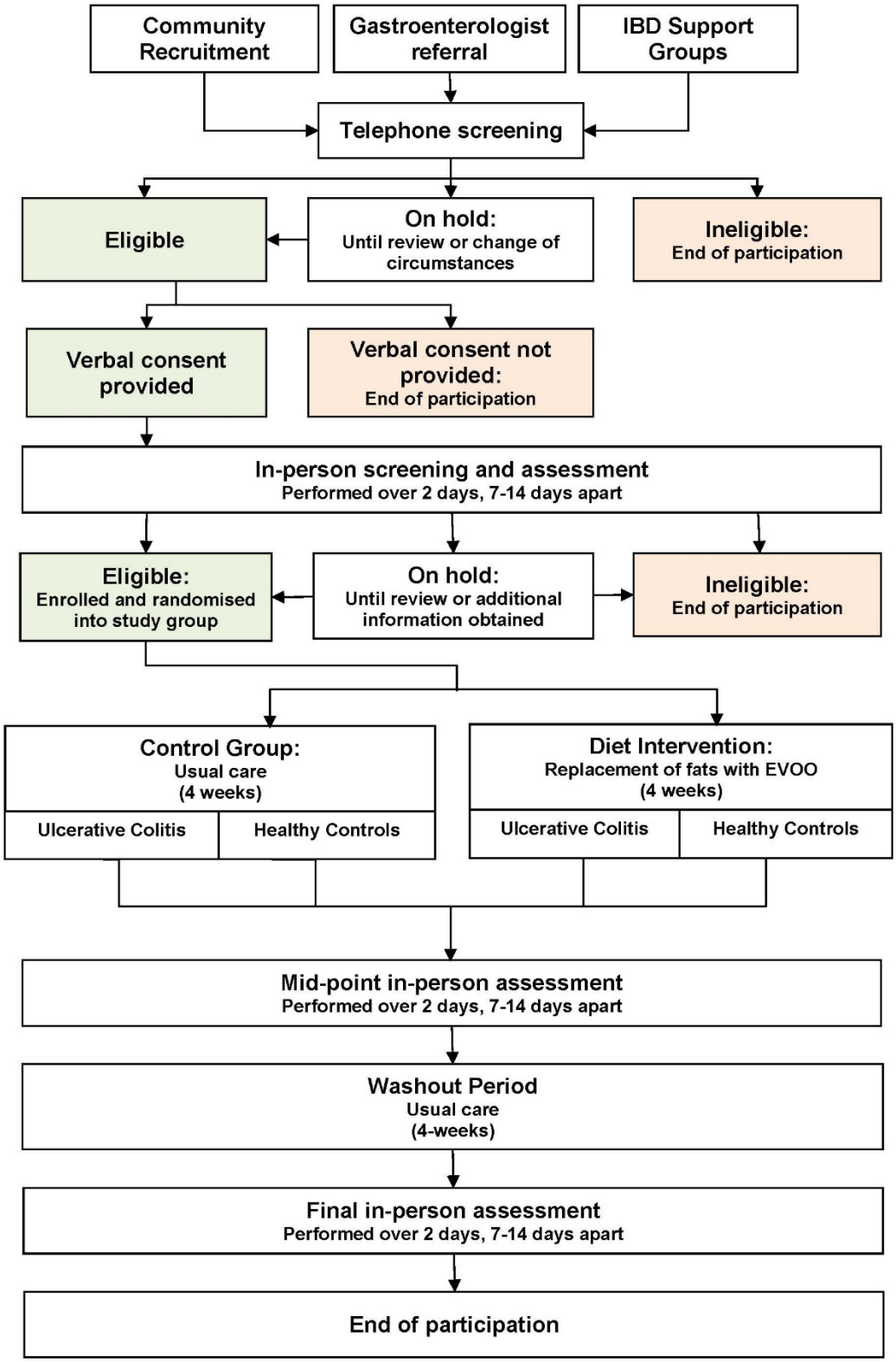
Informed consent	
□	Review of participant information sheet (PIS)
□	Written informed consent
Assessment 1	
□	Participant demographics
□	Physician Screen
□	Disease severity scoring
□	Patient Health Questionnaire (PHQ-9)
□	Hospital Anxiety and Depression Scale (HADS)
□	Short Form 36 (SF-36)
□	Inflammatory Bowel Disease Questionnaire (IBDQ-32)
□	Food-related Quality of Life Questionnaire (FRQoL-29)
□	Resting electrocardiogram (ECG), exercise stress test with ECG.
□	Food Choice Questionnaire (FCQ)
□	Inflammatory Bowel Disease Fatigue Scale (IBD-F)
□	Patient Sleep Quality Index (PSQI)
□	1 repetition maximum tests
□	Muscle Power
□	Fitting with AX3 3-axis accelerometer for 7 days

7-14 days between Assessment 1 and Assessment 2	
□	3-day weighted food diary
□	Physical activity diary
□	Sleep diary
□	Provision of stool sampling kit
□	Collection of stool sample

Assessment 2	
□	Weight
□	Height
□	DXA (body composition and bone mineral density)
□	Blood test (serum, plasma)
□	Review of 3-day weighted food diary forms
□	Repeat of 1 repetition maximum tests
□	Repeat of muscle power

Note: Assessment 2 was done while the participant was in a fasted state for weight, height, DXA, and blood test. Morning meals supplied by the investigating team comprising of breakfast cereals, milk and milk alternatives, and fruit were provided following the assessment prior to review of 3-day weighted food diary forms, repeats of 1 repetition maximum tests and muscle power.

Figure 2.2. **COLONiC Study Design and Group Randomization**



This figure summarizes the COLONiC study design. Both participants with UC and healthy controls (generally healthy subjects) will undergo the processes outlined in this flowchart.

Table 2.1. Power Calculation for COLONiC

Citation	Intervention	Intervention Length	Outcome	Baseline	Post intervention	Mean difference	Effect size	Sample Size Per Study Arm
Morvaridi, et al., [80]	EVOO	20 days	hs-CRP	2.31 ± 1.89	1.00 ± 0.72	- 1.31	1.132353	9
Konijeti et al., [153]	Autoimmune Protocol Diet	6 weeks	Partial Mayo Score	5.8 ± 1.2	1.2 ± 2.0	- 4.6	-2.87	4

*Note: Sample size calculation was estimated using the statistical power analysis program G*Power 3.1. [152] setting alpha at 0.05 and beta 0.2 Primary outcomes for participants with UC were selected from each of the studies. Conservative estimated effect sizes calculation for Konijeti et al., [153] was calculated based on a 2-point reduction to the Partial Mayo Score rather than the reported 4.6-point reduction.*

Appendix 1. Weekly Activity Log for XIBD and COLONiC

Weekly Activity Log

Study ID:			Participant Name:			
Monday	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**	**Sunday**
DD/MM/YYYY	DD/MM/YYYY	DD/MM/YYYY	DD/MM/YYYY	DD/MM/YYYY	DD/MM/YYYY	DD/MM/YYYY
Have you undertaken any intentional/ purposeful exercise today? ☐ Yes ☐ No If yes, please describe: - Type(s) of exercise ________________ ________________ - Duration of exercise (minutes) ________________ - Level of exertion (using exertion scale below) ________________	Have you undertaken any intentional/ purposeful exercise today? ☐ Yes ☐ No If yes, please describe: - Type(s) of exercise ________________ ________________ - Duration of exercise (minutes) ________________ - Level of exertion (using exertion scale below) ________________	Have you undertaken any intentional/ purposeful exercise today? ☐ Yes ☐ No If yes, please describe: - Type(s) of exercise ________________ ________________ - Duration of exercise (minutes) ________________ - Level of exertion (using exertion scale below) ________________	Have you undertaken any intentional/ purposeful exercise today? ☐ Yes ☐ No If yes, please describe: - Type(s) of exercise ________________ ________________ - Duration of exercise (minutes) ________________ - Level of exertion (using exertion scale below) ________________	Have you undertaken any intentional/ purposeful exercise today? ☐ Yes ☐ No If yes, please describe: - Type(s) of exercise ________________ ________________ - Duration of exercise (minutes) ________________ - Level of exertion (using exertion scale below) ________________	Have you undertaken any intentional/ purposeful exercise today? ☐ Yes ☐ No If yes, please describe: - Type(s) of exercise ________________ ________________ - Duration of exercise (minutes) ________________ - Level of exertion (using exertion scale below) ________________	Have you undertaken any intentional/ purposeful exercise today? ☐ Yes ☐ No If yes, please describe: - Type(s) of exercise ________________ ________________ - Duration of exercise (minutes) ________________ - Level of exertion (using exertion scale below) ________________

Rating of Perceived Exertion (0-10 scale) – PLEASE RATE FOR EACH DAY OF EXERCISE

0	1	2	3	4	5	6	7	8	9	10
Normal	Very, very weak	Weak	Moderate	Somewhat strong	Strong (heavy)		Very Strong		Very, very strong (almost maximal)	Maximal

Weekly Activity Log

Study ID:
Participant Name:
Monitor Placement Sacrum

☐Removal Date (Day 8) DD / MM / YYYY

- If the monitor falls off your body, please note date and time it fell off. If you are unsure, time estimates are fine.
- If you do attempt to re-attach the monitor, please also note the time its placed back onto your lower back.
- Please circle "Yes" or "No" to the questions below.

Monitoring Period | *Start (dd/mm/yy):* | *End (dd/mm/yy):*

DD/MM/YYYY **Monday**	DD/MM/YYYY **Tuesday**	DD/MM/YYYY **Wednesday**	DD/MM/YYYY **Thursday**	DD/MM/YYYY **Friday**	DD/MM/YYYY **Saturday**	DD/MM/YYYY **Sunday**
Time you woke up	Time you woke up	Time you woke up	Time you woke up	Time you woke up	Time you woke up	Time you woke up
____:____ am/pm	____:____ am/pm	____:____ am/pm	____:____ am/pm	____:____ am/pm	____:____ am/pm	____:____ am/pm
Time you got out of bed	Time you got out of bed	Time you got out of bed	Time you got out of bed	Time you got out of bed	Time you got out of bed	Time you got out of bed
____:____ am/pm	____:____ am/pm	____:____ am/pm	____:____ am/pm	____:____ am/pm	____:____ am/pm	____:____ am/pm
Did you sleep during the day? ☐NO ☐YES If **YES**, write down the specific times you fell asleep: ___:___to___:___ am/pm	**Did you sleep during the day?** ☐NO ☐YES If **YES**, write down the specific times you fell asleep: ___:___to___:___ am/pm	**Did you sleep during the day?** ☐NO ☐YES If **YES**, write down the specific times you fell asleep: ___:___to___:___ am/pm	**Did you sleep during the day?** ☐NO ☐YES If **YES**, write down the specific times you fell asleep: ___:___to___:___ am/pm	**Did you sleep during the day?** ☐NO ☐YES If **YES**, write down the specific times you fell asleep: ___:___to___:___ am/pm	**Did you sleep during the day?** ☐NO ☐YES If **YES**, write down the specific times you fell asleep: ___:___to___:___ am/pm	**Did you sleep during the day?** ☐NO ☐YES If **YES**, write down the specific times you fell asleep: ___:___to___:___ am/pm
Get into bed time	Get into bed time	Get into bed time	Get into bed time	Get into bed time	Get into bed time	Get into bed time
____:____ am/pm	____:____ am/pm	____:____ am/pm	____:____ am/pm	____:____ am/pm	____:____ am/pm	____:____ am/pm
Did you go straight to sleep? ☐YES ☐NO	Did you go straight to sleep? ☐YES ☐NO	Did you go straight to sleep? ☐YES ☐NO	Did you go straight to sleep? ☐YES ☐NO	Did you go straight to sleep? ☐YES ☐NO	Did you go straight to sleep? ☐YES ☐NO	Did you go straight to sleep? ☐YES ☐NO
If NO, what time did you attempt to go to sleep?	**If NO**, what time did you attempt to go to sleep?	**If NO**, what time did you attempt to go to sleep?	**If NO**, what time did you attempt to go to sleep?	**If NO**, what time did you attempt to go to sleep?	**If NO**, what time did you attempt to go to sleep?	**If NO**, what time did you attempt to go to sleep?
____:____ am/pm	____:____ am/pm	____:____ am/pm	____:____ am/pm	____:____ am/pm	____:____ am/pm	____:____ am/pm
Have you had any medications that may affect your sleep? (Please circle for each day)						
Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Have you had any prebiotics including probiotic drinks, supplement, yoghurt, and keffir? (please circle for each day and specify)						
Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Have you had any caffeine, nicotine or alcohol less than 2 hours before bed? (Please circle for each day)						
Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N

Do you have a bed partner who moves a lot at night? Y / N
Do you sleep on a water bed or rocking chair? Y / N

Appendix 2. Paper Based Food Record

THE UNIVERSITY OF SYDNEY

Name:_____

Study ID:_____

Date:_____

COLONIC

3-day Food Record

Instructions

- Please fill in this food intake record on **3 days, including 2 weekdays and 1 weekend day**.
- The days in which food intake is recorded do not need to be consecutive, but need to be within the same 1 week period.
- You should **fill in the details immediately after you eat or drink, for each meal or snack. Do not** wait till the end of the day to remember everything.
- Detailed directions for how to fill in the food record are at the top of each day. An example of one day is on the following page.

When you have completed the food record please bring it along with you to your next appointment with us, or email it back to us at: kenneth.daniel@sydney.edu.au

If you have any questions about how you should complete the food record, please contact Ken on 02 9351 9138 or kenneth.daniel@sydney.edu.au

Instructions for completing the food record

- **Write down everything that you eat and drink over one day from waking to going to sleep. It is important that you do this straight away after you eat or drink, rather than waiting till the end of the day. This also includes any snacks, water and vitamin and mineral supplements you have.**
- Use a new line for each food, drink or supplement.
- Record the type of eating occasion in the appropriate column. For example, breakfast, lunch, dinner, morning tea, afternoon tea or snack.
- Record each food individually. For example, while you may state *'tuna sandwich'* in the first row for lunch, you should then list each of the individual foods contained in the sandwich in the rows below, together with their amounts.
- Include the amounts in household measures or natural portion sizes. For example, 2 slices of bread, ½ cup rice, ¼ cup peas. Please use the set of standard spoon, cup and jug measures we have provided to assist in recording this information.
    - If you wish to use abbreviations for spoon measures please use the following:
        - 1 teaspoon = 1 tsp
        - 1 tablespoon = 1 TBSP
- You can also weigh food items on the digital scales provided, if preferred. Make sure you first 'zero/tare' the scales before placing a food item for weighing on it.
- Record the cooking method used, where applicable. For example, grilled, BBQ, dry fried, deep fried, baked, boiled, steamed, stir fried etc.
- Give a detailed description of the food or drink and include brand names where possible. For example, Arnott's Milk Arrowroot® biscuit, Yalla Humus or Cobram Estate Extra Virgin Olive Oil robust flavour.
- Don't forget to include any sauces, mayonnaise, dressings or gravies that are used. We are interested to find out about <u>your</u> usual eating patterns, so please keep your food intake as usual.
- If your food item is from a recipe, please record the entire recipe on a separate piece of paper and attach to your food record. This means jotting down all the ingredients and the number of serves the recipe made. Then estimate the proportion of the recipe that you personally ate and record the amount on your food record.
- If you record a day that is not typical, please indicate in the box at the end of each food record day and tell us how it differs from your usual intake. For example, I attended a wedding.

Example of one day

Date: 22/03/2015			Day: Friday		
Location	**Time**	**Meal/Eating Occasion**	**Foods/Drinks/Water/Supplements**	**Cooking Method (where applicable)**	**Amount/Size EATEN**
Home	7am	Breakfast	Skim milk (Dairy Farmers)	-	1 cup
			Weet-bix	-	2 Weet-bix
			White sugar	-	1 tsp
			Toast – white bread (Tip Top)	-	2 slices
			Margarine (Gold'n Canola)	-	2 tsp
			Strawberry jam (Coles)	-	2 tsp
Home	9am	Supplement	Berocca Performance	-	1 tablet
Neighbours place	10am	Morning tea	Coffee, instant	-	1 cup
			HeartActive milk (Dairy Farmer's)	-	1 TBSP
			Doughnut, home made	Deep fried	1
Home	12md	Lunch	*Cheese and salad sandwich:* White bread (Tip Top) Margarine (Meadow-lea) Tasty cheese (Coon) Lettuce, shredded Tomato, sliced Carrot, grated Beetroot, sliced	-	 2 slices 2 tsp 1 slice 1 leaf 2 slices 1 TBSP 1 large slice
Home	1pm		Water		1 cup
Home	3pm	Snack	Tim Tams chocolate biscuits (Arnott's)	-	2
			Orange cordial (Home Brand)	-	1 cup
At the Club	6:30pm	Dinner	2 thin beef sausages	Grilled	2 thin, length 10 cm
			Potato, peeled	Steamed	1 medium
			Carrots, peeled	Steamed	¼ cup
			Green peas, frozen	Boiled	¼ cup
			Red wine, shiraz (Penfolds)	-	300 ml
			Vanilla ice cream (Dairy Farmer's)	-	2 small scoops
			Chocolate sauce (Cottees)	-	2 tablespoons
Home	8pm	Snack	Banana	-	1 medium
Home	9pm	Supper	HeartActive milk (Dairy Farmer's)	-	1 cup

Was your intake unusual in any way? No ☐ Yes √

If yes, in what way? __Had dinner at the Club, which I do once per month__

DAY 1 FOOD INTAKE RECORD (WEEKDAY)

- ✓ **Write down everything that you eat and drink over one day from waking to going to sleep. It is important that you do this straight away after you eat or drink, rather than waiting till the end of the day. This also includes any snacks, water and vitamin and mineral supplements you have.**
- ✓ Use a new line for each food, drink or supplement.
- ✓ Record the type of eating occasion in the appropriate column. For example, breakfast, lunch, dinner, morning tea, afternoon tea or snack.
- ✓ Record each food individually. For example, while you may state *'tuna sandwich'* in the first row for lunch, you should then list each of the individual foods contained in the sandwich in the rows below, together with their amounts.
- ✓ Include the amounts in household measures or natural portion sizes. For example: 2 slices of bread, ½ cup rice, ¼ cup peas. Please use the set of standard spoon, cup and jug measures we have provided.
- ✓ Record the cooking method used, where applicable. For example, grilled, BBQ, dry fried, deep fried, baked, boiled, steamed, stir fried etc.
- ✓ Give a detailed description of the food or drink and include brand names where possible. For example, Arnott's Milk Arrowroot® biscuit, biscuit, Yalla Humus or Cobram Estate Extra Virgin Olive Oil robust flavour.
- ✓ Don't forget to include any sauces, mayonnaise, dressings or gravies that are used. We are interested to find out about <u>your</u> usual eating patterns, so please keep your food intake as usual.
- ✓ If you record a day that is not typical, please indicate in the box at the end of each food record day and tell us how it differs from your usual intake. For example, I attended a wedding.

Date:			**Day:**		
Location	**Time**	**Meal/Eating occasion**	**Foods/Drinks/Water/Supplements**	**Cooking method (where applicable)**	**Amount/Size EATEN**

Was your intake unusual in any way? No ☐ Yes ☐

If yes, in what way? _____

DAY 2 FOOD INTAKE RECORD (WEEKDAY)

- ✓ **Write down everything that you eat and drink over one day from waking to going to sleep. It is important that you do this straight away after you eat or drink, rather than waiting till the end of the day. This also includes any snacks, water and vitamin and mineral supplements you have.**
- ✓ Use a new line for each food, drink or supplement.
- ✓ Record the type of eating occasion in the appropriate column. For example, breakfast, lunch, dinner, morning tea, afternoon tea or snack.
- ✓ Record each food individually. For example, while you may state *'tuna sandwich'* in the first row for lunch, you should then list each of the individual foods contained in the sandwich in the rows below, together with their amounts.
- ✓ Include the amounts in household measures or natural portion sizes. For example: 2 slices of bread, ½ cup rice, ¼ cup peas. Please use the set of standard spoon, cup and jug measures we have provided.
- ✓ Record the cooking method used, where applicable. For example, grilled, BBQ, dry fried, deep fried, baked, boiled, steamed, stir fried etc.
- ✓ Give a detailed description of the food or drink and include brand names where possible. For example, Arnott's Milk Arrowroot® biscuit, biscuit, Yalla Humus or Cobram Estate Extra Virgin Olive Oil robust flavour.
- ✓ Don't forget to include any sauces, mayonnaise, dressings or gravies that are used. We are interested to find out about <u>your</u> usual eating patterns, so please keep your food intake as usual.
- ✓ If you record a day that is not typical, please indicate in the box at the end of each food record day and tell us how it differs from your usual intake. For example, I attended a wedding.

Date:			**Day:**		
Location	**Time**	**Meal/Eating occasion**	**Foods/Drinks/Water/Supplements**	**Cooking method (where applicable)**	**Amount/Size EATEN**

Was your intake unusual in any way? No ☐ Yes ☐

If yes, in what way? _____

DAY 3 FOOD INTAKE RECORD (WEEKEND)

- ✓ **Write down everything that you eat and drink over one day from waking to going to sleep. It is important that you do this straight away after you eat or drink, rather than waiting till the end of the day. This also includes any snacks, water and vitamin and mineral supplements you have.**
- ✓ Use a new line for each food, drink or supplement.
- ✓ Record the type of eating occasion in the appropriate column. For example, breakfast, lunch, dinner, morning tea, afternoon tea or snack.
- ✓ Record each food individually. For example, while you may state *'tuna sandwich'* in the first row for lunch, you should then list each of the individual foods contained in the sandwich in the rows below, together with their amounts.
- ✓ Include the amounts in household measures or natural portion sizes. For example: 2 slices of bread, ½ cup rice, ¼ cup peas. Please use the set of standard spoon, cup and jug measures we have provided.
- ✓ Record the cooking method used, where applicable. For example, grilled, BBQ, dry fried, deep fried, baked, boiled, steamed, stir fried etc.
- ✓ Give a detailed description of the food or drink and include brand names where possible. For example, Arnott's Milk Arrowroot® biscuit, biscuit, Yalla Humus or Cobram Estate Extra Virgin Olive Oil robust flavour.
- ✓ Don't forget to include any sauces, mayonnaise, dressings or gravies that are used. We are interested to find out about <u>your</u> usual eating patterns, so please keep your food intake as usual.
- ✓ If you record a day that is not typical, please indicate in the box at the end of each food record day and tell us how it differs from your usual intake. For example, I attended a wedding.

Date:			**Day:**		
Location	**Time**	**Meal/Eating occasion**	**Foods/Drinks/Water/Supplements**	**Cooking method (where applicable)**	**Amount/Size EATEN**

Appendix 3 Dietitian Checklist

Dietitian Assisted Food Record Checklist

Purpose: to ask about forgotten foods/drinks in 3 day food record; what and how much consumed; brands (where relevant as FoodWorks maps to generic foods except sodium) and cooking methods; query and record serves/omissions by 'gold standard' dietetic probing with open ended questions.

Occasion	Context specific prompts
Breakfast	• Water - lemon • Cold drink – juice (100%/fruit juice drink), smoothie (dairy/alternative) • Hot drink – sweetener, milk/type, coffee style, caffeinated, flavouring • Cereal – RTE/cooked, sugar/honey, nut/seed sprinkles, dairy/alternative, fruit (if canned syrup type/water) • Bread/toast – yellow fat spread, other spreads • Protein (eggs/meat/baked beans) – fat/oil, salt, spices/herbs • Yoghurt – plain/flavoured/diet/fat content/non-dairy • Weekend - bacon/sausages, vegetables, pastries
Lunch	• Sandwich/wrap – spread, sauce/mayo, filling • Soup – bread/roll, spread • Salad – protein (drainage for canned fish), carbs, nuts/croutons, oil/acid/mayo, salt, herbs • Leftovers – as for dinner • Yoghurt (plain/flavoured/diet/fat content/non-dairy), fruit, cake (icing/dried fruit), biscuits (savoury/sweet) • Cold drink – canned/bottled • Hot drink – sweetener, milk/type, coffee style, caffeinated, flavouring
Dinner	• Soup – bread/roll, spread • Protein – meat cut/fat trimming, oil/fat, crumbed/battered/cooking method, sauce, salt • Carbs (rice/pasta/grains) – oil/fat, cooking method, sauce, salt • Vegetables/salad – dressing/mayo, butter/oil, salt, acid, nut/seed sprinkles • Bread/rolls – spread • Mixed dishes – check ingredients, cooking method, fats/oils, paste, salt, serves • Dessert – ice cream/custard (flavour), fruit (if canned, syrup type/water) • Cheese (cream/fat content) and biscuits/crackers • Cold drink - soft drink/cordial/energy drinks/juice/milk • Hot drink – sweetener, milk/type, coffee style, caffeinated, flavouring • Alcohol - 150 ml wine, 375 ml beer stubbie/can, nip spirits
Snacks (prompt after dinner e.g. TV viewing)	• Crisps/hot chips • Biscuits/muffins/pastries • Cheese and biscuits/crackers • Lollies/chocolates • Nuts (salt)/dried fruits/fresh fruit/canned fruit (syrup type/water)
Throughout the day	• Water – tap/mineral/flavoured • Soft drinks/cordials/energy drinks/juice/milk • Hot drink – sweetener, milk/type, coffee style, caffeinated, flavouring
Other information	• Brands/names of takeaway outlets/restaurants • Herbs/spices for breakfast/lunch/dinner • Quantity if portions appear too small/large • Check composite dishes for added fats/oils, sugar, salt, cream etc. • If composite dishes are incomplete, record recipe with total serves in FoodWorks 'Notes' and analyse later

Appendix 4. General Diet Questionnaire

Confidential

General Diet Q

Please complete the questions to the best of your ability. There are no right or wrong answers, we are just hoping to better understand your dietary choices and past experiences.

For the final question, we list a few common diet strategies. If you have attempted any of those on the list, please note if it has been beneficial or helpful for your symptoms or health goals.

If not, you may mark not applicable/never attempted and continue down.

Full name:	_____
Date of survey	_____

Overview of current eating patterns

Are you currently following any type of special diet?	◯ Yes ◯ No
If yes, please select the diet that best describes your current eating pattern	☐ Gluten free ☐ Wheat free ☐ Low FODMAP or elimination diet ☐ Special Carbohydrate Diet (SCD) ☐ IBD-AID Diet ☐ Low Fibre / Low Residue ☐ Low Fat ☐ Paleo ☐ Low Carbohydrate ☐ Ketogenic ☐ Mediterranean ☐ Vegetarian (includes dairy and eggs) ☐ Vegan ☐ Intermittent Fasting or the 5:2 Diet ☐ High energy high protein diet ☐ Clear fluids ☐ Full fluids ☐ Liquid diet or juicing ☐ AIP (Autoimmune Protocol Diet) ☐ Other (please specify)
How long have you followed your current diet?	_____

You have selected that you're either on a low FODMAP or elimination diet. If you have identified what food(s) or food components you're sensitive to please indicate on this field. If you are currently doing some food challenges, please comment as well.	_____
Please describe what "other" diet you're currently following	_____
Please choose the reason(s) that you are currently following a special diet	☐ Manage symptoms related to IBD ☐ Manage other health conditions (please specify the condition) ☐ Religious reasons ☐ Ethical/social reasons/personal reasons ☐ Recommendations of a health professional (please indicate the profession) ☐ Aiming to improve general health ☐ Weight loss ☐ Weight gain ☐ Other reasons
Please describe the health condition related to your current dietary pattern	_____
Please indicate the health profession providing the dietary recommendation, and if this person is your current nominated healthcare/medical professional	_____
Please indicate other reason(s) you are currently following your current eating pattern	_____
Do you have any specific nutritional concerns or goals?	◯ Yes ◯ No
If yes, please indicate your nutritional goals from the checklist below (more than one selection may be made)	☐ Reduce Weight ☐ Gain Weight ☐ Improve Energy Levels ☐ Manage a nutritional deficiency (please indicate type of deficiency and if a healthcare professional provided the diagnosis) ☐ Manage symptoms of IBD ☐ Other (please specify)
You have indicated that one of your nutrition goals is to manage a past or current deficiency. Please outline what deficiency that you have/had, and the healthcare professional providing the diagnosis (if one was provided)	_____
Please outline any other nutrition goals you have not listed in the above checklist	_____

Food Allergies and Intolerances	
Have you ever been diagnosed with a food allergy or intolerance independent from your IBD symptoms?	◯ Yes ◯ No
Health professional providing the diagnosis	_____
Year diagnosed	_____
What food(s) or food components do you have a known allergy towrds?	_____
Do you have a suspected food allergy or intollerance unrelated to your IBD?	◯ Yes ◯ No
What symptoms do you demonstrate when consuming foods that you may be sensitive to?	_____
If yes, please indicate what food(s) or food components you usually avoid	_____
Do you have any other foods/beverages which you are currently avoiding in relation to your IBD symptoms (but not related to an allergy or known intollerance)?	◯ Yes ◯ No
If yes, please outline what food(s) or food components do you actively avoid in order to manage your IBD symptoms	_____
If yes, please specify if these are avoided at all times or only during flares or active symptoms	_____

Social Situation	
Are you the person responsible for shopping in your household?	◯ Yes ◯ No ◯ Shared
If no or shared, who is responsible for shopping in your household?	_____
Are you the person responsible for cooking your own meals in your household?	◯ Yes ◯ No ◯ Shared
If no or shared, who else is responsible for preparing meals in your household?	_____

Fasting	
Do you regularly skip meals OR practice any form of fasting? This includes the 5:2 diet, religious, or for cultural reasons. This does not include forgoing food when symptoms arise, or occasionally skipping meals e.g. breakfast.	◯ Yes ◯ No
If yes, what type of fasting do you practice? (e.g. food avoidance, limiting certain food groups, etc)	_____
If yes, what is the frequency of your fasting?	◯ Daily ◯ Weekly ◯ Monthly ◯ Yearly
How long do you typically fast for (please describe your regiment, and include the duration of the fast)	_____
During your time with our study, have you or will you plan on fasting?	◯ Yes ◯ No

Below you will find a list of common diet strategies that are used to manage gastrointestinal symptoms. For this question, please mark ALL diets that you are either currently doing, or have previously attempted. If you have had experience with a particular diet, please note if you noticed any changes to gastrointestinal related symptoms.

If you never attempted any of the diets listed below, please mark off not applicable.

If you have tried another type of eating pattern not listed below; please make a note on the comment box below.

	Improves flare / GI symptoms	Triggers flare	Makes flares worse	Triggers other GI symptoms	No effect	Unsure	Not applicable/ never attempted
Intentional fasting (e.g., 5:2 diet, 16:8, intermittent fasting)	☐	☐	☐	☐	☐	☐	☐
Skipping meals (unintentional)	☐	☐	☐	☐	☐	☐	☐
Large meal portions / overeating	☐	☐	☐	☐	☐	☐	☐
Small meal portions / portion control	☐	☐	☐	☐	☐	☐	☐
Small frequent meals (grazing)	☐	☐	☐	☐	☐	☐	☐
Vegetarian diet	☐	☐	☐	☐	☐	☐	☐
Vegan diet (no animal products of any type)	☐	☐	☐	☐	☐	☐	☐

Paleolithic style diet (Paleo)	☐	☐	☐	☐	☐	☐	☐
Low carbohydrate diet (e.g., Atkins, South Beach diets, etc)	☐	☐	☐	☐	☐	☐	☐
Ketogenic diet	☐	☐	☐	☐	☐	☐	☐
Mediterranean diet	☐	☐	☐	☐	☐	☐	☐
Specific Carbohydrate Diet	☐	☐	☐	☐	☐	☐	☐
IBD Aid Diet	☐	☐	☐	☐	☐	☐	☐
Low FODMAP	☐	☐	☐	☐	☐	☐	☐
RPA Elimination Diet	☐	☐	☐	☐	☐	☐	☐
Juice/liquid diet	☐	☐	☐	☐	☐	☐	☐
"Detox" and "cleansing" diets of any description	☐	☐	☐	☐	☐	☐	☐

Any other comment's you'd like to make about current/past strategies?

Appendix 5. DXA checklist

Screening ID: _____
Participant ID: _____
Date: _____

DEXA SCAN
RECORD FORM

Image Acquisition Technician: _____

1. **Have you removed all metals** (e.g. jewellery, watches, piercings, belts)?

a. Spine	☐ Small box ☐ Medium box ☐ Large box	☐ Thin ☐ Medium ☐ Thick	
b. Left hip		☐ Thin ☐ Medium ☐ Thick	
c. Right hip		☐ Thin ☐ Medium ☐ Thick	
d. Whole body	☐ Fit in bed markings ☐ Arms against body ☐ Mummy wrap ☐ Pillow	☐ Thin ☐ Medium ☐ Thick	

Analysis performed by: _____

1. Analysis variants (eg profiles altered)		
2. Area graphed in spine analysis Comments:	☐ L1 ☐ L2 ☐ L3 ☐ L4	☐ L1 – L3 ☐ L1 – L4 ☐ L2 – L3 ☐ L3 – L4
3. Area graphed in hip analysis Comments:		

COLONIC_DXA_RECORD_FORM

Appendix 6. Stool Sampling Instructions and Checklist

Participants' handout – Baseline Stool Collection Procedure at Home

BEFORE YOU START:

- Please wear gloves **at all times** while collecting samples.
- Please do not open the stool collection lid until ready to collect the sample.
- Stool samples for collection should be the **FIRST bowel motion of the day**
- Last day of the food diary should be completed for the **day before stool collection** (e.g. if last day of food diary is Monday, 12th March 2019, stool sampling should be done for the first bowel motion of Tuesday, 13th March 2019.
- Please note, you may be asked to replicate Day 3 of the Food Diary before each stool collection.
- If you are unable to produce the sample as planned on that morning, experience constipation, or irregular bowel movements, please collect when bowels open. If this occurs on the next day, please note this down on this sheet.

CHEKLIST

☐ 3-day food diary completed (2 weekdays + 1 weekend)

- Day 1_____
- Day 2_____
- Day 3_____

☐ Stool sampling date should immediately follow Day 3 of food diary

Date of sampling: _____Time: _____

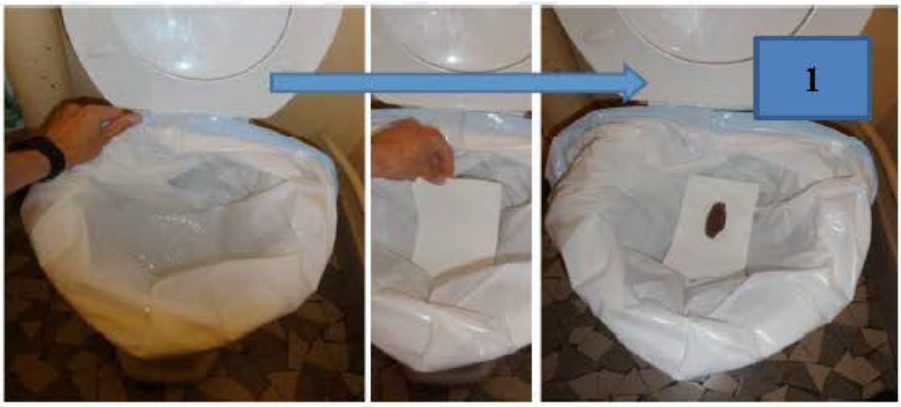
Stool Type as per Bristol Stool Chart_____

☐ 7-day Axivity and Activity log has been completed prior to sampling

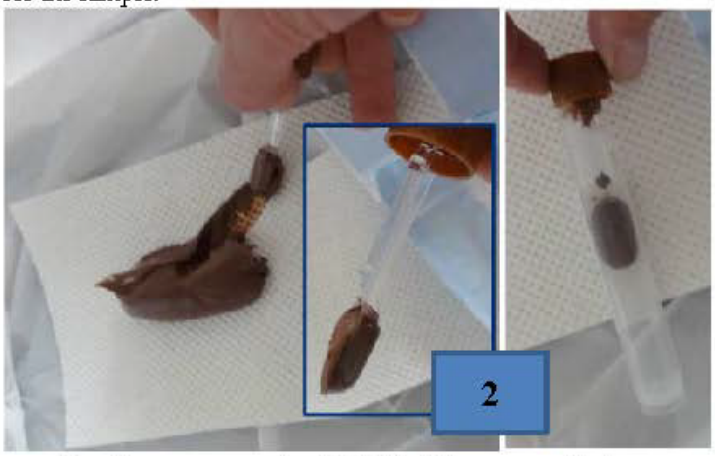
☐ Stool sample immediately kept in fridge at the coldest section (please do not freeze)

☐ Next planned clinic visit date_____
If next clinic date is more than 3 days after sampling, please contact us to arrange a pick up.

1) Set the toilet lining in a secure position. You can use sticky tape to attach this to the sides of the toilet.



2) Use the scoop built inside the cup lid to collect the sample from 4 locations across the sample.



3) Please collect 4 scoops, enough to fill 1/3rd of the cup provided

4) Close the tubes tightly. Please fill out the DATE and TIME of sampling on the label outside the cup with a pen.

5) Place the SEALED and LABELED tube in the biological hazard bag provided to you.

6) Once the bag is sealed, place it in the fridge at the coldest section (**not the fridge door**).

7) Tip away any unused sample in the toilet bowl, and dispose the toilet liner as you would dispose a diaper. Note that the **toilet liner should not be flushed down as it may clog your toilet.**

8) Please bring the sealed bag containing the stool sample and the coversheet of this instructions with you in your next visit, which should be within 24 hours to 3 days after sampling.

If you are not scheduled for further visits or cannot attend your appointment in the next 3 days, please let us know at your earliest convenience. We will organise a pick up from your preferred location.

If you have any concerns on collection and storage; please contact Kenneth via e-mail; Kenneth.daniel@sydney.edu.au OR for urgent matters; mobile on 0433 899 305

Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. **Entirely Liquid**

Reference
Heaton, K W & Lewis, S J 1997, 'Stool form scale as a useful guide to intestinal transit time'. *Scandinavian Journal of Gastroenterology*, vol 32, no 9, pp 920 - 924. Retrieved on 19/07/2019

CHAPTER 3: DIETARY ATTITUDES, FOOD INTAKE, AND QUALITY OF LIFE– A CROSS-SECTIONAL STUDY OF AUSTRALIAN ADULTS LIVING WITH INFLAMMATORY BOWEL DISEASE

Authors: Kenneth Daniel [1], Luis Vitetta, M.D., PhD [2], Helen O'Connor, PhD[1] , Daniel Hackett, PhD [1] Maria A. Fiatarone Singh, M.D. [1,2,3]

[1]Sydney School of Health Sciences, Faculty of Medicine and Health, The University of Sydney, NSW, Australia

[2]Sydney Medical School, Faculty of Medicine and Health, The University of Sydney, Sydney 2000, Australia

[3]The Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts, USA

[1] Deceased 13 January 2020

3.1. Abstract

Background: Many patients with Inflammatory Bowel Disease (IBD) adopt dietary strategies for the management of their condition and symptoms control. Although several IBD-specific diets have shown potential in facilitating remission and attenuating symptoms, conclusive evidence of benefit is lacking. Additionally, the adoption of nutritional interventions presents challenges due to difficulties in implementation, personal food beliefs, and individual dietary preferences. Therefore, understanding individual perspectives and identifying dietary patterns is vital for the development of personalised, evidence-based nutritional strategies which may optimise both disease outcomes and overall quality of life in those living with IBD.

Aims: This cross-sectional study aimed to analyse relationships among dietary intake, lifestyle habits, and food-related quality of life in individuals living with Crohn's disease (CD) or ulcerative colitis (UC) to inform future research and clinical applications of nutritional interventions for IBD.

Methods: Participants aged 18–75 years with a confirmed diagnosis of CD or UC for >3 months were recruited from the Greater Sydney Region for two assessments at the University of Sydney. Assessments included medical history, body composition analysis, assessment of physical activity participation and dietary intake, collection of stool and blood samples, and self-reported health-related questionnaires.

Results: A total of 38 participants were enrolled in the study (21 with CD, 17 with UC, 50% female), with 36 completing both visits (50% female). The average age was 34.7 ± 10.6 (range 19-62) years. Adoption of specialised diets was limited; however, food avoidance was frequently reported, and few reported professional dietary guidance since initial diagnosis. All participants consumed less than their estimated daily energy intake requirements, 55% reported musculoskeletal impairments and low appendicular skeletal muscle mass was identified in 100% of participants. Depression, anxiety, fatigue, impaired sleep quality, and below average quality of life scores were commonly reported in this cohort. Dietary intake patterns, food-related quality of life, and health-related quality of life were similar between CD and UC patients. Compared to women, men had significantly higher energy, carbohydrate, starch, protein, fat intakes, and alcohol consumption. Significantly higher total body fat % was observed in men, differences in skeletal muscle mass and bone mineral density were not statistically significant between sexes. Depression, anxiety, fatigue, impaired sleep quality and below average quality of life scores were more commonly reported in women.

Conclusion: We observed high heterogeneity in dietary patterns in participants enrolled in this study, however few received professional dietary advice. Likewise, many reported restricting food choices without evidence to support their decisions. Low energy intakes, low muscle mass, musculoskeletal symptoms and impairments to psychosocial wellbeing and quality of life were common in this cohort, with no clear difference between CD and UC, but generally lower nutritional intake in women. Our findings highlight a clear need for robust empirical studies to provide evidence to guide nutritional recommendations in IBD, in order to advance clinical care and outcomes for this cohort.

3.2. Introduction

Living with inflammatory bowel disease (IBD) is difficult, due to alternating periods of remission and relapse, unpredictability of the disease course, frequent non-response to therapy, and fears of surgery or development of cancer, leading to high levels of psychosocial distress. [1-3] Disruptions to activities of daily living are frequently reported, negatively impacting social and interpersonal relationships, education, employment, and self-esteem. [4-7] It is unsurprising therefore, that IBD, including both Crohn's disease (CD) and ulcerative colitis (UC), may profoundly reduce the quality of life of those living with the condition. [8, 9]

Individuals with IBD will often adopt a range of health-promoting behaviours for the management of their condition and symptoms, in an attempt to improve health outcomes, quality of life, and gain a sense of control over their illness. This may include lifestyle modifications involving dietary changes, [10-12] the use of complementary and alternative therapies, [13, 14] physical activity participation, [15, 16] and stress management strategies including cognitive-behavioural therapy and mindfulness-based stress reduction. [17-19] Amongst these strategies, dietary changes are often the first line approach for many with the condition, particularly as IBD most commonly manifests as gastrointestinal distress. Unfortunately, dietary behaviours in IBD often consist of self-imposed dietary restrictions based on subjective intolerances identified through trial and error, rather than inclusion of potentially beneficial foods into the existing diet. A scoping review of 29 studies observed that 27.4-89% of patients reported food avoidance, and 41-93% practiced dietary restrictions with the primary purpose of preventing IBD relapse and/or symptom management. [20] Dietary restrictions may be undertaken regardless of disease activity, [21-24] and in severe instances may manifest in the form of eating disorders such as anorexia nervosa and orthorexia nervosa. [25,

[26] Thus, it is unsurprising that nutritional deficiencies are frequently described in this cohort, with malnutrition identified in 16-49.5% of IBD patients [27-29] and prevalence of sarcopenia in CD and UC reported at above 30%. [30-32] Considering these risk factors, identification of effective dietary management strategies is critical in IBD care.

At the time of writing, there is no single diet which is widely advocated for the management of IBD. Instead, a range of pre-defined diets have been described in literature with the aim of improving remission rates, reducing risk of flares, managing symptoms associated with IBD or preventing nutritional inadequacies. Unfortunately, many of the published studies on diet consist of small participant numbers and uncontrolled trials, with heterogeneous outcomes reported. [33-36] This is further complicated by challenges in recruiting sufficient numbers of participants in IBD studies, [37, 38] and substantive attrition rates due to difficulties implementing dietary interventions or loss of interest. [39-41] These barriers highlight a key limitation in designing robust, sufficiently powered diet trials in IBD.

To bridge this gap, understanding nutrition habits, perceptions, beliefs, and motivations of patients living with IBD is a vital step in identifying and designing interventions which are sufficiently flexible, sustainable, and practical. Cross-sectional studies are an important tool for this purpose, with existing studies examining various aspects of health-related quality of life, [9, 42] perceptions towards lifestyle modifications, [15, 21, 43] and dietary habits in IBD. [44-46] However, few studies (to our knowledge) have concurrently examined these parameters.

3.3. Aim

Thus, the aim of this cross-sectional study was to describe and compare lifestyle habits of individuals living with IBD and compare dietary habits, beliefs, nutrition support and food-related quality of life between individuals living with CD and UC. The secondary aim of this study was to describe in detail the body composition, health-related quality of life, sleep quality, fatigue, and physical activity participation in individuals living with IBD.

3.4. Method

3.4.1. Study Design

Methods for this study are outlined in Chapter 2. Participants completed all assessments at the University of Sydney, Faculty of Health Sciences, Cumberland Campus. Ethics application was approved by the University of Sydney Human Ethics Committee (Protocol no. 2018/734).

3.4.2. Participants

Prospective participants were sought within the greater Sydney region through social media advertising, flyers, and through IBD support networks. Participants who were both eligible and expressed interest from other projects running concurrently with this study; COLONiC: Consequences of OLive Oil replacemenNt on ulcerative Colitis (University of Sydney Human Ethics Committee Protocol no. 2018/981) and PRE-BIOTIC: Progressive Resistance Exercise-BIOTa and Inflammation in Crohn's & colitis (University of Sydney Human Ethics Committee Protocol no. 2018/029) were also included.

3.4.3. Inclusion and exclusion criteria

Participants with a confirmed diagnosis of IBD 3 months prior to enrolment were included in the study. Participants with Ulcerative Colitis (UC) were eligible if they scored 0-6 out of 9 (remission to moderate disease) on the Partial Mayo Score [47] at baseline in addition to confirmation from their specialist. Participants with Crohn's Disease (CD) were eligible if they scored ≤ 450 (remission to moderate disease) on the Crohn's Disease Activity Index (CDAI).[48] Participants with severe disease as evidenced by their disease activity scores, modifying their medication, planning to travel and/or currently enrolled in another clinical trial in which concurrent participation was deemed inappropriate were placed on a 3-month waiting list.

3.5. Assessments

Participants completed two in-person assessments over a 2-week period included a physician screen, stress test, body composition assessment, habitual physical activity, dietary intake, strength testing and questionnaires in accordance with the procedures outlined in Chapter 2.

3.5.1. Outcome Measures

Disease activity was examined using the Partial Mayo Score [47] for participants with UC, and the Crohn's Disease Activity Index [48] for participants with CD during the physician screen during the first in-person assessment. Quality of life was evaluated using the Inflammatory Bowel Disease Questionnaire (IBDQ-32)[49] and the Food-related Quality of Life (FRQoL-29) scales. [50]

Depression and anxiety were examined using the Patient Health Questionnaire 9 (PHQ-9) [51] and the Hospital Anxiety and Depression Index (HADS). [52] Sleep quality was determined via the Patient Sleep Quality Index (PSQI), [53] while self-reported fatigue was assessed through the Inflammatory Bowel Disease Fatigue scale (IBD-F). [54] Total and regional body composition and bone mineral density were examined whilst fasting using the Lunar Prodigy Dual X-ray Absorptiometry (DXA) system (GE Healthcare, Vienna, Austria) following standard procedures.

Diet history and past habits was examined through a semi-structured interview with the study dietitian (K.D.), while dietary beliefs were captured via the Food Choice Questionnaire (FCQ). [55] Habitual diet was assessed through completion of a 3-day weighed food diaries (Chapter 2, Appendix 2.3) and analysed using FoodWorks 9 Professional (Xyris Pty Ltd, Brisbane, Australia). Exercise participation was examined through completion of a 7-day prospective self-reported physical activity log recorded while wearing the AX3 3-axis accelerometer (Axivity, Newcastle upon Tyne, United Kingdom) between Assessment 1 and Assessment 2 (see Chapter 2).

3.5.2. Changes to Methods after Commencement

As noted in Chapter 2, evaluation of habitual physical activity data captured via the AX3 3-axis accelerometers, intestinal microbiome through 16S rRNA sequencing of faecal samples, and inflammatory markers through fasting plasma and serum samples collected at the second in-person assessment could not be completed due to funding limitations.

3.5.3. Statistics

Data analysis was completed using SPSS® Statistics version 28.0 (IBM®, Chicago, IL, USA). Normality of data distribution was determined by the Shapiro-Wilk tests. Unpaired t-tests were used to analyse differences in continuous variables between UC and CD as well as between sexes. One-way ANOVA was used to analyse relationships between dietary intake and disease severity categories. Relationships between categorical variables of interest were evaluated using Pearsons's chi-squared tests. Potential relationship between disease severity, body composition, quality of life and diet were evaluated using Pearson correlation coefficient where values (r) ≥ 0.7 are defined as strong, between 0.4 and 0.7 moderate, and between 0.1 and 0.4 weak.[56] Confidence intervals were set at 95% and p values <0.05 were defined as statistically significant. Missing data was excluded from the analyses.

3.6. Results

A total of 89 prospective participants expressing interest were contacted, of whom 35 had UC, 43 had CD, and 11 participants who did not disclose the type of IBD prior to final contact and were thus excluded from the study. No participants with indeterminate colitis (IC) were identified during recruitment. Ability to contact participants following provision of the participant information sheet (n=17), time commitment (n=8), and study suspension due to external circumstances (n=8) were the greatest barrier for enrolment into the study.

Following the first stage telephone screening, 38 prospective participants completed Assessment 1. Two participants with CD withdrew between Assessment 1 and Assessment 2 due to inability to commit for the remainder of the study. (*Figure 1*)

3.6.1. Participant Characteristics and Medical History

Participant demographics are outlined in **Table 3.1**. A greater number of men with CD and women with UC completed the study. Average age was similar between men (34.84 ± 10.42) and women (34.05 ± 11.01) and comparable between CD and UC. The majority of participants in both groups (79%) identified as being of European ancestry.

Across both CD and UC participant groups, most participants (>82%) reported living with either a family or a partner, with more than 50% living in their own home. Except for 1 retired participant in the CD group, all participants reported ongoing work commitments (CD: 31.6 ± 15.7 hours per week, UC: 29.3 ± 14.3 hours per week, $p = 0.656$). Caregiving responsibilities for young children were reported by 6/21 (29%) of participants with CD and 4/17 (24%) of participants with UC. None of the participants were current smokers at the time of the study. Smoking history was reported by 8/21 (38%) participants with CD (7.5 ± 11.8 pack-years) and 3/17 (18%) participants with UC (5.1 ± 4.9 pack-years). No associations were observed between IBD types and smoking history.

More than 89% (34/38) of participants reported taking medication for the management of IBD, with 5-aminosalicylates more prevalent in the UC group (12/17, 71%) and biologics in the CD

group (10/21, 48%). Supplements included calcium (n=4), vitamin D (n=4), iron (n=4), multivitamins (n=3), folate (n=2), vitamin B12 (n=3), magnesium (n=3), selenium (n=1), probiotics (n=3), fish oil/omega-3 (n=2) and turmeric (n=1). More participants with UC (n=4) were consuming either calcium and/or vitamin D supplementation compared to CD (n=2). Four participants (2 with CD, 2 with UC) were not on any medication for the management of IBD at the time of the assessment, all in remission. Neither IBD types nor sex differences were associated with the type of medication prescribed nor the likelihood of taking supplements (*p* values = 0.052 – 0.956).

No differences in functional gastrointestinal symptoms were reported between IBD types (*p* = 0.244) nor sex (*p* = 0.158). Musculoskeletal conditions were reported in 55% of participants including low bone mineral density (n=13), arthritis (n=8), inflammatory joint disease (n=3), osteogenesis imperfecta (n=1), and ankylosing spondylitis (n=1). Joint pain was reported by 17/38 (45%) participants and a history of fractures were identified in 5/38 (13%) participants. Clinical diagnosis of depression based on reported medical history was greater in CD (6/21, 29%) compared to UC (1/17, 6%), while 24% of participants with CD (5/21, 24%) and UC (3/17, 18%) reported a diagnosis of anxiety disorder. No statistically significant differences were observed between the prevalence of anxiety and depression between IBD types (*p* value*s* = 0.076 – 0.654). Similar rates of depression (men 4/19, 21%, women 3/19, 16%, *p* = 0.686) and depression (both 4/19, 21%, *p* = 1.0) were also observed between both sexes.

Family history of CD was more commonly reported in participants living with CD than with UC; 4/21 (29%) participants reported a parent or sibling living with the condition and 2/21 (10%) participants with an extended family relative (cousin, grandparent) with CD compared with 1/17 (6%) each in UC, however these differences were non-significant (*p* values =0.244 – 0.689). Family history of "other GI conditions" was significantly more common in UC (*p* =0.015).

Reported family history of "other" gastrointestinal conditions was also significantly more common in women (*p* =0.037). No associations between sex and a positive family history of IBD were observed (*p* values = 0.324 – 0.642) (**Table 3.2**).

3.6.2. Body Composition

Body composition measures are reported in **Table 3.3.1**. Body composition results could not be evaluated in 2 women living with CD due to withdrawal prior to examination (n=1) and refusal of a full body scan (n=1). This participant, however, consented to and completed spine and bilateral hip scans to evaluate bone mineral density in these regions.

Comparing sexes, men had significantly higher measurements for height, weight, android/gynoid ratios, total lean mass, ALM, ALMI, ASM and ASMI ($p<0.001$). Women had significantly higher total fat % and gynoid fat % distribution ($p<0.001$). Moderate positive correlation was observed between BMI and total fat %, $r\ (36) = 0.596$, $p < 0.001$, and between BMI and ALMI, $r\ (36) = 0.362$, $p < 0.05$.No statistical difference in height, weight, android/gynoid ratios, total lean mass, ALM, ALMI, ASM and ASMI were observed between CD and UC (*p* values = 0.075 – 0.950).

Appendicular lean muscle indices (ALMI) for men (8.47 ± 1.12) and women (6.35 ± 0.49) of most participants were above published thresholds for low lean mass for men [standardised mean difference [SMD (95%); 0.71 (-0.16, 1.58)] and women [SMD 0.48 (-1.45, 0.59)]; $p > 0.05$ for both sexes. Within the entire cohort, 3 participants with CD (1 man and 2 women) were below published thresholds (ALMI < 5.50),[57] while one female participant with CD was considered a borderline case with an ALMI of 5.51 kg/m^2.

Bone mineral content (BMC) and bone mineral density (BMD) measures are reported in **Table 3.3.2**. Men had higher BMC than women, but the difference was not statistically significant (p = 0.028). No difference in BMD were observed between sexes. Comparing IBD phenotypes, abnormal BMD as indicated by a T-score ≤ -1.0 [58] was more prevalent in CD (6/19, 32% for L2-L4 spine, 7/19, 37% for bilateral hip) compared to UC (3/17, 18% for L2-L4 spine, 2/17, 12% for bilateral hip). Low spine BMD was more prevalent in men, while low hip BMD was more frequently observed in women, however no significant differences were observed (p values = 0.114 – 0.565). The T-scores could not be evaluated for 1 female participant with CD due to her age being outside of the reference database. [58]

3.6.3. Physical Activity

No differences between the frequency and type of physical activity participation were observed between sexes. Most participants (17/21, 81% participants living with CD and 14/17, 82% participants living with UC) reported intentional physical activity between Assessment 1 and Assessment 2. No differences in exercise frequency (CD: 2.7 ± 2.4 days, UC: 2.5 ± 2.0 days, p =

0.738), nor duration (CD: 0.7 ± 0.5 hours/session, UC: 0.6 ± 0.5 hours/session, $p = 0.828$) were observed between IBD types. Resistance exercises or combined resistance/aerobic classes (weight training, gym classes, CrossFit, F45) were more frequently reported in UC (11/17, 65%) compared to CD (7/21, 33%). Aerobic exercises (running and jogging) were more frequently reported in CD (7/21, 33%) compared to UC (2/17, 12%); however, differences were not statistically different ($p = 0.078$). Likewise, no significant differences were observed between sexes for duration, frequency, and type of physical activity participation (p values = 0.148 – 0.447).

Analysing the type and volume of self-reported physical activities, only 7/21 (33%) participants with CD and 6/17 (35%) participants with UC met Physical Activity Guidelines for adults (18 to 64 years). [59] The proportion of participants who met these guidelines did not differ between types of IBD, X^2 (1, N = 38) = 0.016, $p = 0.899$ nor sex, X^2 (1, N = 38) = 2.923, $p = 0.087$. Nine participants (CD 5/21, 24%, UC 4/17, 24%) did not report any physical activity during the recording period. Time (n=3), fatigue (n=3), and motivation (n=2) were cited as primary barriers. One participant with UC reported fear of IBD relapse as a barrier for exercise participation.

3.6.4. Diet

3.6.4.1. Dietary Habits

Most participants (13/21, 62% participants with CD and 13/17, 76% participants with UC) reported being involved with meal preparation at home. Adherence to specific diets was reported by 6/21 (29%) participants with CD and 4/17 (24%) participants with UC. Two participants reported following diets for the maintenance of general health unrelated to the management of IBD (low

sugar diet, n=1 with UC) and to support his partner's dietary needs (low Glycemic Index diet, n=1 with CD). Other reported health goals included weight loss (n=9), improvement in energy levels (n=6), management of IBD symptoms (n=5), and preservation of muscle and/or bone mass (n=3). No obvious differences in nutritional goals were reported between participants with CD and UC nor between sexes.

Current dietary patterns are outlined in **Table 3.4.1.** Three participants with CD reported following concurrent diets; ketogenic and vegan (n=1), low FODMAP and vegetarian (n=1), and a combination of low FODMAP, [60] Specific Carbohydrate Diet™ (SCD™), [61] Inflammatory Bowel Disease Anti-inflammatory Diet (IBD-AID) [62] and the Mediterranean diet (n=1). None of the participants following the Low FODMAP diet reported attempting the challenge phase. All diets were self-managed, and none of the participants with specific diets reported current advice or support from an accredited practicing dietitian. Dietary advice from a gastroenterologist (ketogenic diet n=1, avoid spices n=1) was reported by 2/21 participants with CD. Prior dietetic support was reported by 4/21 (19%) participants with CD and 4/17 (24%) participants with UC since initial diagnosis of IBD. One participant with UC commented on the need to do their own online research as they never received any formal guidance nor dietetic referral since diagnosis. One participant with CD disclosed distrust of Accredited Practising Dietitians during the session due to poor past experiences. From the entire cohort, only one participant with UC reported ongoing support by a private practice Accredited Practising Dietitian for the management of gastrointestinal symptoms at the time of the study, with the most recent advice being to 'avoid caffeine'. Reasons for not seeking formal nutrition support were not examined in this study, however 4 participants with UC reported never receiving referral for dietetic services.

The proportion of participants reporting past or a current prescribed diet was similar between participants living with 59% of UC (10/17) and 52% of CD (11/21) having tried at least 1 diet ($p>0.05$). No association was found between the type nor frequency of prescribed diets and sex. The highest number of diets attempted was reported by one participant living with UC (9 prior diets), who was not following specific dietary pattern at the time of recruitment. The low FODMAP diet was the most frequently reported diet strategy attempted (9/38, 24%); 5/38 (13%) participants described improvements to IBD symptoms while 4/38 (11%) participants were either unsure (n=1) or reported no effects (n=4). Two participants reported difficulty with following the low FODMAP diet was cited as the main barrier for continuation, while the remaining participants used the low FODMAP phase of the diet as a transient strategy for the management of severe symptoms. Meal portion sizes and frequency were reported to have no effect on IBD symptoms by 8/38 (21%) participants, while smaller meals were viewed favorably by 6/38 (16%) participants for symptoms management. Skipping meals was seen as a viable strategy to improve IBD symptoms in 5/38 (13%) participants, with at least one participant reporting using this strategy during severe flares. A table outlining the different diets and participant perceptions is presented in **Table 3.4.2**.

Confirmed diagnosis of a food allergy or intolerance was reported by only 3/38 (8%) participants, which included lactose, gluten and apples. By comparison, food avoidance or restrictions related to *suspected* intolerances were reported by >50% of participants, with similar frequencies between CD and UC. Symptoms included increased bowels opening, urgency, bloating, stomach cramps, diarrhea, constipation, feeling “blocked up”, and vomiting. More participants living with CD

avoided spicy foods (5/21, 24%), vegetables (onions, garlic, mushroom, fibrous vegetables) (5/21, 24%), meat (red meat, oysters) (3/21, 14%) and alcohol (2/21, 10%). By comparison, more participants with UC avoided dairy (5/17, 29%), coffee (3/17, 18%), and fruit (strawberries, dried fruit) (2/17, 12%). One participant living with UC reported avoiding chicken and fish due to increased urgency. Across both groups, most participants (16/38, 42%) reported avoiding trigger foods "sometimes" or being mindful of amounts, while a greater number of participants with CD reported complete avoidance of trigger foods (4/21, 19%) compared to UC (1/17, 6%). Avoidance of foods relating to structuring disease in CD was reported by 3 participants (fibrous vegetables, n=2 and whole nuts, n=1). (**Table 3.4.2)**

3.6.4.2. Food Choice Questionnaire

Thirty-one participants (16/21, 76% participants living with CD and 15/17, 88% participants living with UC) completed the Food Choice Questionnaire (FCQ), with missing records attributed to participant withdrawal prior to Assessment 2 (n=2) and incomplete records (n=5). Women in both groups ascribed greater importance to health, mood, convenience, and weight control when choosing meals, with the convenience difference being significant (women: 3.2 ± 0.6, men: 2.28 ± 0.64, $p<0.001$). Higher average ratings indicating greater importance for all domains were observed in participants living with UC, however the differences were not statistically significant. (**Table 3.4.4**) From all the components of the FCQ, greater ratings for "health" had weak negative correlation with disease severity scores r (29) = -0.361, $p < 0.05$, while the relationship with all other domains of the FCQ were negligible.

3.6.4.3. 3-day Weighed Food Diaries

Thirty participants (18/21 participants with CD, 12/17 with UC) submitted 3-day weighed food diaries and completed the review session alongside the study dietitian confirming reported food intakes. Missing records are attributed to participant withdrawal prior to Assessment 2 (n=2) and incomplete 3-day weighed food diary (n=6). All participants completing the food diaries reported habitual food intake during the assessment period. Equal numbers of men and women submitted completed food diaries for analysis (n=15).

Significantly higher intakes of energy, protein, carbohydrates, and starch were reported by men in the study ($p<0.001$) (**Table 3.4.5**). Men were closer to meeting their estimated energy needs (EER) compared to women (men; 92% EER CD, 87% EER UC vs. women 71% EER CD, 79% EER UC). Men reported a significantly higher weekly alcohol consumption compared to women in this study (men: 6.6 ± 6.7, women: 2.6 ± 2.5 standard drinks, $p<0.001$) Alcohol intake above Australian alcohol safety guidelines (≥ 10 standard drinks per week) [63] was observed in 4/18 (22%) participants with CD and 2/12 (17%) participants with UC.

No significant differences in estimated energy intakes nor any of the nutrients examined were observed between disease types or severities. Protein consumption below recommended daily intakes (women: 0.75 g/kg body weight, men: 0.84 g/kg body weight) [64] were observed in in 3/18 (17%) participants with CD and 1/12 (8%) participant with UC. Fibre was below Australian and New Zealand recommendations for adequate intake in both CD and UC (women ≥25 g/day, men ≥30 g/day), [64] with slightly lower average intakes observed in CD (CD: 22.83 ± 10.39, UC: 23.98

± 6.95 g/day). Total fat intake and omega-3 fatty acids were lower in participants with UC vs. CD. The highest saturated fat intake was observed in men with UC (46.02 ± 9.25 g/day). Correlations between physical activity participation, estimated energy intake and all macronutrients were either weak or negligible ($r < 0.4$).

3.6.5. Quality of Life

3.6.5.1. Food-related Quality of Life (FRQoL-29)

Thirty-one participants who completed the FCQ (**Table 3.4.4**) also completed the 29-item Food-related Quality of Life (FRQoL-29) questionnaire. Higher average scores, indicating better quality of life, were observed in men and participants with UC compared to women and CD, respectively. These differences were nearly statistically significant between sexes ($p = 0.051$) but not between IBD phenotype ($p = 0.455$). (**Table 3.5.1**) No relationships were observed between FRQoL-29 and estimated intake from the 3-day weighted food diaries,

3.6.5.2. Inflammatory Bowel Disease Questionnaire (IBDQ-32)

Higher total IBDQ and IBDQ sub-scores, indicating better quality of life, were observed in men. women and participants living with UC vs. CD. Significant differences in systemic system sub-scores were observed between sexes (men: 26.95 ± 4.2, women: 21.21 ± 6.04, $p<0.001$). (**Table 3.5.2**) No other statistically significant differences in average total scores or sub-scores were observed. Total IBDQ-32 scores were strongly correlated with the FRQoL-29 scores, r (29) = 0.722, $p < 0.001$. We also observed moderate positive correlations between the total IBDQ-32 scores and PHQ-9, r (36) = 0.683, $p < 0.001$.

3.6.5.3. Patient Health Questionnaire (PHQ-9)

Across the entire cohort, 18/38 (47%) of participants returned scores suggestive of mild depression or higher. Scores suggestive of mild or greater depression were found in 10/19 (52%) of women and 8/19 (42%) of men, but the difference was not statistically significant. The proportion of participants with scores suggestive of mild or greater depression were similar in CD (10/21, 48%) and UC (8/17, 47%) (**Table 3.5.3**) None of the participants reported severe depression (PHQ-9 score >19) [51] during the assessment.

3.6.5.4. Hospital Anxiety and Depression Scale (HADS)

Borderline or abnormal scores for anxiety was observed in 11/38 (29%) across the entire cohort. Women had a significantly higher average HADS-A score (women: 7.32 ± 3.65, men: 4.68 ± 4.11, $p = 0.044$), and greater prevalence of anxiety (women 8/19, 42% vs. men 3/19, 16%). Participants with UC had a higher average HADS-A score and greater prevalence of borderline or abnormal cases for anxiety (7/17, 41%) compared to CD (4/21, 19%).

Borderline or abnormal scores for depression were observed in 8/38 (21%) across the entire cohort. Average HADS-A scores were similar between men and women (men: 3.37 ± 3.8, women: 3.53 ± 3.31, $p = 0.892$) with no difference in prevalence (4/19, 21%). Participants with CD had a higher average HADS-D score and greater prevalence of borderline or abnormal cases for depression (5/21, 24%) compared to UC (3/17, 18%), although the differences were not statistically significant. **(Table 3.5.4)** Strong positive correlation was observed between HADS-A and HADS-

D, r (36) = 0.716, $p < 0.001$. Both sub-scores were also strongly correlated with PHQ-9 scores (HADS-A, $r = 0.811$, HADS-D, $r = 0.731$, $p < 0.001$).

3.6.6. Fatigue and Sleep Quality

3.6.6.1. Inflammatory Bowel Disease Fatigue (IBD-F) Self-assessment

Nearly all participants (37/38, 97%) described some level of fatigue in the past 2 weeks, and most (30/38, 79%) reported their fatigue occurs intermittently **(Table 3.6.1)**. Total IBD-F scores were higher in women (women: 37.79 ± 22.82, men: 21.05 ± 13.76, $p = 0.010$). No significant difference between CD and UC were observed for IBD-F. More participants with CD compared to UC described their fatigue as being "constant". Both work (14/38, 37%) and impaired sleep (14/38, 37%) were the most frequently reported contributors for fatigue. Medical reasons for fatigue included medication side effects (n=2), joint pain (n=1), allergies (n=1), gastrointestinal symptoms (n=1), celiac disease (n=1), and kidney disease (n=1). Other reasons cited for fatigue included moving house (n=1), lack of exercise (n=1), ageing (n=1), being overweight (n=1), and financial stress (n=1). IBD-F scores were strongly correlated with total-IBDQ-32 scores ($r = 0.711$), PHQ-9 ($r = 0.811$), and HADS-A ($r = 0.739$). Moderate correlations were observed with FRQoL-29 ($r = 0.584$) and HADS-D ($r = 0.645$).

3.6.6.2 Sleep Quality

Sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI) is presented in **Table 3.6.2** Two thirds of participants (66%) reported impaired sleep quality as indicated by a PSQI total score ≥ 5. Domains for subjective sleep quality, sleep latency, sleep disturbance and daytime dysfunction

received the highest average scores for all participants, compared to sleep duration, sleep efficiency, and use of sleep medications. Higher scores indicating greater sleep impairments were reported by women vs. men, however differences between sexes were not statistically significant. High and similar rates of poor sleep quality were observed both in UC (11/17, 65%) and CD (12/21, 57%), but significantly greater impairments to the sleep efficiency component of the PSQI were reported in UC compared to CD (UC: 0.6 ± 0.9 vs. CD: 0.1 ± 0.3, $p<0.001$). The PSQI total and sub-scores were weakly correlated with IBD-F except for daytime dysfunction scores, r (35) = 0.516, p = 0.001. Weak negative correlation was observed between the PSQI and total IBDQ-32 scores (r = -0.398), while systemic symptoms sub-scores demonstrated the greatest relationship (r = - 0.537) from all the components of the IBDQ-32.

3.6.7. Adverse events

No adverse events were reported by any participant for the duration of the study.

3.7. Discussion

We conducted a cross-sectional study comparing dietary habits, food- and health-related quality of life, body composition, sleep quality, fatigue, and physical activity participation in both CD and UC. We recruited 38 participants, 50% women, with an average age of 34.7 ± 10.6 years into the study, with a higher proportion of women with UC (65%) compared to CD (38%). Few participants had adopted special diets for the management of IBD at time of the assessment, however above 50% of those in both groups had attempted at least 1 diet for the management of their condition since initial diagnosis. These self-prescribed dietary choices met with varying levels of success,

leading some participants to attempt alternative strategies, with the highest number of attempts reported at 9 different diets. Similarly, although diagnosis of food allergies and/or intolerance was low at 8%, more than 50% of participants in both groups reported self-imposed dietary restrictions for the management of their symptoms, with vegetables and spicy foods mostly avoided by patients with CD, while dairy, fruit and caffeine avoided by patients with UC. Our findings suggest that these dietary restrictions were not only unsuccessful but may have resulted in significant health risks. Specifically, we found a high prevalence of sub-optimal energy intake in this cohort, as well lean mass measures below normative thresholds in participants with CD, raising significant concerns for long term adverse clinical consequences of these dietary patterns in addition to the risks of the chronic inflammatory disease process itself. [27-31, 65] Additional concerns for future fracture risk are suggested by the low bone mineral density (BMD) identified in 25% of participants despite their young age. The risk factors for this low BMD are likely multifactorial, including not only dietary restrictions including dairy avoidance in 18% minimal use of calcium or vitamin D supplementation (16%), chronic inflammation, and use of immunosuppressant drug therapy. [66] Our findings of low bone density and muscle mass are consistent with previous studies in this cohort. [32, 67]

Contrary to previous findings reporting low exercise participation in IBD, [68] more than 80% of participants engaged with planned physical activity, with half meeting Australian physical activity guidelines for adults (18-64 years). [59] A higher proportion of participants with UC (65%) reported engaging in resistance exercise compared to those with CD (33%), although it remains unclear whether these differences are attributed to disease presentation or other factors. Additionally, no significant differences in exercise type by sex were observed, suggesting that sex distribution

between CD and UC did not influence exercise preferences. However, due to the small sample size, these findings should be interpreted with caution. Physical activity interventions have been demonstrated to support maintenance of clinical remission and improvements in quality of life in IBD, with the potential to complement other lifestyle interventions such as diet.[69] Unfortunately, most published trials are limited by small participant numbers and variability of outcome measures, [70-73] with well-designed and sufficiently powered studies warranted to define optimal exercise prescriptions in this cohort.

Few participants had low muscle mass as indicated by appendicular lean mass measurements below published threshold for sarcopenia in older adults,[57] which may reflect the younger average study cohort and high amounts of physical activity participation. It is notable however that published cut-offs can vary significantly and depend on the method of assessment, outcomes measured and reference population,[74] thus the need to interpret these findings pragmatically considering other risk factors identified in this population including malnutrition, reduced physical activity participation particularly during active disease, and physiological changes associated with disease presentation.

Fatigue was reported in nearly all participants recruited in the study (97%), compared to an estimated 20% estimated in adult populations.[75] Primary causes of fatigue in the study cohort was poor sleep (37%) and work-related stress (37%). Primary causes of fatigue in this cohort were not IBD-specific which is consistent with findings that most participants had quiescent disease. It was notable however that the prevalence of fatigue in this cohort greatly exceeds the estimated 24-87%

cited in literature. [76] Given that the IBD-F assesses the 'main' contributors to fatigue and the multifactorial nature of fatigue, it remains unclear if the prevalence of fatigue is a greater due to a combination of both IBD-specific and external variables such as work-related stressors and suboptimal lifestyle, nor is it clear if this relationship is bi-directional. Similarly, there is significant heterogeneity of the definitions and tools used to evaluate fatigue in research which should be considered in interpreting these findings.[77]

We observed a high prevalence of poor sleep with 60% of participants reporting sleep related impairments, however correlations with fatigue as examined by the IBD-F were weak. which could have contributed towards the high rates of fatigue described in this population, however it is unclear if these impairments could be attributed to IBD symptoms alone or other factors. Significant disruptions to sleep efficiency were reported by participants with UC but not in CD, however due to small participant numbers further studies are required to assess this relationship. Poor sleep, fatigue, and external stressors may have also contributed to sub-optimal health-related quality of life outcomes observed in this study consistent with current literature. [76]

We identified substantial rates of anxiety (21%) and depression (18%) reported in medical histories; however, prevalence of psychological distress was even greater when participants were assessed using HADS-D (21%), HADS-A (29%) and PHQ-9 (47%). By comparison, data from the National Study of Mental Health and Wellbeing (2020-22) suggest 12-month prevalence of any anxiety disorder is 17.2%, while depressive episodes is 4.9% . [78] Thus, our results demonstrate a higher prevalence of psychological impairments compared to the general population. Indeed,

lifetime risk of psychological impairments in IBD is significantly higher compared to the general population, with a 3- to 5-fold increase for anxiety and 2- to 4-times increase for depressive disorders. [79, 80] High rates of psychological impairments have previously been described in this population, with ranges between 21-25.2% for depression and 19.1-35.1% for anxiety. [81] Strong evidence suggests that elevated inflammatory markers, commonly present in IBD, may play a role in the pathophysiology of anxiety and depression. [82-88] Furthermore, the use of immunosuppressive medications such as corticosteroids, frequently used in IBD, have also been associated with glucocorticoid-induced mood changes and neuropsychiatric symptoms. [89] Concerningly, both anxiety and depression have been associated with worsening outcomes in IBD, including shortened period of remission, [90] loss of response to therapy, [91] malnutrition, [92] and higher risk of complications requiring surgical interventions. [93] As such, it is important to consider comprehensive support strategies addressing both the management of IBD and psychological comorbidities.

3.7.1. Diet and Inflammation

Growing evidence points towards the role of diet in attenuating inflammation as an important mechanism in managing chronic conditions, including IBD and psychological distress. [94-96] To this end, several tools examining the relationship between dietary components and inflammatory markers have been developed. The Dietary Inflammatory Index (DII) which was first published in 2009 [97] and revised in 2014 [98] examined 6500 peer reviewed articles to create an a priori index of 45 foods and assign each with an overall inflammatory effect score. Separately, Harvard's Empirical Dietary Inflammatory Pattern score (EDIP) [99] examined the diet records and inflammatory markers of 5230 participants enrolled in the Nurses' Health Study (NHS) [100] to

develop a shortlist of 18 food groups categorised by their impact on inflammation. Although conceptually different, some overlap exist between these two tool with modest correlation. [101]

Based on these tools, a wide range of foods and nutrients have been identified as having anti-inflammatory potential including garlic, ginger, onion, turmeric, leafy green vegetables, coffee, fibre, omega-3 fatty acids, polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA) and flavonoids. By contrast, processed meat, red meat, refined grains, sugar sweetened beverages, saturated fats, and trans fats were considered pro-inflammatory. [98, 99] Many of the foods identified seem to match observational study data describing risk factors for the development and progression of IBD, [102-106] however investigations applying DII and EDIP in IBD have produced mixed results. Greater DII and EDIP scores (indicating a higher proportion of pro-inflammatory food components in the diet) were positively associated with increased faecal calprotectin [107] and disease activity, [107, 108] while a cross sectional study of 143 IBD patients found no association between DII, EDIP, and disease severity. [109] Few studies have examined this relationship in IBD, and the inconsistent findings highlight a gap in the evidence. While anti-inflammatory foods and diets may have a therapeutic role in IBD evident through adoption of dietary strategies such as the SCD [61] and IBD-AID [62] diet in this cohort, more data from randomised controlled trials are required to establish their efficacy. Similarly, the underlying mechanisms through which anti-inflammatory diets and ingredients might influence IBD pathophysiology also remain unclear in these dietary prescriptions. Despite these diets being attempted by several participants in this study, only one participant continued to use these diets in an intermittent fashion indicating limitations on sustainability in maintaining long term adherence. Similarly, it should be considered that many of the anti-inflammatory foods described in literature such as spices, onions, and garlic are also

trigger foods actively avoided by participants in this cohort. This incompatibility illustrates some of the challenges in applying the evidence on diet in IBD, and the need for individualised support by accredited nutrition professionals experienced to support patient outcomes.

3.7.2. The Potential Role for Exercise Interventions

To address some of the impairments described in this study, emerging evidence suggests that physical activity may confer protective effects against IBD-related complications including bone loss, low bone mineral density, and sarcopenia, while also positively influencing fatigue, psychological health and wellbeing. [110-112] Despite these potential benefits and generally favourable view towards physical activity expressed by patients, [111] barriers to physical activity participation remain high.

Concerns around exacerbation of symptoms, joint pain, fatigue and embarrassment are frequently reported barriers to exercise by individuals living with IBD, [68, 113, 114] which was acknowledged by one participant in the study as a deterrent. Notably, most participants in this study cited time and motivation as primary barriers for exercise rather than IBD related symptoms. Most participants in this study were in disease remission, which may explain the greater exercise participation observed in this study and barriers to exercise. Currently there are no specific guidelines on physical activity recommendations effective in IBD across disease severities and presentations, despite the potential to improve health outcomes in this cohort.[115] Likewise, the impact of these strategies on other lifestyle approaches unexplored such as dietary changes is poorly understood.[70]

3.7.3. Gaps in Nutrition Support

Concerningly, less than one-quarter of participants (21%) reported having received support from dietetic services since their initial diagnosis, despite their interest in this topic. Dietetic support is a frequently underutilised resource in IBD care, with services predominantly focused on nutrition screening and management of EEN and prevention of malnutrition. [116, 117] Recent reviews highlight the emerging role of dietetic services to manage nutrition needs and disease-related complications, optimise diet therapy, and improve patient outcomes in IBD, both within acute care settings and in community-based or outpatient settings. [118, 119] Unfortunately, several studies have reported low referral rates for nutrition support, with fewer than 50% of patients receiving appropriate dietetic referrals. [120, 121] This is further complicated by variable access to specialist dietitians working in IBD, [122, 123] long wait times in outpatient settings [124] and associated costs of accessing healthcare services. [125] Amongst patients who do receive support, several studies have highlighted that unmet patient expectations regarding nutrition advice from healthcare professionals contribute towards distrust and dissatisfaction among individuals living with IBD. [45, 126, 127] This disconnect may stem from perceived inadequacies in dietary guidance, lack of personalisation, or inconsistencies in recommendations, ultimately influencing patient adherence and engagement with medical nutrition therapy. As such, nutritional intakes may remain suboptimal, even among patients receiving dietary advice.

These gaps in nutritional support and guidance may also contribute to the use of alternative sources of information to address unmet needs. Although gastroenterologist are often cited as the primary source of nutrition information following diagnosis, internet sources (9-60%) and non-dietetic professionals (84.7%) are a substantial source of information for individuals living with

IBD.[126, 128] a Disparity between the number of past diets attempted and number of patients on a specific diet at the time of the study may indicate a sustainability issue, with many specialised dietary patterns frequently adopted and then discarded in IBD. Many of the diets described were restrictive in nature, and long-term adherence is often challenging due to factors such as personal dietary beliefs, financial constraints, time demands, and psychosocial commitment. [62, 129-132] Adopting these diets can also be particularly challenging for some patients due to concerns about specific dietary components. For example, fibre restrictions are frequently reported in IBD due to fears of complications such as stricturing disease, [133] potentially limiting adherence to high fibre diets such as the Mediterranean diet despite limited evidence supporting the need for such restrictions. [104, 134, 135] This uncertainty around the role of diet, in addition to limited guidance and conflicting information, is further highlighted with many patients reporting that they were unsure if the diets trialed had any effect on their IBD (**Table 3.4.2**). Dietary confusion and misinformation is highlighted by the one patient who had attempted up to 9 dietary strategies, and the one participant concurrently trialing 4 diets at once.

Beyond descriptions of any specific diet, avoidance of individual food components through trial and error may be a less regimented and therefore a more attractive approach. Each of the 5 major food groups were represented in the foods avoided in our study, with vegetables, dairy, and grains and cereals frequently reported. Notably, unsaturated fats and oils were not identified as a trigger by any participant in this study. Some of the foods avoided are key sources of energy and calcium in the diet, which is particularly concerning due to the prevalence of low bone mineral density and sarcopenia in IBD and in our cohort specifically. [30-32] However, it is important to acknowledge the limitations of dietary assessments, particularly the possibility of under-reporting in 3-day weighed

food diaries, which remains a potential source of bias. Literature suggests under reporting or misreporting of food records results in an underestimation of energy intake by up to 30%, [136] and a proportion of participants (24%) reported weight loss as a personal health goal during the session, which may skew these results. Furthermore, the limitations of using prediction equations to estimate energy needs must be acknowledged, as these methods are prone to inaccuracies. Studies indicate that only 28–52% of adult patients have energy estimates that fall within 10% of values obtained through indirect calorimetry, highlighting the potential for miscalculations in energy requirements. [137]

Finally, our findings demonstrate variability in the level of support received among participants, based on self-reported medical histories and dietary guidance since diagnosis. Participants with UC were more likely to trial specific dietary patterns, had a higher prevalence of anxiety, poorer sleep quality, and were less likely to receive dietetic referrals. By contrast, participants with CD exhibited higher rates of depression, musculoskeletal abnormalities, and lower energy intakes. Additionally, therapeutic approaches differed between the two groups. Despite these distinctions, many dietary strategies and nutrition research continue to apply a uniform approach to IBD, often overlooking differences in disease phenotype. Future trials should consider a more targeted approach to disease phenotype and symptom burden.

3.7.4. Strengths and Limitations

One of the key strengths of this study was the range of variables examined, including medical history, body composition, diet, exercise, food- and health-related quality of life, sleep quality,

fatigue, and patient perspectives. We recruited a similar number of participants with CD and UC, with balanced sex and age distribution.

This study was also subject to several limitations. Recruitment was constrained by the 2019–20 Australian bushfire season, the COVID-19 pandemic, and the subsequent relocation of the research clinic, limiting the number of participants enrolled. The placement of participants with severe disease in the 3-month wait list may limit the generalisability of our findings to individuals with quiescent disease. Study attrition was likely influenced by the extensive assessments and multiple site visits required, in addition to circumstances relating to the 2019–20 Australian bushfire season and COVID-19 pandemic. Additionally, assessment outcomes such as analysis of 7-day habitual physical activity from the AX-3 accelerometer, intestinal microbiome diversity, fecal calprotectin levels, and serum inflammatory markers could not be assessed at this time due to funding constraints. Future research may consider more comprehensive dietary assessments, such as 7-day weighed food records to capture longer-term intake patterns and variations, whilst health related quality of life, strength and power, and body composition could be examined as a separate trial to reduce the number of assessments and manage participant burden. Further evaluations could also consider examination for muscle function using handgrip strength to assess for sarcopenia, serum levels of vitamin D3 and iron, examination of dietary quality, and dietary screeners to examine disordered eating patterns in IBD.

3.8. Conclusion

Patients with IBD experience significant disease burden that affects multiple aspects of daily life, including dietary habits, physical activity, overall health, and psychosocial wellbeing. While similarities exist between CD and UC, each patient faces unique challenges in adapting their lifestyle, emphasizing the need for individualised approaches in IBD management. The lack of robustly designed dietary studies in this area has led to unmet needs for evidence-based, practical, and flexible dietary strategies that do not rely on unnecessary restrictions. Larger studies are needed to further investigate differences between IBD subtypes and sex-based variations observed in this study. Future diet trials should consider a more targeted approach, focusing on individual IBD subtypes and develop simpler, sustainable dietary strategies.

3.9. References

1 DuBois KE, Blake CE, Rudisill C, Harrison SE, Hébert JR. Use of Treatment and Self-Management Methods: Perspectives and Decisions of Patients With Ulcerative Colitis. *American Journal of Lifestyle Medicine*. 2024:15598276241243300.

2 Sajadinejad MS, Asgari K, Molavi H, Kalantari M, Adibi P. Psychological Issues in Inflammatory Bowel Disease: An Overview. *Gastroenterology Research and Practice*. 2012;2012(1):106502.

3 Stevens TW, Matheeuwsen M, Lönnkvist MH, et al. Systematic review: predictive biomarkers of therapeutic response in inflammatory bowel disease—personalised medicine in its infancy. *Alimentary Pharmacology & Therapeutics*. 2018;48(11-12):1213-1231.

4 Han SW, McColl E, Barton JR, James P, Steen IN, Welfare MR. Predictors of Quality of Life in Ulcerative Colitis.: The Importance of Symptoms and Illness Representations. *Inflammatory Bowel Diseases*. 2005;11(1):24-34.

5 Mitchell A, Guyatt G, Singer J, et al. Quality of Life in Patients with Inflammatory Bowel Disease. *Journal of Clinical Gastroenterology*. 1988;10(3).

6 Schirbel A, Reichert A, Roll S, et al. Impact of pain on health-related quality of life in patients with inflammatory bowel disease. *World J Gastroenterol*. 2010;16(25):3168-3177.

7 Byron C, Cornally N, Burton A, Savage E. Challenges of living with and managing inflammatory bowel disease: A meta-synthesis of patients' experiences. *Journal of Clinical Nursing*. 2020;29(3-4):305-319.

8 Knowles SR, Graff LA, Wilding H, Hewitt C, Keefer L, Mikocka-Walus A. Quality of Life in Inflammatory Bowel Disease: A Systematic Review and Meta-analyses-Part I. *Inflamm Bowel Dis*. 2018;24(4):742-751.

9 Mavroudis G, Simrén M, Öhman L, Strid H. Health-related quality of life in patients with long-standing ulcerative colitis in remission. *Therap Adv Gastroenterol*. 2022;15:17562848211062406.

10 Jowett SL, Seal CJ, Phillips E, Gregory W, Barton JR, Welfare MR. Dietary beliefs of people with ulcerative colitis and their effect on relapse and nutrient intake. *Clinical Nutrition*. 2004;23(2):161-170.

11 Kennedy ED, To T, Steinhart HA, Detsky A, Llewellyn-Thomas HA, McLeod RS. Do patients consider postoperative maintenance therapy for Crohn's disease worthwhile? *Inflammatory Bowel Diseases*. 2008;14(2):224-235.

12 Prince A, Whelan K, Moosa A, Lomer MCE, Reidlinger DP. Nutritional problems in inflammatory bowel disease: The patient perspective. *Journal of Crohn's and Colitis*. 2011;5(5):443-450.

13 Yanai H, Salomon N, Lahat A. Complementary Therapies in Inflammatory Bowel Diseases. *Curr Gastroenterol Rep*. 2016;18(12):62.

14 Lindberg A, Fossum B, Karlen P, Oxelmark L. Experiences of complementary and alternative medicine in patients with inflammatory bowel disease – a qualitative study. *BMC Complementary and Alternative Medicine*. 2014;14(1):407.

15 Chae J, Yang HI, Kim B, Park SJ, Jeon JY. Inflammatory Bowel Disease Patients' Participation, Attitude and Preferences Toward Exercise. *Int J Sports Med*. 2016;37(08):665-670.

16 Jones K, Naisby J, Baker K, Tew GA. Exercise Perceptions and Experiences in Adults With Crohn's Disease Following a Combined Impact and Resistance Training Program: A Qualitative Study. *Crohn's & Colitis 360*. 2023;5(2):otad019.

17 Lovén Wickman U, Yngman-Uhlin P, Hjortswang H, Riegel B, Stjernman H, Hollman Frisman G. Self-Care Among Patients With Inflammatory Bowel Disease: An Interview Study. *Gastroenterol Nurs*. 2016;39(2):121-128.

18 Mikocka-Walus A, Bampton P, Hetzel D, Hughes P, Esterman A, Andrews JM. Cognitive-behavioural therapy has no effect on disease activity but improves quality of life in subgroups of patients with inflammatory bowel disease: a pilot randomised controlled trial. *BMC Gastroenterology*. 2015;15(1):54.

19 Lyall K, Beswick L, Evans S, Cummins RA, Mikocka-Walus A. Mindfulness Practice Is Associated With Subjective Wellbeing Homeostasis Resilience in People With Crohn's Disease but Not Ulcerative Colitis. *Frontiers in Psychiatry*. Original Research. 2022;13.

20 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;167:105650.

21 Crooks B, McLaughlin J, Matsuoka K, Kobayashi T, Yamazaki H, Limdi JK. The dietary practices and beliefs of people living with inactive ulcerative colitis. *European Journal of Gastroenterology & Hepatology*. 2021;33(3).

22 Limdi JK, Aggarwal D, McLaughlin JT. Dietary Practices and Beliefs in Patients with Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. 2016;22(1):164-170.

23 Zallot C, Quilliot D, Chevaux J-B, et al. Dietary beliefs and behavior among inflammatory bowel disease patients. *Inflammatory Bowel Diseases*. 2012;n/a(n/a).

24 Baars JE, Nuij VJAA, Oldenburg B, Kuipers EJ, van der Woude CJ. Majority of Patients with Inflammatory Bowel Disease in Clinical Remission Have Mucosal Inflammation. *Inflammatory Bowel Diseases*. 2012;18(9):1634-1640.

25 Wabich J, Bellaguarda E, Joyce C, Keefer L, Kinsinger S. Disordered Eating, Body Dissatisfaction, and Psychological Distress in Patients with Inflammatory Bowel Disease (IBD). *Journal of Clinical Psychology in Medical Settings*. 2020;27(2):310-317.

26 Wardle RA, Thapaliya G, Nowak A, et al. An Examination of Appetite and Disordered Eating in Active Crohn's Disease. *Journal of Crohn's and Colitis*. 2018;12(7):819-825.

27 Liu J, Ge X, Ouyang C, et al. Prevalence of Malnutrition, Its Risk Factors, and the Use of Nutrition Support in Patients with Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. 2022;28(Supplement_2):S59-S66.

28 Gold SL, Rabinowitz LG, Manning L, et al. High Prevalence of Malnutrition and Micronutrient Deficiencies in Patients With Inflammatory Bowel Disease Early in Disease Course. *Inflamm Bowel Dis*. 2023;29(3):423-429.

29 Pulley J, Todd A, Flatley C, Begun J. Malnutrition and quality of life among adult inflammatory bowel disease patients. *JGH Open*. 2020;4(3):454-460.

30 Dhaliwal A, Quinlan JI, Overthrow K, et al. Sarcopenia in Inflammatory Bowel Disease: A Narrative Overview. *Nutrients*. 2021;13(2).

31 Ryan E, McNicholas D, Creavin B, Kelly ME, Walsh T, Beddy D. Sarcopenia and Inflammatory Bowel Disease: A Systematic Review. *Inflammatory Bowel Diseases*. 2019;25(1):67-73.

32 Fatani H, Olaru A, Stevenson R, et al. Systematic review of sarcopenia in inflammatory bowel disease. *Clinical Nutrition*. 2023;42(8):1276-1291.

33 Weber AT, Shah ND, Sauk J, Limketkai BN. Popular Diet Trends for Inflammatory Bowel Diseases: Claims and Evidence. *Curr Treat Options Gastroenterol*. 2019;17(4):564-576.

34 Limketkai BN, Godoy-Brewer G, Parian AM, et al. Dietary Interventions for the Treatment of Inflammatory Bowel Diseases: An Updated Systematic Review and Meta-analysis. *Clinical Gastroenterology and Hepatology*. 2023;21(10):2508-2525.e2510.

35 Comeche JM, Gutierrez-Hervás A, Tuells J, Altavilla C, Caballero P. Predefined Diets in Patients with Inflammatory Bowel Disease: Systematic Review and Meta-Analysis. Nutrients, Vol. 13, 2021

36 Knight-Sepulveda K, Kais S, Santaolalla R, Abreu MT. Diet and Inflammatory Bowel Disease. *Gastroenterol Hepatol (N Y)*. 2015;11(8):511-520.

37 Ha C, Ullman TA, Siegel CA, Kornbluth A. Patients Enrolled in Randomized Controlled Trials Do Not Represent the Inflammatory Bowel Disease Patient Population. *Clinical Gastroenterology and Hepatology*. 2012;10(9):1002-1007.

38 Johnson C, Barnes EL, Zhang X, Long MD. Trends and Characteristics of Clinical Trials Participation for Inflammatory Bowel Disease in the United States: A Report From IBD Partners. *Crohn's & Colitis 360*. 2020;2(2):otaa023.

39 Lewis JD, Sandler RS, Brotherton C, et al. A Randomized Trial Comparing the Specific Carbohydrate Diet to a Mediterranean Diet in Adults With Crohn's Disease. *Gastroenterology*. 2021;161(3):837-852.e839.

40 Kaplan HC, Opipari-Arrigan L, Yang J, et al. Personalized Research on Diet in Ulcerative Colitis and Crohn's Disease: A Series of N-of-1 Diet Trials. *Official journal of the American College of Gastroenterology | ACG*. 2022;117(6):902-917.

41 Crichton GE, Howe PR, Buckley JD, Coates AM, Murphy KJ, Bryan J. Long-term dietary intervention trials: critical issues and challenges. *Trials*. 2012;13:111.

42 Sarid O, Slonim-Nevo V, Schwartz D, et al. Differing Relationship of Psycho-Social Variables with Active Ulcerative Colitis or Crohn's Disease. *International Journal of Behavioral Medicine*. 2018;25(3):341-350.

43 Horne R, Parham R, Driscoll R, Robinson A. Patients' Attitudes to Medicines and Adherence to Maintenance Treatment in Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. 2009;15(6):837-844.

44 Walton M, Alaunyte I. Do patients living with ulcerative colitis adhere to healthy eating guidelines? A cross-sectional study. *British Journal of Nutrition*. 2014;112(10):1628-1635.

45 Marsh A, Kinneally J, Robertson T, Lord A, Young A, Radford –Smith G. Food avoidance in outpatients with Inflammatory Bowel Disease – Who, what and why. *Clinical Nutrition ESPEN*. 2019;31:10-16.

46 Day AS, Davis R, Costello SP, Yao CK, Andrews JM, Bryant RV. The Adequacy of Habitual Dietary Fiber Intake in Individuals With Inflammatory Bowel Disease: A Systematic Review. *J Acad Nutr Diet*. 2021;121(4):688-708.e683.

47 Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis*. 2008;14(12):1660-1666.

48 Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology*. 1976;70(3):439-444.

49 Guyatt G, Mitchell A, Irvine EJ, et al. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology*. 1989;96(3):804-810.

50 Hughes LD, King L, Morgan M, et al. Food-related Quality of Life in Inflammatory Bowel Disease: Development and Validation of a Questionnaire. *Journal of Crohn's and Colitis*. 2016;10(2):194-201.

51 Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. *Journal of General Internal Medicine*. 2001;16(9):606-613.

52 Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Vol. 67. United Kingdom: Blackwell Publishing, 1983:361-370

53 Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193-213.

54 Czuber-Dochan W, Norton C, Bassett P, et al. Development and psychometric testing of inflammatory bowel disease fatigue (IBD-F) patient self-assessment scale. *Journal of Crohn's and Colitis*. 2014;8(11):1398-1406.

55 Steptoe A, Pollard TM, Wardle J. Development of a measure of the motives underlying the selection of food: the food choice questionnaire. *Appetite*. 1995;25(3):267-284.

56 Schober P, Boer C, Schwarte LA. Correlation Coefficients: Appropriate Use and Interpretation. *Anesthesia & Analgesia*. 2018;126(5).

57 Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age and Ageing*. 2019;48(1):16-31.

58 Henry MJ, Pasco JA, Pocock NA, Nicholson GC, Kotowicz MA. Reference ranges for bone densitometers adopted Australia-wide: Geelong osteoporosis study. *Australas Radiol*. 2004;48(4):473-475.

59 Australian Government Department of Health and Aged Care. Physical activity and exercise guidelines for all Australians. Vol. 2024, 2021

60 Gibson PR, Shepherd SJ. Evidence-based dietary management of functional gastrointestinal symptoms: The FODMAP approach. *Journal of Gastroenterology and Hepatology*. 2010;25(2):252-258.

61 Suskind DL, Cohen SA, Brittnacher MJ, et al. Clinical and Fecal Microbial Changes With Diet Therapy in Active Inflammatory Bowel Disease. *J Clin Gastroenterol*. 2018;52(2):155-163.

62 Olendzki BC, Silverstein TD, Persuitte GM, Ma Y, Baldwin KR, Cave D. An anti-inflammatory diet as treatment for inflammatory bowel disease: a case series report. *Nutr J*. 2014;13:5.

63 (Australia) NHaMRC. *Australian guidelines to reduce health risks from drinking alcohol*. National Health and Medical Research Council; 2020.

64 Nutrient reference values for Australia and New Zealand : including recommended dietary intakes. [Canberra, A.C.T. :: National Health and Medical Research Council], 2006

65 Cederholm T, Jensen GL, Correia MITD, et al. GLIM criteria for the diagnosis of malnutrition – A consensus report from the global clinical nutrition community. *Journal of Cachexia, Sarcopenia and Muscle*. 2019;10(1):207-217.

66 Kao FC, Hsu YC, Tu YK, Chen TS, Wang HH, Lin JC. Long-Term Use of Immunosuppressive Agents Increased the Risk of Fractures in Patients with Autoimmune Diseases: An 18-Year Population-Based Cohort Study. *Biomedicines*. 2023;11(10).

67 Neelam PB, Pal R, Gupta P, et al. Sarcopenia is common in ulcerative colitis and correlates with disease activity. *Intest Res*. 2024;22(2):162-171.

68 Gatt K, Schembri J, Katsanos KH, et al. Inflammatory Bowel Disease [IBD] and Physical Activity: A Study on the Impact of Diagnosis on the Level of Exercise Amongst Patients With IBD. *Journal of Crohn's and Colitis*. 2019;13(6):686-692.

69 Lamers CR, de Roos NM, Heerink HH, van de Worp-Kalter LA, Witteman BJM. Lower Impact of Disease on Daily Life and Less Fatigue in Patients With Inflammatory Bowel Disease Following a Lifestyle Intervention. *Inflammatory Bowel Diseases*. 2022;28(12):1791-1799.

70 Jones K, Kimble R, Baker K, Tew GA. Effects of structured exercise programmes on physiological and psychological outcomes in adults with inflammatory bowel disease (IBD): A systematic review and meta-analysis. *PLoS One*. 2022;17(12):e0278480.

71 Demers K, Bak MTJ, Bongers BC, et al. Scoping review on health-related physical fitness in patients with inflammatory bowel disease: Assessment, interventions, and future directions. *World J Gastroenterol*. 2023;29(38):5406-5427.

72 Raman M, Rajagopalan V, Kaur S, et al. Physical Activity in Patients With Inflammatory Bowel Disease: A Narrative Review. *Inflammatory Bowel Diseases*. 2022;28(7):1100-1111.

73 Eckert KG, Abbasi-Neureither I, Köppel M, Huber G. Structured physical activity interventions as a complementary therapy for patients with inflammatory bowel disease – a scoping review and practical implications. *BMC Gastroenterology*. 2019;19(1):115.

74 Walowski CO, Braun W, Maisch MJ, et al. Reference Values for Skeletal Muscle Mass – Current Concepts and Methodological Considerations. *Nutrients*. 2020;12(3):755.

75 Yoon JH, Park NH, Kang YE, Ahn YC, Lee EJ, Son CG. The demographic features of fatigue in the general population worldwide: a systematic review and meta-analysis. *Front Public Health*. 2023;11:1192121.

76 D'Silva A, Fox DE, Nasser Y, et al. Prevalence and Risk Factors for Fatigue in Adults With Inflammatory Bowel Disease: A Systematic Review With Meta-Analysis. *Clin Gastroenterol Hepatol*. 2022;20(5):995-1009.e1007.

77 Borren NZ, van der Woude CJ, Ananthakrishnan AN. Fatigue in IBD: epidemiology, pathophysiology and management. *Nature Reviews Gastroenterology & Hepatology*. 2019;16(4):247-259.

78 Australian Bureau of Statistics. National Study of Mental Health and Wellbeing. Vol. 2025: ABS, 2020-2022

79 Irving P, Barrett K, Nijher M, de Lusignan S. Prevalence of depression and anxiety in people with inflammatory bowel disease and associated healthcare use: population-based cohort study. *BMJ Ment Health*. 2021;24(3):102-109.

80 Hu S, Chen Y, Chen Y, Wang C. Depression and anxiety disorders in patients with inflammatory bowel disease. *Frontiers in psychiatry*. 2021;12:714057.

81 Bisgaard TH, Allin KH, Keefer L, Ananthakrishnan AN, Jess T. Depression and anxiety in inflammatory bowel disease: epidemiology, mechanisms and treatment. *Nature Reviews Gastroenterology & Hepatology*. 2022;19(11):717-726.

82 Duivis HE, Vogelzangs N, Kupper N, de Jonge P, Penninx BWJH. Differential association of somatic and cognitive symptoms of depression and anxiety with inflammation: Findings from the Netherlands Study of Depression and Anxiety (NESDA). *Psychoneuroendocrinology*. 2013;38(9):1573-1585.

83 Milaneschi Y, Kappelmann N, Ye Z, et al. Association of inflammation with depression and anxiety: evidence for symptom-specificity and potential causality from UK Biobank and NESDA cohorts. *Molecular Psychiatry*. 2021;26(12):7393-7402.

84 Vogelzangs N, Beekman ATF, de Jonge P, Penninx BWJH. Anxiety disorders and inflammation in a large adult cohort. *Translational Psychiatry*. 2013;3(4):e249-e249.

85 Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med*. 2009;71(2):171-186.

86 Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67(5):446-457.

87 Abautret-Daly Á, Dempsey E, Riestra S, et al. Association between psychological measures with inflammatory anddisease-related markers of inflammatory bowel disease. *International Journal of Psychiatry in Clinical Practice*. 2017;21(3):221-230.

88 Martin-Subero M, Anderson G, Kanchanatawan B, Berk M, Maes M. Comorbidity between depression and inflammatory bowel disease explained by immune-inflammatory, oxidative, and nitrosative stress; tryptophan catabolite; and gut–brain pathways. *CNS Spectrums*. 2016;21(2):184-198.

89 Ali S, Paul S, Yakkali S, et al. Glucocorticoids-Induced Neuropsychiatric Disorders in Patients With Inflammatory Bowel Disease: A Systematic Review. *Cureus*. 2022;14(9):e28981.

90 Mikocka-Walus A, Pittet V, Rossel J-B, et al. Symptoms of depression and anxiety are independently associated with clinical recurrence of inflammatory bowel disease. *Clinical Gastroenterology and Hepatology*. 2016;14(6):829-835. e821.

91 Persoons P, Vermeire S, Demyttenaere K, et al. The impact of major depressive disorder on the short- and long-term outcome of Crohn's disease treatment with infliximab. *Aliment Pharmacol Ther*. 2005;22(2):101-110.

92 Addolorato G, Capristo E, Stefanini GF, Gasbarrini G. Inflammatory Bowel Disease: A Study of the Association between Anxiety and Depression, Physical Morbidity, and Nutritional Status. *Scandinavian Journal of Gastroenterology*. 1997;32(10):1013-1021.

93 Kochar B, Barnes EL, Long MD, et al. Depression Is Associated With More Aggressive Inflammatory Bowel Disease. *Official journal of the American College of Gastroenterology | ACG*. 2018;113(1).

94 Phillips CM, Shivappa N, Hébert JR, Perry IJ. Dietary inflammatory index and mental health: A cross-sectional analysis of the relationship with depressive symptoms, anxiety and well-being in adults. *Clinical Nutrition*. 2018;37(5):1485-1491.

95 Tian Z, Zhuang X, Zhao M, et al. Index-Based Dietary Patterns and Inflammatory Bowel Disease: A Systematic Review of Observational Studies. *Adv Nutr*. 2021;12(6):2288-2300.

96 Ramos-Lopez O, Martinez-Urbistondo D, Vargas-Nuñez JA, Martinez JA. The Role of Nutrition on Meta-inflammation: Insights and Potential Targets in Communicable and Chronic Disease Management. *Current Obesity Reports*. 2022;11(4):305-335.

97 Cavicchia PP, Steck SE, Hurley TG, et al. A New Dietary Inflammatory Index Predicts Interval Changes in Serum High-Sensitivity C-Reactive Protein. *The Journal of Nutrition*. 2009;139(12):2365-2372.

98 Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. 2014;17(8):1689-1696.

99 Tabung FK, Smith-Warner SA, Chavarro JE, et al. Development and Validation of an Empirical Dietary Inflammatory Index. *The Journal of Nutrition*. 2016;146(8):1560-1570.

100 Colditz GA, Hankinson SE. The Nurses' Health Study: lifestyle and health among women. *Nature Reviews Cancer*. 2005;5(5):388-396.

101 Tabung FK, Smith-Warner SA, Chavarro JE, et al. An Empirical Dietary Inflammatory Pattern Score Enhances Prediction of Circulating Inflammatory Biomarkers in Adults. *The Journal of Nutrition*. 2017;147(8):1567-1577.

102 Andersen V, Olsen A, Carbonnel F, Tjønneland A, Vogel U. Diet and risk of inflammatory bowel disease. *Digestive and Liver Disease*. 2012;44(3):185-194.

103 Khalili H, Håkansson N, Chan SS, et al. Adherence to a Mediterranean diet is associated with a lower risk of later-onset Crohn's disease: results from two large prospective cohort studies. *Gut*. 2020;69(9):1637-1644.

104 Brotherton CS, Martin CA, Long MD, Kappelman MD, Sandler RS. Avoidance of Fiber Is Associated With Greater Risk of Crohn's Disease Flare in a 6-Month Period. *Clinical Gastroenterology and Hepatology*. 2016;14(8):1130-1136.

105 Rashvand S, Somi MH, Rashidkhani B, Hekmatdoost A. Dietary fatty acid intakes are related to the risk of ulcerative colitis: a case–control study. *International Journal of Colorectal Disease*. 2015;30(9):1255-1260.

106 John S, Luben R, Shrestha SS, Welch A, Khaw K-T, Hart AR. Dietary n-3 polyunsaturated fatty acids and the aetiology of ulcerative colitis: a UK prospective cohort study. *European Journal of Gastroenterology & Hepatology*. 2010;22(5).

107 Vagianos K, Shafer LA, Witges K, et al. Association Between Change in Inflammatory Aspects of Diet and Change in IBD-related Inflammation and Symptoms Over 1 Year: The Manitoba Living With IBD Study. *Inflammatory Bowel Diseases*. 2021;27(2):190-202.

108 Lamers CR, de Roos NM, Witteman BJM. The association between inflammatory potential of diet and disease activity: results from a cross-sectional study in patients with inflammatory bowel disease. *BMC Gastroenterology*. 2020;20(1):316.

109 Mirmiran P, Moslehi N, Morshedzadeh N, et al. Does the inflammatory potential of diet affect disease activity in patients with inflammatory bowel disease? *Nutrition Journal*. 2019;18(1):65.

110 Protano C, Gallè F, Volpini V, et al. Physical activity in the prevention and management of inflammatory bowel disease: a systematic review. *Journal of Public Health*. 2024.

111 Lamers CR, de Roos NM, Koppelman LJM, Hopman MTE, Witteman BJM. Patient experiences with the role of physical activity in inflammatory bowel disease: results from a survey and interviews. *BMC Gastroenterology*. 2021;21(1):172.

112 Bilski J, Brzozowski B, Mazur-Bialy A, Sliwowski Z, Brzozowski T. The role of physical exercise in inflammatory bowel disease. *Biomed Res Int*. 2014;2014:429031.

113 DeFilippis EM, Tabani S, Warren RU, Christos PJ, Bosworth BP, Scherl EJ. Exercise and Self-Reported Limitations in Patients with Inflammatory Bowel Disease. *Digestive Diseases and Sciences*. 2016;61(1):215-220.

114 Chan D, Robbins H, Rogers S, Clark S, Poullis A. Inflammatory bowel disease and exercise: results of a Crohn's and Colitis UK survey. *Frontline Gastroenterology*. 2014;5(1):44-48.

115 Sabir G, Abdelhady HA, Oumar Abakar A, et al. The Potential Benefits of Exercise in Managing Inflammatory Bowel Disease: A Systematic Review. *Cureus*. 2024;16(9):e68948.

116 Purcell L, Mutsekwa R, Angus R, Shukla D, Palmer M. Is the frequency of dietitian support associated with greater clinical improvements in adults with Crohn's disease undertaking exclusive enteral nutrition? *Journal of Human Nutrition and Dietetics*. 2022;35(3):435-443.

117 Dua A, Corson M, Sauk JS, Jaffe N, Limketkai BN. Impact of malnutrition and nutrition support in hospitalised patients with inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*. 2023;57(8):897-906.
118 Fitzpatrick JA, Melton SL, Yao CK, Gibson PR, Halmos EP. Dietary management of adults with IBD - the emerging role of dietary therapy. *Nat Rev Gastroenterol Hepatol*. 2022;19(10):652-669.
119 Halmos EP, Gibson PR. Dietary management of IBD—insights and advice. *Nature Reviews Gastroenterology & Hepatology*. 2015;12(3):133-146.
120 Baldwin C, McGough C, Norman AR, Frost GS, Cunningham DC, Andreyev HJN. Failure of dietetic referral in patients with gastrointestinal cancer and weight loss. *European Journal of Cancer*. 2006;42(15):2504-2509.
121 Gout BS, Barker LA, Crowe TC. Malnutrition identification, diagnosis and dietetic referrals: Are we doing a good enough job? *Nutrition & Dietetics*. 2009;66(4):206-211.
122 Czuber-Dochan W, Morgan M, Hughes LD, Lomer MCE, Lindsay JO, Whelan K. Perceptions and psychosocial impact of food, nutrition, eating and drinking in people with inflammatory bowel disease: a qualitative investigation of food-related quality of life. *Journal of Human Nutrition and Dietetics*. 2020;33(1):115-127.
123 Massuger W, Moore GTC, Andrews JM, et al. Crohn's & Colitis Australia inflammatory bowel disease audit: measuring the quality of care in Australia. *Intern Med J*. 2019;49(7):859-866.
124 Mutsekwa RN, Canavan R, Whitfield A, Spencer A, Angus RL. Dietitian first gastroenterology clinic: an initiative to reduce wait lists and wait times for gastroenterology outpatients in a tertiary hospital service. *Frontline Gastroenterology*. 2019;10(3):229-235.
125 Forsyth A, Beck E, Kruger R, et al. Public perceptions of dietetics services in Australia and New Zealand. *Nutrition & Dietetics*. 2024;81(5):480-496.
126 Bernstein KI, Promislow S, Carr R, Rawsthorne P, Walker JR, Bernstein CN. Information needs and preferences of recently diagnosed patients with inflammatory bowel disease. *Inflammatory Bowel Diseases*. 2011;17(2):590-598.
127 Wong S, Walker JR, Carr R, et al. The Information Needs and Preferences of Persons with Longstanding Inflammatory Bowel Disease. *Canadian Journal of Gastroenterology and Hepatology*. 2012;26(8):735386.
128 Miglioretto C, Beck E, Lambert K. A scoping review of the dietary information needs of people with inflammatory bowel disease. *Nutrition & Dietetics*. 2024;81(1):79-93.
129 Rivera N, Nguyen K, Kalami V, Blankenburg R, Ming Yeh A. Perspectives on Specific Carbohydrate Diet Education from Inflammatory Bowel Disease Patients and Caregivers: A Needs Assessment. *JPGN Rep*. 2022;3(3):e222.

130 Schwartz NRM, McNichol SR, Devine B, Phipps AI, Roth JA, Suskind DL. Assessing Barriers to use of the Specific Carbohydrate Diet in Pediatric Inflammatory Bowel Disease: A Qualitative Study. *JPGN Rep*. 2022;3(3):e239.

131 Halmos EP, Gibson PR. Controversies and reality of the FODMAP diet for patients with irritable bowel syndrome. *Journal of Gastroenterology and Hepatology*. 2019;34(7):1134-1142.

132 Lopes Neri LdC, Guglielmetti M, Fiorini S, et al. Adherence to ketogenic dietary therapies in epilepsy: A systematic review of literature. *Nutrition Research*. 2024;126:67-87.

133 Cox SR, Clarke H, O'Keeffe M, et al. Nutrient, Fibre, and FODMAP Intakes and Food-related Quality of Life in Patients with Inflammatory Bowel Disease, and Their Relationship with Gastrointestinal Symptoms of Differing Aetiologies. *Journal of Crohn's and Colitis*. 2021;15(12):2041-2053.

134 Ritchie JK, Wadsworth J, Lennard-Jones JE, Rogers E. Controlled multicentre therapeutic trial of an unrefined carbohydrate, fibre rich diet in Crohn's disease. *British Medical Journal (Clinical research ed)*. 1987;295(6597):517-520.

135 Levenstein S, Prantera C, Luzi C, D'Ubaldi A. Low residue or normal diet in Crohn's disease: a prospective controlled study in Italian patients. *Gut*. 1985;26(10):989-993.

136 Poslusna K, Ruprich J, de Vries JHM, Jakubikova M, van't Veer P. Misreporting of energy and micronutrient intake estimated by food records and 24 hour recalls, control and adjustment methods in practice. *British Journal of Nutrition*. 2009;101(S2):S73-S85.

137 Weijs PJM, Kruizenga HM, van Dijk AE, et al. Validation of predictive equations for resting energy expenditure in adult outpatients and inpatients. *Clinical Nutrition*. 2008;27(1):150-157.

138 McCarthy C, Tinsley GM, Bosy-Westphal A, et al. Total and regional appendicular skeletal muscle mass prediction from dual-energy X-ray absorptiometry body composition models. *Scientific Reports*. 2023;13(1):2590.

139 Yu S, Appleton S, Chapman I, et al. An Anthropometric Prediction Equation for Appendicular Skeletal Muscle Mass in Combination With a Measure of Muscle Function to Screen for Sarcopenia in Primary and Aged Care. *Journal of the American Medical Directors Association*. 2015;16(1):25-30.

140 Dodds RM, Syddall HE, Cooper R, et al. Grip strength across the life course: normative data from twelve British studies. *PLoS One*. 2014;9(12):e113637.

141 de la O V, Zazpe I, Martínez JA, et al. Scoping review of Paleolithic dietary patterns: a definition proposal. *Nutrition Research Reviews*. 2021;34(1):78-106.

142 Thiele EA. Assessing the Efficacy of Antiepileptic Treatments: The Ketogenic Diet. *Epilepsia*. 2003;44(s7):26-29.

143 Davis C, Bryan J, Hodgson J, Murphy K. Definition of the Mediterranean Diet; A Literature Review. *Nutrients*. 2015;7(11):9139-9153.

144 Swain AR. RPAH elimination diet handbook : with food & shopping guide. In: Soutter VL, Loblay RH eds. Camperdown, N.S.W. :: Allergy Unit, Royal Prince Alfred Hospital, 2011

145 Tuck CJ, Biesiekierski JR, Schmid-Grendelmeier P, Pohl D. Food Intolerances. *Nutrients*. 2019;11(7):1684.

146 Klein AV, Kiat H. Detox diets for toxin elimination and weight management: a critical review of the evidence. *Journal of Human Nutrition and Dietetics*. 2015;28(6):675-686.

147 Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr*. 1985;39 Suppl 1:5-41.

Figure 3.1. Participant recruitment flowchart

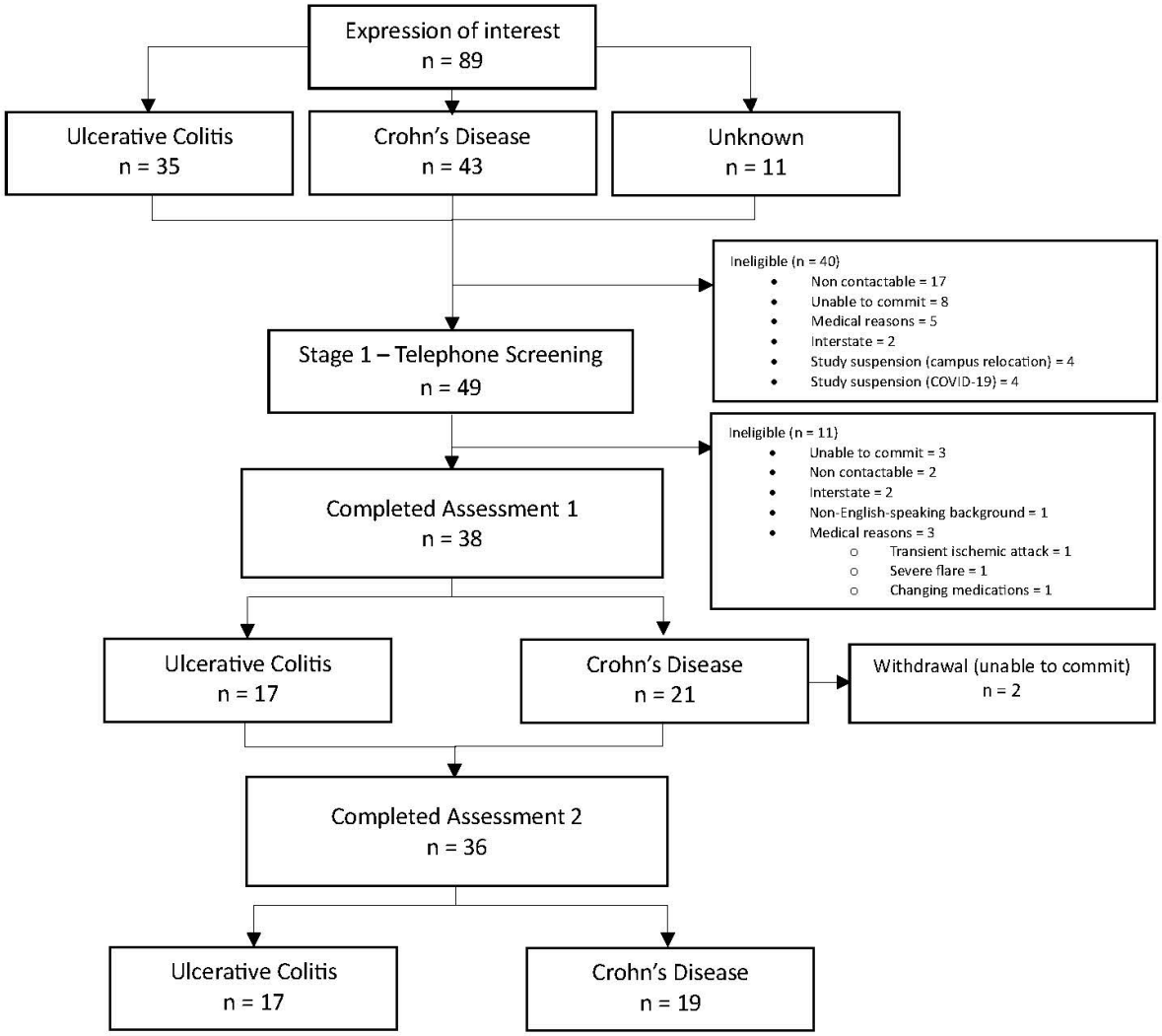


Table 3.1. Participant characteristics

	Crohn's Disease			Ulcerative Colitis			Total		
	Women (n = 8)	Men (n = 13)	Total (n = 21)	Women (n = 11)	Men (n = 6)	Total (n = 17)	Women (n = 19)	Men (n = 19)	Total (n = 38)
Age (years), mean ± SD	30.3 ± 7.9	36.7 ± 12.1	34.2 ± 11.0	36.8 ± 12.4	30.8 ± 3.4	34.7 ± 10.4	34.1 ± 11.0	34.8 ± 10.4	34.7 ± 10.6
Age range (years)	19 - 40	22 - 60	19 - 60	21 – 62	25 - 33	21 - 62	19 - 62	22 - 60	19 - 62
Ethnicity, n (%)									
European	6 (75)	11 (85)	17 (81)	7 (64)	6 (100)	13 (76)	13 (68)	17 (89)	30 (79)
Ashkenazi Jewish	1 (13)	1 (8)	2 (10)				1 (5)	1 (5)	2 (5)
South Asian				1 (9)		1 (6)	1 (5)		1 (3)
East Asian				1 (9)		1 (6)	1 (5)		1 (3)
Middle Eastern	1 (13)		1 (5)				1 (5)		1 (3)
Mixed heritage		1 (8)	1 (5)	1 (9)		1 (6)	1 (5)	1 (5)	2 (5)
Prefer not to answer				1 (9)		1 (6)	1 (5)		1 (3)

Notes. SD, *standard deviation*

Table 3.2. Participant medical history

	Crohn's Disease			Ulcerative Colitis			Total		
	Women (n = 8)	Men (n = 13)	Total (n = 21)	Women (n = 11)	Men (n = 6)	Total (n = 17)	Women (n = 19)	Men (n = 19)	Total (n = 38)
Years since diagnosis, mean ± SD (range)	10.1 ± 7.6 (1 - 23)	11.8 ± 8.3 (2 - 26)	11.1 ± 7.9 (1 - 26)	8.2 ± 7.9 (1 - 28)	4.2 ± 2.3 (2 - 8)	6.9 ± 6.9 (1 - 28)	9.0 ± 7.6 (1 - 29)	9.7 ± 7.9 (2 - 26)	9.3 ± 7.8 (1 - 28)
n Remission (%)	7 (88)	10 (77)	17 (81)	9 (82)	2 (33)	10 (59)	16 (84)	11 (58)	27 (71)
Medical History									
Musculoskeletal	4 (50)	9 (69)	13 (62)	6 (55)	2 (33)	8 (47)	10 (53)	11 (58)	21 (55)
Anxiety	3 (38)	2 (15)	5 (24)	1 (9)	2 (33)	3 (24)	4 (21)	4 (21)	8 (21)
Depression	3 (38)	3 (23)	6 (29)		1 (17)	1 (6)	3 (16)	4 (21)	7 (18)
Small intestine resection	1 (13)	2 (15)	3 (14)				1 (5)	2 (11)	3 (8)
Currently on medication for IBD, n (%)	6 (75)	13 (100)	19 (90)	10 (91)	5 (83)	15 (88)	16 (84)	18 (95)	34 (89)
n Types of medication for IBD, mean ± SD	0.8 ± 0.64	1.92 ± 0.49	1.52 ± 0.75	1.91 ± 1.04	1.50 ± 1.05	1.76 ± 1.03	1.47 ± 1.02	1.79 ± 0.71	1.63 ± 0.88
(range)	(0-2)	(1-3)	(0-3)	(0-4)	(0-4)	(0-4)	(0-4)	(0-3)	(0-4)
5-Aminosalicylates	2 (25)	7 (54)	9 (43)	9 (82)	3 (50)	12 (71)	11 (58)	10 (53)	21 (55)
Biologics	3 (38)	7 (54)	10 (48)	2 (18)	1 (17)	3 (18)	5 (26)	8 (42)	13 (34)
Immunomodulators		8 (62)	8 (38)	7 (64)	2 (33)	9 (53)	7 (37)	10 (53)	17 (45)
Corticosteroids	1 (13)	1 (8)	2 (10)	1 (9)	1 (17)	2 (12)	2 (11)	2 (11)	4 (11)
Supplements, n (%)	4 (50)	4 (31)	8 (38)	5 (45)	1 (17)	6 (35)	9 (47)	5 (26)	14 (37)
Family history, n (%)									
Crohn’s Disease	3 (38)	3 (23)	6 (29)	1 (9)	1 (17)	2 (12)	4 (21)	4 (21)	8 (21)
Ulcerative Colitis	1 (13)		1 (5)				1 (5)		1 (3)
Other GI conditions									

Irritable Bowel Syndrome (IBS)	2 (15)	2 (10)	2 (18)	1 (17)	3 (18)	2 (11)	3 (16)	5 (13)
Colorectal cancer			1 (9)		1 (6)	1 (5)		1 (3)
Bowel cancer			1 (9)		1 (6)	1 (5)		1 (3)
Diverticulitis			2 (18)		2 (12)	2 (11)		2 (5)
Non-specific GI condition	1 (8)	1 (5)	2 (18)		2 (12)	2 (11)	1 (5)	3 (8)

Notes. SD, standard deviation. GI, gastrointestinal.

Remission for participants with Crohn's disease was assessed through the Crohn's Disease Activity Index (CDAI) which includes weighted sub-scores for 8-items including liquid or very soft stools, abdominal pain, general wellbeing, physical findings, use of antidiarrheals, presence of abdominal mass, blood haematocrit, and body weight. Remission was defined as a sum score of ≤ 150. [48] *Remission for participants with Ulcerative Colitis was assessed through the Partial Mayo Score which includes sub-scores for self-reported stool frequency, rectal bleeding, and a physician global assessment. Remission was defined as a Partial Mayo Score of ≤ 2.* [47]

Table 3.3.1. Body composition

	Crohn's Disease			Ulcerative Colitis			Total		
	Women (n = 6)	Men (n = 13)	Total (n = 19)	Women (n = 11)	Men (n = 6)	Total (n = 17)	Women (n = 17)	Men (n = 19)	Total (n = 36)
Height (cm)	168.6 ± 7.3	180 ± 6.5	176 ± 8.6	161.2 ± 7.7	184.4 ± 4.9	169.4 ± 13.2	164.1 ± 8.2	181.4 ± 6.3	173 ± 11.3
Weight (kg)	65.6 ± 6.6	80.9 ± 17	75.5 ± 15.9	65.2 ± 14	87 ± 10.6	72.9 ± 16.5	65.4 ± 11.4	82.8 ± 15.3	74.3 ± 16
Body mass index (kg/m^2)	23.1 ± 2.2	24.9 ± 5	24.3 ± 4.3	25.2 ± 6	25.6 ± 2.7	25.3 ± 5	24.4 ± 4.9	25.1 ± 4.3	24.8 ± 4.6
Fat mass (kg)	21844.3 ± 6964.8	17109.9 ± 8220.1	18605 ± 7977.1	24388.1 ± 12920.3	19158.2 ± 8492.9	22542.2 ± 11554.7	23490.3 ± 11002.9	17756.7 ± 8126.5	20464.2 ± 9886
Android / gynoid ratio	0.8 ± 0.2	1.1 ± 0.2	1 ± 0.3	0.9 ± 0.3	1.1 ± 0.2	1 ± 0.3	0.8 ± 0.2	1.1 ± 0.2	1 ± 0.3
Android (% fat)	37.2 ± 14.5	34 ± 11.2	35 ± 12	39.6 ± 15.7	29.2 ± 10	35.9 ± 14.6	38.7 ± 14.9	32.5 ± 10.8	35.5 ± 13.1
Gynoid (% fat)	45.2 ± 7.1	29.9 ± 8.1	34.8 ± 10.5	45.2 ± 8.9	26.3 ± 10.3	38.5 ± 13	45.2 ± 8.1	28.8 ± 8.7	36.5 ± 11.8
Fat free mass (g)	41457.3 ± 6320.8	63990.1 ± 18392.1	56874.5 ± 18772.5	41075.5 ± 3804.8	68608.5 ± 6767.9	50793.1 ± 14398	41210.3 ± 4644.2	65448.6 ± 15591.7	54002.7 ± 16896.3
Whole body lean mass (g)	38754.8 ± 6172.8	57187 ± 7670.8	51366.3 ± 11282.6	38604.8 ± 3629.3	64760.8 ± 6559.3	47836.4 ± 13699.7	38657.8 ± 4488.4	59578.7 ± 8016.3	49699.4 ± 12428.1
Arms lean mass (g)	4067.8 ± 949.3	6846 ± 1274.4	5968.7 ± 1758.8	4037.5 ± 460.3	9484.5 ± 1544.8	5959.9 ± 2842.1	4048.2 ± 643.6	7679.2 ± 1825.8	5964.6 ± 2298.6
Legs lean mass (g)	12839.5 ± 1978.9	18946.2 ± 2844.4	17017.8 ± 3871.3	12475.6 ± 1258.1	21956 ± 2598.7	15821.6 ± 4990.8	12604.1 ± 1498.4	19896.7 ± 3055.4	16452.9 ± 4411.4
ALM (g)	16907.3 ± 2792.2	25792.2 ± 3705.4	22986.5 ± 5415.1	16513.1 ± 1571.1	31440.5 ± 3869.2	21781.6 ± 7764.6	16652.2 ± 2004.2	27575.9 ± 4537.4	22417.5 ± 6558.5

Total SM (g)	18306.2 ± 3127.3	28257 ± 4150.0	25114.9 ± 6064.9	17864 ± 1759.6	34583.4 ±4333.5	23765.4 ± 8696.4	18020.5 ± 2244.7	30255.0 ± 5081.9	24477.6 ± 7345.5
Arm SM (g)	2509.3 ± 550.6	4120.7 ± 739.1	3611.8 ± 1020.1	2491.7 ± 267	5651 ± 896	3606.8 ± 1648.4	2497.9 ± 373.3	4603.9 ± 1058.9	3609.4 ± 1333.2
Leg SM (g)	8944.8 ± 1543.6	13708.1 ± 2218.6	12203.9 ± 3019.6	8661 ± 981.3	16055.7 ± 2027	11270.9 ± 3892.8	8761.2 ± 1168.7	14449.4 ± 2383.2	11763.3 ± 3440.9
ASM (g)	11454.2 ± 2008.4	17828.7 ± 2699.1	15815.7 ± 3904.5	11152.7 ± 1157.1	21706.7 ± 2747.6	14877.7 ± 5497.6	11259.1 ± 1455.8	19053.4 ± 3222.4	15372.7 ± 4677.9
ASMI (kg/m^2)	4.07 ± 0.41	5.49 ± 0.76	5.05 ± 0.94	4.29 ± 0.31	6.37 ± 0.63	5.02 ± 1.11	4.21 ± 0.35	5.77 ± 0.82	5.04 ± 1.01

Notes. ALM, Appendicular Lean Mass. ALMI, Appendicular Lean Mass Index. SM, Skeletal Muscle. ASM, Appendicular Skeletal Muscle, ASMI, Appendicular Skeletal Muscle Index. Body mass index was calculated using weight (in kg) divided by the squared height (in m). Android/gynoid ratio was calculated using android (% fat) divided by gynoid (% fat). Arms lean mass (g) is defined as the sum of both limbs (arm left lean and arm right lean, in grams) examined through the whole body DXA scan. Legs lean mass (g) is defined as the sum of both limbs (leg left lean and leg right lean, in grams) examined through the whole body DXA scan. ALM (g) was calculated by adding arms lean mass (g) and legs lean mass (g). ALMI was calculated using ALM (in kg) divided by the squared height (in m). Total SM, arm SM, and leg SM were calculated using previously published equations, [138] where:

Total SM (g) was calculated using the equation $1.12 \times ALM\ (g) - 0.63$

Arm SM (g) was calculated using the equation $0.58\ \times (arms\ lean\ mass) + 0.15$

Leg SM (g) was calculated using the equation $0.78\ \times (legs\ lean\ mass) - 1.07$

ASM (g) was the sum of arms SM (g) and leg SM (g)

ASMI was calculated using ASM (in kg) divided by the squared height (in m). [138, 139]

ALMI cutoff values using the updated European Working Group on Sarcopenia in Older People (EWGSOP2, version 2019) was <7.0 kg/m^2 for men and <5.5 kg/m^2 for women to define low muscle mass [57] Cut-off values used young health adult means of a European population reference group [140] and set at -2 standard deviations. [57] No published cut-offs are available for ASMI at the time of writing.

Table 3.3.2. Bone mineral content and bone mineral density

	Crohn's Disease			Ulcerative Colitis			Total		
	Women (n = 7)	Men (n = 13)	Total (n = 19)	Women (n = 11)	Men (n = 6)	Total (n = 17)	Women (n = 17)	Men (n = 19)	Total (n = 36)
Total body BMC (g)	2626.2 ± 335.3	2821 ± 995.5	2759.5 ± 837	2480.3 ± 342.5	3702.2 ± 595.2	2911.5 ± 739.1	2531.8 ± 337	3099.3 ± 967.5	2831.3 ± 784.8
Total body BMD (mean, g/cm2)	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.4 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.3 ± 0.1	1.2 ± 0.1
T-score	0.8 ± 1	0.2 ± 1.3	0.4 ± 1.2	0.6 ± 0.9	1.8 ± 0.9	1 ± 1	0.7 ± 0.9	0.7 ± 1.4	0.7 ± 1.2
Spine BMC L2 – L4 (g)	53.2 ± 13.8	59.4 ± 13.1	57.2 ± 13.3	50.8 ± 7.7	68.9 ± 10.9	57.2 ± 12.4	51.7 ± 10.1	62.4 ± 12.9	57.2 ± 12.7
L2	15.6 ± 4.5	17.9 ± 4.1	17.1 ± 4.3	14.8 ± 2.1	20.5 ± 3.8	16.8 ± 3.9	15.1 ± 3.2	18.7 ± 4.1	17 ± 4.1
L3	17.9 ± 4.1	19.8 ± 4.3	19.1 ± 4.2	17 ± 2.5	23.6 ± 3.1	19.3 ± 4.2	17.3 ± 3.2	21 ± 4.2	19.2 ± 4.1
L4	19.7 ± 5.1	21.7 ± 5.7	21 ± 5.5	18.9 ± 3.4	24.8 ± 4.6	21 ± 4.7	19.2 ± 4.1	22.7 ± 5.5	21 ± 5.1
Spine BMD L2- L4 (mean, g/cm2)	1.22 ± 0.17	1.16 ± 0.17	1.18 ± 0.17	1.2 ± 0.2	1.3 ± 0.2	1.2 ± 0.2	1.21 ± 0.16	1.22 ± 0.18	1.21 ± 0.17
T-score	-0.13 ± 1.34	-0.64 ± 1.42	-0.48 ± 1.38	-0.31 ± 1.29	0.8 ± 1.29	0.08 ± 1.36	-0.25 ± 1.27	-0.18 ± 1.51	-0.21 ± 1.38
T score between -1.0 and -2.5 (n)	1	3	4	2		2	3	3	6
T score ≤ -2.5 (n)		2	2	1		1	1	2	3
Bilateral Total Hip BMC (g)	29.4 ± 5.3	34.6 ± 6.1	32.8 ± 6.2	29.4 ± 4.6	47.7 ± 7.4	35.9 ± 10.6	29.4 ± 4.7	38.7 ± 8.9	34.2 ± 8.5
Bilateral Total Hip BMD (mean, g/cm^2)	1 ± 0.2	1 ± 0.1	1 ± 0.2	1 ± 0.1	1.2 ± 0.2	1.1 ± 0.2	1 ± 0.1	1.1 ± 0.2	1 ± 0.2
T-score	-0.5 ± 1.5	-0.9 ± 1.2	-0.8 ± 1.3	-0.3 ± 1	1.2 ± 1.5	0.2 ± 1.4	-0.4 ± 1.1	-0.3 ± 1.6	-0.3 ± 1.4
T score between -1.0 and -2.4 (n)	2	3	5	2		2	4	3	7

T score ≤ -2.5 (n)	1	1	2		1	1	2	

Notes. BMC, Bone Mineral Content. BMD, Bone Mineral Density. L2, Lumbar Spine Vertebrae 2. L3, Lumbar Spine Vertebrae 3. L4, Lumbar Spine Vertebrae 4. Total hip include measurements for the femur neck, greater trochanter and lesser trochanter. Normal bone mineral density is defined as T-score ≥-1.0 SD, Osteopenia T-score between -1.0 and -2.4 SD, Osteoporosis T-score ≤ 2.5. Young healthy Caucasian men and women aged ≥ 20 years were the reference database used to determine T-scores. [58]

Table 3.4.1. Current dietary strategies during study recruitment

	Crohn's Disease (n=21)	Ulcerative Colitis (n=17)	Total (n=38)
Specific diets, n	6	4	10
Low FODMAP	2		2
Specific Carbohydrate Diet™	1	1	2
Ketogenic diet	2		2
Vegetarian	1	1	2
Vegan	1		1
Lactose free	1		1
Gluten free		1	1
Mediterranean diet	1		1
Wheat free		1	1
IBD-AID	1		1
Low GI	1		1
Low sugar		1	1
Number of previous diets attempted, mean ± SD (range)	1.2 ± 1.6 (0 – 5)	1.6 ± 2.3 (0 – 9)	1.4 ± 1.9 (0 – 9)

Notes. Combination of specific diets are recorded alongside individual diets reported by participants i.e., "ketogenic vegan" was reported as ketogenic diet = 1, vegan diet =1. Three participants with CD reported concurrent diets: ketogenic & vegan (n=1), low

FODMAP & vegetarian (n=1), and a combination of low FODMAP, Specific Carbohydrate Diet™ (SCD™), IBD-AID and Mediterranean diet (n=1). Fasting diets include any dietary prescription which involves an element of fasting either daily or weekly, for example, intermittent fasting, the 5:2 diet, and 18:5 diet. Vegetarian diets refer to an eating pattern which excludes meats, poultry and fish. The vegan diet refers to an eating pattern which excludes all animal products including meats, poultry, fish, eggs, and dairy. The paleolithic diet refers to a dietary pattern with is purported to mimic dietary patterns of hunter gatherers during the paleolithic era. Interpretations of the diet varies, however the diet predominantly allows red meat and poultry, fish, eggs, vegetables, fruit, tree nuts, while restricting grains, legumes, dairy, and seed oils.[141] The low carbohydrate diet is a diet which restricts consumption of carbohydrates relative to the average diet, emphasizing higher intakes of protein and fat. The ketogenic diet is a derivative of the low carbohydrate diet which involves a high fat, moderate protein, and very low carbohydrate eating pattern designed to induce ketosis, which shifts the primary fuel source to ketone bodies derived from fat metabolism. [142] The Mediterranean diet is a traditional dietary pattern emphasizing extra virgin olive oil, fibre-rich foods (whole grains, vegetables, fruits, legumes, nuts), and moderate consumption of fish, meat, and dairy. [143] The low FODMAP diet refers to a dietary approach which restricts consumption of fermentable carbohydrates (oligosaccharides, disaccharides, monosaccharides, and polyols). The diet involves a 3-step process which includes a 2-6 week period consuming low FODMAP foods, an 8-12 week FODMAP reintroduction phase, and personalisation based on individual tolerance. [60] The Specific Carbohydrate Diet™ is a grain free, low sugar and low lactose diet which includes a list of "allowed" and "prohibited" foods. [61] The Anti-inflammatory Diet for Inflammatory Bowel Disease (IBD-AID) is a derivative of the Specific Carbohydrate Diet™ involving restriction of grains (except oats and barley), corn, milk, soft cheeses, emulsifiers, foods high

in trans fats and refined sugar. The diet advocates for daily inclusion of probiotics (fermented foods such as yogurt, kimchi, miso, tempeh, sauerkraut) and prebiotic foods (fiber, especially soluble fiber). The diet involves 3 phases which increases the amount of fiber and textures based on individual tolerance. [62] *The RPAH diet is a elimination diet designed to identify intolerances to salicylates, amines, glutamates, and food additives which are known contributors to food sensitivities.* [144] *The low salicylate, low amine diet is similar to the RPAH diet however primarily focuses on salicylates and amines rather than a systematic approach of eliminating a broader range of 'food chemicals.'* [145] *Texture modified diets relate to consumption of foods which have undergone texture modification including achieved through cooking or blending. This includes soft, cooked foods, purees, and liquid diets taken over a specified period not including diets prescribed during hospital admission. 'Detox' style diet refers to a range of dietary approaches designed to eliminate toxins from the body and promote health. Participants were queried on the type of detox diet attempted.* [146]

Table 3.4.2. Summary of Attempted Dietary Patterns and Patient Comments on Efficacy

Study code	Sex	IBD Subtype	Fasting diets	Vegetarian	Vegan	Palaeolithic diet	Low carbohydrate diets	Ketogenic diets	Mediterranean diet	Low FODMAP	Specific Carbohydrate Diet™	IBD-AID	RPAH elimination diet	Low salicylate low amine	Texture modified diets	Detox' style diets	n Diets attempted
Subject 1	M	CD															0
Subject 2	M	CD								No effect							1
Subject 3	M	CD															0
Subject 4	M	CD		No effect													1
Subject 5	M	CD															0
Subject 6	F	CD															0
Subject 7	M	CD			Improves			Unsure									2
Subject 8	M	CD	No effect					No effect	No effect								3
Subject 9	F	CD		No effect													1
Subject 10	M	CD								Improves			No effect				2
Subject 11	M	CD															0
Subject 12	M	CD		Unsure					Unsure	Improves	Improves	Improves					5
Subject 13	M	CD															0
Subject 14	F	CD															0
Subject 15	F	CD					Unsure										1
Subject 16	F	CD						No effect		Unsure				No effect			3
Subject 17	F	CD								No effect							1
Subject 18	F	CD		Improves	Improves				Improves	No effect					Improves		5
Subject 19	F	CD															0
Subject 20	M	CD															0
Subject 21	M	CD															0
Subject 22	F	UC	No effect	Unsure													2
Subject 23	F	UC				Improves					Improves						2
Subject 24	M	UC															0
Subject 25	F	UC					Worsens									Worsens	2

Subject 26	F	UC									Improves					1
Subject 27	F	UC					No effect		No effect							2
Subject 28	F	UC														0
Subject 29	F	UC														
Subject 30	F	UC														0
Subject 31	M	UC	No effect	Unsure												2
Subject 32	M	UC														0
Subject 33	F	UC		Improves												1
Subject 34	M	UC									Improves			Improves	Worsens	3
Subject 35	F	UC														0
Subject 36	F	UC		Worsens					No effect		Improves				Improves	4
Subject 37	M	UC														0
Subject 38	M	UC	Improves		Worsens	Improves	Improves	Improves	No effect			Improves	No effect		Worsens	9

Notes. M, male. F, female. CD, Crohn's disease. UC, ulcerative colitis.

Fasting diets include any dietary prescription which involves an element of fasting either daily or weekly, for example, intermittent fasting, the 5:2 diet, and 18:5 diet. Vegetarian diets refer to an eating pattern which excludes meats, poultry and fish. The vegan diet refers to an eating pattern which excludes all animal products including meats, poultry, fish, eggs, and dairy. The paleolithic diet refers to a dietary pattern with is purported to mimic dietary patterns of hunter gatherers during the paleolithic era. Interpretations of the diet varies, however the diet predominantly allows red meat and poultry, fish, eggs, vegetables, fruit, tree nuts, while restricting grains, legumes, dairy, and seed oils.[141] The low carbohydrate diet is a diet which restricts consumption of carbohydrates relative to the average diet, emphasizing higher intakes of protein and fat. The ketogenic diet is a derivative of the low carbohydrate diet which involves a high fat, moderate protein, and very low carbohydrate eating pattern designed to induce ketosis, which shifts the primary fuel source to ketone bodies derived from fat metabolism. [142] The Mediterranean diet is a traditional dietary pattern emphasizing extra

virgin olive oil, fibre-rich foods (whole grains, vegetables, fruits, legumes, nuts), and moderate consumption of fish, meat, and dairy. [143] *The low FODMAP diet refers to a dietary approach which restricts consumption of fermentable carbohydrates (oligosaccharides, disaccharides, monosaccharides, and polyols). The diet involves a 3-step process which includes a 2-6 week period consuming low FODMAP foods, an 8-12 week FODMAP reintroduction phase, and personalisation based on individual tolerance.* [60] *The Specific Carbohydrate Diet™ is a grain free, low sugar and low lactose diet which includes a list of "allowed" and "prohibited" foods.* [61] *The Anti-inflammatory Diet for Inflammatory Bowel Disease (IBD-AID) is a derivative of the Specific Carbohydrate Diet™ involving restriction of grains (except oats and barley), corn, milk, soft cheeses, emulsifiers, foods high in trans fats and refined sugar. The diet advocates for daily inclusion of probiotics (fermented foods such as yogurt, kimchi, miso, tempeh, sauerkraut) and prebiotic foods (fiber, especially soluble fiber). The diet involves 3 phases which increases the amount of fiber and textures based on individual tolerance.* [62] *The RPAH diet is a elimination diet designed to identify intolerances to salicylates, amines, glutamates, and food additives which are known contributors to food sensitivities.* [144] *The low salicylate, low amine diet is similar to the RPAH diet however primarily focuses on salicylates and amines rather than a systematic approach of eliminating a broader range of 'food chemicals.'* [145] *Texture modified diets relate to consumption of foods which have undergone texture modification including achieved through cooking or blending. This includes soft, cooked foods, purees, and liquid diets taken over a specified period not including diets prescribed during hospital admission. 'Detox' style diet refers to a range of dietary approaches designed to eliminate toxins from the body and promote health. Participants were queried on the type of detox diet attempted.*[146]

Table 3.4.3. Food allergies, intolerance, and triggers

	Crohn's Disease (n=21)	Ulcerative Colitis (n=17)	Total (n=38)
Diagnosed food allergy, n (%)	2 (10)	1 (6)	3 (8)
Lactose	1 (5)		1 (3)
Gluten		1 (6)	1 (3)
Apples	1 (5)		1 (3)
Foods avoided, n (%)	13 (62)	10 (59)	23 (61)
Dairy	2 (10)	5 (29)	7 (18)
Grains and cereals	3 (14)	3 (18)	6 (16)
Legumes	1 (5)	2 (12)	3 (8)
Ground nuts and tree nuts	1 (5)	1 (6)	2 (5)
Meat	3 (14)	1 (6)	4 (11)
Vegetables	5 (24)	3 (18)	8 (21)
Fruit		2 (12)	2 (5)
Spicy foods	5 (24)	3 (18)	8 (21)
Coffee		3 (18)	3 (8)
Alcohol	2 (10)		2 (5)
Frequency of food avoidance, n (%)			
Always	4 (19)	1 (6)	5 (13)

Sometimes	7 (33)	9 (58)	16 (42)
During active disease	2 (10)		2 (5)

Notes. Diagnosed food allergies were confirmed by a healthcare provider – investigations were completed by a gastroenterologist (lactose, gluten) and a general practitioner (apples). Dairy foods avoided include milk, cheese, Milo® and lactose containing products. Grains and cereals included wheat, white pasta, and bread. Legumes included beans, lentils, and chickpeas. Ground nuts and tree nuts referred to avoidance of peanuts and cashews, particularly whole nuts. Meats avoided included red meat, chicken, fish, and oysters. Vegetables avoided include "fibrous vegetables", capsicum, mushrooms, onions, and garlic. Fruit included strawberries and dried fruit of any type. Spicy foods were a broad description and included any foods with spice or chillies. Coffee included avoidance of caffeine. Alcohol of all types were included in the alcohol category, however one participant noted better tolerance to beer compared to wines and spirits (although wine is the preferred beverage).

Table 3.4.4. Food choice questionnaire

	Crohn's Disease			Ulcerative Colitis			Total		
	Women (n = 6)	Men (n = 10)	Total (n = 16)	Women (n = 9)	Men (n = 6)	Total (n = 15)	Women (n = 15)	Men (n = 16)	Total (n = 31)
Health	2.67 ± 0.54	2.47 ± 0.76	2.54 ± 0.67	2.89 ± 0.7	2.31 ± 0.68	2.66 ± 0.73	2.8 ± 0.63	2.41 ± 0.71	2.6 ± 0.69
Mood	2.53 ± 0.83	1.73 ± 0.42	2.03 ± 0.7	2.7 ± 0.93	2.17 ± 0.94	2.49 ± 0.94	2.63 ± 0.86	1.9 ± 0.67	2.25 ± 0.84
Convenience	3 ± 0.72	2.22 ± 0.75	2.51 ± 0.81	3.33 ± 0.5	2.37 ± 0.48	2.95 ± 0.68	3.2 ± 0.6	2.28 ± 0.64	2.72 ± 0.77
Sensory appeal	2.42 ± 0.72	2.65 ± 0.46	2.56 ± 0.56	3.33 ± 0.52	2.67 ± 0.34	3.07 ± 0.55	2.97 ± 0.74	2.66 ± 0.41	2.81 ± 0.6
Natural content	2.44 ± 0.98	2.43 ± 0.85	2.44 ± 0.87	2.96 ± 1.2	1.83 ± 0.62	2.51 ± 1.13	2.76 ± 1.11	2.21 ± 0.81	2.47 ± 0.99
Price	2.72 ± 1.14	2.07 ± 0.75	2.31 ± 0.94	2.48 ± 0.63	2.22 ± 0.81	2.38 ± 0.69	2.58 ± 0.84	2.13 ± 0.75	2.34 ± 0.81
Weight control	2.17 ± 0.86	1.87 ± 0.65	1.98 ± 0.72	2.56 ± 0.73	1.78 ± 0.75	2.24 ± 0.81	2.4 ± 0.78	1.83 ± 0.67	2.11 ± 0.77
Familiarity	1.94 ± 0.83	2 ± 0.7	1.98 ± 0.72	2.33 ± 0.78	2.39 ± 0.39	2.36 ± 0.64	2.18 ± 0.8	2.15 ± 0.62	2.16 ± 0.7
Ethics	1.67 ± 0.84	1.8 ± 0.57	1.75 ± 0.66	2.19 ± 1.04	1.67 ± 0.56	1.98 ± 0.9	1.98 ± 0.97	1.75 ± 0.55	1.86 ± 0.78

Food Choice Questionnaire (FCQ) is a 36-item questionnaire examining 9 factors which influence food selection and rates them based on level of importance (from 1, not important at all, to 4, very important).[55] *No reference timeframe is assigned on how participants rate these individual items. Each domain is an average of individual questions, with higher scores reflecting greater importance assigned by the participant. All values are reported as mean ± standard deviation, with a maximum score of 4 for each domain.*

Table 3.4.5. 3-day Weighted Food Diary Analysis

	Crohn's Disease			Ulcerative Colitis			Total		
	Women (n = 7)	Men (n = 11)	Total (n = 18)	Women (n = 8)	Men (n = 4)	Total (n = 12)	Women (n = 15)	Men (n = 15)	Total (n = 30)
EER (kJ)	9555.1 ± 1279.1	11781.8 ± 1456.2	10915.9 ± 1752.8	9270.8 ± 1050.9	13631.5 ± 1754.2	10724.3 ± 2480.3	9403.5 ± 1129.1	12275.1 ± 1700.3	10839.3 ± 2035.6
Energy Intake (kJ)	6813.1 ± 1645.1	10844.7 ± 3315.3	9276.8 ± 3392.7	7336.4 ± 1713.7	11826.3 ± 2553.4	8833 ± 2921.3	7092.2 ± 1643.6	11106.5 ± 3074.1	9099.3 ± 3167.6
Protein (g)	73.61 ± 17.91	111.81 ± 36.93	96.95 ± 35.82	78.24 ± 23.24	129.80 ± 12.12	95.43 ± 32.06	76.08 ± 20.33	116.61 ± 32.76	96.34 ± 33.80
Carbohydrates (g)	152.39 ± 54.56	273.44 ± 77.68	226.37 ± 91.03	177.43 ± 35.22	315.74 ± 89.39	223.53 ± 87.22	165.74 ± 45.42	284.72 ± 79.98	225.23 ± 88.01
Sugars (g)	56.68 ± 19.77	99.91 ± 34.01	83.10 ± 35.90	74.49 ± 25.97	95.45 ± 40.66	81.48 ± 31.41	66.18 ± 24.28	98.72 ± 34.42	82.45 ± 33.62
Starch (g)	95.59 ± 38.62	169.69 ± 52.55	140.87 ± 59.43	102.21 ± 42.36	219.02 ± 60.85	141.15 ± 73.89	99.12 ± 39.34	182.84 ± 57.24	140.98 ± 64.36
Dietary fibre (g)	19.98 ± 12.27	24.64 ± 9.15	22.83 ± 10.39	22.05 ± 6.91	27.82 ± 6.01	23.98 ± 6.95	21.08 ± 9.46	25.49 ± 8.35	23.29 ± 9.05
Total fat (g)	76.71 ± 23.12	96.31 ± 31.74	88.69 ± 29.63	70.48 ± 29.04	106.65 ± 35.20	82.54 ± 34.52	73.39 ± 25.71	99.07 ± 31.74	86.23 ± 31.24
Monounsaturated fat (g)	24.98 ± 5.11	38.59 ± 15.37	33.30 ± 13.95	27.11 ± 11.53	38.51 ± 18.53	30.91 ± 14.48	26.12 ± 8.88	38.57 ± 15.56	32.34 ± 13.97

Polyunsaturated fat (g)	8.98 ± 3.42	14.67 ± 5.95	12.46 ± 5.75	12.37 ± 5.78	15.31 ± 5.27	13.35 ± 5.56	10.79 ± 4.98	14.84 ± 5.60	12.82 ± 5.60
Saturated fat (g)	33.27 ± 13.22	35.02 ± 12.76	34.34 ± 12.58	24.05 ± 10.18	46.02 ± 9.25	31.37 ± 14.36	28.36 ± 12.22	37.95 ± 12.65	33.15 ± 13.16
Trans fatty acids (g)	1.71 ± 1.04	1.44 ± 0.75	1.54 ± 0.86	0.99 ± 0.53	1.66 ± 0.61	1.21 ± 0.62	1.33 ± 0.86	1.49 ± 0.70	1.41 ± 0.78
Cholesterol (mg)	275.93 ± 192.38	354.06 ± 176.06	323.67 ± 181.19	293.39 ± 177.59	402.77 ± 216.43	329.85 ± 189.07	285.25 ± 178.08	367.05 ± 180.76	326.15 ± 181.15
Omega-3 fatty acids (g)	3.75 ± 8.63	0.48 ± 0.52	1.75 ± 5.40	0.40 ± 0.74	0.10 ± 0.05	0.30 ± 0.61	1.96 ± 5.93	0.38 ± 0.47	1.17 ± 4.21
Linoleic acid (g)	6.90 ± 3.34	12.57 ± 5.60	10.36 ± 5.52	10.41 ± 4.92	13.33 ± 3.54	11.38 ± 4.57	8.77 ± 4.49	12.77 ± 5.02	10.77 ± 5.10
ALA (g)	1.09 ± 0.62	1.92 ± 0.92	1.60 ± 0.90	1.26 ± 0.62	1.71 ± 0.87	1.41 ± 0.71	1.18 ± 0.60	1.87 ± 0.88	1.52 ± 0.82
EPA (g)	1.80 ± 4.28	0.17 ± 0.20	0.80 ± 2.68	0.13 ± 0.28	0.03 ± 0.02	0.10 ± 0.23	0.91 ± 2.94	0.13 ± 0.18	0.52 ± 2.08
DPA (g)	0.09 ± 0.13	0.11 ± 0.10	0.10 ± 0.10	0.09 ± 0.13	0.04 ± 0.02	0.07 ± 0.10	0.09 ± 0.12	0.09 ± 0.09	0.09 ± 0.10
DHA (g)	1.85 ± 4.35	0.20 ± 0.24	0.84 ± 2.72	0.18 ± 0.34	0.03 ± 0.03	0.13 ± 0.28	0.96 ± 2.99	0.15 ± 0.21	0.56 ± 2.12
% MUFA	38.2 ± 5.4	42.9 ± 5.9	41.1 ± 6	42.6 ± 4.9	37.3 ± 7.5	40.8 ± 6.1	40.5 ± 5.5	41.4 ± 6.6	41 ± 6
% PUFA	13.2 ± 3.2	16.7 ± 4.2	15.4 ± 4.1	19.2 ± 3.4	15.3 ± 1.1	17.9 ± 3.4	16.4 ± 4.4	16.3 ± 3.6	16.3 ± 4
% saturated fat	48.6 ± 6.5	40.4 ± 8.9	43.6 ± 8.9	38.3 ± 7.1	47.4 ± 7.1	41.3 ± 8.1	43.1 ± 8.4	42.3 ± 8.8	42.7 ± 8.5
Ash (g)	12.74 ± 4.70	20.19 ± 6.24	17.29 ± 6.68	13.47 ± 2.96	23.37 ± 1.20	16.77 ± 5.45	13.13 ± 3.74	21.04 ± 5.50	17.08 ± 6.13
Alcohol (g)	3.45 ± 3.87	20.19 ± 36.46	13.68 ± 29.28	8.48 ± 8.99	11.15 ± 11.49	9.37 ± 9.44	6.13 ± 7.32	17.78 ± 31.54	11.95 ± 23.26
Alcohol standard drinks/week, mean ± SD (range)	2 ± 1.5 (0 – 4.5)	7.1 ± 7.6 (0 – 20)	5.1 ± 6.4 (0 – 20)	4.0 ± 3.9 (0 – 10)	5.5 ± 4.8 (0.25 – 14)	4.0 ± 3.9 (0 – 14)	2.6 ± 2.5 (0 – 10)	6.6 ± 6.7 (0 – 20)	4.6 ± 5.4 (0 – 20)

Water (g)	2163.8 ± 886.3	2099.6 ± 1196.8	2124.6 ± 1058.7	1632.7 ± 768	2595.8 ± 231.6	1953.7 ± 784.1	1880.6 ± 840.7	2231.9 ± 1042.2	2056.2 ± 947.3

Notes. EER, *estimated energy requirements.* ALA*, alpha linoleic acid,* EPA *eicosapentaonic acid,* DPA*, docosapentaenoic acid,* DHA *docosahexaenoic acid,* MUFA *monounsaturated fatty acid,* PUFA *polyunsaturated fatty acid.*

EER was estimated using sex- and age- specific Schofield equations [147] based on weight and height to estimate basal metabolic rate (BMR), which was then multiplied by estimated physical activity levels (PAL) derived from self-reported habitual physical activity. (60-62)

Table 3.5.1 Food-related Quality of Life (FRQoL-29) Scores

Crohn's Disease			Ulcerative Colitis			Total		
Women (n = 6)	Men (n = 10)	Total (n = 16)	Women (n = 9)	Men (n = 6)	Total (n = 15)	Women (n = 15)	Men (n = 16)	Total (n = 31)
72.17 ± 35.21	104.2 ± 25.27	92.19 ± 32.45	96.67 ± 33.99	106.67 ± 23.4	100.67 ± 29.69	86.87 ± 35.46	105.13 ± 23.82	96.29 ± 30.92

Food-related Quality of Life (FRQoL-29) is a 29-item self-reported questionnaire comprising of a 5-point Likert scale delivered through a semi structured interview. The tool examines psychosocial aspect of eating and drinking in IBD. Total scores range from 29 to 145, with higher scores reflecting better food related quality of life. [50]

Table 3.5.2 Inflammatory Bowel Disease Questionnaire (IBDQ-32)

	Crohn's Disease			Ulcerative Colitis			Total		
	Women (n = 8)	Men (n = 13)	Total (n = 21)	Women (n = 11)	Men (n = 6)	Total (n = 17)	Women (n = 19)	Men (n = 19)	Total (n = 38)
IBDQ Total Score (224)	151.25 ± 41.45	187.54 ± 21.5	173.71 ± 34.71	176.82 ± 23.26	192.67 ± 10.93	182.41 ± 20.89	166.05 ± 33.72	189.16 ± 18.64	177.61 ± 29.31
Bowel Score (70)	48.88 ± 14.98	60.46 ± 7.34	56.05 ± 12.01	58.91 ± 8.6	60.67 ± 2.66	59.53 ± 7.01	54.68 ± 12.42	60.53 ± 6.16	57.61 ± 10.11
Systemic symptoms (35)	19.75 ± 5.95	26.92 ± 4.5	24.19 ± 6.1	22.27 ± 6.17	27 ± 3.85	23.94 ± 5.81	21.21 ± 6.04	26.95 ± 4.2	24.08 ± 5.9
Emotional function (84)	54.88 ± 15.54	66.54 ± 10.96	62.1 ± 13.79	63.18 ± 9.5	71.83 ± 5.19	66.24 ± 9.11	59.68 ± 12.72	68.21 ± 9.69	63.95 ± 11.96
Social function (35)	27.75 ± 7.91	33.62 ± 2.22	31.38 ± 5.77	32.45 ± 3.17	33.17 ± 1.94	32.71 ± 2.76	30.47 ± 5.97	33.47 ± 2.09	31.97 ± 4.66

Inflammatory Bowel Disease Questionnaire (IBDQ-32) is a 32-item questionnaire comprising of a 7-point Likert scale examining 4-domains (Bowel Score, Systemic Symptoms, Emotional Function, and Social Function) in the past 2-weeks. Total scores are reported, which range from 32 to 224. Higher scores reflect better quality of life, with no established cut-offs for impairments.[49]

Table 3.5.3 Patient Health Questionnaire-9

	Crohn's Disease			Ulcerative Colitis			Total		
	Women (n = 8)	Men (n = 13)	Total (n = 21)	Women (n = 11)	Men (n = 6)	Total (n = 17)	Women (n = 19)	Men (n = 19)	Total (n = 38)
Patient Health Questionnaire 9 (27)	7.13 ± 4.61	5.54 ± 4.56	6.14 ± 4.53	5.64 ± 3.93	3.67 ± 3.08	4.94 ± 3.68	6.26 ± 4.17	4.95 ± 4.16	5.61 ± 4.16
n mild depression	3	4	7	5	2	7	8	6	14
n moderate depression		1	1	1		1	1	1	2
n mod-severe depression	1	1	2				1	1	2
n severe depression			0			0			0

Patient Health Questionnaire 9 (PHQ-9) is a self-reported, 9-item questionnaire assessing depression severity over the past 2 weeks. Each item is scaled based on frequency, ranging from not at all (0) to nearly every day (3). Scores range from 0 to 27, with higher scores correlated with greater depression symptoms and severity. PHQ-9 scores <5 is defined as having no or minimal depression. Mild depression is defined as a PHQ-9 score between 5-9, moderate depression is defined as a PHQ-9 score between 10-14, mod-severe depression is defined as a PHQ-9 score between 15-19, and severe depression is defined as a PHQ-9 score >19. [51]

Table 3.5.4 Hospital Anxiety and Depression Scale

	Crohn's Disease			Ulcerative Colitis			Total		
	Women (n = 8)	Men (n = 13)	Total (n = 21)	Women (n = 11)	Men (n = 6)	Total (n = 17)	Women (n = 19)	Men (n = 19)	Total (n = 38)
HADS-D (21)	4.88 ± 3.52	3.69 ± 3.95	4.14 ± 3.75	2.55 ± 2.91	2.67 ± 3.72	2.59 ± 3.1	3.53 ± 3.31	3.37 ± 3.8	3.45 ± 3.52
n normal cases	6	10	16	9	5	14	15	15	30
n borderline cases	2	1	3	2	1	3	4	2	6
n abnormal cases		2	2					2	2
HADS-A (21)	7.38 ± 3.66	5 ± 4.78	5.9 ± 4.45	7.27 ± 3.82	4 ± 2.28	6.12 ± 3.66	7.32 ± 3.65	4.68 ± 4.11	6 ± 4.06
n normal cases	6	11	17	5	5	10	11	16	27
n borderline cases				4	1	5	4	1	5
n abnormal cases	2	2	4	2		2	4	2	6

The Hospital Anxiety and Depression Scale (HADS) is a self-reported 14-item questionnaire to screen for anxiety and depression symptoms in the past week. The tool was administered in the form of a semi-structured clinical interview. The depression subscale (HADS-D) is comprised of 7 questions scored on a 4-point Likert scale (range 0 to 3), with a total score out of 21. Higher scores represent worse depression symptoms, with scores greater than 8 defined as"possible" cases while scores greater than 11 defined as

"probable" cases. The anxirty subscale (HADS-A) is comprised of 7 questions scored on a 4-point Likert scale (range 0 to 3), with a total score out of 21. Higher scores represent worse anxiety symptoms, with scores greater than 8 defined as"possible" cases while scores greater than 11 defined as "probable" cases. [52]

Table 3.6.1 Inflammatory Bowel Disease Fatigue (IBD-F) Self-assessment Scale

	Women (n = 8)	Men (n = 13)	Total (n = 21)	Women (n = 11)	Men (n = 6)	Total (n = 17)	Women (n = 19)	Men (n = 19)	Total (n = 38)
IBDF Total Score (140)	46.38 ± 23.23	24.38 ± 15.24	32.76 ± 21.17	31.55 ± 21.39	13.83 ± 5.74	25.29 ± 19.3	37.79 ± 22.82	21.05 ± 13.76	29.42 ± 20.43
Section 1 score (20)	9.25 ± 2.6	6.92 ± 3.97	7.81 ± 3.63	8.45 ± 3.72	4 ± 2.61	6.88 ± 3.95	8.79 ± 3.24	6 ± 3.79	7.39 ± 3.75
Section 2 score (120)	37.13 ± 21.54	17.46 ± 12.62	24.95 ± 18.81	23.09 ± 18.28	9.83 ± 3.76	18.41 ± 16	29 ± 20.42	15.05 ± 11.11	22.03 ± 17.68
Fatigue duration	3.75 ± 3.3	3.38 ± 3.62	3.52 ± 3.42	4.08 ± 3.84	1.18 ± 1.24	3.05 ± 3.43	3.94 ± 3.53	2.69 ± 3.2	3.31 ± 3.38
Frequency of fatigue									
Intermittent	6 (75)	8 (62)	14 (67)	10 (91)	6 (100)	16 (94)	16 (84)	14 (74)	30 (79)
Constant	2 (25)	4 (31)	6 (29)	1 (9)		1 (6)	3 (16)	4 (21)	7 (18)
None		1 (8)	1 (5)					1 (5)	1 (3)
Reasons for fatigue									
Work related	2	4	6	5	3	8	7	7	14
Poor sleep	3	5	8	3	3	6	6	8	14
Diet	3	3	6	1	1	2	4	4	8
Medical reasons	2	1	3	2	2	4	4	3	7
Mental health reasons	1	3	4		2	2	1	5	8
Caregiving		2	2	1		1	1	2	3
Other reasons		1	1	3	1	4	3	2	5

The Inflammatory Bowel Disease Fatigue (IBD-F) self-assessment scale is a questionnaire which is used to examine and monitor fatigue severity, frequency, and duration over the past 2-week period. It comprises of 3 sections; level and duration of fatigue (Section 1, 5 questions), impact of fatigue on daily activities (Section 2, 30 questions), and other factors related to fatigue (Section 3, 5 questions). Questions in sections 1 and 2 are scored on a 5-point Likert scale from 0 to 4, with a total score of 140. Section 3 is not

scored but used to describe circumstances associated with fatigue. Higher scores represent worse fatigue symptoms, with Section 1 indicating worsening levels of fatigue and Section 2 greater impact on the individual. [54]*. Adjusted scores were used to calculate Section 2 scores to account for "N/A' in the provided responses using the formula* $adjusted\ score = \frac{Section\ 2\ score}{120-(number\ of\ "NA"s\ x\ 4)} \times 120$. *Cut-offs have yet to be defined for this tool.*

Table 3.6.2 Pittsburgh Sleep Quality Index (PSQI)

	Crohn's Disease			Ulcerative Colitis			Total		
	Women (n = 8)	Men (n = 13)	Total (n = 21)	Women (n = 11)	Men (n = 6)	Total (n = 17)	Women (n = 19)	Men (n = 19)	Total (n = 38)
Pittsburgh Sleep Quality Index (PSQI) (21)	6.1 ± 2.4	4.4 ± 3.4	5 ± 3.1	6.4 ± 4.4	5 ± 3.2	5.9 ± 4	6.3 ± 3.6	4.6 ± 3.2	5.4 ± 3.5
Subjective sleep quality (3)	1.1 ± 0.6	0.9 ± 0.8	1 ± 0.7	1.3 ± 0.6	0.5 ± 0.5	1 ± 0.7	1.2 ± 0.6	0.8 ± 0.7	1 ± 0.7
Sleep latency (3)	1.5 ± 1.1	0.8 ± 0.8	1.1 ± 0.9	1.4 ± 1.1	1.5 ± 1.2	1.4 ± 1.1	1.4 ± 1.1	1 ± 1	1.2 ± 1
Sleep duration (3)	0.5 ± 0.8	0.8 ± 0.8	0.7 ± 0.7	0.9 ± 0.8	0.5 ± 0.5	0.8 ± 0.8	0.7 ± 0.8	0.7 ± 0.7	0.7 ± 0.7
Sleep efficiency (3)	0.1 ± 0.4	0.1 ± 0.3	0.1 ± 0.3	0.5 ± 1	0.7 ± 0.5	0.6 ± 0.9	0.4 ± 0.8	0.3 ± 0.5	0.3 ± 0.7
Sleep disturbance (3)	1.3 ± 0.5	1 ± 0.4	1.1 ± 0.4	1 ± 0.4	1 ± 0.6	1 ± 0.5	1.1 ± 0.5	1 ± 0.5	1.1 ± 0.5
Use of sleep medication (3)	0.1 ± 0.4	0.4 ± 0.9	0.3 ± 0.7	0.3 ± 0.9	0 ± 0	0.2 ± 0.7	0.2 ± 0.7	0.3 ± 0.8	0.2 ± 0.7
Daytime dysfunction (3)	1.5 ± 0.5	0.8 ± 0.8	1.1 ± 0.8	1 ± 0.9	0.8 ± 0.4	0.9 ± 0.7	1.2 ± 0.8	0.8 ± 0.7	1 ± 0.8
n Poor sleep quality (%)	6 (75)	6 (46)	12 (57)	7 (64)	4 (67)	11 (65)	13 (68)	10 (53)	23 (61)

The Pittsburgh Sleep Quality Index (PSQI) examines overall sleep quality by assessing 7 components; subjective sleep quality, sleep latency, duration, habitual sleep efficiency, sleep disturbances, use of medication for sleep and daytime dysfunction over a 1 month retrospective priod. The tool is administered in the form of a semi-structured interview. Each component is scored on a range of 0 to 3, with a global score achieved by summing all the components for a maximum score of 21. Higher scores are indicative of more impairment, with a cut-off score of ≥ 5 used for poor sleep quality. [53].

AUTHORSHIP STATEMENT

This chapter was published in The British Journal of Nutrition

Volume 128 Issue 8 in April 2022. https://doi.org/10.1017/S0007114521001999

The co-authors of the paper "Effects of olives and their constituents on the expression of ulcerative colitis: a systematic review of randomised controlled trials" confirm that Kenneth Daniel has made the following contributions:

- Conception and design of the research
- Conduct and management of study
- Writing of the paper and critical appraisal of the content

As the primary supervisor for the candidate upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Professor Maria A. Fiatarone Singh, 28 February 2025

CHAPTER 4: EFFECTS OF OLIVES AND THEIR CONSTITUTENTS ON THE EXPRESSION OF ULCERATIVE COLITIS: A SYSTEMATIC REVIEW OF RANDOMISED CONTROLLED TRIALS

Authors: Kenneth Daniel [1], Luis Vitetta, M.D., PhD [2], Helen O'Connor, PhD [1 a], Maria A. Fiatarone Singh, M.D. [1,2,3]

[1]Sydney School of Health Sciences, Faculty of Medicine and Health, The University of Sydney,

NSW 2050, Australia

[2]Sydney Medical School, Faculty of Medicine and Health, The University of Sydney, NSW 2050, Australia

[3]The Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts, USA

[a] Deceased 13 January 2020

4.1 Abstract

Background: Extra virgin olive oil (EVOO) is often associated with anti-inflammatory and antioxidant properties. Its effects on inflammatory conditions such as Ulcerative Colitis (UC) however has yet to be defined. As such, we aimed to conduct a systematic review and meta-analysis of studies investigating olive-based interventions in UC.

Methods: A comprehensive database search for randomised controlled trials was performed between 9th July 2018 and 16th August 2018. Studies identified from search alerts were included up to the 22nd of June 2020. Both individuals living with UC at any disease stage and murine models of UC were included in this review.

Results: No human trials meeting the eligibility criteria were identified, while nineteen animal studies comprised of 849 murine models of UC were included in this review. Pooling of the data could not be performed due to heterogeneous outcomes, however general trends favouring olive-based interventions were identified. Milder disease expression including weight maintenance, reduced rectal bleeding and well-formed stools favouring olive-based interventions was statistically significant in 16/19 studies, with moderate-to-large effect sizes (ESs -0.66 (95% CI -1.56, 0.24) to -12.70 (95% CI -16.8, -8.7)). Olive-based interventions did not prevent the development of colitis-like pathologies in any study. In conclusion, effects of olive-based interventions on murine models of UC appear promising, with milder disease outcomes favouring the intervention in most trials and effect sizes suggesting potential clinical relevance. However, the lack of published randomised controlled human trials warrants further investigation to determine if these effects would translate to individuals living with UC.

4.2 Introduction

Ulcerative Colitis (UC) is a chronic condition characterised by inflammation and ulcerations along the colonic mucosa. The disease predominantly affects the large bowel and develops from the rectum to other parts of the colon in a progressive fashion. Symptoms occur intermittently, cycling between active disease and periods of remission. These range from gastrointestinal issues such as loose stools, urgency, frequency, and bleeding, to systemic issues such as fatigue, joint pain, malnutrition and the development of colon cancer. As such, those living with this condition often report a significant impact on quality of life, although overall lifespan is not reduced.[1] Along with other Inflammatory Bowel Diseases (IBDs), the prevalence of UC is increasing globally.[2] The reason for this trend is not well understood, however a combination of environmental,[3] lifestyle,[4] and genetic risk factors[3, 5] has been proposed.

Diet has been a key lifestyle focus for both clinicians and patients. Its role in modifying disease risk factors, disease severity, and symptoms have previously been reported in prospective studies and small trials.[5, 6] In contrast to medical therapy, dietary approaches are often viewed as an attractive option due to the side effects of conventional treatment such as immunosuppressive therapy and monoclonal antibodies.[7] As such, patients often report a range of self-prescribed dietary behaviours and restrictions with potentially negative implications for health outcomes and quality of life.[8] Unfortunately, the efficacy of such practices remains unclear due to the lack of robust evidence.[9]

Amongst the various dietary strategies proposed, the Mediterranean diet is one approach that has gained interest in recent years. Early findings suggest dietary patterns which emulate the Mediterranean Diet was associated with reduced faecal calprotectin,[10, 11] reduced inflammatory

markers, and improvements to anthropometric measures and quality of life measures.[12] Definitions of the diet tends to vary and may extend to include social aspects of food consumption and lifestyle thus it can be challenging to identify how specific elements of the diet impact health outcomes.

Amongst the various elements of the diet, Extra Virgin Olive Oil (EVOO) consumption is one aspect of the diet which is often credited with positive health outcomes.[13] Epidemiological studies have shown associations between higher olive oil consumption with lower UC prevalence.[14-16] However, it is unknown whether such observational associations indicate any causal relationships between olive oil and disease risk.[15, 16] By contrast, one uncontrolled trial in 8 adults with UC using 1 gram olive oil capsules demonstrated no effects on UC disease activity scores after a 12-month period.[17] However, higher doses have yet to be investigated, no randomised controlled trials (RCTs) or systematic review of human or animal trials has been published to our knowledge.

4.3 Aim

We aimed to systematically review and if appropriate, perform a meta-analysis of interventions using EVOO from table olives (*Olea europaea*) or their constituents on disease outcomes of individuals living with UC and murine models of UC at any stage of the disease.

4.4. Method

Searches for eligible articles for the systematic literature review commenced on the 9th of July 2018 and concluded on the 16th of August 2018. Inclusion of hand-searched literature and new trials identified through alerts and the Cochrane central registry of clinical trials concluded on the 22nd of June 2020. This systematic literature review adhered to PRISMA guidelines[18] and

was prospectively registered with the international prospective register of systematic reviews (PROSPERO) under CRD42018103754 on 09 August 2018.

4.4.1. Search Strategy

A systematic literature search was conducted using the following databases; MEDLINE (1946 to August 2018), AMED (1985 to August 2018), CINAHL (1981 to August 2018), EMBASE (1947 to August 2018), Web of Science (1900 to August 2018), Google Scholar (first 100 results from 2008 to August 2018), and Cochrane central registry of clinical trials (1955 to 22 June 2020). Alerts were established for MEDLINE, AMED, CINAHL, EMBASE, Web of Science and Google Scholar and additional references found were included up until 22nd of June 2020. Search alerts for potentially eligible human studies were maintained until the 3rd of January 2025. Search strategy included a combination of 'Population' (UC) AND 'Intervention'(olives/constituents) terms. 'Comparison intervention' or 'Outcome' terms were not used, to optimize sensitivity. Searches using the following terms; ("ulcerative colitis" or "colitis" or "colitis, ischemic" or "colitis, microscopic" or "colitis, ulcerative" or "proctocolitis" or "inflammatory bowel diseases" or "inflammatory bowel disease" or "IBD" or "Crohn disease" or "proctitis" or "enterocolitis") AND ("dietary fats" or "dietary fat" or "olive oil" or "olive" or "virgin olive oil" or "fatty acid" or "monounsaturated" or "diet" or "monounsaturated fat" or "phenols" or "polyphenols" or "flavonoids" or "phenyl ethyl alcohol" or "antioxidant" or "olea" or "tyrosol" or "hydroxytyrosol" or "oleocanthal" or "plant oils" or "plant extracts" or "fatty acids" or "fatty acids, unsaturated" or fatty acids, monounsaturated" or "dietary fats, unsaturated"). Due to the range of phenols present in olives, we explicitly searched for phenols specific to olives which have been examined in previous clinical trials[19] in addition to broad search terms such as "phenols" and "plant extracts" (see online, Supplementary Material). Reference list of articles meeting the inclusion criteria were

also examined to identify studies which may be eligible. No limitations were set for publication year, language, or study location. Both human and animal studies were included. Potentially eligible abstracts not in English were translated to determine eligibility.

4.4.2. Selection of Eligible Studies

Inclusion criteria for both human and animal studies were as follows:

1) randomised experimental trials including a control arm,
2) peer-reviewed publication, either full length articles or chapters,
3) clinical validation of UC in humans at any stage of disease or comparative pathology in animals,
4) ability to assess UC as an independent study arm,
5) *in vivo* intervention,
6) interventions using the olive fruit (*Olea europaea*) and its products including olive oil, paste, freeze dried powdered products, and capsules, or phenolic compounds (hydroxytyrosol, tyrosol, oleuropein, oleocanthal). Studies using olives or its constituents as part of a broader dietary intervention were also included.
7) administration of the intervention either orally or rectally
8) ability to isolate the effects of the olive fruit or its components as an intervention,
9) disease activity outcomes via disease activity score, weight loss, mortality, histology, or inflammatory markers,

No limitations were set on disease severity or duration. Other conditions not meeting the definition of UC[20] such as Crohn's Disease, Inflammatory Bowel Disease Unclassified (IBDU) and indeterminate colitis were excluded. Animal studies fulfilling the selection criteria were further screened for 1) mammalian models of the disease, 2) equivalent condition matching UC

pathologies comprising of both experimental and sporadic disease.[21-23] Mammalian models were selected due to the relative similarity of intestinal function and morphology to humans.[21] Other transient forms of colitis such as acute or episodic colitis, allergic colitis, and stress colitis were excluded from this review. Studies which include olive-based interventions as part of a broader dietary intervention were considered.

The reference management software Endnote X9.3.3 was used for this review. The primary author (K.D.) was responsible for database searches, collation of studies, and removal of duplicates and screening of eligible studies. Full text of remaining articles was assessed by authors K.D. and M.A.F.S. When agreement could not be reached, author L.V. was consulted. All eligible articles were included in this systematic review.

4.4.3. Data Extraction and Analysis

Data extraction of eligible studies was completed by the first author (K.D.). A second reviewer (M.A.F.S.) verified extracted data and discrepancies for review. Summary of data extracted at each study level (aggregate) was reported. A meta-analysis for each outcome was considered if appropriate. Human and animal studies were analyzed separately.

Data extraction included the following: 1) Publication metrics (first author surname, publication year, volume and number of publication), 2) Population characteristics (sex, age, number recruited/studied, co-variates), 3) Disease & co-morbidities, 4) Description of intervention, 5) Duration and dose, and 6) Study outcomes and statistical analysis.

4.4.4. Outcome Assessment

Due to the breadth of outcomes, assessments tools identified were in accordance with what was described in the literature, with some general trends identified. For both Disease Activity Index (DAI) scores and histology scores, an increase in the scores correspond to greater damage to colon tissue. Specific outcomes and assigned sub-scores varied between tools and are outlined accordingly in the results.

Similarly, colon shortening and increased colon weight are hallmarks of inflammation and indicators for disease progression in experimental colitis in animal models.[23] As such, increased colon weight/length ratios compared to non-colitis animals are typically considered a hallmark of disease severity. Negative effect sizes for DAI, histology score, and colon weight/length ratio are indicative of milder disease expression favouring the intervention, with the reverse true for controls. Colon lengths and weight outcomes independent from colon weight/length ratios reported were included in the analysis.

Quantification of inflammatory cytokines and gut microbiome outcomes may vary between studies dependent on the techniques used and the measures selected. Outcomes extracted in the results were dependent on what was described in text, with no assumptions made in the event that no measurement value was described.

WebPlotDigitizer Version 4.1 was used to extract graphical data in the absence of raw values. All results are expressed as *mean* ± *standard deviation* unless stated otherwise. Post-study outcomes were analyzed in all studies due to incomplete baseline data. Standard deviations between groups were assumed to be the same if data were not available and when such assumptions were made this was identified within tables. Mean values were used for studies

expressing population numbers as ranges. An effect size calculator published by the Centre of Evaluation & Monitoring was used to calculate Hedge's bias corrected ESs and 95% CIs using values extracted from the literature.[24] Interpretation of ESs was determined based on the benchmark proposed by Cohen [25] with effects categorized as small (d = 0.2), medium (d = 0.5), and large (d = 0.8).

4.4.5. Quality Assessment

Two review authors K.D. and M.A.F.S. performed the risk of bias assessment independently. Human studies were evaluated using the Cochrane Collaboration Risk of Bias tool[26] which examines 6 types of bias comprising of selection, performance, detection, attrition, reporting, and other bias. The tool assigns each aspects of the trial with high, low, or unclear risk of bias. Animal trials were evaluated using the SYRCLE's Risk of Bias Tool which was developed based on the Cochrane Collaboration Risk of Bias tool. The tool is comprised of 10 questions which are assigned high, low, or unclear risk of bias on aspects of the study pertinent to animal interventions.[27] No final score is assigned for the studies assessed, and outcomes are summarized in the form of tables. Inter-observer variability was evaluated using Kappa statistics based on evaluations by authors K.D. and M.A.F.S.

4.5. Results

Thirty-two potentially eligible studies were identified through electronic searches and search alerts (*Figure 4.1*). All human trials identified were excluded due to uncontrolled study design (n=1) and dietary interventions in which the effects of olives could not be isolated (n=2). Ten murine studies were excluded due to non-olive interventions (n=6), interventions bypassing the gastrointestinal tract (n=2) and combined interventions in which the effects of olive

components could not be isolated (n=2). This resulted in a total of 19 eligible animal studies, with no eligible human trials. Studies were heterogeneous which precluded a meta-analysis, however effect sizes were calculated to demonstrate the magnitude of effect of olive based intervention in each study.

4.5.1. Risk of Bias

The overall study quality for eligible studies was deemed to be low. An average of 6/10 items on in the risk of bias tool were not reported (NR) across all studies. Two of 19 studies described allocation sequences through simple randomisation[28] or by weight[29] with no additional description. Eight of 19 studies reported assessing representative histology specimens within each study arm, however the sampling process was not described in any text (**Table 4.1**).

4.5.2. Study Characteristics

4.5.2.1. Characteristics of animals

Twelve mouse studies and 7 rat studies, representing more than 849 animals were identified. The most common strains used were 6-to-8-week-old C57BL/6 mice and Wistar rats, and 10/19 studies used female animals. In all studies reporting age at baseline, all animals had reached sexual maturity but none could be considered old.[30] Study populations could not be assessed in 3 studies.[31-33] (**Table 4.2**).

4.5.2.2. Environmental and Control Conditions

Husbandry conditions were poorly reported, with only 3/19 studies adequately describing number of animals per cage.[34-36] The American Institute of Nutrition (AIN) purified rodent diet[37, 38] with modified fat content was the most common food used (7/19 studies), while remaining studies reported various commercial or non-specific diets. Energy content of the diet

was described in 4/19 studies and ranged between 2900 and 3970 kcal/kg,[28, 31, 33, 35] while fat content ranged from 4-10% by weight (**Table 4.2**). Calorie-matched diets between study groups was reported in only 1/19 study,[35] while 5/19 studies[34, 39-42] described matched fat, protein and carbohydrate content between diets. Sunflower oil was the most commonly used fat source in control diets,[34, 36, 40-42] while corn oil[39] or soybean oil[35] were used in the remaining studies.

4.5.3.3. Induction of Colitis

Chemically induced colitis models were the most common method of simulating UC (17/19 studies), which was achieved predominantly using Dextran Sulfate Sodium (DSS) (14/19 studies). Despite variances between study protocols, the overall procedures were similar. Briefly, DSS solution was prepared daily to the desired concentration (wt./vol.) using distilled water. This solution was provided in place of drinking water which could be consumed *ad libitum.* Duration of DSS exposure and concentration used varied between studies; acute models were induced between 3-15 days with a DSS concentration of 2 – 5%, while chronic colitis models was induced between 28 and 259 days using 0.7 – 2%. The remaining studies used either 2,4,6-trinitrobenzenesulfonic acid (TNBS)[28] or rectal administrations of acetic acid.[43, 44] Two studies reported using transgenic HLA-B27 rats[39] or IL-10 knockout mice[45] predisposed to inflammation (**Table 4.3**).

4.5.4.4. Intervention

Interventions comprised of olive oil (virgin and refined oils), oleuropein, hydroxytyrosol acetate (Hty-Ac), and tyrosol administered between 5 and 273 days, with a median of 30 days. Most studies combined olive-based intervention into dietary preparations, with 9/19 having enough information to estimate doses. These included 0.2-2.25 mL/day olive oil,[28, 39, 46] 10-40

mg/day oleuropein,[31, 33, 47] 1.2 – 4.0 mg/day Hty-Ac,[32, 40] and 3.6-5.0 mg/day Tyorosol.[48] Doses in 8 studies could not be calculated due to unreported food consumption, 1 study due to unreported animal weights[44] and 1 study in which the olive oil was combined with a reagent prior to administration.[28] Voltes, et al.[28] was the only study to intervene post-colitis, while all remaining studies administered the intervention either prior to, or concurrent with, colitis induction. (**Table 4.4**).

Five studies reported food consumption, with mice consuming 3-4 g/day,[33-35, 49] and HLAB-27 rats 15 g/day.[39] One study[39] described the method of evaluating food consumption. Lower food intake in untreated animals was reported in 1 study[49] while 4 studies reported no difference between groups.[33-35, 39] None of the studies intervening via oral gavage[29, 43, 44, 46-48] or rectal administration[28] of an olive-based therapy described matching for potential energy contributions of the intervention.

4.5.3. Study Outcomes

4.5.3.1. Mortality

Mortality was reported in 7/19 studies,[31, 33, 39, 40, 43, 45, 49] and ranged from 0 – 40%. Animals in the olive-based interventions had lower mortality rates (2.9 ± 6.6%) compared to controls (13.9 ± 16.9%), with 3 studies reporting no mortality in either group. (**Table 4.5**). Deceased animals were included in the DAI analysis in one study,[40] while two studies did not report if deceased animals were included in any outcome analyses.[43, 49] None of the studies documented cause of death.

4.5.3.2 Disease Activity

All experimental models of colitis in this review demonstrated intestinal inflammation and mucosal damage and symptoms consistent with UC, including rectal bleeding, loose stools, weight changes, altered colon morphology, altered histology, and upregulation of inflammatory markers.[23, 50] Disease severity was reported in 11/19 studies[31-36, 40-42, 47, 49] as DAI; comprised of sub-scores for rectal bleeding, weight loss, and stool consistency. One study reported rectal bleeding scores and weight loss to characterise disease activity without using a scoring index.[29]

Colitis induction increased the DAI in all studies, while cessation of reagents used improved DAI outcomes, although they did not return to non-colitis levels in any study. Inclusion of an olive-based intervention reduced disease activity scores (between -0.07 to -2.1 points) compared to control-colitis animals, indicating milder symptoms, in 10 of 12 studies[29, 31-35, 41, 42, 47, 49] reporting this outcome. The differences between groups were statistically significant in 9 studies[29, 31-35, 41, 42, 49], with all but 1 of these[34] reporting moderate-to-large effects (ESs -0.66 (95% CI -1.56, 0.24) to -12.70 (95% CI -16.8, -8.7)). Disease activity improvements were not seen in transgenic HLAB-27 rats, however.[39] (**Table 4.6**). Improvements to stool consistency[33] and reduced rectal bleeding[31] were the greatest contributors to the differences in DAI, however only 3 studies reported these sub-scores[31, 33, 34]. Comparing studies using the same intervention, higher intervention doses for hydroxytyrosol[32, 40, 51] and oleuropein[31, 33, 47] were associated with greater DAI differences between groups.

4.5.3.3. Weight Changes Post Study

Ten of 19 studies[28, 29, 32, 36, 39, 41, 42, 45, 46, 49] reported weight changes as an outcome independent of the DAI score. Seven of 10 studies showed benefit in the intervention group indicated by

reduced weight loss (-19 ± 21.3 % from baseline measures in the intervention group, -28 ± 25.3 % from baseline measures in controls)[29, 32, 41, 42, 45, 46] or greater weight gain at study completion (246 ± 18.4 grams in the intervention group, 184 ± 18.4 grams in animals receiving control diets).[49]

Among the studies reporting outcomes favouring the intervention, 4 were statistically significant ($p< 0.05$ - 0.001),[29, 32, 41, 42] and 6 studies reported large ESs between 0.97 (95% CI 0.12, 1.82) and 8.73 (95% CI 6.14, 11.33).[29, 32, 41, 45, 46, 49] Within the remaining studies, one study using DSS mouse models[36] and HLA-B27 rats[39] reported greater weight gain in controls, while a study using TNBS colitis models reported non-significant outcomes with no examinable data.[28] No differences were observed between studies using acute[28, 32, 36, 39, 42, 46] vs. chronic[41, 49] models of colitis (**Table 4.7**). None of the studies investigated the source of weight loss, thus it is unknown if weight changes were attributed to anorexia, secondary effects of inflammation, altered fluid balance, or other physiological changes.

4.5.3.4. Colon Morphology

4.5.3.4.1. Histology Score

Sixteen of 19 studies[28, 29, 32-36, 39-42, 44-46, 48, 49] reported histology outcomes using parameters of colonic damage.[52, 53] Grading methods varied between studies, with scores ranging between 4 – 120. Fourteen studies reported blinded assessments.[28, 32-36, 39-42, 45, 46, 48, 49]

Improved histology outcomes favouring the intervention group were demonstrated in 14 of 16 studies,[28, 29, 32-35, 40-42, 44-46, 48, 49] with 9 studies[29, 32, 33, 40, 41, 44, 46, 48, 49] showing large ESs between -0.81 (95% CI -1.64, 0.02) to -4.51 (95% CI -6.16, -2.86). Microscopic outcomes were reported in 1 study,[48] with statistically significant improvements in mucosal architecture, cell

infiltration, crypt abscess formation and preservation of goblet cells (ESs -0.5 (95% CI -0.78, 1.98) to -1.15 (95% CI -0.01, 2.89), p<0.001). Five studies using DSS-colitis models reported sub-scores for proximal, middle, and distal colon sections with the greatest difference noted in middle[41] and distal[32, 40, 42, 49] colon sections. (**Table 4.8**).

4.5.3.4.2 Colon Weight/Length Ratio

Nine of 19 studies[31, 33-36, 40-42, 47] reported colon weight/length ratios which were expressed as either mg/cm in 5 studies[31, 33, 35, 36, 40], g/cm[34] or percentages compared to non-colitis animals in 2 studies [41, 42]. Favourable weight/length ratios in intervention animals were reported in 6 studies; with a mean difference of -11.9 ± 3.1 mg/cm[31, 33, 35, 40] and -67.5 ± 10.6% [41, 42] compared to controls. Four studies showed large effects with an ES between -1.31 (95% CI -2.27, -0.34) to -2.41 (95% CI -3.56, -1.26).[31, 33, 41, 42] Results were omitted in one paper reporting no statistically significant differences between groups[47] (**Table 4.9**).

4.5.3.4.3 Colon Length

Colon length was reported by 6/19 studies, comprised of 4 mouse studies[32, 33, 36, 46] and 2 rat studies.[44, 49] Average colon length of non-colitis animals was 7.9 ± 0.7 cm for mice and 17.3 ± 2.8 cm for rats, which was shortened in all animals induced with colitis, a sign of inflammation and colonic injury. Olive-based interventions attenuated this change, with longer colon lengths reported in intervention animals (mean 6.3 ± 0.6 cm in mice, 13.1 ± 1.4 cm in rats) compared to controls (mean 5.9 ± 0.6 cm in mice, 11.2 ± 1.3 cm in rats). One of 6 studies reported statistical significance favouring the intervention,[44] while 4/6 studies[32, 33, 44, 49] reported large ESs between +0.88 (95% CI 0.04, 1.72) to +2.36 (95% CI 1.22, 3.50) (**Table 4.10**).

4.5.3.5. Inflammatory Cytokines

4.5.3.5.1. Tumour Necrosis Factor alpha (TNF-α)

Fourteen studies reported TNF-α outcomes post-sacrifice;[33-36, 39-44, 46-49] 9 studies reported concentrations in colon tissue,[33-36, 43, 44, 47-49] 3 studies quantified TNF-α mRNA in tissue samples,[39, 41, 42] 1 study expressed TNF-α in percentages compared to non-colitis animals,[40] and 1 study reported number of cells expressing antibodies.[46] Twelve of 14 studies[33-35, 39-44, 46-48] reported lower TNF-α expression in the intervention group compared to controls, with 9 studies statistically significant ($p < 0.001$ to 0.05).[33, 39, 40, 42-44, 46-48] ES ranged from -0.34 (95% CI -1.15, 0.48) to -4.63 (95% CI -6.31, -2.95), with 9 of 14 moderate-to-large favouring the intervention.[33, 35, 39, 42-44, 46-48] One study reported outcomes favouring controls[36] which was not statistically significant but had a large ES (+0.95, 95% CI 0.00, 1.89). (**Table 4.11**).

4.5.3.5.2. Interleukins

Four families were identified in this systematic review; Interleukin-1β, Interleukin 6, Interleukin 10, and Interleukin 17.

I Interleukin-1β (IL-1β)

Nine studies assessed pro-inflammatory IL-1β expressed as quantities in tissue,[31, 33, 36, 44] relative gene expression,[29, 39] percentages compared to non-colitis animals,[40] and number of stained cells in sampled colon tissue.[46] Induction of experimental colitis resulted in higher IL-1β expression compared to non-colitis animals in all studies. Animals receiving an olive-based intervention showed a lower expression of IL-1β in 6/9 studies (ESs -0.54 (95% CI -1.61, 0.52) to -3.57 (95% CI -5.40, -1.75).[29, 31, 33, 39, 44, 46] Statistical significance ($p < 0.05$) was reported in 3/9 studies,[29, 33, 44] all favouring the intervention. Results were omitted in one paper reporting no statistically significant differences between groups.[49] (**Table 4.12**).

II. Interleukin-6 (IL-6)

Ten studies examined pro-inflammatory IL-6 expressed as tissue concentration,[31, 33, 34, 36, 44, 47, 48] number of stained cells in colon samples[46] or relative gene expression.[29] Nine of 10 studies[29, 31, 33, 34, 36, 44, 46-48] reported lower IL-6 favouring the intervention group, with 6/10 statistically significant ($p<0.01$ to $p<0.001$).[29, 31, 33, 44, 47, 48] Seven of 10 studies had large ESs between -0.84 (95%CI -1.76, 0.07) and -2.81 (95% CI -4.29, -1.33).[29, 31, 33, 44, 46-48] Results were omitted in one paper reporting no statistically significant differences between groups.[49] (**Table 4.13**)

III Interleukin-10 (IL-10)

Three studies reported anti-inflammatory IL-10 outcomes which were expressed using varying units of measure.[31, 36, 40] Colitis induction reduced IL-10 expression in all the animals, which was attenuated by olive-based interventions in 2/3 studies[31, 40]. Measures of IL-10 was 34-43% greater in intervention animals compared to controls at sacrifice. Outcomes from two studies were statistically significant, with large ESs of + 0.99 (95% CI 0.13, 1.85)[40] and +10.33 (95% CI 6.30, 14.17).[31] Results were omitted in one paper reporting no statistically significant differences between groups.[36]

IV. Interleukin-17 (IL-17)

Park, et al. was the only study reporting pro-inflammatory IL-17 outcome, expressed as number of positive cells.[46] Mean cell count expressing IL-17 in non-colitis animals was 10.5±5.4 cells, while induction of colitis resulted in a marked increase in IL-17 expression. This increase was milder in intervention animals (55.9±12.0 cells) compared to controls (71.2±5.0 cells). This outcome was not statistically significant; however, calculated ES was -1.49 (95% CI -2.89 to -0.09).

4.5.4.5.3 Interferon Gamma (IFNγ)

Pro-inflammatory IFNγ was reported in 2/19 studies through enzyme immunoassay [34] and RT-PCR [39]. Colitis induction increased IFNγ expression in both studies, and olive-based interventions did not significantly influence outcomes; ESs were -0.40 (95% CI -1.02, 0.23) [34] and +0.31 (95% CI -0.78, 1.41) [39] showing small non-significant effects both in favour and against the intervention.

4.5.3.6. Other Outcomes

Microbiome outcomes were reported in only 1/19 studies,[44] expressed as colony forming units (CFU) of 3 bacteria families. Experimental colitis reduced *Lactobacillus* spp. and *Bifidobacterium* spp. counts in all study arms, while *Clostridium perfringens* counts remained stable. Animals supplemented with olive oil maintained greater *Lactobacillus* spp. counts compared to controls post induction of colitis while *Bifidobacterium* spp. counts were not impacted by the intervention.

4.6. Discussion

To our knowledge, this is the first systematic review investigating the effects of olive-based interventions on the expression of UC in both humans and animal models. A significant body of work has been done in murine models of colitis, while no randomised controlled trials in humans have been published at the time of writing. Studies were heterogeneous, which precluded a meta-analysis; however general trends were identified, as discussed below.

4.6.1. Overall effects of olive-based interventions

Animals receiving olive-based interventions had milder UC severity in most studies, as shown by lower disease activity scores and favourable inflammatory markers compared to controls at sacrifice. Interestingly, such findings were not replicated in HLA-B27 rats[39] and one study using C57BL/6 mice.[36] All remaining studies using C57BL/6 mice models demonstrated outcomes favouring the intervention,[29, 31, 32, 34, 36, 40-42, 46, 47] while no other study used HLA-B27 models. Other rat models however demonstrated outcomes favouring olive-based interventions,[28, 35, 43, 44, 48, 49] thus it is unclear if the use of HLA-B27 rat models or other experimental variables influenced these outcomes.

Insufficient intervention doses may have contributed to this discrepancy. Polyphenol content was not described in one study,[36] while Bigagli., et al., reported hydroxytyrosol concentration of 15 mg/kg olive oil; equivalent to a daily dose of 90 μg/kg body weight in HLA-B27 rats.[39] By contrast, findings from other studies in this review suggests clinically significant outcomes were associated with polyphenol concentrations above 0.4 mg/kg body weight.[40, 41] Similarly, in this review we identified greater attenuation of disease scores at higher concentration of hydroxytyrosol[32, 40, 51] and oleuropein.[31, 33] It should be noted that adverse effects may occur at higher doses,[54] however this was not evident in any study in this review. Furthermore, a dose response relationship cannot yet be established due to the small sample sizes, heterogeneity of studies, and variable reporting of experimental methods.

4.6.2. Effects on body weight

Weight loss and malnutrition are known complications associated with colitis in both animal models[55, 56] and human cohorts.[9, 57] Anorexia, malabsorption, dietary restrictions and gut microbiome disturbances are some of the contributors to this phenomenon.[58-60] In this

systematic review, olive-based interventions improved weight outcomes concordant with milder disease activity, as indicated by weight maintenance or increased weight gain. Energy density of control and intervention diets were matched in most studies however, such precautions were not evident in studies intervening through oral gavage or rectal administration. As such, it is unknown if these interventions influenced daily energy intake and subsequent weight outcomes. Similarly, housing conditions and husbandry were poorly described in most studies and potential confounders for feeding behaviour and subsequent weight outcomes.[61, 62]

Interestingly, olive oil supplementation increased oral intake in one study.[49] Although exact mechanisms are unclear, associations between gastrointestinal dysfunction and feeding behaviours are plausible,[60] as milder symptoms may promote feeding behaviour. In conjunction with these changes, mucosal healing as indicated by stool consistency and histology outcomes may offer greater opportunity for fluid and nutrient absorption along the gastrointestinal tract. In combination, these changes may ultimately contribute towards favourable weight outcomes in intervention animals. This relationship remains speculative as few studies quantified oral intake, further complicated by multiple animals per cage and *ad libitum* feeding.

Finally, gut microbiome favourable shifts mediated by olive interventions may have contributed to the outcomes observed. Reduced gut bacterial diversity and abundance of commensal species have been associated with disease severity in both UC and experimental colitis.[63] Such changes are significant considering the microbiome's role in supporting gut barrier integrity, gut inflammatory tone and intestinal immunity through the production of short chain fatty acids (e.g., butyrate) and other host interactions. By contrast, previous studies has

shown that olive oil supplementation promotes alpha diversity of commensal bacterial species and accumulation of lean muscle mass in healthy C57BL/6J mice,[64] a finding which was replicated in this review.[44] No other study assessed microbiome outcomes, thus any conclusions are premature.

4.6.3. Colon Morphology

Chemically induced colitis results in several features which differ depending on the reagent and dosage used. DSS-colitis models exhibit loss of surface epithelium which subsequently increases mucosal permeability, predominantly impacting the distal colon. Administration of TNBS results in thickening of the proximal colon accompanied by loss of haustration while intra-rectal administration of acetic acid solution results in necrosis of intestinal mucosa and submucosa.[23] Despite the variability of these changes, several shared features such as oedema, ulcerations, granulocyte infiltration and dysplasia can be used to ascertain severity of experimental colitis.

Findings from this review suggest that olive-based interventions may have a role in preserving colonic architecture and metabolic-immunological function in experimental UC. This was evident through milder microscopic and macroscopic outcomes, histology scores, and normalized weight/length ratios favouring intervention animals. It should be noted that olive-based interventions did not *prevent* intestinal injury in any study, however the degree of damage was considerably lower compared to animals in the control arm.

Comparing sub-sections of the colon, middle and distal sections are known to be most affected by colitis.[65, 66] Importantly, these sub-sections showed the greatest improvements in response to olive-based interventions, suggesting specific protection on these sites. Promotion of wound

healing and protection against oxidative damage of intestinal cells mediated by olive polyphenols have previously been demonstrated[31] which may explain how olive-based interventions protect against chemically induced colitis.

Beneficial alterations to the microbiome mediated by olive polyphenols may have conferred additional protective effects against experimental colitis. Consumption of olive oil and olive polyphenols have been demonstrated to facilitate growth of butyrate producing bacteria such as *Lactobacillus and Bifidobacterium,*[67] increase mucosal concentrations of short chain fatty acids,[67] and inhibit growth of pathogenic species associated with inflammation.[68] Short chain fatty acids such as butyrate play a vital role in preserving intestinal epithelial barrier and serve as fuel for colonocytes.[69, 70] Furthermore, short chain fatty acids have been demonstrated to exert anti-inflammatory effects in the intestinal mucosa.[69] Metabolism of short chain fatty acids is impaired in UC and has been correlated with poorer histology and endoscopy outcomes.[71] As such, strategies targeting both the microbiome and short chain fatty acid production may assist in maintaining colon homeostasis, however current evidence remains inconsistent and further investigations are warranted.

4.6.4. Inflammatory markers

Many health outcomes of olive-based interventions have been ascribed to component effects on inflammatory responses. Olive oil is predominantly composed of the monounsaturated fatty acid oleic acid, which has been shown to protect against oxidative stress, regulate immune function in intestinal smooth muscle cells, and disrupt arachidonic acid and NF-κB signalling pathways associated with chronic inflammation.[29, 72] Prospective studies in healthy cohorts suggest an inverse association between oleic acid consumption and risk of developing UC,[16] although such findings have yet to be replicated in larger studies.[73] Similarly, associations

between dietary oleic acid and disease severity in individuals living with UC remain inconclusive despite promising findings in pre-clinical and clinical data.[74]

Consumption of olive oil may confer additional benefits through displacing less desirable fatty acids in the diet. Specific fatty acids such as omega-6 polyunsaturated fatty acids, saturated fats, trans fats, and high fat diets have been associated with increased markers of pro-inflammatory cytokines,[75] increased risk of developing UC,[16] and worsening symptoms in individuals living with UC and animal models.[75, 76] Similarly, inclusion of omega-3 fatty acids have been demonstrated to exert protective effects against experimental colitis[77, 78] however its role in prevention and treatment of UC remains controversial.[79-81] Finally, although dietary fat manipulation through olive oil consumption may confer some benefits on inflammatory markers and disease outcomes, it is unlikely that the effects observed in this review could be attributed to the fatty acid profile alone.

Previous experiments have highlighted the bioavailability and anti-inflammatory properties of olive oil polyphenols such as oleuropein, hydroxytyrosol, and oleocanthal in the gut.[82] In this review we identified dose-dependent associations between hydroxytyrosol and oleuropein interventions with lower cytokine expression in concert with improved disease outcomes in murine models of UC. These findings further support previous *in vitro* studies on colonic biopsies of UC cohorts [83] and healthy cohorts,[84, 85] in which cytokine expression was reduced by olive polyphenols such as hydroxytyrosol and oleuropein.

Regulation of inflammatory markers has been identified as a potential therapeutic target in IBD, as increased secretion of pro-inflammatory (TNF-α, IL-1β, IL-6) and reduction of anti-inflammatory cytokines (IL-10) are associated with chronic inflammation and symptoms.[86-88]

However, limited evidence is available on the specific markers associated with UC outcomes and their response to olive based interventions, with several inconsistencies identified in the literature. Moraes et al found minimal differences in cytokine expression between a cross-sectional study of UC cohorts with and without gastrointestinal symptoms.[89] Similarly, an uncontrolled study comparing 50 mL/day EVOO and canola oil interventions in UC cohorts reported alleviation of gastrointestinal symptoms and reduction of hs-CRP without alterations to serum TNF-α favouring EVOO, although no other markers were quantified.[90] Finally, a meta-analysis in non-IBD populations similarly reported no changes to TNF-α despite favourable CRP and IL-6 outcomes with olive oil interventions.[91] The discrepancies between animal data in this review and human studies highlight the limitations of translating our findings to human cohorts and current gaps in the evidence. As such, although olive-based interventions appear to influence disease activity and symptoms as well as attenuation of pro-inflammatory cytokine expression in experimental UC models, it is unknown if findings would be replicated in human trials. Therefore, further investigations are warranted.

4.6.5. Limitations of this review methodology

The search strategy for this review was comprehensive, although no unpublished studies were sought, and no non-English language databases were searched, which could have limited the number of trials available for review. In addition, only one author (K.D.) performed the search and initial selection of eligible articles. However, the final selection was agreed upon by all authors.

4.6.6. Limitations of the literature to date

The studies identified were heterogeneous, with variations between experimental models, outcome measures, and methods of evaluating disease severity. Chemically induced colitis

models formed the majority of the evidence, which may limit the translation of our findings to other models of UC and human cohorts. Scaling up of olive oil doses described in this review for individuals living with UC should consider the feasibility and safety of implementing these interventions. Furthermore, quality of the evidence through the SYRCLE's Risk of Bias tool was sub-optimal due to limited reporting of key domains such as animal characteristics and husbandry; factors known to influence disease severity and experimental outcomes (such as individual animal stool volumes), as well as determine actual individual animal consumption of both food and olive-based product.[92, 93] Moreover, strength to murine models of IBD would be further enhanced if researchers conducting the histology studies were unsighted to the collected colon samples.

Most of the studies intervened prior to, or during induction of, experimental colitis, limiting our ability to determine the efficacy of such strategies post-colitis. It does lend support to epidemiological data on consumption patterns and risk of developing disease.[14-16] However, translation to therapeutic interventions in cohorts who have established UC or similar conditions require explicit human studies with robust experimental designs.

4.7. Conclusion

Olive-based interventions exerted protective effects against chemically induced colitis in murine models. Despite these promising outcomes, conclusions are limited by the overall low quality of existing animal trials due to sub-optimal reporting of key parameters. Future investigations should include well-defined baseline characteristics, greater transparency regarding randomisation, blinding, and husbandry as well as mortality. Most importantly, translation of these basic studies to human trials are warranted given the absence of robustly

designed trials investigating the relationship between olive-based interventions and outcomes in UC cohorts.

4.8. References

1 Winther KV, Jess T, Langholz E, Munkholm P, Binder V. Survival and cause-specific mortality in ulcerative colitis: follow-up of a population-based cohort in Copenhagen County. *Gastroenterology*. 2003;125(6):1576-1582.

2 Bernstein CN. Epidemiologic clues to inflammatory bowel disease. *Current Gastroenterology Reports*. Review. 2010;12(6):495-501.

3 Abegunde AT, Muhammad BH, Bhatti O, Ali T. Environmental risk factors for inflammatory bowel diseases: Evidence based literature review. *World Journal of Gastroenterology*. Review. 2016;22(27):6296-6317.

4 Chapman-Kiddell CA, Davies PSW, Gillen L, Radford-Smith GL. Role of diet in the development of inflammatory bowel disease. *Inflammatory Bowel Diseases*. Review. 2010;16(1):137-151.

5 Aleksandrova K, Romero-Mosquera B, Hernandez V. Diet, Gut Microbiome and Epigenetics: Emerging Links with Inflammatory Bowel Diseases and Prospects for Management and Prevention. *Nutrients*. Review. 2017;9(9):30.

6 Haskey N, Gibson DL. An examination of diet for the maintenance of remission in inflammatory bowel disease. *Nutrients*. Review. 2017;9(3).

7 Carter MJ, Lobo AJ, Travis SPL. Guidelines for the management of inflammatory bowel disease in adults. *Gut*. 10.1136/gut.2004.043372. 2004;53(suppl 5):v1.

8 Casanova M, Chaparro M, Molina B, et al. Prevalence of malnutrition and nutritional characteristics of patients with inflammatory bowel disease. *Journal of Crohn's and Colitis*. Conference Abstract. 2016;10 (Supplement 1):S208-S209.

9 Alastair F, Emma G, Emma P. Nutrition in inflammatory bowel disease. *Journal of Parenteral and Enteral Nutrition*. Review. 2011;35(5):571-580.

10 Godny L, Reshef L, Pfeffer-Gik T, et al. Adherence to the Mediterranean diet is associated with decreased fecal calprotectin in patients with ulcerative colitis after pouch surgery. *Eur J Nutr*. 2020;59(7):3183-3190.

11 Strisciuglio C, Cenni S, Serra MR, et al. Effectiveness of Mediterranean Diet's Adherence in Children with Inflammatory Bowel Diseases. *Nutrients*. 2020;12(10):3206.

12 Chicco F, Magrì S, Cingolani A, et al. Multidimensional Impact of Mediterranean Diet on IBD Patients. *Inflammatory Bowel Diseases*. 2020.

13 Santangelo C, Varì R, Scazzocchio B, et al. Anti-inflammatory activity of extra virgin olive oil polyphenols: Which role in the prevention and treatment of immune-mediated inflammatory diseases? *Endocrine, Metabolic and Immune Disorders - Drug Targets*. Review. 2018;18(1):36-50.

14 Triantafillidis JK, Emmanouilidis A, Manousos ON, et al. Ulcerative colitis in Greece: clinicoepidemiological data, course, and prognostic factors in 413 consecutive patients. *J Clin Gastroenterol*. 1998;27(3):204-210.

15 Shivananda S, Lennard-Jones J, Logan R, et al. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut*. 1996;39(5):690-697.

16 De Silva P, Luben R, Mc Taggart A, Khaw KT, Hart A. Dietary arachidonic acid and the aetiology of ulcerative colitis: Data from a UK prospective cohort study, using 7-day food diaries. *Gut*. Conference Abstract. 2011;1):A140.

17 Greenfield SM, Green AT, Teare JP, et al. A randomized controlled study of evening primrose oil and fish oil in ulcerative colitis. *Alimentary Pharmacology and Therapeutics*. Clinical Trial Randomized Controlled Trial. 1993;7(2):159-166.

18 Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Medicine*. 2009;6(7):e1000097.

19 Cicerale S, Lucas LJ, Keast RSJ. Antimicrobial, antioxidant and anti-inflammatory phenolic activities in extra virgin olive oil. *Current Opinion in Biotechnology*. 2012;23(2):129-135.

20 Geboes K, Dewit O, Moreels TG, Faa G, Jouret-Mourin A. Inflammatory Bowel Diseases. In: Jouret-Mourin A, Faa G, Geboes K, eds. *Colitis: A Practical Approach to Colon and Ileum Biopsy Interpretation*. Cham: Springer International Publishing; 2018:107-140.

21 Jiminez JA, Uwiera TC, Douglas Inglis G, Uwiera RRE. Animal models to study acute and chronic intestinal inflammation in mammals. *Gut pathogens*. 2015;7:29-29.

22 Mizoguchi A. Animal Models of Inflammatory Bowel Disease. In: Conn PM, ed. *Progress in Molecular Biology and Translational Science*. Vol. 105. Academic Press; 2012:263-320.

23 Randhawa PK, Singh K, Singh N, Jaggi AS. A Review on Chemical-Induced Inflammatory Bowel Disease Models in Rodents. *Korean J Physiol Pharmacol*. 2014;18(4):279-288.

24 Centre for Evaluation & Monitoring. Effect Size Calculator. Vol. 2019: Centre for Evaluation & Monitoring, 2020

25 Cohen J. *Statistical power analysis for the behavioral sciences*. Academic press; 2013.

26 Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj*. 2011;343:d5928.

27 Hooijmans CR, Rovers MM, de Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC Medical Research Methodology*. 2014;14(1):43.

28 Voltes A, Bermúdez A, Rodríguez-Gutiérrez G, et al. Anti-Inflammatory Local Effect of Hydroxytyrosol Combined with Pectin-Alginate and Olive Oil on Trinitrobenzene Sulfonic Acid-Induced Colitis in Wistar Rats. *Journal of Investigative Surgery*. Article in Press. 2018:1-7.

29 Cariello M, Contursi A, Gadaleta RM, et al. Extra-Virgin Olive Oil from Apulian Cultivars and Intestinal Inflammation. *Nutrients*. 2020;12(4).
30 Dutta S, Sengupta P. Men and mice: Relating their ages. *Life Sciences*. 2016;152:244-248.
31 Giner E, Recio MC, Ríos JL, Giner RM. oleuropein protects against dextran sodium sulfate-induced chronic colitis in mice. *Journal of Natural Products*. Article. 2013;76(6):1113-1120.
32 Sánchez-Fidalgo S, Villegas I, Aparicio-Soto M, et al. Effects of dietary virgin olive oil polyphenols: Hydroxytyrosyl acetate and 3, 4-dihydroxyphenylglycol on DSS-induced acute colitis in mice. *Journal of Nutritional Biochemistry*. Article. 2015;26(5):513-520.
33 Giner E, Andújar I, Recio MC, Ríos JL, Cerdá-Nicolás JM, Giner RM. oleuropein ameliorates acute colitis in mice. *Journal of Agricultural and Food Chemistry*. Article. 2011;59(24):12882-12892.
34 Sánchez-Fidalgo S, Villegas I, Cárdeno A, et al. Extra-virgin olive oil-enriched diet modulates DSS-colitis-associated colon carcinogenesis in mice. *Clinical Nutrition*. Article. 2010;29(5):663-673.
35 Camuesco D, Gálvez J, Nieto A, et al. Dietary olive oil supplemented with fish oil, rich in EPA and DHA (n-3) polyunsaturated fatty acids, attenuates colonic inflammation in rats with DSS-induced colitis. *Journal of Nutrition*. Article. 2005;135(4):687-694.
36 de Paula do Nascimento R, Lima AV, Oyama LM, et al. Extra virgin olive oil and flaxseed oil have no preventive effects on DSS-induced acute ulcerative colitis. *Nutrition*. 2020;74:110731.
37 Nutrition AIo. Report of the American Institute of Nutrition Ad Hoc Committee on Standards for Nutritional Studies. *The Journal of Nutrition*. 1977;107(7):1340-1348.
38 Bieri JG. Second Report of the ad hoc Committee on Standards for Nutritional Studies. *The Journal of Nutrition*. 1980;110(8):1726-1726.
39 Bigagli E, Toti S, Lodovici M, et al. Dietary Extra-Virgin Olive Oil Polyphenols Do Not Attenuate Colon Inflammation in Transgenic HLAB-27 Rats but Exert Hypocholesterolemic Effects through the Modulation of HMGCR and PPAR-alpha Gene Expression in the Liver. *Lifestyle genomics*. 2019:1-10.
40 Sánchez-Fidalgo S, Sánchez De Ibargüen L, Cárdeno A, Alarcón De La Lastra C. Influence of extra virgin olive oil diet enriched with hydroxytyrosol in a chronic DSS colitis model. *European Journal of Nutrition*. Article. 2012;51(4):497-506.
41 Sánchez-Fidalgo S, Cárdeno A, Sánchez-Hidalgo M, Aparicio-Soto M, De la Lastra CA. Dietary extra virgin olive oil polyphenols supplementation modulates DSS-induced chronic colitis in mice. *Journal of Nutritional Biochemistry*. Article. 2013;24(7):1401-1413.
42 Sánchez-Fidalgo S, Cárdeno A, Sánchez-Hidalgo M, et al. Dietary unsaponifiable fraction from extra virgin olive oil supplementation attenuates acute ulcerative colitis in mice. *European Journal of Pharmaceutical Sciences*. Article. 2013;48(3):572-581.

43 Hamam GG, Raafat MH, Shoukry Y. Possible protective effect of dietary extra-virgin olive oil on experimentally induced acute colitis in adult male albino rats: A histological and immunohistochemical study. *Egyptian Journal of Histology*. Article. 2014;37(2):373-385.

44 Wu C-C, Tung Y-T, Chen S-Y, Lee W-T, Lin H-T, Yen G-C. Anti-Inflammatory, Antioxidant, and Microbiota-Modulating Effects of Camellia Oil from Camellia brevistyla on Acetic Acid-Induced Colitis in Rats. *Antioxidants (Basel)*. 2020;9(1):58.

45 Hegazi RAF, Saad RS, Mady H, Matarese LE, O'Keefe S, Kandil HM. Dietary fatty acids modulate chronic colitis, colitis-associated colon neoplasia and COX-2 expression in IL-10 knockout mice. *Nutrition*. Article. 2006;22(3):275-282.

46 Park JS, Choi J, Hwang SH, et al. Cottonseed Oil Protects Against Intestinal Inflammation in Dextran Sodium Sulfate-Induced Inflammatory Bowel Disease. *J Med Food*. 2019.

47 Huguet-Casquero A, Xu Y, Gainza E, Luis Pedraz J, Beloqui A. Oral delivery of oleuropein-loaded lipid nanocarriers alleviates inflammation and oxidative stress in acute colitis. *International Journal of Pharmaceutics*. 2020:119515.

48 Guvenc M, Cellat M, Ozkan H, et al. Protective Effects of Tyrosol Against DSS-Induced Ulcerative Colitis in Rats. *Inflammation*. 2019.

49 Takashima T, Sakata Y, Iwakiri R, et al. Feeding with olive oil attenuates inflammation in dextran sulfate sodium-induced colitis in rat. *Journal of Nutritional Biochemistry*. Article. 2014;25(2):186-192.

50 Waldner MJ, Neurath MF. Chemically Induced Mouse Models of Colitis. *Current Protocols in Pharmacology*. 2009;46(1):5.55.51-55.55.15.

51 Rosillo MA, Sánchez-Hidalgo M, González-Benjumea A, Fernández-Bolaños JG, Lubberts E, Alarcón-de-la-Lastra C. Preventive effects of dietary hydroxytyrosol acetate, an extra virgin olive oil polyphenol in murine collagen-induced arthritis. *Molecular Nutrition and Food Research*. Article. 2015;59(12):2537-2546.

52 Solomon L, Mansor S, Mallon P, et al. The dextran sulphate sodium (DSS) model of colitis: an overview. *Comparative Clinical Pathology*. journal article. 2010;19(3):235-239.

53 Brenna O, Furnes MW, Drozdov I, et al. Relevance of TNBS-colitis in rats: a methodological study with endoscopic, histologic and Transcriptomic [corrected] characterization and correlation to IBD. *PLoS One*. 2013;8(1):e54543.

54 Kouka P, Tekos F, Papoutsaki Z, et al. Olive oil with high polyphenolic content induces both beneficial and harmful alterations on rat redox status depending on the tissue. *Toxicology Reports*. 2020;7:421-432.

55 Goyal N, Rana A, Ahlawat A, Bijjem KRV, Kumar P. Animal models of inflammatory bowel disease: a review. *Inflammopharmacology*. 2014;22(4):219-233.

56 Antoniou E, Margonis GA, Angelou A, et al. The TNBS-induced colitis animal model: An overview. *Annals of Medicine and Surgery*. 2016;11:9-15.

57 Cabré E, Gassull MA. Nutrition in inflammatory bowel disease: Impact on disease and therapy. *Current Opinion in Gastroenterology*. Review. 2001;17(4):342-349.
58 Scaldaferri F, Pizzoferrato M, Lopetuso LR, et al. Nutrition and IBD: Malnutrition and/or Sarcopenia? A Practical Guide. *Gastroenterology Research and Practice*. 2017;2017:8646495.
59 Mijač DD, Janković GLJ, Jorga J, Krstić MN. Nutritional status in patients with active inflammatory bowel disease: Prevalence of malnutrition and methods for routine nutritional assessment. *European Journal of Internal Medicine*. 2010;21(4):315-319.
60 Tuzun A, Uygun A, Yesiolva Z, et al. Leptin levels in the acute stage of ulcerative colitis. *Journal of Gastroenterology and Hepatology*. 2004;19(4):429-432.
61 Yamauchi C, Fujita S, Obara T, Ueda T. Effects of Room Temperature on Reproduction, Body and Organ Weights, Food and Water Intakes, and Hematology in Mice. *Experimental Animals*. 1983;32(1):1-11.
62 Nicholson A, Malcolm RD, Russ PL, et al. The response of C57BL/6J and BALB/cJ mice to increased housing density. *J Am Assoc Lab Anim Sci*. 2009;48(6):740-753.
63 Fabia R, Ar'Rajab A, Johansson ML, et al. Impairment of bacterial flora in human ulcerative colitis and experimental colitis in the rat. *Digestion*. 1993;54(4):248-255.
64 Patterson E, O' Doherty RM, Murphy EF, et al. Impact of dietary fatty acids on metabolic activity and host intestinal microbiota composition in C57BL/6J mice. *British Journal of Nutrition*. 2014;111(11):1905-1917.
65 Diaz-Granados N, Howe K, Lu J, McKay DM. Dextran Sulfate Sodium-Induced Colonic Histopathology, but not Altered Epithelial Ion Transport, Is Reduced by Inhibition of Phosphodiesterase Activity. *Am J Pathol*. 2000;156(6):2169-2177.
66 Chassaing B, Aitken JD, Malleshappa M, Vijay-Kumar M. Dextran sulfate sodium (DSS)-induced colitis in mice. *Current Protocols in Immunology*. 2014;(SUPPL.104) (no pagination)(15.25).
67 Farràs M, Martinez-Gili L, Portune K, et al. Modulation of the Gut Microbiota by Olive Oil Phenolic Compounds: Implications for Lipid Metabolism, Immune System, and Obesity. *Nutrients*. 2020;12(8):2200.
68 Rodríguez-García C, Sánchez-Quesada C, Algarra I, Gaforio JJ. The High-Fat Diet Based on Extra-Virgin Olive Oil Causes Dysbiosis Linked to Colorectal Cancer Prevention. *Nutrients*. 2020;12(6):1705.
69 Parada Venegas D, De la Fuente MK, Landskron G, et al. Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases. *Frontiers in immunology*. 2019;10:277-277.
70 Rivière A, Selak M, Lantin D, Leroy F, De Vuyst L. Bifidobacteria and Butyrate-Producing Colon Bacteria: Importance and Strategies for Their Stimulation in the Human Gut. *Frontiers in microbiology*. 2016;7:979-979.

71 De Preter V, Arijs I, Windey K, et al. Impaired butyrate oxidation in ulcerative colitis is due to decreased butyrate uptake and a defect in the oxidation pathway. *Inflammatory Bowel Diseases*. Article. 2012;18(6):1127-1136.

72 Gálvez J, Camuesco D, Rodríguez-Cabezas ME, Zarzuelo A. Chapter 113 - Intestinal Anti-inflammatory Activity of Dietary Olive Oil. In: Preedy VR, Watson RR, eds. *Olives and Olive Oil in Health and Disease Prevention*. San Diego: Academic Press; 2010:1049-1055.

73 Hart AR, Luben R, Olsen A, et al. Diet in the aetiology of ulcerative colitis: A European prospective cohort study. *Digestion*. Article. 2008;77(1):57-64.

74 Barnes EL, Nestor M, Onyewadume L, et al. High Dietary Intake of Specific Fatty Acids Increases Risk of Flares in Patients With Ulcerative Colitis in Remission During Treatment With Aminosalicylates. *Clinical Gastroenterology and Hepatology*. Article. 2017;15(9):1390-1396.e1391.

75 Wiese DM, Horst SN, Brown CT, et al. Serum fatty acids are correlated with inflammatory cytokines in ulcerative colitis. *PLoS ONE*. Article. 2016;11(5).

76 Nishida T, Miwa H, Shigematsu A. Increased arachidonic acid composition of phopsholipids in colonic mucosa from patients with active ulcerative colitis. *Gut*. 1987;28(8):1002-1007.

77 Dennis EA, Norris PC. Eicosanoid storm in infection and inflammation. *Nature Rev Immunol*. 2015;15(8):511-523.

78 Bosco N, Brahmbhatt V, Oliveira M, et al. Effects of increase in fish oil intake on intestinal eicosanoids and inflammation in a mouse model of colitis. *Lipids in Health and Disease*. Article. 2013;12(1).

79 Barbalho SM, Goulart RDA, Quesada K, Bechara MD, De Carvalho ADCA. Inflammatory bowel disease: Can omega-3 fatty acids really help? *Annals of Gastroenterology*. Review. 2016;29(1):37-43.

80 Cabré E, Mañosa M, Gassull MA. Omega-3 fatty acids and inflammatory bowel diseases-a systematic review. *British Journal of Nutrition*. Review. 2012;107(SUPPL. 2):S240-S252.

81 Turner D, Shah PS, Steinhart AH, Zlotkin S, Griffiths AM. Maintenance of remission in inflammatory bowel disease using omega-3 fatty acids (fish oil): A systematic review and meta-analyses. *Inflammatory Bowel Diseases*. Article. 2011;17(1):336-345.

82 Corona G, Tzounis X, Assunta DessÌ M, et al. The fate of olive oil polyphenols in the gastrointestinal tract: Implications of gastric and colonic microflora-dependent biotransformation. *Free Radical Research*. 2006;40(6):647-658.

83 Larussa T, Oliverio M, Suraci E, et al. oleuropein decreases interleukin-17 and attenuates inflammatory damage in colonic mucosa from ulcerative colitis patients. *Journal of Crohn's and Colitis*. Conference Abstract. 2017;11 (Supplement 1):S130.

84 Martin-Pelaez S, Castaner O, Sola R, et al. Influence of Phenol-Enriched Olive Oils on Human Intestinal Immune Function. *Nutrients*. 2016;8(4).

85 Papageorgiou N, Tousoulis D, Psaltopoulou T, et al. Divergent anti-inflammatory effects of different oil acute consumption on healthy individuals. *European Journal of Clinical Nutrition*. 2011;65(4):514-519.
86 Cioffi M, Rosa AD, Serao R, Picone I, Vietri MT. Laboratory markers in ulcerative colitis: Current insights and future advances. *World J Gastrointest Pathophysiol*. 2015;6(1):13-22.
87 Pearl DS, Shah K, Whittaker MA, et al. Cytokine mucosal expression in ulcerative colitis, the relationship between cytokine release and disease activity☆, ☆☆. *Journal of Crohn's and Colitis*. 2013;7(6):481-489.
88 Reimund JM, Wittersheim C, Dumont S, et al. Mucosal inflammatory cytokine production by intestinal biopsies in patients with ulcerative colitis and Crohn's disease. *J Clin Immunol*. 1996;16(3):144-150.
89 Moraes L, Magnusson MK, Mavroudis G, et al. Systemic Inflammatory Protein Profiles Distinguish Irritable Bowel Syndrome (IBS) and Ulcerative Colitis, Irrespective of Inflammation or IBS-Like Symptoms. *Inflammatory Bowel Diseases*. 2020;26(6):874-884.
90 Morvaridi M, Jafarirad S, Seyedian SS, Alavinejad P, Cheraghian B. The effects of extra virgin olive oil and canola oil on inflammatory markers and gastrointestinal symptoms in patients with ulcerative colitis. *Eur J Clin Nutr*. 2020.
91 Schwingshackl L, Christoph M, Hoffmann G. Effects of Olive Oil on Markers of Inflammation and Endothelial Function-A Systematic Review and Meta-Analysis. *Nutrients*. 2015;7(9):7651-7675.
92 Mähler M, Bristol IJ, Leiter EH, et al. Differential susceptibility of inbred mouse strains to dextran sulfate sodium-induced colitis. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 1998;274(3):G544-G551.
93 Bramhall M, Flórez-Vargas O, Stevens R, Brass A, Cruickshank S. Quality of methods reporting in animal models of colitis. *Inflammatory bowel diseases*. 2015;21(6):1248-1259.
94 Cooper HS, Murthy SN, Shah RS, Sedergran DJ. Clinicopathologic study of dextran sulfate sodium experimental murine colitis. *Laboratory investigation; a journal of technical methods and pathology*. 1993;69(2):238-249.
95 Gommeaux J, Cano C, Garcia S, et al. Colitis and colitis-associated cancer are exacerbated in mice deficient for tumor protein 53-induced nuclear protein 1. *Molecular and cellular biology*. 2007;27(6):2215-2228.
96 Melgar S, Karlsson L, Rehnstrom E, et al. Validation of murine dextran sulfate sodium-induced colitis using four therapeutic agents for human inflammatory bowel disease. *Int Immunopharmacol*. 2008;8(6):836-844.
97 Melgar S, Karlsson A, Michaëlsson E. Acute colitis induced by dextran sulfate sodium progresses to chronicity in C57BL/6 but not in BALB/c mice: correlation between symptoms and

inflammation. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2005;288(6):G1328-G1338.

98 Stucchi AF, Shofer S, Leeman S, et al. NK-1 antagonist reduces colonic inflammation and oxidative stress in dextran sulfate-induced colitis in rats. *Am J Physiol Gastrointest Liver Physiol*. 2000;279(6):G1298-1306.

99 Berg DJ, Davidson N, Kühn R, et al. Enterocolitis and colon cancer in interleukin-10-deficient mice are associated with aberrant cytokine production and CD4(+) TH1-like responses. *J Clin Invest*. 1996;98(4):1010-1020.

100 Dieleman LA, Palmen MJ, Akol H, et al. Chronic experimental colitis induced by dextran sulphate sodium (DSS) is characterized by Th1 and Th2 cytokines. *Clin Exp Immunol*. 1998;114(3):385-391.

101 Hunter MM, Wang A, Hirota CL, McKay DM. Neutralizing anti-IL-10 antibody blocks the protective effect of tapeworm infection in a murine model of chemically induced colitis. *Journal of immunology (Baltimore, Md : 1950)*. 2005;174(11):7368-7375.

102 Castagnini C, Luceri C, Toti S, et al. Reduction of colonic inflammation in HLA-B27 transgenic rats by feeding Marie Menard apples, rich in polyphenols. *British Journal of Nutrition*. Evaluation Studies
Research Support, Non-U.S. Gov't. 2009;102(11):1620-1628.

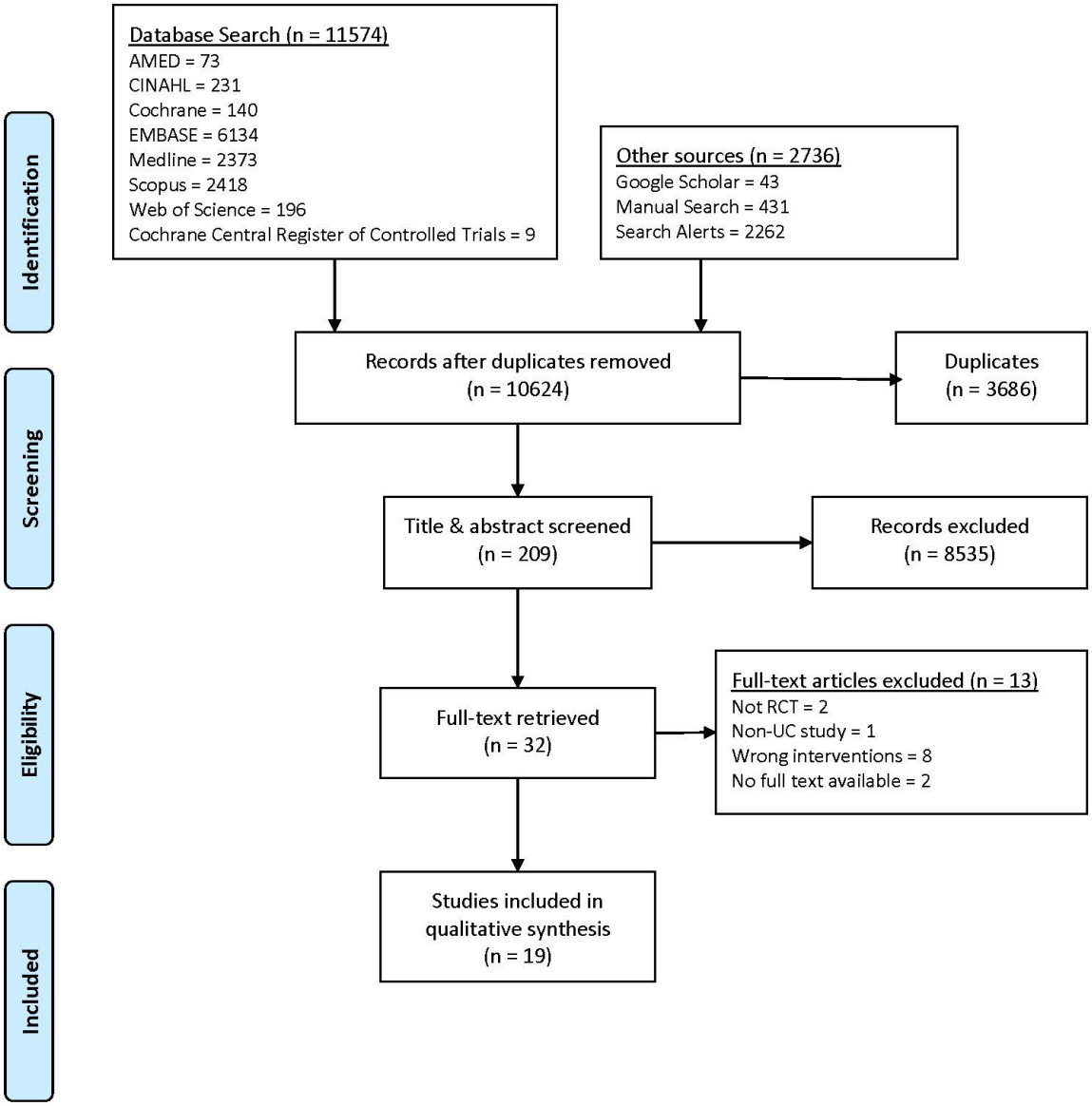
103 Han ES, Oh JY, Park HJ. Cordyceps militaris extract suppresses dextran sodium sulfate-induced acute colitis in mice and production of inflammatory mediators from macrophages and mast cells. *Journal of Ethnopharmacology*. Research Support, Non-U.S. Gov't. 2011;134(3):703-710.

104 Morris GP, Beck PL, Herridge MS, Depew WT, Szewczuk MR, Wallace JL. Hapten-induced model of chronic inflammation and ulceration in the rat colon. *Gastroenterology*. 1989;96(3):795-803.

105 Lee C-P, Shih P-H, Hsu C-L, Yen G-C. Hepatoprotection of tea seed oil (Camellia oleifera Abel.) against CCl4-induced oxidative damage in rats. *Food and Chemical Toxicology*. 2007;45(6):888-895.

106 Riddell RH, Goldman H, Ransohoff DF, et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Pathol*. 1983;14(11):931-968.

Figure 4.1. **PRISMA flow diagram**



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Table 4.1. SYRCLE's risk of bias assessment

Study	Allocation Sequence	Baseline Similarity	Concealed Allocation	Random Housing	Caregiver Blinding	Random Assessment	Blinded Assessment	Incomplete Outcomes Addressed	Reporting Bias Addressed	Other Bias
Camuesco, et al.[35]	NR	✔	✔	NR	✔	NR	✔	✔	✘	✔
Hegazi, et al.[45]	NR	NR	NR	NR	NR	NR	✔	✔	NR	✔
Sánchez-Fidalgo, et al.[34]	NR	✔	NR	NR	NR	NR	NR	✘	NR	✔
Giner, et al.[33]	NR	✔	NR	NR	NR	NR	NR	✘	✔	✔
Sánchez-Fidalgo, et al.[40]	NR	✔	NR	NR	NR	NR	NR	✘	NR	NR
Sánchez-Fidalgo, et al.[41]	NR	✔	✔	NR	✔	NR	✔	✘	✘	✔
Sánchez-Fidalgo, et al.[42]	NR	✔	✔	NR	✔	NR	✔	✘	✘	✔
Giner, et al.[31]	NR	✔	NR	NR	NR	NR	NR	✘	✘	NR
Takashima, et al.[49]	NR	✔	NR	NR	NR	NR	NR	✘	✘	✘
Hamam, et al.[43]	NR	✔	NR	NR	NR	NR	NR	✘	✘	✘

Sánchez-Fidalgo, et al.[32]	NR	✔	✔	NR	✔	NR	✔	✔	✔	✘
Voltes, et al.[28]	NR	✔	NR	NR	NR	NR	✔	✔	✘	✔
Bigagli, et al.[39]	NR	✔	NR	NR	NR	NR	✔	✔	✔	✔
Park, et al.[46]	NR	✔	NR	NR	NR	NR	✔	✔	NR	✔
Güvenç, et al.[48]	NR	NR	NR	NR	NR	NR	NR	✔	NR	✔
Wu, et al.[44]	NR	NR	NR	NR	✘	NR	NR	✔	✔	✔
Cariello, et al.[29]	NR	✔	NR	NR	NR	NR	NR	✔	✔	✔
de Paula do Nascimento, et al.[36]	NR	✔	NR	NR	✔	NR	✔	✘	✘	✔
Huguet-Casquero, et al.[47]	NR	NR	NR	NR	NR	NR	NR	✘	✘	✔

NR, Not Reported in text, variables could not be assessed,

✓*= satisfied.* *X= not satisfied.*

Table 4.2. Design characteristics of eligible animal studies

Study	Location	Animal	Strain	Sex	Age	Baseline Wt (g)	n	Housing	Cages	Temperature (°C)	Humidity (%)	Day/Night cycle	Base Diet	% Fat (by wt)
Camuesco, et al.[35]	Spain	Rats	Wistar	F	NR	180-200	40	Individual	Makrolon® cages	"AC atmosphere"	"AC atmosphere"	12D/12N	Semi-synthetic diet	4%
Hegazi, et al.[45]	USA	Mice	IL-10 knockout	NR	8 week	NR	92	NR	NR	NR	NR	NR	Defatted regular mouse chow (Bio-Serv)	7%
Sánchez-Fidalgo, et al.[34]	Spain	Mice	C57BL/6	F	6 weeks	NR	84	5-6 per cage	NR	24-25	"constant"	12D/12N	Modified AIN-76A Diet	10%
Giner, et al.[33]	Spain	Mice	BALB/c	F	6-8 weeks	18-20	40*	NR	NR	22	60	12D/12N	“Standard Laboratory	NR

													Rodent Diet”	
Sánchez-Fidalgo, et al.[40]	Spain	Mice	C57BL/6	F	6 weeks	NR	75	NR	NR	24-25	70-75	12D/12N	AIN standard reference diet	10%
Sánchez-Fidalgo, et al.[41]	Spain	Mice	C57BL/6	F	6 weeks	NR	80	NR	NR	24-25	70-75	12D/12N	AIN standard reference diet	10%
Sánchez-Fidalgo, et al.[42]	Spain	Mice	C57BL/6	F	6 weeks	NR	60	NR	NR	24-25	70-75	12D/12N	AIN standard reference diet	10%
Giner, et al.[31]	Spain	Mice	C57BL/6	F	6-8 weeks	18-20	40*	NR	NR	22	60	12D/12N	“Standard Laboratory	NR

													Rodent Diet”	
Takashima, et al.[49]	Japan	Rats	Sprague–Dawley	M	6 weeks	NR	41	NR	NR	24-25	"constant"	12D/12N	Modified AIN-76A Diet	5%
Hamam, et al.[43]	Egypt	Rats	Albino	M	3-5 months	200-225	35	NR	"standard cages"	NR	NR	NR	"Standard diet"	NR
Sánchez-Fidalgo, et al.[32]	Spain	Mice	C57BL/6	F	6 weeks	NR	36*	NR	NR	24-25	70-75	12D/12N	"Standard diet"	NR
Voltes, et al.[28]	Spain	Rats	Wistar	F	NR	205-294	40	NR	NR	NR	NR	NR	“Standard laboratory feed”	NR
Bigagli, et al.[39]	Italy	Rats	HLA-B27	M	6-8 weeks	200-230	26	NR	NR	NR	NR	NR	Modified AIN76 diet	10%

Park, et al.[46]	Korea	Mice	C57BL/6	M	8 weeks	22-25	27	NR	NR	21-22	NR	12D/12N	"Standard mouse chow"	NR
Güvenç, et al.[48]	Turkey	Rats	Wistar-Albino	M	NR	180-250	35	NR	NR	20-22	NR	12D/12N	"Standard commercial feed"	NR
Wu, et al.[44]	Taiwan	Rats	Sprague–Dawley	M	6 weeks	NR	36	NR	NR	NR	NR	NR	NR	NR
Cariello, et al.[29]	Italy	Mice	C57BL/6	M	8 weeks	NR	50	NR	NR	23	NR	12D/12N	NR	NR
de Paula do Nascimento, et al.[36]	Brazil	Mice	C57BL/6	F	8-9 weeks	NR	80	2 per cage	NR	23-27	60-70	12D/12N	AIN-93M diet	10%
Huguet-Casquero, et al.[47]	Belgium	Mice	C57BL/6	M	8 weeks	21 - 26	48	NR	NR	NR	NR	NR	"Standard laboratory feed"	NR

F, Female.

NR, Not Reported in text.

12D/12N: 12-hour daylight and 12-hour night cycles.

AIN, American Institute of Nutrition.

M, Male.

***Total number of animals quantified from study results with the assumption of no mortality.*

Table 4.3. Method of inducing colitis

Study	Reagent	Dose (wt/v)	Route	Colitis Model	Duration of Induction
Camuesco, et al.[35]	DSS	5% and 2% cycles	Drinking water	Acute	15 days (5/10 day cycles)
Hegazi, et al.[45]	N/A	N/A	N/A	NR	N/A
Sánchez-Fidalgo, et al.[34]	DSS	0.7%	Drinking water	Chronic	259 days
Giner, et al.[33]	DSS	5%	Drinking water	Acute	7 days
Sánchez-Fidalgo, et al.[40]	DSS	3%	Drinking water	Acute	5 days
Sánchez-Fidalgo, et al.[41]	DSS	3%	Drinking water	Chronic	5 days
Sánchez-Fidalgo, et al.[42]	DSS	3%	Drinking water	Acute	5 days
Giner, et al.[31]	DSS	1% and 2% cycles	Drinking water	Chronic	28 days (14/14 day cycles)
Takashima, et al.[49]	DSS	4%	Drinking water	Chronic	35 days
Hamam, et al.[43]	Acetic acid	2%	Intra-rectal	Acute	3 days
Sánchez-Fidalgo, et al.[32]	DSS	3%	Drinking water	Acute	5 days
Voltes, et al.[28]	TNBS	0.5 mL	Intra-rectal	Acute	3 days
Bigagli, et al.[39]	N/A	N/A	N/A	Chronic	N/A
Park, et al.[46]	DSS	3%	Drinking water	Acute	4 days

Güvenç, et al.[48]	DSS	4%	Drinking water	Acute	7 days
Wu, et al.[44]	Acetic acid	4%	Intra-rectal	Acute	21 days
Cariello, et al.[29]	DSS	5%	Drinking water	NR	10 days
de Paula do Nascimento, et al.[36]	DSS	3%	Drinking water	Acute	5 days
Huguet-Casquero, et al.[47]	DSS	3%	Drinking water	Acute	5 days

wt/v, Weight / Volume.

DSS, Dextran sulfate sodium.

N/A, Not Applicable.

NR: Not Reported in text.

TNBS, 2,4,6-trinitrobenzene sulfonic acid.

Table 4.4. Characteristics of the intervention and comparator study arms

Study	Control	n	Intervention	n	Time Point Intervention	Route	Consumption	Estimated Dose	Treatment Duration
Camuesco, et al.[35]	SD + SBO	10	SD + EVOO (4%)	10	Pre UC & Concurrent	Diet	NR	Unable to calculate	29 days
Hegazi, et al.[45]	SD + CO	28	SD + OO (7%)	29	Concurrent	Diet	NR	Unable to calculate	84 days
Sánchez-Fidalgo, et al.[34]	SD + SFO	20	SD + EVOO (10%)	20	Pre UC & Concurrent	Diet	NR	Unable to calculate	273 days
Giner, et al.[33]	SD	NR	SD + oleuropein (1%)	NR	Concurrent	Diet	4 g food / day	40 mg oleuropein/ day	7 days
Sánchez-Fidalgo, et al.[40]	SD + SFO	17	SD + EVOO (0.04% Hty-Ac)	17	Pre UC & Concurrent	Diet	3 g food / day	1.2 mg Hty-Ac / day	51 days
Sánchez-Fidalgo, et al.[41]	SD + SFO	12	SD + EVOO (10%)	12	Pre UC & Concurrent	Diet	NR	Unable to calculate	30 days

Sánchez-Fidalgo, et al.[42]	SD + SFO	12	SD + EVOO (10%)	12	Pre UC & Concurrent	Diet	NR	Unable to calculate	39 days
Giner, et al.[31]	SD	Between 7-10	SD + oleuropein (0.25%)	Between 7-10	Concurrent	Diet	4 g food / day	10 mg oleuropein/ day	56 days
Takashima, et al.[49]	SD	17	SD + EVOO (5%)	12	Pre UC & Concurrent	Diet	NR	Unable to calculate	35 days
Hamam, et al.[43]	None	10	EVOO	10	Pre UC & Concurrent	Oral Gavage	1 mL / 100 g body weight	2.00-2.25 mL EVOO / day	10 days
Sánchez-Fidalgo, et al.[32]	SD	NR	SD + Hty-Ac (0.10%)	12	Pre UC & Concurrent	Diet	4 g food / day	4 mg Hty-Ac / day	28 days + 10 days*
Voltes, et al.[28]	Pectin/ alginate	10	Pectin/alginate + EVOO	10	Post UC	Rectal	2 mL solution / day	Unable to calculate	5 days
Bigagli, et al.[39]	SD + CO	6	SD + EVOO (10%)	7	Concurrent	Diet	15 g food / day	1.5 g EVOO / day (4.3 mg/kg polyphenols/day)	84 days

Park, et al.[46]	None	5	OO	5	Concurrent	Oral gavage	0.2 mL / day	0.2 mL / day	10 days
Güvenç, et al.[48]	None	7	Saline solution + Tyrosol	7	Pre UC & Concurrent	Oral gavage	20 mg / kg body weight	3.6 -5.0 mg /day	21 days
Wu, et al.[44]	SBO	6	OO	6	Pre UC	Oral gavage	2 mL/kg body weight	Unable to calculate	21 days
Cariello, et al.[29]	0.9% NaCl solution	10	OO (Monocultivar Coratina)	10	Pre UC & Concurrent	Oral gavage	NR	Unable to calculate	11 days
de Paula do Nascimento, et al.[36]	SD + SFO	Between 10-12	SD + EVOO	Between 10-12	Pre UC	Diet	NR	Unable to calculate	30 days
Huguet-Casquero, et al.[47]	Deionized water	8	oleuropein + deionized water	8	Concurrent	Oral gavage	0.5 g/kg body weight	10.5 - 13 mg/day	5 days

SD, Standard Diet.

SBO, Soy Bean Oil.

EVOO, Extra Virgin Olive Oil.

Pre UC, prior to induction of experimental colitis.

Concurrent, intervention and induction of colitis occurring at the same timepoints

NR, Not Reported in text.

CO, Corn Oil.

OO, Olive Oil.

SFO, Sunflower Oil.

Hty-Ac, Hydroxytyrosol Acetate.

NaCl, Sodium chloride.

Table 4.5. Animal mortality at study completion

Study	Control Colitis	Intervention Colitis
Camuesco, et al.[35]	NR	NR
Hegazi, et al.[45]	1/27 (4%)	1/29 (3%)
Sánchez-Fidalgo, et al.[34]	NR	NR
Giner, et al.[33]	0/10 (0%)	0/10 (0%)
Sánchez-Fidalgo, et al.[40]	7/17 (40%)	3/17 (17.6%)
Sánchez-Fidalgo, et al.[41]	NR	NR
Sánchez-Fidalgo, et al.[42]	NR	NR
Giner, et al.[31]	0/10 (0%)	0/10 (0%)
Takashima, et al.[49]	4/17 (23.5%)	0/12 (0%)
Hamam, et al.[43]	3/10 (30%)	0/10 (0%)
Sánchez-Fidalgo, et al.[32]	NR	NR
Voltes, et al.[28]	NR	NR
Bigagli, et al.[39]	0/6 (0%)	0/7 (0%)
Park, et al.[46]	NR	NR
Güvenç, et al.[48]	NR	NR
Wu, et al.[44]	NR	NR
Cariello, et al.[29]	NR	NR
de Paula do Nascimento, et al.[36]	NR	NR
Huguet-Casquero, et al.[47]	NR	NR

NR, Not reported in text.

Table 4.6. Post-study Disease Activity Index (DAI) score

Study	Scoring Method	Max Score	Control			Intervention			Mean Difference	Effect Size (95% CI)	Reported p-value
			Mean	SD	n	Mean	SD	n			
Camuesco, et al.[35]	Cooper, et al.[94]	4	3.1	1.58	10	1.9	1.9	10	-1.2	-0.66 (-1.56, -0.24)	P < 0.05
Sánchez-Fidalgo, et al.[34]	Gommeaux, et al.[95]	3	0.29	0.13	20	0.22	0.18	20	-0.07	-0.43 (-1.06, 0.19)	p < 0.05
Giner, et al.[33]	Unknown	4	2.6	0.32	10	1.5	0.63	10	-1.1	-2.11 (-3.20, -1.02)	p < 0.01
Sánchez-Fidalgo, et al.[40]	Melgar, et al.[96]	3	0.53	1.07	17	0.63	0.7	25	0.1	0.18 (-0.44, 0.79)	NS
Sánchez-Fidalgo, et al.[41]	Melgar, et al.[97], modified	3	0.77	0.35	12	0	0.35*	12	-0.77	-2.12 (-3.12, -1.12)	p < 0.001
Sánchez-Fidalgo, et al.[42]	Melgar, et al.[97], modified	3	1.8	0.69	12	1.1	0.69	12	-0.7	-0.98 (-1.83, 0.13)	p < 0.001
Giner, et al.[31]	Unknown	4	1	0.41	10	0.47	0.25	10	-0.53	-1.49	p < 0.01

										(-2.49, -0.50)	
Takashima, et al.[49]	Gommeaux, et al.[95]	3	1.8	0.36	13	0.8	0.69	12	-1	-1.78 (-2.71, -0.85)	$p < 0.01$
Sánchez-Fidalgo, et al.[32]	Melgar, et al.[97], modified	3	2	0.69	12	0.9	0.35	12	-1.1	-5.30 (-6.99, -3.60)	$p < 0.001$
Cariello, et al.[29]	Unknown	4	3.8	0.1	10	1.7	0.2	10	-2.1	-12.7 (-16.8, -8.7)	$p < 0.05$
de Paula do Nascimento, et al.[36]	Gommeaux, et al.[95]	3	1.16	0.33	11	1.38	0.46	11	0.22	0.49 (-0.36, 1.34)	NS
Huguet-Casquero, et al.[47]	Melgar, et al.[97]	3	1.46	0.62	8	1.36	0.76	8	-0.1	0.14 (-1.12, 0.85)	NS

SD, Standard Deviation.

NS, Not Significant as reported by the authors.

**SD values unavailable in the intervention group, assumed to be same with controls.*

Negative effect size indicates lower disease activity scores and reduced severity.

Mean difference, Hedges' g Effect Size, and Confidence Intervals for Effect Sizes are all post-study outcomes comparing colitis animals between study arms.

Effect Sizes calculated using post-test measures at sacrifice divided by pooled Standard Deviation

Table 4.7. Post-study weight changes

Author	Measure	Control Colitis			Intervention Colitis			Mean difference		Effect Size (95% CI)	Reported p-value
		Mean	SD	n	Mean	SD	n	Raw Weight (g)	Weight change (%)		
Hegazi, et al.[45]	Weight loss (g)	-0.46	0.36	26	0	0.16	27	0.46	Unable to calculate	1.76 (1.13, 2.40)	NS
Sánchez-Fidalgo, et al.[41]	% Weight Change	-7.6	2.1	12	11.2	2.1	12	Unable to calculate	18.8	8.73 (6.14, 11.33)	$p < 0.001$
Sánchez-Fidalgo, et al.[42]	% Weight Change	-23.7	NR	12	-17.6	NR	12	Unable to calculate	6.1	Unable to calculate	$p < 0.001$
Takashima, et al.[49]	Post Weight (g)	329	39	17	376	25	12	47	62	3.28 (2.16, 4.40)	NS
Sánchez-Fidalgo, et al.[32]	% Weight Change	-26	11.4	12	-18	8.7	12	Unable to calculate	8	0.97 (0.12, 1.82)	$p < 0.001$
Voltes, et al.[28]	Weight loss (g)	NR	NR	NR	NR	NR	NR	Unable to calculate	Unable to calculate	Unable to calculate	0.91
Bigagli, et al.[39]	Post Weight (g)	319	NR	6	306	NR	7	-13	Unable to calculate	NR	NS

	Net Weight Gain (g)	99	93	6	95	116	7	-4	Unable to calculate	-0.03 (-1.13, 1.06)	NS
Park, et al.[46]	Post Weight (g)	17.0	0.6	5	17.9	1.4	5	0.9	Unable to calculate	1.79 (0.32, 3.25)	NS
	% From Baseline Weight	74	1.5	5	80	4.0	5	Unable to calculate	6	5.42 (2.74, 8.09)	NS
Cariello, et al.[29]	% From Baseline Weight	18.9	6.6	10	40	6.9	10	Unable to calculate	20.7	2.94 (1.67, 4.20)	$p < 0.05$
de Paula do Nascimento, et al.[36]	Post Weight (g)	20.3	1.3	11	19.5	2.3	11	-0.8	Unable to calculate	-0.79 (-1.66, 0.07)	NS

SD, Standard Deviation.

NS, Not Significant as reported by the authors.

NR, Not Reported in text.

Positive effect sizes indicate higher weights in the study intervention.

Studies reporting "% From Baseline Weight" and "% Weight Change" assumes animals are 100% at baseline.

Mean difference, Hedges' g Effect Size, and Confidence Intervals for Effect Sizes are all post-study outcomes comparing colitis animals between study arms.

Effect Sizes calculated using post-test measures at sacrifice divided by pooled Standard Deviation

Table 4.8. Histology score from colon samples

Study	Colon Site	Score Method	Max Score	Control			Intervention			Mean Difference	Effect Size (95% CI)	Reported p-value
				Mean	SD	n	Mean	SD	n			
Camuesco, et al.[35]	Full Length	Modified Histology Score[98]	27	15.1	3.5	10	10.3	24	10	-4.8	-0.27 (-1.15, 0.61)	NS
Hegazi, et al.[45]	Full Length	Colitis Score[99]	4	2.0	1.0	26	2.3	1.6	27	0.3	0.22 (-0.32, 0.76)	NS
		% Animals with dysplasia	100	15	NR	26	4	NR	27	-11	Unable to calculate	$p < 0.05$
		ACF	4	1.4	1.0	26	1.3	1.0	27	-0.1	-0.10 (-0.63, 0.44)	NS
		Crypt Index	Unknown	127.7	76.5	26	121.6	50.4	27	-6.1	-0.09 (-0.63, 0.45)	NS
Giner, et al.[33]	Full Length	Histology Score	10	8.5	4.7	10	2.5	4.7	10	-6	-1.21 (-2.16, -0.26)	$p < 0.01$

Sánchez-Fidalgo, et al.[40]	Proximal	Modified Histology Score[96]	4	1	1.73	3	0.33	0.57	3	-0.7	-0.41 (-2.03, 1.20)	NS
	Distal		4	1.67	1.16	3	0.67	0.57	3	-1	-0.87 (-2.55, 0.80)	NS
	Rectum		4	3.67	0.57	3	1.33	0.57	3	-2.3	-3.27 (-5.71, -0.82)	NS
Sánchez-Fidalgo, et al.[41]	Proximal	Colitis Score[100]	40	9.5	12.5	12	2.1	0.07	12	-7.4	-0.81 (-1.64, 0.02)	$p < 0.001$
	Distal		40	36.5	2.08	12	18.4	23.6	12	-18.1	-1.05 (-1.90, -0.19)	$p < 0.001$
	Rectum		40	16	6.24	12	15.5	17.7	12	-0.5	-0.04 (-0.84, 0.76)	NS
Sánchez-Fidalgo, et al.[42]	Proximal	Histology Score[100]	40	2.6	0.69	12	1.9	2.08	12	-0.7	-0.44 (-1.25, 0.37)	NS
	Distal		40	35.7	1.73	12	23.6	26.7	12	-12.1	-0.62 (-1.44, 0.20)	$p < 0.05$

	Rectum		40	34.2	6.24	12	20.1	35.3	12	-14.1	-0.54 (-1.35, 0.28)	$p < 0.001$
Takashima, et al.[49]	Proximal	Histology Score[96]	6	3.2	0.45	5	3	0.11	5	-0.2	-0.55 (-1.82, 0.71)	$p < 0.05$
	Distal		6	3.3	0.45	5	3	0.11	5	-0.3	-0.83 (-2.12, 0,46)	NS
	Rectum		6	5.3	0.67	5	3.9	0.67	5	-1.4	-1.88 (-3.37, -0.39)	$p < 0.05$
Sánchez-Fidalgo, et al.[32]	Distal colon	Histology Score[100]	40	27.5	19.9	12	8.6	5.2	12	-18.9	-1.25 (-2.13, -0.38)	$p < 0.01$
Voltes, et al.[28]	Full Length	Modified Hunter Score[101]	8	3.4	2.63	10	2.6	1.36	10	-0.8	-0.37 (-1.25, 0.52)	NS
Bigagli, et al.[39]	Full Length	Colitis Score[102]	7	1.83	0.91	6	2	0.9	7	0.2	0.18 (-0.92, 1.27)	NS

Park, et al.[46]	Full Length	Modified Histology Score[103]	12	11.7	0.3	5	11	1	5	-0.7	-0.86 (-2.15, 0.44)	NS
Güvenç, et al.[48]	Full Length	Macroscopic damage[104]	5	4.26	0.85	7	1.97	1.22	7	-2.29	-2.03 (-3.32, -0.74)	$p < 0.001$
Wu, et al.[44]	NR	Focal Hemorrhage	Unknown	3.67	1.37	6	2.17	1.18	6	-1.5	-1.08 (-2.30, 0.13)	$p < 0.05$
	NR	Injury Score[105]	Unknown	25	5.44	6	20.17	6.25	6	-4.83	-0.76 (-1.93, 0.41)	NS
Cariello, et al.[29]	Distal colon	Histology Score[96]	6	4.6	0.3	10	3.4	0.2	10	-1.2	-4.51 (-6.16, -2.86)	$p < 0.05$
de Paula do Nascimento, et al.[36]	Distal colon	Histology Score[100]	Unknown	1.01	0.79	10	1.94	0.85	10	0.93	1.08 (0.14, 2.02)	NS
	Distal colon	Histology Score[98]	Unknown	10.7	6.83	10	16.55	7.65	10	5.85	0.77 (-0.14, 1.68)	NS

Sánchez-Fidalgo, et al.[34]	Low Grade Dysplasia	Dysplasia[106]	100	100	NR	20	100	NR	20	0	Unable to calculate	NS
	High Grade Dysplasia		100	85	NR	20	55.55	NR	20	-29	Unable to calculate	NS
	Adeno-carcinoma		100	55	NR	20	22.2	NR	20	-33	Unable to calculate	NS
	Tumour		100	30	NR	20	0	NR	20	-30	Unable to calculate	NS

SD, Standard Deviation.

NS, Not Significant as reported by the authors.

ACF, Aberrant Crypt Foci.

For all scoring methods, lower scores indicate less damage on the colon samples.

Negative effect size indicates lower histology scores and less tissue damage

Mean difference, Hedges' g Effect Size, and Confidence Intervals for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at sacrifice divided by pooled Standard Deviation.

Table 4.9. Colon Weight/Length ratio

Study	Unit	Control Colitis			Intervention Colitis			Mean Difference	Effect Size (95% CI)	Reported p-value
		Mean	SD	n	Mean	SD	n			
Camuesco, et al.[35]	mg/cm	100.6	19	10	84.2	18	10	-16.4	-0.85 (-1.76, 0.07)	$p < 0.05$
Hegazi, et al.[45]	NR	NR	NR	26	NR	NR	27	Unable to calculate	Unable to calculate	NS
Sánchez-Fidalgo, et al.[34]	g/cm	105.9	37.1	20	107.1	18.3	20	1.2	0.04 (-0.72, 0.80)	NS
Giner, et al.[33]	mg/cm	40.5	6.01	10	29.1	2.21	10	-11.4	-2.41 (-3.56, -1.26)	NS
Sánchez-Fidalgo, et al.[40]	mg/cm	118.3	47.4	10	108	33.7	14	-10.32	-0.25 (-1.06, 0.56)	NS
Sánchez-Fidalgo, et al.[41]	% *	215	52	12	140	34.6	12	-75	-1.64 (-2.56, -0.71)	$p < 0.001$
Sánchez-Fidalgo, et al.[42]	% *	147	52	12	87	24.3	12	-60	-1.43	$p < 0.001$

									(-2.33, -0.53)	
Giner, et al.[31]	mg/cm	53.7	0.95	10	44.2	9.8	10	-9.5	-1.31 (-2.27, -0.34)	$p < 0.05$
de Paula do Nascimento, et al.[36]	mg/cm	26.1	4.3	11	26.8	4	11	0.7	0.16 (-0.67, 1.00)	NS

SD, Standard Deviation.

NR, Not Reported in text.

NS, Not Significant as reported by the authors.

**Percentage of colon weight/length ratios compared to non-colitis control animals at sacrifice; control animals were assumed to be 100%.*

Negative effect size indicates lower weight/length ratio in the intervention

Mean difference, Hedges' g Effect Size, and Confidence Intervals for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at sacrifice divided by pooled Standard Deviation

Table 4.10. Colon length between study arms

Author	Animal	Group	Control			Intervention			Mean difference	Effect Size (95% CI)	Reported p-value
			Mean (cm)	SD	n	Mean (cm)	SD	n			
Giner, et al. [33]	Mice	non-colitis	8.86	0.95	10	NR	NR	NR	Unable to calculate	2.36 (1.22, 3.50)	NS
		colitis	5.35	0.16	10	6.65	0.73	10	1.3		
Takashima, et al. [49]	Rat	non-colitis	18.0	3.12	12	NR	NR	NR	Unable to calculate	1.28 (0.41, 2.14)	NS
		colitis	11.2	0.61	13	12.65	1.46	12	1.45		
Sánchez-Fidalgo, et al. [32]	Mice	non-colitis	7.5	0.7	12	7.3	0.7	12	-0.2	0.88 (0.04, 1.72)	NS
		colitis	6.5	0.7	12	7	0.4	12	0.5		
Park, et al [46]	Mice	non-colitis	6.20	0.10	2	NR	NR	NR	Unable to calculate	-0.55 (-1.81, 0.72)	NS
		colitis	4.24	0.38	5	4.01	0.38	5	-0.23		
Wu, et al. [44]	Rats	non-colitis	159.1	22.1	6	NR	NR	NR	Unable to calculate	1.20 (-0.03, 2.42)	$p < 0.05$

		colitis	112.1	22.5	6	141.3	11.8	6	29.2		
de Paula do Nascimento, et al. [36]	Mice	non-colitis	7.6	0.3	10	NR	NR	NR	Unable to calculate	-0.29 (-1.13, 0.55)	NS
		colitis	6.5	0.7	10-12	6.3	0.7	10 -12	-0.2		

SD, Standard Deviation.

NR, Not Reported in text.

NS, Not Significant as reported by the authors.

Positive effect sizes indicate greater colon lengths favouring the intervention arm.

Mean difference, Hedges' g Effect Size, and Confidence Intervals for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at sacrifice divided by pooled Standard Deviation.

In studies not reporting colon lengths of non-colitis intervention animals (NR), Mean ± Standard Deviation values assumed to be the same as non-colitis controls.

Table 4.11. TNF-α in colon tissue post sacrifice

Author	Units of measurement	Control Colitis			Intervention Colitis			Mean difference	Effect Size (95% CI)	Reported p-value
		Mean	SD	n	Mean	SD	n			
Camuesco, et al. [35]	pmol/g tissue	846.1	295.7	10	596.9	235.0	10	-249.2	-0.89 (-1.81, 0.03)	NS
Sánchez-Fidalgo, et al. [34]	pg/mg tissue	4	2.2	20	3.2	1.8	20	-0.8	-0.39 (-1.02, 0.23)	NS
Giner, et al. [33]	pg/mL	37.1	4.8	7	22	9.5	7	-15.1	-1.86 (-3.12, -0.61)	$p < 0.01$
Sánchez-Fidalgo, et al.[40]	% compared to non-UC controls	170.4	34.5	10	149.6	71.8	14	-20.8	-0.34 (-1.15, 0.48)	$p < 0.05$
Sánchez-Fidalgo, et al. [41]	NR	8.1	5.0	4	6.3	3.4	4	-1.8	-0.37 (-1.76, 1.03)	NS
Sánchez-Fidalgo, et al. [42]	NR	13.95	9.84	4	4.78	0.74	4	-9.17	-1.14 (-2.64, 0.35)	$p < 0.001$

Takashima, et al. [49]	NR	NR	NR	NR	NR	NR	NR	Unable to calculate	Unable to calculate	NS
Hamam, et al. [43]	% area expressing TNF-α	31.45	6.18	10	7.65	3.22	10	-23.8	-4.63 (-6.31, -2.95)	$p < 0.05$
Bigagli, et al. [39]	NR	1.33	0.15	6	1.19	0.08	7	-0.14	-1.11 (-2.28, 0.06)	$p < 0.05$
Park, et al. [46]	n cells	227.71	28.29	5	139.16	65.99	5	-88.55	-1.57 (-2.99, -0.16)	$p < 0.05$
Güvenç, et al. [48]	pg/mL	2.77	0.95	7	1.32	0.053	7	-1.446	-1.99 (-3.28, -0.71)	$p < 0.05$
Wu, et al. [44]	pg/mg tissue	55.1	35.5	6	11.2	8.1	6	-43.9	-1.57 (-2.87, -0.28)	$p < 0.05$
de Paula do Nascimento, et al. [36]	pg/mg tissue	0.5	0.3	7 - 12	1.1	0.7	7 - 12	0.57	0.95 (0.00, 1.89)	NS
Huguet-Casquero, et al. [47]	pg/g protein	2650	876	7 - 8	1340	356	7 - 8	-1310	-1.84 (-3.05, -0.63)	$p < 0.05$

SD, Standard Deviation.

NS, Not Significant as reported by the authors.

NR, Not Reported in text.

Negative effect size indicates lower colon TNF-α expression in the intervention group.

Mean difference, Hedges' g Effect Size, and Confidence Intervals for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at sacrifice divided by pooled Standard Deviation

Table 4.12. Interleukin-1β in colon tissue post sacrifice

Author	Units of measurement	Control Colitis			Intervention Colitis			Mean difference	Effect Size (95% CI)	Reported p-value
		Mean	SD	n	Mean	SD	n			
Giner, et al. [33]	pg/mL	175.1	15.9	7	133.9	23.6	7	-41.2	-1.91 (-3.17, -0.64)	$p < 0.05$
Sánchez-Fidalgo, et al. [40]	% *	162.4	35.1	10	180.8	55.0	14	18.90	0.37 (-0.45, 1.19)	NS
Giner, et al. [31]	pg/mL	34.5	27.5	7	23.1	2.4	7	-13.70	-0.54 (-1.61, 0.52)	NS
Takashima, et al.[49]	NR	NR	NR	NR	NR	NR	NR	Unable to calculate	Unable to calculate	NS
Bigagli, et al. [39]	NR	3.53	0.3	6	2.95	0.5	7	-0.58	-1.34 (-2.54, -0.13)	NS
Park, et al. [46]	n cells	125	6.7	5	94.4	17.9	5	-30.5	-2.06 (-3.59, -0.52)	NS
Wu, et al. [44]	pg/mg tissue	175.9	24.5	6	60	34.5	6	-115.9	-3.57 (-5.40, -1.75)	$p < 0.05$
Cariello, et al. [29]	Relative gene expression	1.62	1.96	10	0.31	0.51	10	-1.31	-0.88 (-1.79, 0.04)	$p < 0.05$
de Paula do Nascimento, et al. [36]	pg/mg tissue	12.7	11.4	7-12	37	35.1	7-12	24.3	0.89 (-0.05, 1.83)	NS

SD, Standard Deviation.

NS, Not Significant as reported by the authors.

NR, Not Reported in text.

** Expressions in % refer to proportions compared to non-colitis control animals at time of sacrifice.*

Negative effect size indicates lower expression of Interleukin-1β in the intervention group.

Mean difference, Hedges' g Effect Size, and Confidence Intervals for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at sacrifice divided by pooled Standard Deviation

Table 4.13. Interleukin-6 post sacrifice

Author	Units of measurement	Control Colitis			Intervention Colitis			Mean difference	Effect Size (95% CI)	Reported p-value
		Mean	SD	n	Mean	SD	n			
Sánchez-Fidalgo, et al.[34]	pg/mg tissue	2.2	2.24	20	2 (1.79)	1.79	20	-0.20	-0.10 (-0.72, 0.52)	NS
Giner, et al. [33]	pg/mL	101.0	16.67	7	57.4	17.46	7	-43.60	-2.38 (-3.74, -1.01)	$p < 0.01$
Giner, et al. [31]	pg/mL	121.4	30.43	7	76.5	16.40	7	-44.90	-1.71 (-2.93, -0.48)	$p < 0.05$
Takashima, et al. [49]	NR	NR	NR	NR	NR	NR	NR	Unable to calculate	Unable to calculate	NS
Park, et al. [46]	n cells	51.04	4.63	5	33.13	9.85	5	-17.91	-2.10 (-3.64, -0.56)	NS
Güvenç, et al. [48]	pg/mL	1.841	0.317	7	1.142	0.079	7	-0.70	-2.81 (-4.29, -1.33)	$p < 0.001$
Wu, et al. [44]	pg/mg tissue	69.7	37.2	6	37.1	20.8	6	-32.60	-1.00 (-2.20, 0.20)	$p < 0.05$
Cariello, et al. [29]	gene expression	1.65	2.53	10	0.07	0.22	10	-1.58	-0.84 (-1.76, 0.07)	$p < 0.05$

de Paula do Nascimento, et al. [36]	pg/mg tissue	34.8	31.1	7 - 12	23.9	24.7	7 - 12	-10.90	-0.37 (-1.28, 0.54)	NS
Huguet-Casquero, et al. [47]	pg/g protein	1840	301	7 - 8	920	411	7 - 8	-920	-2.41 (-3.74, -1.08)	$p < 0.01$

SD, Standard Deviation.

NS, Not Significant as reported by the authors.

NR, Not Reported in text.

Negative effect size indicates lower expression of Interleukin-6 in the intervention group.

Mean difference, Hedges' g Effect Size, and Confidence Intervals for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at sacrifice divided by pooled Standard Deviation

CHAPTER 5: EXTRA VIRGIN OLIVE OIL CONSUMPTION AND HEALTH OUTCOMES IN ULCERATIVE COLITIS: A PILOT STUDY OF A RANDOMISED TRIAL

Authors: Kenneth Daniel [1], Luis Vitetta, M.D., PhD [2], Helen O'Connor, PhD[1] [a], Maria A. Fiatarone Singh, M.D. [1,2,3]

[1]Sydney School of Health Sciences, Faculty of Medicine and Health, The University of Sydney,

NSW 2050, Australia

[2]Sydney Medical School, Faculty of Medicine and Health, The University of Sydney, NSW 2050, Australia

[3]The Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts, USA

[a] Deceased 13 January 2020

5.1. Abstract

Background: Emerging studies have explored the impact of extra virgin olive oil (EVOO) both as a standalone intervention and as part of a diet intervention in inflammatory bowel disease (IBD), however evidence is predominantly composed of pre-clinical animal studies with limited human studies.

Methods: This pilot randomised controlled trial aimed to address this research gap by investigating the effects of substituting usual cooking fats and oils with EVOO in ulcerative colitis (UC) and in generally healthy populations. We hypothesised improvements in disease severity scores, symptoms, and therefore quality of life measures following inclusion of EVOO in the usual diet based on evidence from pre-clinical studies. We also hypothesise that these changes would diminish towards the end of the wash-out period. Participants randomised to the intervention group will substitute all forms of fats added in meal preparation with EVOO provided by the study over a 4-week period, followed by 4 weeks of usual care (wash-out). Participants in the control group will maintain usual care over 8 weeks.

Results: Three eligible participants in the UC group were identified, two completed the study, one in each study arm. No eligible participants were identified for the generally healthy controls for this study. Descriptive statistics were used to report study findings due to paucity of participants. No adverse effects were reported and both participants completing the study were compliant. Increase in total energy, total fat, and fibre during the intervention was observed while no changes were observed in the control participants. Clinically meaningful improvements to Partial Mayo Score were observed in the intervention and sustained following the wash-out period at 8 weeks. Improvements to health-related quality of life scores were observed in all participants, however greater changes were observed in the intervention group.

Improvements in the Inflammatory Bowel Disease Questionnaire (IBDQ-32), the 36-Item Short Form (SF-36®) Health Survey, Food Related Quality of Life (FR-QoL-29), Patient Health Questionnaire 9 (PHQ-9), Hospital Anxiety and Depression Index (HADS), and Inflammatory Bowel Disease Fatigue (IBD-F) Self-assessment Scale were observed in all participants at 4 weeks with greater changes observed in the two Intervention participants. These changes were sustained at 8 weeks following cessation of the intervention. For the Control participant receiving usual care, clinically meaningful improvements to the Mental Component Summary (MCS) Score of the SF-36® and anxiety sub score of the HADS were observed at 4 weeks, which returned to baseline at 8 weeks.

Conclusions: Although preliminary evidence of benefit in subjective symptoms related to UC was observed with EVOO as the source of dietary fat, due to small participant numbers, and the fact that the Control participant also improved slightly, these findings cannot be generalised to other individuals living with IBD. Larger, carefully controlled trials are warranted.

5.2. Introduction

Ulcerative Colitis (UC) is a complex, chronic gastrointestinal condition characterised by inflammation and ulceration of the colonic mucosa, which extends proximally from the rectum and may involve the whole colon (pancolitis). The condition falls under the broader category of Inflammatory Bowel Disease (IBD), which manifests in both gastrointestinal and extraintestinal symptoms in an intermittent fashion. The aetiology of UC remains inconclusive; however a combination of genetic host factors, host immune function, environmental triggers, and gut microbiome have been proposed. [1]

Due to increasing global prevalence of IBD, UC is emerging as a public health challenge. Preliminary reports suggest Australia has among the highest incidence and prevalence of the disease globally. [2, 3] Hospital costs attributable to IBD are estimated at $100 million AUD annually, while yearly productivity losses are estimated to be greater than $361 million AUD according to a 2012 Crohn's & Colitis Australia report, [4] and likely much greater at the time of writing. Likewise, the condition poses significant physical and psychological burden to the individual, with only 30% of Australian respondents living with UC describing their health as being either "good" or "excellent" in a 2017-8 survey. [5] Such findings are often mirrored in health-related quality of life surveys indicating reduced quality of life across physical, emotional, and psychosocial domains, particularly during active disease. [6, 7] Concerningly, past studies suggest a tendency for patients to normalise higher burden of disease, regardless of disease severity or symptoms. [5, 8, 9]

Variable access to IBD services, referral pathways to specialist care, and funding across the Australian public health system present a challenge for participants seeking medical care, adjustments to their existing plan, or advice pertaining to their self-management. [4] Whilst

pharmacological therapy is broadly effective and well accepted by individuals living with UC, complicated dosing regimens, cost, frequency of treatment, number of medications, [10] medication side effects, [11, 12], long-term risks of immunosuppressive agents [12, 13] and differing expectations between care providers and patients [11, 14] are known barriers for individuals seeking effective treatment. This is further complicated by the variability of disease presentation and changes in therapeutic response when opting for appropriate interventions, with up to 30% of patients failing advanced therapy and thus requiring surgery. [15-19]

Given these barriers, it is unsurprising that nonadherence to therapy has been commonly reported in UC, resulting in worsening disease and increased symptoms. [10, 20, 21] Likewise, there is interest in non-invasive and preventative approaches to the management of active disease. Nutritional interventions are one popular approach, and remain among the top 10 research priorities in IBD for both patients and clinicians. [22] Patient surveys in individuals with inactive UC indicate 31% believe diet contributed to the development of their condition, while 37% believe diet could trigger disease relapse. [23] Personal experience tends to shape dietary beliefs, with avoidance of trigger foods reported in 40-60% [23, 24] of patients surveyed, while 22% reported increased intake of foods believed to be protective. [24]

Amongst the various dietary strategies cited in literature, the Mediterranean diet pattern and its role on gastrointestinal health outcomes has emerged as a topic of interest. [25, 26] Epidemiological data suggest regions following traditional dietary patterns such as the Mediterranean diet report lower incidence of IBD compared to those following a more "Western" style diet. [1, 3, 27-29] A recent prospective cohort study of 83,147 Swedish adults found reduced risk of Crohn's Disease (CD) in those adhering to a Mediterranean diet pattern, although this relationship was unclear in UC. [30] One uncontrolled study using a 6-month

Mediterranean diet intervention found statistically significant improvements in C-reactive protein, faecal calprotectin and quality of life measures in UC. [31] Finally, the first (to our knowledge) published randomised controlled trial using a 12-week Mediterranean diet intervention in 28 patients with quiescent UC found beneficial changes to the gut microbiome composition, inflammatory biomarkers, bowel symptoms and diet quality, [32] warranting further investigations in this space.

Despite these promising preliminary results, there are several limitations when translating these results to clinical practice. Firstly, parameters defining the Mediterranean diet and tools used to examine adherence vary across published literature, [31-35] posing a challenge for interventions aiming to replicate these results. Furthermore, many elements of the Mediterranean diet including consumption of fibre-rich wholegrains, fruit, and vegetables may pose a barrier for individuals who may present with intolerances, especially during active disease. [33, 36, 37] Dietary modification and elimination style diets may be applied; however, it is unclear if these changes would influence overall outcomes. [38, 39] Finally, with comprehensive dietary interventions there are challenges in isolating the effects of specific nutrients within the food matrix or interactions between food components which would provide insights into mechanisms and direction for future treatment strategies. [40]

The use of olive products, especially extra virgin olive oil (EVOO) in meal preparations, is one of the most recognizable aspects of the traditional Mediterranean diet pattern. [34, 41] This is further supported by its presence in the majority of tools used to examine Mediterranean diet adherence. [35] The health impacts of the Mediterranean diet have been attributed in part to regular consumption of EVOO due to its fatty acid and polyphenols content, [42] with potential implications for IBD. [43] Our previous systematic literature review (see Chapter 4) identified a

clear gap in robustly designed human trials, with animal studies comprising all but one investigation. [44, 45] In the first published human trial, Morvaridi et al reported in a randomised cross over trial that EVOO consumption resulted in reduced gastrointestinal symptoms and intestinal inflammation markers compared to canola oil in a cohort of 32 patients with stable UC. [46] Interestingly, there were some improvements observed in the canola oil intervention, and it is unclear if the increased oil consumptions contributed to these observations. At the time of writing, no other human trials exploring the relationship of EVOO specifically to UC have been published to our knowledge.

5.3. Aim

Considering these gaps in existing evidence, this study aimed to investigate the effects of EVOO consumption on health outcomes in UC in comparison to usual care. The secondary aim of this study was to explore carry-over effects of EVOO intervention following return to usual care. A healthy control group with no history of UC was included to compare the effects of EVOO on health outcomes between UC and healthy controls and contrast the intestinal microbiome of UC participants and healthy controls under usual care conditions.

We hypothesised that EVOO consumption would improve disease activity in individuals with mild to moderate disease activity. We also hypothesised that these impacts would be reflected in quality-of-life outcomes. We hypothesised intestinal microbiome changes are a driving factor for these changes and would differ between participants receiving the intervention and controls. We hypothesised that the EVOO benefits would diminish during the 4-week wash-out period.

5.4. Method

5.4.1. Study Design

The COLONiC (Consequences of OLive Oil replacemenNt on ulcerative Colitis) study was a parallel, randomised controlled trial examining the impact of EVOO supplementation on the disease activity and intestinal microbiome of individuals living with UC in comparison to generally healthy controls. Both participants with UC and generally healthy controls were randomly allocated to one of two groups in addition to their usual medical care and physical activity levels: 1) an intervention group in which participants were provided Australian EVOO (Cobram Estate Pty Ltd, Classic Flavour, Southbank, Australia) to use in place of their usual cooking oil and fats daily over 4 weeks, followed by a 4-week wash-out period during which they resumed usual care and lifestyle, and 2) a control group in which participants were asked to maintain their usual diet and lifestyle over an 8-week period.

Participants completed all assessments at the University of Sydney, Faculty of Health Sciences, Cumberland Campus. The study was prospectively registered with ANZCTR (Trial ID ACTRN12619000150145) and conducted between the 24th of April 2019 and the 14th of December 2021. Written consent was obtained, and the ethics application was approved by the University of Sydney Human Ethics Committee (Protocol no. 2018/981). A study flowchart is outlined in Chapter 2, *Figure 2.2.*

5.4.2. Patient Recruitment

Two groups of participants were recruited for the study: individuals living with UC and individuals with no history of inflammatory bowel disease or gastrointestinal symptoms (generally healthy controls). Prospective participants were sought through online advertising through the University of Sydney Volunteer for Research Study Webpage, Crohn's and Colitis

Australia, posters in the University of Cumberland Campus, and public hospitals within the greater Sydney region.

Inclusion and exclusion criteria

Participants were eligible if they were between the ages of 18 and 75 at the time of recruitment, could attend the in-person assessment at the University of Sydney research clinic and were able to commit to the study duration. History of faecal microbial transplant, antibiotic or anti-tuberculosis treatment during the study period or preceding 4 weeks, resection of the gastrointestinal tract, bariatric surgery, biological or monoclonal antibody agents during the study period or the preceding 12 weeks, unstable medical conditions requiring further investigations, pregnancy, and/or planned major surgery within the first 3 months after study enrolment were exclusion criteria for all participants.

Regular consumption of olive leaf extract, olive oil tablets, Echinacea, or probiotic supplementation, (defined as being consumed more than 3 times a week), dietary requirements which precluded the participant from consuming the intervention product, and/or consumption of any amount of EVOO at a frequency of more than 3 days a week were exclusions from the study. Regular use of light or refined olive oil was not an exclusion for study participation.

Participants living with UC were included in the study if their diagnosis was confirmed more than 3 months prior to enrolment and they scored 0-6 out of 9 (remission to moderate disease) on the Partial Mayo Score [47] at baseline in addition to confirmation from their specialist. Generally healthy participants were included if they reported no past medical history of chronic diseases of any type confirmed during the study screening. Prospective participants were excluded if they reported any sensitivity or intolerance to the intervention.

Participants under medical supervision for the management of unstable disease or in the process of modifying their medication regime (including tapering), planning to travel, and/or currently enrolled in another clinical trial in which concurrent participation was deemed inappropriate, were placed on a 12-week wait list and re-invited to participate at conclusion of the waiting period.

Estimation of Effect Sizes

Sample size for the primary outcome was estimated using data from two papers using the statistical power analysis program G*Power 3.1. [48]. The first paper was a randomised cross-over study comparing daily consumption of EVOO and canola oil on high sensitivity C-reactive protein (hs-CRP) in UC. [46] The second paper investigated the effects of a 6-week uncontrolled diet intervention on clinical scores in both Crohn's (Harvey Bradshaw Index) and UC (Partial Mayo Score). [49] Hedges' bias corrected effect size calculated from the published outcomes (*mean* ± *standard deviation*) was 1.132 for hs-CRP and 1.25 for a 2-point reduction of Partial Mayo Scores in UC. Using the more conservative effect size of 1.132, setting alpha at 0.05 and beta 0.2 (80% power) we estimated 9 participants were required for each study arm. Allowing for a 17.5% attrition rate in literature, [46] we aimed to recruit 11 participants in each study arm: 22 participants with UC and another 22 generally healthy matched participants for a total sample size of 44 participants.

5.4.3. Assessment

Prospective participants underwent a two-stage screening process which included a telephone screen following initial expression of interest, and an in-person comprehensive assessment at the University of Sydney Cumberland Campus clinic. In person assessments were completed over a 2-week period and included a physician screen, stress test, body composition

assessment, habitual physical activity, dietary intake, strength testing and questionnaires in accordance with the procedures outlined in Chapter 2.

Briefly, once the telephone screening form was vetted by the lead investigator, participants were invited to attend the first in-person assessment (Assessment 1) which included strength testing, questionnaires, fitting with a AX3 3-axis accelerometer (Axivity, Newcastle upon Tyne, United Kingdom), and instructions to complete a 3-day weighed food diary, 7-day habitual physical activity log, and procedures for stool sampling and storage prior to the second in-person assessment.

The second visit (Assessment 2) was scheduled between 7 and 14 days following the first assessment. This session was comprised of fasting assessments including collection of fasting blood serum and plasma, body composition assessment, collection of the stool sample and review of completed diaries by the study investigators. Assessments were repeated across 3 time-points; at baseline prior to randomisation, at completion of the 4-week intervention prior to the study wash-out period, and final assessment at 8 weeks following study-wash-out.

5.4.4. Randomisation

Concealed randomisation in randomly permuted blocks of 4-8 was prepared by an independent researcher not otherwise involved with the study, with a planned allocation ratio of 1:1 between the study intervention and controls. Stratification was based on a prior diagnosis of UC (Yes, No) and sex (Male, Female). Randomisation sequence was generated using the website Randomization.com (http://www.randomization.com) [50] and uploaded into a university-managed research database (REDCap). Once uploaded, the randomisation sequence remained inaccessible to study investigators and automatically allocated participants to either an

intervention or control group at completion of baseline assessment. Allocation was then confirmed with the independent researcher generating the sequence, and at confirmation, participants were informed verbally of their allocation in person. At the end of the baseline assessment, participants were provided with study-related materials in accordance with their study randomisation. Study assessor blinding could not be implemented due to staffing limitations, and participants could not be blinded due to the need to include a control oil to blind them, which might have influenced habitual intake.

5.4.5. Study Intervention

5.4.5.1. Intervention group

Participants in the intervention arm were supplied with 24 x 200 mL Australian EVOO (Cobram Estate Pty Ltd, Classic Flavour, Southbank, Australia) with a labelled harvest date of 2019 and best before date of December 2020, stored in dark opaque glass bottles following randomisation. Participants were instructed to replace all fats including oils, butter, margarine, vegetable shortening and lard in their diet with EVOO over the 4-week intervention. No restrictions were made on how the oil was used in meal preparations or how much was to be consumed. However, participants were recommended to store the oils away in a cool dark space away from heat and light in line with manufacturer recommendations. Participants were instructed to maintain all other aspect of their usual physical activity levels and dietary habits, and an education session was facilitated by the study dietitian to demonstrate how EVOO could be incorporated into habitual food intake based on 3-day weighed food diaries completed prior to randomisation. During the intervention period, participants finishing their last bottle were instructed to contact the research team who would provide an additional box (6 x 200 mL) of replacement bottles. Participants consuming EVOO outside the supplied intervention were requested to estimate the amounts consumed and log it in a supplied diary. Adherence was

defined as consumption of the intervention product or other sources of EVOO ≥ 4 days a week, assessed through weekly status checks over the phone and completion of the supplied diary to record EVOO use. Volume of olive oil consumed was examined during this period but not considered as a measure of adherence to account for variations in oil consumption amongst participants and lack of specified amount to be consumed. Participants were instructed to continue the intervention during the mid-point assessment (Week 4) until commencement of the wash-out period.

At completion of the final component of the mid-point assessment (Week 4), participants in the intervention group were asked to return all used and unused bottles of EVOO to the research team prior to commencing the 4-week wash-out period to allow for quantification. During this time participants were instructed to resume their habitual food intake prior to the intervention over a 4-week period and record consumption of EVOO as part of their usual intake until the final assessment.

5.4.5.2. Control group

Blinding using a placebo oil was considered in the control group, however deemed to be unsuitable due to the potential impact to habitual food intake and the likelihood of identifying the intervention by taste. Participants in the control group were instructed to maintain habitual intake and physical activity throughout the study duration.

5.4.6. Outcome Measures

Disease activity for the UC participants was selected as a primary outcome and assessed using the Partial Mayo Score which includes sub-scores for self-reported stool frequency, rectal bleeding, and a physician global assessment [47] at baseline, 4-week, and 8-week timepoints.

Secondary outcomes included quality of life using the 36-Item Short Form (SF-36®) Health Survey, [51] the Inflammatory Bowel Disease Questionnaire (IBDQ-32), [52] and Food-related Quality of Life (FRQoL-29). [53] Depression and anxiety were examined using the Patient Health Questionnaire 9 (PHQ-9) [54] and Hospital Anxiety and Depression Index (HADS). [55] Sleep quality was examined through the Patient Sleep Quality Index (PSQI), [56] while self-reported fatigue was assessed through the Inflammatory Bowel Disease Fatigue scale (IBD-F). [57] Habitual diet was assessed through completion of a 3-day weighed food diary comprised of 2 weekdays and 1 weekend within a 7-day period. The lead investigator, an accredited practising dietitian, reviewed the diaries for accuracy alongside the study participant. Data were then entered and analysed using FoodWorks 9 Professional (Xyris Pty Ltd, Brisbane, Australia). Habitual physical activity was assessed through completion of a 7-day self-reported physical activity diary prior to attending the clinic for fasting assessments. Adverse events, self-reported disease activity, compliance with the study intervention and changes to habitual care were assessed through weekly status checks completed over the phone.

5.4.7. Changes to Methods after Commencement

Evaluation of intestinal microbiome through 16S rRNA sequencing of faecal samples and inflammatory markers through fasting plasma and serum samples collected at baseline, 4 weeks post-intervention and after completion of the study wash-out at 8 weeks could not be completed by the time of thesis submission due to funding limitations, but samples collected have been retained at -80 degrees Celsius and will be analysed when funding permits.

Planned sample size could not be reached due to the recruitment coinciding with the 2019-20 Australian bushfire season, recruitment suspension during the COVID-19 pandemic, followed

by the relocation from Cumberland Campus to the Susan Wakil Health building, Camperdown campus, during which all clinical trial activities were prohibited.

5.4.8. Statistics

Analysis of the randomised controlled trial using linear mixed models and intention to treat design was planned during study development. Due to the paucity of participants, descriptive statistics and presentation of data in graphs were used to report findings from this study.

5.5. Results

A total of 48 prospective participants expressing interest were contacted, of whom 32 reported a history of IBD (25 individuals living with UC, 7 individuals with Crohn's disease which was therefore ineligible for the study) and 6 expressing interest to participate in the "generally healthy" group. History of IBD could not be determined for 10 prospective participants due to them being uncontactable following the initial expression of interest. No eligible participants were identified from the "generally healthy" group following stage 1 screening. Across all participant groups, time commitment (n = 10), and regular consumption of EVOO which meant the intervention would make no difference to usual care (n = 8) posed the greatest barrier for enrolment into the study. Comparing participant groups, time commitment was the most frequently reported reason for withdrawal in the "generally healthy" group (n=5), inability to contact participants following initial expression of interest was most frequent in the "unknown health status" group (n=7), and regular consumption of EVOO was most frequent in the participants with UC (n=6).

Following the first stage telephone screening, four prospective participants completed baseline assessments. One participant withdrew prior to randomisation due to COVID-19 restrictions in

New South Wales and three were randomised into the study. From the three participants enrolled, one participant from the intervention group (Intervention 2) withdrew at the mid-point assessment (Week 4) due to the 2019-20 Australian bushfire season affecting her residential area. Two participants completed the entire study protocol, one for each study arm (*Figure 5.1*). Analysis was performed on the 3 participants who completed baseline and randomisation.

5.5.1. Participant Demographics and Medical History

Participant demographics are outlined in **Table 5.1**. Family history of chronic gastrointestinal conditions was reported by all participants including diverticulitis (n=1), irritable bowel syndrome (n=1), colorectal cancer (n=1). None disclosed a family history of IBD. One participant with a Partial Mayo Scoring Index of 3/9 (Intervention 1) scored 2/3 for rectal bleeding and 1/3 for the physician global assessment at baseline. All participants were in remission at study recruitment as confirmed by a gastroenterologist.

A maintenance dose of immunosuppressant medications was reported by two participants: azathioprine (n=1) and methotrexate (n=1). One participant was not taking any medication for the management of IBD at time of assessment. All participants disclosed taking the recommended dosage of medications prescribed during baseline assessment.

5.5.2. Baseline Body Composition

Baseline body composition measures are reported in **Table 5.2.1**. Intervention participant 2 disclosed an unplanned 10 kg weight gain in the past 12 months which was stable 3 months prior to enrolment. Appendicular skeletal muscle indices (ASMI) for all participants were below published thresholds for sarcopenia in women (< 5.5 kg/m^2). [58]

Baseline bone mineral content (BMC) and bone mineral density (BMD) measures are reported in **Table 5.2.2**. Bone density measures for total body and L2-L4 spine were within normal ranges for all participants (T-score ≥ -1.0). [59] Left femoral neck T-score of the Control participant was indicative of osteopenia which aligned with her medical history.

Weight change throughout the study duration was reported by Intervention participant 2, with a 1.5 kg intentional weight loss through increased physical activity reported at the end of her study participation (4 weeks). All other participants were weight stable at completion of the final assessment and did not report any variations in their weight during the study duration.

5.5.3. Physical Activity

Intentional physical activity throughout the study duration was reported by two of 3 participants enrolled in the study (Intervention 1 and Control), who also completed the self-reported physical activity diary at baseline, mid-point (4 weeks) and study completion (8 weeks) (**Table 5.3**). Intervention participant 2 did not complete the physical activity diary provided, however described incidental activity in the form of physical labour (chain sawing, moving firewood) 4 hours once a week and walking around her property about 30 minutes per day. Self- reported ratings for exertion or habitual physical activity could not be examined for this participant.

Increased daily average step counts from 9000 steps at baseline and mid-point assessment (4 weeks) to 10,000 steps at study completion (8 weeks) was observed in Intervention participant 1. The other 2 participants maintained their level of physical activity throughout the study duration. None of the participants met Australian Physical Activity Guidelines for adults (18

to 64 years) nor strength training guidelines [60] based on prospective physical activity logs or self-reported physical activity.

5.5.4. Diet

None of the eligible participants reported following a particular diet for the management of their UC nor other purposes prior to commencing the study. However, all participants disclosed trialling one or more diets since their initial diagnosis. Two of 3 participants (Intervention 2 and Control) reported trialling 2 diets prior to commencing the study which included a low carbohydrate diet, a Mediterranean diet and one non-specified "detox" diet. Both the "detox" diet and low carbohydrate diet were ceased by the Control? participant due to adverse gastrointestinal symptoms attributed to dietary change. One participant (Intervention 1) described trialling the Monash low FODMAP diet for symptom control which was ceased prior to study enrolment due to symptom improvements. No participant described any specific nutrition support, guidance, nor dietetic services after UC diagnosis. One participant (Intervention 1) was an Accredited Practising Dietitian and self-managing diet. Motivations for current dietary habits at baseline included weight management and improving general energy levels. One participant reported aiming to increase dietary sources of probiotics (yogurt) intake following recommendations from a television health program. All participants reported taking an active role in the household groceries and food preparation

Restriction of specific foods due to suspected intolerances were reported by all participants. Coffee and caffeine-containing products including teas and chocolate, wheat products, vegetables (capsicum, raw onions), fruit (strawberries), dairy (fat-free cow's milk, cream, and lactose), cashews, and foods containing sulphur (dried fruit, wine) were identified as potential triggers. None previously had a confirmed food allergy or prior investigations for intolerances.

Regular consumption of alcohol was reported by two of 3 participants, both averaging 5 standard drinks a week in the form of red wine. Primary types of cooking fat reported prior to study enrolment were grape seed oil (Intervention 2), light olive oil (Intervention 1 and Control), and butter (Intervention 1).

5.5.4.1. 3-day Weighed Food Diary and EVOO consumption

All participants completed a 3-day weighed food diary at baseline, comprised of 2 weekdays and 1 weekend within a 7-day period. The lead investigator, an accredited dietitian, entered and analysed the data using FoodWorks 9 Professional (Xyris Pty Ltd, Australia). An average of estimated macro- and micronutrients is outlined in **Table 5.4**. Intervention participant 2 withdrew from the study at 4 weeks and did not complete 3-day food diaries during the mid-point assessment prior to wash-out (4 weeks) nor 4 weeks after the wash-out period (8 weeks). Estimated energy intake for Intervention participant 1 increased at 4 weeks compared to baseline and was sustained throughout the study period. By contrast, participant in the Control arm decreased her total energy intake at 4- week and 8-week follow-up. Average daily monounsaturated fat consumption from 3-day weighed food diary increased in the Intervention participant 1 at 4 weeks and was reduced at 8 weeks, however remained at a greater amount compared to baseline. Percentage of saturated fat in the diet similarly decreased during the 4-week intervention, returning to baseline levels at completion of the wash-out period at 8 weeks. By comparison, estimates for monounsaturated fatty acid intake and percentages of monounsaturated, polyunsaturated, and saturated fatty acids were unchanged in the Control participant throughout the study duration. Finally, an increase in fibre intake was observed in the Intervention participant at 4 weeks which returned to baseline at 8 weeks. By comparison, estimated fibre intake was stable in the control participant throughout the study duration.

Calculated average consumption of EVOO was 1 tablespoon (15 mL) daily for both Intervention 1 and Intervention 2, with both reporting consumption more than 4 days a week during the study duration (**Table 5.5.1** and **Table 5.5.2**). Main barriers for adherence were travelling away for work-related duties and eating out which both limited opportunities to incorporate the intervention product.

5.5.4.2. Food Choice Questionnaire (FCQ)

All participants assigned the greatest importance to different values (convenience, natural content and ethics). Similar ratings for natural content and ethics were noted for participants in the Intervention group compared to Control, however no general trends could be drawn from the results. (**Table 5.6**)

5.5.5. Partial Mayo Score

Intervention participant 1 reported a Partial Mayo Score suggesting mild disease (3/9) at baseline which reduced to remission (0/9) after 4 weeks. This change was consistent with the minimum clinically meaningful difference defined as at least 3 points on this scale. [47] Scores increased for Intervention 2 by 2 points however remained at remission (≤ 2) at 4 weeks. This less than clinically meaningful change was due to an increase in stool frequency over a 3-day period (3-4 stools more than normal) which the participant attributed to a suspected food poisoning unrelated to the intervention or UC symptoms. Score for the Control participant was stable in remission (≤ 2) over the same duration. (*Figure 5.2.1*).

During the wash-out period participants in both Intervention and Control sustained their Partial Mayo Scores at remission (≤ 2). However, the Control participant reported an increase Partial Mayo Score at follow-up due to streaks of blood identified in stools (rectal bleeding score 1).

(*Figure 5.2.2*). Intervention participant 1 reported a reduction of toileting frequency and normal stool consistency which was captured in the weekly status checks during wash-out (**Table 5.5.2.**)

5.5.6. Quality of Life

5.5.6.1. Short Form health Survey (SF-36 v2™)

Physical and Mental Component Summary scores from the 36-item Short Form Health Survey Version 2 (SF-36 v2™) were calculated using the factor score coefficient of the Australian population from the 1995 Australian National Health Survey [61]. The tool examines both current physical and emotional health (Q1-Q3, Q11) and overall health in the past 4 weeks. (Q4-Q10) Physical Component Summary (PCS) scores and Mental Component Summary (MCS) scores are aggregates of 8 individual sub-scores (physical function, role-physical, role-emotional, vitality, bodily pain, general health, social functioning, and mental health), with individual scores provided in **Table 5.7**. The PCS scores increased (improved) for all participants at completion of the 4-week intervention period and the change of 6.7 points was clinically meaningful for Intervention participant 1 (*Figure 5.3.1*). These score changes were sustained post-wash-out. (*Figure 5.3.2*)

The MCS scores increased (improved) for both participants in the Intervention group, with clinically meaningful changes for participant Intervention 2 prior to study withdrawal. By comparison, MCS scores decreased in the Control participant at completion of the 4-week intervention period (*Figure 5.3.3*). The change score in Intervention participant 1 was sustained at completion of the wash-out period. A clinically meaningful improvement (absolute score change ≥ 3) was observed in the Control participant during the 4-week wash-out period (*Figure 5.3.4*).

5.5.6.2 Food-related Quality of Life (FRQOL-29)

The 29-item Food-related Quality of Life (FRQOL-29) scores increased (improved) for all participants upon completion of the 4-week intervention period between 5 and 55 points. Greater changes were observed in the Intervention group, with increased scores ranging between 12 and 55 points, while the control group reported a 5-point increase (*Figure 5.4.1*). The greatest increase was reported by Intervention 2. Minimum clinically important differences have not been reported for this scale.

FRQoL-29 scores were maintained in the Intervention participant 1 following cessation of the intervention over 4 weeks. An additional 6-point score increase was observed in the Control participant during the same timeframe. (*Figure 5.4.2*)

5.5.6.3. Inflammatory Bowel Disease Questionnaire (IBDQ-32)

Total scores for the Inflammatory Bowel Disease quality of life questionnaire (IBDQ-32) increased (improved) for all participants at 4 weeks post intervention/control period. Clinically meaningful change (> 30-point) [62-64] was reported by 1 participant (Intervention 2). Greater changes were observed in the Intervention group (41 and 23 points) compared to the Control participant (9 points) at completion of the 4-week intervention (*Figure 5.5.1*). Scores were sustained at completion of the wash-out period (*Figure 5.5.2*)

The greatest changes to all sub-scores occurred during the 4-week intervention period for all groups, with systemic symptoms exhibiting the greatest change (8-13 points). Raw scores for each domain are provided in **Table 5.8**.

5.5.6.4. Patient Health Questionnaire (PHQ-9)

Intervention participant 2 reported a baseline score suggestive of mild depression (9/27) which was reduced (improved) at 4 weeks post intervention (5/27) (*Figure 5.6.1*). Scores for all remaining participants were below the cut-off for mild depression (5/27) throughout the 8-week study period. (*Figure 5.6.2*).

5.5.6.5. Hospital and Anxiety Depression Scale (HADS)

Baseline score for Intervention participant 2 (who had a prior diagnosis of anxiety) was in the "borderline" range for anxiety (10/21) and decreased to "normal" ranges (≤7) at completion of the 4-week intervention. Changes to Anxiety sub-scores were clinically meaningful for all participants, defined as a sub-score change of ≥ 2 (*Figure 5.7.1*). Anxiety scores for the two remaining participants (Intervention 1 and Control) were maintained within "normal" ranges at 4 weeks (*Figure 5.7.1*) and 8 weeks (*Figure 5.7.2*). Depression scores for all participants throughout the study were in "normal" ranges at 4 weeks (*Figure 5.7.3*) and 8 weeks (*Figure 5.7.4*).

5.5.7. Fatigue and Sleep Quality

5.5.7.1. Inflammatory Bowel Disease Fatigue self-assessment scale (IBD-F)

Greater total scores were observed in both Intervention participants at baseline compared to Control. Following the 4-week intervention scores reduced (improved) in the Intervention group by 15.5 and 24 points but increased (worsened) in the Control participant by 3 points. (*Figure 5.8.1*). Observed changes were sustained at the end of the wash-out period (8 weeks) (*Figure 5.8.2*). All participants described their fatigue as being intermittent, with a duration ranging between 2 and 10 years. Sub-scores for Section 1, Section 2, and responses to Section 3 are provided in **Table 5.9**.

5.5.7.2. Patient Sleep Quality Index (PSQI)

All participants returned a score suggestive of impaired sleep quality at baseline (PSQI global score ≥ 5). Greatest reduction to the PSQI at post intervention (4 weeks) was observed in Intervention participant 2, while all other participants' scores were unchanged (*Figure 5.9.1*). At completion of the wash-out period (8 weeks), the Control participant reduced her score by 2 points while the Intervention 1 participant scores were unchanged (*Figure 5.9.2*). Sub-scores for the 7 components of the PSQI for each participant are presented in **Table 5.10**.

5.5.8. Adverse Events

None of the participants reporting adverse events during the study period attributed their symptoms to the intervention. Similarly, none of the events occurring were attributed to UC symptoms. Food intolerances, food poisoning and cold and flu-like symptoms were the primary contributors to reported events during the study. Cumulative adverse events recorded during each weekly status checks are outlined in **Table 5.5**.

5.6. Discussion

In this study we conducted a randomised controlled trial to compare the effects of EVOO intervention with usual care on gastrointestinal symptoms and quality of life in quiescent UC. Clinically meaningful improvement as indicated by Partial Mayo Scores was observed in one Intervention participant completing the study, with score changes sustained 4 weeks following cessation of the intervention. Despite worsening scores observed in the Intervention 2 participant at 4 weeks following the intervention, and Control participant at 8 weeks following usual care, these changes were not clinically significant [47] and both participants remained at remission throughout the study period. Small positive changes to health-related quality of life (HRQoL) favouring the Intervention were observed at 4 weeks, with score changes sustained

following the 4-week wash-out period. Quality of life measures for the Control participant were stable throughout the study period as indicated by clinically non-meaningful changes apart from two measures (MCS score of the SF-36 v2™ and HADS-A) which improved at 4 weeks and returned to baseline at 8 weeks.

At the time of writing, only one human study (46) has aimed to isolate the effects of EVOO in experimental trials, to extend pre-clinical studies using rodent models of UC, [45] although in human studies EVOO forms part of a broader dietary intervention such as the Mediterranean Diet. [32, 65] Findings from rodent models suggest olive-based interventions improve UC disease expression as evidenced by reduced mortality, [66-69] reduced rectal bleeding, [70] weight maintenance, [66, 71-73] better stool consistency, [74] and preservation of mucosal architecture, as detailed in the systematic review in Chapter 4. [67, 72-76] Despite these promising results, the variability of rodent models used to represent UC in humans, poor reporting of experimental parameters and limited human data suggest generalisability of these outcomes to humans should be approached cautiously. [43, 45]

In 2020 Morvaridi et al published the first human cross-over trial comparing supplementation using 50 mL of EVOO and Canola Oil in UC outpatients over 20 days. The study reported improvements to gastrointestinal symptoms (bloating, constipation, faecal urgency, incomplete defecation) and inflammatory markers (high sensitive C-reactive protein, erythrocyte sedimentation rate) favouring EVOO. Interestingly, no difference to Partial Mayo Scores were observed between intervention and control periods. [46] By contrast, our pilot study found clinically meaningful improvements to Partial Mayo Scores following 4 weeks of EVOO intervention in one participant, however no significant changes were observed in the remaining Intervention and Control participants. These variations are likely attributed to the pilot nature

this study and may suggest individual response to the intervention, although limitations to the Partial Mayo score should also be acknowledged.

The Partial Mayo Score, which consists of the non-invasive components of the full Mayo Score (stool frequency, rectal bleeding, and a global physician assessment) is a validated tool which demonstrates good specificity and sensitivity in classifying disease activity in UC. [47, 77, 78] Despite its frequent use in clinical trials, there is limited guidance in how the tool should be administered and variability in the cut-off scores used to define remission in literature. [78, 79] As noted in our observations (*Figure 2.1*), variables unrelated to UC and transient symptoms may influence clinical end points such as stool frequency results in an increased disease severity rating, while there is no scoring assigned for reduction of bowel movements which may be clinically meaningful. Similarly, critics argue the inclusion of subjective end points such as the global physician assessment introduces imprecision. [80] The Partial Mayo Score does perform well compared to other non-invasive indices used in UC with good discriminative validity, construct validity and responsiveness to change, [78] However, using it as a standalone clinical outcome may not be sufficient to describe overall burden of disease in UC.

5.6.1. Quality of Life and Other Secondary Outcomes

Given these limitations of the Partial Mayo Score, the inclusion of HRQoL measures provides additional insights into disease manifestation in UC. Lower HRQoL has been described in both active [7, 81] and quiescent UC [6] compared to generally healthy populations. Considering the multifaceted effects of the condition on health and psychosocial outcomes, evidence recommends a variety of instruments used concurrently to better reflect the unique experiences for individuals living with UC. [62, 81-84]

Both the IBDQ-32 and SF-36 v2™ are frequently used tools to assess HRQoL which also seem to correspond to disease severity and treatment response in UC. [9, 85, 86] We observed consistencies between the direction of effect for these two outcomes following the intervention, which is unsurprising considering the crossover of some of the examined domains. By contrast, these trends were not replicated other tools measuring similar health-related outcomes such as depression in the PHQ-9 ad HADS. Interestingly, score changes to HRQoL outcomes following the intervention were sustained after return to usual care in the intervention group and unchanged in the control group. Neither medication nor diet changes were reported during the same timeframe, however an unplanned increase of physical activity participation was observed, which may explain how HRQoL was sustained, rather than diminishing during wash-out as we had hypothesised. Exercise is significantly associated with improvements to HRQoL outcomes IBDQ-32 and SF-36 v2™ in IBD patients in remission. [87]. Parameters such as gut microbiome outcomes tend to return to baseline levels following cessation of the intervention, [88] however it is unclear if carry-over effects are likely with other outcomes measured in this study due to limited evidence. Likewise, due to the limited number of participants and the relatively short study duration, it is unclear if these effects would be replicated in a larger cohort or sustained over a longer time period after intervention cessation.

We also noted one participant returning a score for mild depression in the PHQ-9 who did not exceed depression cut-offs in the depression components of the HADS (HADS-D). These differences may reflect the different timeframe captured between the two tools where the PHQ-9 captures the past 2 weeks while the HADS captures the past week. Presentation of acute symptoms during the different timeframes captured and patient-specific variables such as disease duration may also influence self-reported HRQoL ratings resulting in these variances. [84] Finally, although the HADS has been shown to have good agreement with other HRQoL

tools in a range of other population groups [89-91] and strong associations with IBD related disability, [92] the sensitivity of HADS-D is lower compared to similar tools. [93] Larger sample sizes would be required to evaluate if these observations would apply more broadly.

Improvements to fatigue (IBDF) appeared to match improvements to IBDQ-32 for all participants, which is unsurprising considering the IBDQ-32 examines both fatigue (Q2) and sleep quality (Q14). Previous findings have also established links between levels of fatigue and depression (HADS scores), [94] which wasn't quite clear in this study due to the limited participant numbers. It is however clear that both fatigue and sleep impairments are a common concern for individuals living with IBD. Prevalence of fatigue in patients living with IBD range between 41-48% for those in remission, [95] increasing up to 72% in active disease. [96] Impaired sleep quality, anxiety, depression and anaemia are amongst the most reported contributors for fatigue resulting in a reduction in HRQoL outcomes. [96] Depending of the pathophysiology of fatigue, diet may play a role by addressing nutritional deficiencies, reduced energy intake, and influencing positive changes to the intestinal microbiome. [97] Likewise there are some interest on the role of "anti-inflammatory foods" in managing fatigue secondary to chronic conditions including IBD, however the evidence on this hasn't been convincing. [98]

Finally, it should be acknowledged that patients living with IBD often receive limited guidance on their diet despite expressing great interest on the topic, [24, 99] and UC in particular is underrepresented in dietary studies targeting IBD. [100] This could be attributed to insufficient high quality evidence exploring nutrition interventions in UC, which is further complicated by the variability of disease expression, transient symptoms, disordered eating patterns and the prevalence of food sensitivities in this cohort. [22, 29, 100, 101] Regardless of the limitation in literature, dietary restrictions are commonly reported as part of the management of IBD, often

with adverse consequences towards nutritional adequacy and quality of life impairments. [24, 40, 102, 103] Findings from our study did not identify notable changes to FRQoL-29 scores between intervention and control participants, however it is notable that improvements were observed in both groups. This seems to mirror changes to HRQoL outcomes despite limited changes to clinical outcomes such as the Partial Mayo Score.

5.6.2. Potential Mechanisms of EVOO Interventions

Consumption of EVOO has been hypothesised to positively influence UC outcomes through several mechanisms including the reduction of oxidative stress markers, downregulation of pro-inflammatory cytokines, and interactions with intestinal microbiome. Both human and animal trials suggest olive oil phenols protect against oxidative stress markers malondialdehyde (MDA), myeloperoxidase (MPO), ferric-reducing ability of plasma (FRAP), and greater lag time of LDL oxidation. [104-106] Similarly, systematic literature reviews of olive oil interventions have previously shown favourable effects on inflammatory markers such as interleukin-6 and serum CRP concentrations. [107-112] It should be noted that phenol content and fatty acid composition may vary between the type of olives, ripeness at the harvesting stage, growing conditions, and level of refinement which in turn may influence its efficacy. [113]

5.6.2.1. EVOO Polyphenols and Gut Microbiome

Although most of the research around olive oil interventions are focused on cardiometabolic outcomes, there are potential implications for gastrointestinal health outcomes. An estimated 55-65% of ingested olive oil phenols including oleuropein, hydroxytyrosol, and tyrosol is absorbed and metabolised in the human body. [114] At the time of writing no upper limits for olive phenols have been established with no adverse events reported in human trials. [115] High doses of hydroxytyrosol at concentrations of 2g/kg were also found to be safe in animal studies.

[116] Experimental models have shown that the majority of tyrosol and hydroxytyrosol absorption occurs in the small intestine, with increased metabolites present in plasma and urine following oral intake. [117] By contrast, oleuropein remains more stable throughout the digestive process thus more likely to reach the large intestine, where it is degraded by the colonic microflora resulting in the formation of several phenolic compounds including hydroxytyrosol. [118, 119] The presence of these bioactive compounds may selectively promote the growth of beneficial gut bacteria while inhibiting pathogenic strains. Olive oil and it's phenols have been demonstrated to exert both antifungal [120] and antimicrobial properties against some common pathogens such as *Escherichia coli*, *Staphylococcus aureus*, and *Listeria monocytogenes* in vitro. [121-124] Likewise, olive phenols and their derivatives have been shown to exert antiviral activity in vitro by inhibiting the production of reverse transcriptase and protease. [125-127]

Supplementation with olive-derived phenols in experimental mouse models fed a high fat diet resulted in reduced *Firmicuites* to *Bacteriodetes* ratio (F/B ratio), increased abundance of *Akkermansia*, and improvements to both insulin resistance and plasma lipid profiles compared to controls. [128] Another pre-clinical study found EVOO supplementation over 12 weeks resulted in statistically significant differences in 10 bacterial families compared to mice fed refined olive oil, butter, and standard chow. [129] Increased abundance of *Lactobacillus sp.* and overall microbial diversity have also been shown in spontaneously hypertensive rats (SHR) following EVOO supplementation. [130] Microbiome diversity is lower in UC cohorts with distinct profiles compared to healthy controls, [131, 132] however, it has been shown to respond to treatment. [133] These microbiome modulations could therefore lead to improved gut barrier integrity through increased production of mucins in colonic tissue, reduced bacterial translocation, and consequently, decreased inflammation. The observed reduction in pro-inflammatory markers (MCP-1, TNF-α, iNOS, COX-2) and modulation of inflammatory

pathways (p38 MAPK, IκB) in pre-clinical studies may be indirect effects of this improved gut health. [43, 134, 135]

5.6.2.2. Dietary Fats and Gut Microbiome

Beyond the impact of olive phenols, it should be acknowledged that olive oil interventions will likely influence the amount and type of fat in the habitual diet, thus resulting in alterations to microbiome diversity and richness observed in studies. Studies have shown increased gut permeability and altered microbiome profiles in animals fed a high fat diet compared to standard chow. [136, 137] It should be noted that increasing dietary fat will displace other nutrients such as carbohydrates and fibre, and as such these perturbations may be a direct response to an increased fat intake, reduced carbohydrate intake, or both. Experiments by Morrison, et al., have suggested that the lack of soluble fibre was the main driver of gut microbiome alterations in C57Bl/6:129 mixed strain mice. [138] Similarly, a systematic literature review comparing low-fat (LFD), low-carbohydrate (LCD), and low-protein diets (LPD) on gut microbiome in human trials reported a greater likelihood of increased alpha diversity following a LFD which likely contains a higher amount of carbohydrates, and reduced abundance following carbohydrate restriction. However, these findings varied between studies and sampling limitations were acknowledged by the authors. [139]

5.6.2.3. Fatty Acids and Ulcerative Colitis

As expected, analysis of the 3-day weighted food records showed an increase in monounsaturated fat and decrease in saturated fats in participants swapping butter for EVOO in the intervention group, while the composition of fatty acids was maintained in the control participant. Part of this increase is likely attributed to oleic acid (C18:1), an omega-9 monounsaturated fatty acid which makes up 55-83% of the triacylglycerols found in EVOO.

Remaining fractions of fatty acids in EVOO are made up of linoleic acid (3.5-21%), palmitic acid (7.5-20%) and stearic acid (0.5-5%). [140]

Manipulation of fatty acids as a strategy to mediate inflammation and disease severity in UC has previously been described in literature. Examination of 7-day food diaries from 25639 men and women from the European Prospective Investigation into Cancer (EPIC)-Norfolk cohort found a positive association between arachidonic acid and UC (OR 6.09, 95% CI 1.05–35.23), and an inverse relationship between higher oleic acid and odds of developing UC (OR 0.03, 95% CI 0.002–0.56). [141] Colonic mucosa biopsy and serum samples comparing patients with active UC and generally healthy controls have also demonstrated decreased oleic acid and palmitoleic acid composition in addition to an increased amounts of arachidonic acid in the UC group. [142, 143] Arachidonic acid, an omega-6 polyunsaturated fatty acid found in red meat, certain oils and margarines, is a component of cell membranes and may be a contributing factor to the development of UC. Arachidonic acid is converted to pro-inflammatory eicosanoids prostaglandin E2 (PG2) and leukotriene B4 (LTB4), which are present in greater amounts in the mucosa of UC patients and correlates with degree of inflammation. [142-145] Therapies such as 5-aminosalicylates inhibit the formation of these pro-inflammatory eicosanoids. [144]

Despite the rationale presented from observational and pre-clinical studies and findings from prospective cohorts, the role of fatty acids in mediating disease severity in UC remains controversial, with inconsistencies in literature. [146] Examinations of the Nurses' Health Study cohorts found no association between omega-6 polyunsaturated fatty acid and risk of developing UC, although it did not specify fatty acid types. [147] Likewise, systematic literature reviews and meta-analysis found no effect of omega-3 polyunsaturated fatty acid on maintaining remission in IBD nor treatment of active disease [148-150] despite supporting evidence

from observational studies. [147, 151, 152] Unfortunately, there are few clinical trials examining the role of omega-9 fatty acids in UC, and it is unclear if outcomes would be a result of the fatty acid itself or reduction of fats considered to be more harmful. Considering the variability of effects observed in literature, confounding factors should also be considered.

An increase in total energy intake, starch, and fibre was observed in the Intervention participant which was not observed in the Control. This is noteworthy, as consumption of fibres and fermentable carbohydrates tends to be lower in IBD cohorts compared to the general population, [37] and an increase is likely to positively influence intestinal microbiome. [138, 139, 153] Dietary fibre has been shown to improve gastrointestinal symptoms and inflammatory markers in UC in a number of studies, however evidence is weak, with inconsistencies in the type of fibres used [153, 154]. Increased oral intake as evidenced by the 17% increase in energy intake in the Intervention participant may have contributed to the increased fibre intake. However, another speculation is that the use of EVOO as a primary fat source may promote changes to meal preparation despite instructions to maintain habitual diet, contributing to the improvements observed. A prospective study of 538 adults using 7-day food diaries found the use of EVOO was associated with greater consumption of salads, vegetables and wholegrains compared to those using sunflower oil as a primary cooking oil. [155] It is unclear if these changes are likely in all IBD cohorts due to concerns around strictures in CD and individual tolerance to fermentable carbohydrates. [156] At the time of writing few studies have explored the impact of modifying one element of the diet towards broader dietary patterns which might explain observations in this study, and further investigations are warranted in this space.

5.6.2.4. Dose of EVOO and Practical Applications

It was notable that a large proportion of prospective participants were ineligible due to existing use of EVOO as part of their habitual diet. Nearly two-thirds (65.4%) of 1248 Australian adults in a 2021 cross-sectional study reported using EVOO as a primary cooking oil, [157] aligning with increased olive oil consumption in Australia in the past 30 years. [158] Likewise, Marsh, et al., previously reported olive oil was consumed by 65% of Australian patients with IBD in a cross-sectional study, however few met the 4 tablespoons a day used in Mediterranean Diet intervention studies and no distinctions were made between regular olive oil and EVOO. [36, 159, 160] Average EVOO intake of 15 mL (1 tablespoon) reported in this study matches amounts of cooking oil used in an Australian cross sectional study. [157] Total fat intake observed in this study was comparable to habitual intakes reported in IBD cohorts and healthy controls. [161, 162] This may suggest that habitual intakes of EVOO and isocaloric conditions may not be sufficient to replicate the healthful effects of Mediterranean Diet interventions and greater fat intakes should be considered for future studies using EVOO interventions.

None of the participants reported restrictions around dietary fats, and FRQoL-29 did not appear to be impaired in the intervention, however increasing fat intake may be a challenging recommendation for individuals living with IBD more broadly. High fat foods and fried foods are commonly avoided by IBD patients due to concerns of worsening symptoms, [163-167] and this may also extend to home cooked meals. Unfortunately, no studies at time of writing have evaluated if these attitudes applied across all fat types and culinary applications, which is further complicated by other factors such as taste preferences and the adoption of low-fat diets beyond IBD management.

5.6.3. Strengths and Limitations

To our knowledge, this is only the second study to examine the effects of a single dietary modification using EVOO in place of usual cooking fats/oils in UC. This study addresses an existing gap on the efficacy and safety of dietary interventions for management of IBD symptoms and maintenance of remission. [22, 100] Inclusion of a review with the study dietitian following the 3-day weighed food record reduced the likelihood of recall bias and incorrect reporting prevalent in dietary assessment. Diet studies which examines a range of health related variables are limited in IBD research, and few studies have examined the role of individual food components on disease management and health outcomes.

One key criticism with current evidence in dietary strategies for the management of IBD is the lack of clarity on how individual components contribute towards outcomes. Extensive modifications to dietary prescription are challenging due to the variability of food sensitivities associated with IBD, individual taste or cultural preferences, and access to foods which may be considered core components of the diet. Furthermore, it is unclear if modification of dietary patterns would influence its efficacy for the management of IBD symptoms and health outcomes. As such there is scope for investigations focusing on individual components of the diet. The use of a single food intervention in the form of EVOO resulted in broader dietary changes and may be applied across different eating patterns beyond the Mediterranean diet. Furthermore, we've included a broad range of parameters to account for potential confounding factors on the study outcomes and better describe participants at each assessment timepoint. These results would allow for the development of sufficiently powered studies in future.

On the other hand, there were several limitations that should be considered when interpreting the findings from this study. Participant numbers were extremely limited due the 2019-20

Australian bushfire season, the COVID-19 pandemic, followed by the relocation of the research clinic to a new campus and building. This was further compounded by the high proportion of participants who were ineligible due to routine use of EVOO, and limitations around study design which was resource intensive and required extensive assessments which may limit participation. There were no eligible participants with no history of IBD (generally healthy controls), thus the effect of EVOO supplementation on this cohort remains unclear. For participants with UC, those randomised to the intervention and control groups were of the same sex and similar age which allowed for some comparison, however generalisability of our study findings to broader populations should be approached with extreme caution due to the limited sample size. Clinical outcome measures such as intestinal microbiome diversity and richness, faecal calprotectin, and serum levels of hydroxytyrosol could not be examined at this time due to funding limitations. Future studies may also consider validated tools to examine symptoms such as the Rome IV Diagnostic Questionnaire for Functional Gastrointestinal Disorders in Adults (R4DQ)[168] and the irritable bowel severity scoring system (IBS-SSS).[169]

Duration of the intervention was shorter compared to diet studies in IBD, however longer than a comparable cross-over study in UC outpatients. [46] The estimated EVOO dose in the intervention was relatively low, however comparable to population norms and aligns with reported daily habits. It is unclear if a longer study duration would influence reported daily intake of the intervention. However, in translating these results, the type, variety, and harvest date of EVOO used should also be considered due to the variability of phenol concentration and fatty acid profiles between products which may be a confounding factor for interventions using EVOO.

5.7. Conclusion

In conclusion, an intervention using EVOO in place of usual cooking fats or oils was safe and well tolerated in 2 individuals with quiescent UC. Clinically meaningful improvements to the Partial Mayo Score were observed in one Intervention participant. Small positive changes to disease severity ratings and HRQoL outcomes such as the IBDQ-32 and FRQoL-29 favouring the Intervention were also observed which included carry-over effects 4 weeks following return to usual care, however these findings should be interpreted with caution due to the small participant numbers.

The need for RCTs in this field is critical, given the findings that Invervention effects were heterogeneous, and some outcomes improved in the Control subject as well in our study. In a chronic disease such as UC, enrolling in a trial may have considerable health benefits (the Hawthorne Effect) which must be distinguished from true intervention effects. Confounding factors such as physical activity participation and unconscious changes to dietary habits despite instructions to maintain usual care should be considered. Larger studies over a longer timeframe including participants living with CD and generally healthy controls are warranted. Future trials should consider the effects of larger EVOO doses to align with Mediterranean Diet interventions in quiescent UC cohorts, inclusion of endoscopic outcomes (Full Mayo Index) and validated questionnaires examining functional gastrointestinal symptoms (R4DQ).

Acknowledgement

Intervention EVOO has been provided in kind by Cobram Estate Pty Ltd. Cobram Estate have not been involved in any aspect of the trial including study design, data collection, reporting of results nor dissemination.

5.8. References

1 Ng SC, Bernstein CN, Vatn MH, et al. Geographical variability and environmental risk factors in inflammatory bowel disease. *Gut*. 2013;62(4):630.

2 Wilson J, Hair C, Knight R, et al. High incidence of inflammatory bowel disease in Australia: A prospective population-based Australian incidence study. *Inflammatory Bowel Diseases*. 2010;16(9):1550-1556.

3 Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet*. 2017;390(10114):2769-2778.

4 Massuger W, Moore GTC, Andrews JM, et al. Crohn's & Colitis Australia inflammatory bowel disease audit: measuring the quality of care in Australia. *Intern Med J*. 2019;49(7):859-866.

5 Connor SJ, Sechi A, Andrade M, Deuring JJ, Witcombe D. Ulcerative Colitis Narrative findings: Australian survey data comparing patient and physician disease management views. *JGH Open*. 2021;5(9):1033-1040.

6 Mavroudis G, Simrén M, Öhman L, Strid H. Health-related quality of life in patients with long-standing ulcerative colitis in remission. *Therap Adv Gastroenterol*. 2022;15:17562848211062406.

7 Gibson PR, Vaizey C, Black CM, et al. Relationship between disease severity and quality of life and assessment of health care utilization and cost for ulcerative colitis in Australia: A cross-sectional, observational study☆. *Journal of Crohn's and Colitis*. 2014;8(7):598-606.

8 Rubin DT, Siegel CA, Kane SV, et al. Impact of Ulcerative Colitis from Patients' and Physicians' Perspectives: Results from the UC: NORMAL survey. *Inflammatory Bowel Diseases*. 2009;15(4):581-588.

9 Yarlas A, Rubin DT, Panés J, et al. Burden of Ulcerative Colitis on Functioning and Well-being: A Systematic Literature Review of the SF-36® Health Survey. *Journal of Crohn's and Colitis*. 2018;12(5):600-609.

10 Kane SV. Systematic review: adherence issues in the treatment of ulcerative colitis. *Alimentary Pharmacology & Therapeutics*. 2006;23(5):577-585.

11 Thompson KD, Connor SJ, Walls DM, et al. Patients with Ulcerative Colitis Are More Concerned About Complications of Their Disease than Side Effects of Medications. *Inflammatory Bowel Diseases*. 2016;22(4):940-947.

12 Navaneethan U, Shen B. Pros and cons of medical management of ulcerative colitis. *Clin Colon Rectal Surg*. 2010;23(4):227-238.

13 Beaugerie L, Kirchgesner J. Balancing Benefit vs Risk of Immunosuppressive Therapy for Individual Patients With Inflammatory Bowel Diseases. *Clinical Gastroenterology and Hepatology*. 2019;17(3):370-379.

14 Boeri M, Myers K, Ervin C, et al. Patient and physician preferences for ulcerative colitis treatments in the United States. *Clinical and Experimental Gastroenterology*. 2019;12(null):263-278.
15 Allez M, Karmiris K, Louis E, et al. Report of the ECCO pathogenesis workshop on anti-TNF therapy failures in inflammatory bowel diseases: Definitions, frequency and pharmacological aspects. *Journal of Crohn's and Colitis*. 2010;4(4):355-366.
16 Marsal J, Barreiro-de Acosta M, Blumenstein I, Cappello M, Bazin T, Sebastian S. Management of Non-response and Loss of Response to Anti-tumor Necrosis Factor Therapy in Inflammatory Bowel Disease. *Front Med (Lausanne)*. 2022;9:897936.
17 Papamichael K, Rivals-Lerebours O, Billiet T, et al. Long-Term Outcome of Patients with Ulcerative Colitis and Primary Non-response to Infliximab. *Journal of Crohn's and Colitis*. 2016;10(9):1015-1023.
18 Ungar B, Chowers Y, Yavzori M, et al. The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. *Gut*. 2014;63(8):1258.
19 Loftus EV, Jr., Davis KL, Wang C-C, Dastani H, Luo A. Treatment Patterns, Complications, and Disease Relapse in a Real-world Population of Patients with Moderate-to-severe Ulcerative Colitis Initiating Immunomodulator Therapy. *Inflammatory Bowel Diseases*. 2014;20(8):1361-1367.
20 Eaden J, Abrams K, Ekbom A, Jackson E, Mayberry J. Colorectal cancer prevention in ulcerative colitis: a case-control study. *Aliment Pharmacol Ther*. 2000;14(2):145-153.
21 Moody GA, Jayanthi V, Probert CS, Mac Kay H, Mayberry JF. Long-term therapy with sulphasalazine protects against colorectal cancer in ulcerative colitis: a retrospective study of colorectal cancer risk and compliance with treatment in Leicestershire. *Eur J Gastroenterol Hepatol*. 1996;8(12):1179-1183.
22 Hart AL, Lomer M, Verjee A, et al. What Are the Top 10 Research Questions in the Treatment of Inflammatory Bowel Disease? A Priority Setting Partnership with the James Lind Alliance. *Journal of Crohn's and Colitis*. 2017;11(2):204-211.
23 Crooks B, McLaughlin J, Matsuoka K, Kobayashi T, Yamazaki H, Limdi JK. The dietary practices and beliefs of people living with inactive ulcerative colitis. *European Journal of Gastroenterology & Hepatology*. 2021;33(3).
24 Jowett SL, Seal CJ, Phillips E, Gregory W, Barton JR, Welfare MR. Dietary beliefs of people with ulcerative colitis and their effect on relapse and nutrient intake. *Clinical Nutrition*. 2004;23(2):161-170.
25 Merra G, Noce A, Marrone G, et al. Influence of Mediterranean Diet on Human Gut Microbiota. *Nutrients*. 2021;13(1):7.
26 Illescas O, Rodríguez-Sosa M, Gariboldi M. Mediterranean Diet to Prevent the Development of Colon Diseases: A Meta-Analysis of Gut Microbiota Studies. *Nutrients*. 2021;13(7):2234.
27 Kaplan GG, Ng SC. Understanding and Preventing the Global Increase of Inflammatory Bowel Disease. *Gastroenterology*. 2017;152(2):313-321.e312.

28 Levine A, Rhodes JM, Lindsay JO, et al. Dietary Guidance From the International Organization for the Study of Inflammatory Bowel Diseases. *Clin Gastroenterol Hepatol*. 2020;18(6):1381-1392.

29 Fitzpatrick JA, Melton SL, Yao CK, Gibson PR, Halmos EP. Dietary management of adults with IBD - the emerging role of dietary therapy. *Nat Rev Gastroenterol Hepatol*. 2022;19(10):652-669.

30 Khalili H, Håkansson N, Chan SS, et al. Adherence to a Mediterranean diet is associated with a lower risk of later-onset Crohn's disease: results from two large prospective cohort studies. *Gut*. 2020;69(9):1637-1644.

31 Chicco F, Magrì S, Cingolani A, et al. Multidimensional Impact of Mediterranean Diet on IBD Patients. *Inflammatory Bowel Diseases*. 2021;27(1):1-9.

32 Haskey N, Estaki M, Ye J, et al. A Mediterranean Diet Pattern Improves Intestinal Inflammation Concomitant with Reshaping of the Bacteriome in Ulcerative Colitis: A Randomised Controlled Trial. *Journal of Crohn's and Colitis*. 2023;17(10):1569-1578.

33 Fiorindi C, Dinu M, Gavazzi E, et al. Adherence to mediterranean diet in patients with inflammatory bowel disease. *Clinical Nutrition ESPEN*. 2021;46:416-423.

34 Davis C, Bryan J, Hodgson J, Murphy K. Definition of the Mediterranean Diet; A Literature Review. *Nutrients*. 2015;7(11):9139-9153.

35 Zaragoza-Martí A, Cabañero-Martínez MJ, Hurtado-Sánchez JA, Laguna-Pérez A, Ferrer-Cascales R. Evaluation of Mediterranean diet adherence scores: a systematic review. *BMJ Open*. 2018;8(2):e019033.

36 Marsh A, Radford-Smith G, Banks M, Lord A, Chachay V. Dietary intake of patients with inflammatory bowel disease aligns poorly with traditional Mediterranean diet principles. *Nutrition & Dietetics*. 2022;79(2):229-237.

37 Day AS, Davis R, Costello SP, Yao CK, Andrews JM, Bryant RV. The Adequacy of Habitual Dietary Fiber Intake in Individuals With Inflammatory Bowel Disease: A Systematic Review. *J Acad Nutr Diet*. 2021;121(4):688-708.e683.

38 Walton M, Alaunyte I. Do patients living with ulcerative colitis adhere to healthy eating guidelines? A cross-sectional study. *British Journal of Nutrition*. 2014;112(10):1628-1635.

39 Comeche JM, Gutierrez-Hervás A, Tuells J, Altavilla C, Caballero P. Predefined Diets in Patients with Inflammatory Bowel Disease: Systematic Review and Meta-Analysis. Nutrients, Vol. 13, 2021

40 Green N, Miller T, Suskind D, Lee D. A Review of Dietary Therapy for IBD and a Vision for the Future. Nutrients, Vol. 11, 2019

41 Bach-Faig A, Berry EM, Lairon D, et al. Mediterranean diet pyramid today. Science and cultural updates. *Public Health Nutrition*. 2011;14(12A):2274-2284.

42 Urpi-Sarda M, Casas R, Chiva-Blanch G, et al. Virgin olive oil and nuts as key foods of the Mediterranean diet effects on inflammatory biomakers related to atherosclerosis. *Pharmacol Res*. 2012;65(6):577-583.

43 Vrdoljak J, Kumric M, Vilovic M, et al. Effects of Olive Oil and Its Components on Intestinal Inflammation and Inflammatory Bowel Disease. *Nutrients*. 2022;14(4).

44 Marsh A, Rindfleish S, Bennett K, Croft A, Chachay V. Outcomes of dietary management approaches in active ulcerative colitis: A systematic review. *Clinical Nutrition*. 2022;41(2):298-306.

45 Daniel K, Vitetta L, Fiatarone Singh MA. Effects of olives and their constituents on the expression of ulcerative colitis: a systematic review of randomised controlled trials. *Br J Nutr*. 2022;127(8):1153-1171.

46 Morvaridi M, Jafarirad S, Seyedian SS, Alavinejad P, Cheraghian B. The effects of extra virgin olive oil and canola oil on inflammatory markers and gastrointestinal symptoms in patients with ulcerative colitis. *Eur J Clin Nutr*. 2020;74(6):891-899.

47 Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis*. 2008;14(12):1660-1666.

48 Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*. 2007;39(2):175-191.

49 Konijeti GG, Kim N, Lewis JD, et al. Efficacy of the Autoimmune Protocol Diet for Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2017;23(11):2054-2060.

50 Dallal GE. Randomization Plans: Randomizing subjects to a single treatment. Vol. 2019. Randomization.com, 2013

51 McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care*. 1994;32(1):40-66.

52 Guyatt G, Mitchell A, Irvine EJ, et al. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology*. 1989;96(3):804-810.

53 Hughes LD, King L, Morgan M, et al. Food-related Quality of Life in Inflammatory Bowel Disease: Development and Validation of a Questionnaire. *Journal of Crohn's and Colitis*. 2016;10(2):194-201.

54 Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. *Journal of General Internal Medicine*. 2001;16(9):606-613.

55 Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Vol. 67. United Kingdom: Blackwell Publishing, 1983:361-370

56 Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193-213.

57 Czuber-Dochan W, Norton C, Bassett P, et al. Development and psychometric testing of inflammatory bowel disease fatigue (IBD-F) patient self-assessment scale. *Journal of Crohn's and Colitis*. 2014;8(11):1398-1406.

58 Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age and Ageing*. 2019;48(1):16-31.

59 Henry MJ, Pasco JA, Pocock NA, Nicholson GC, Kotowicz MA. Reference ranges for bone densitometers adopted Australia-wide: Geelong osteoporosis study. *Australas Radiol*. 2004;48(4):473-475.

60 Australian Government Department of Health and Aged Care. Physical activity and exercise guidelines for all Australians. Vol. 2024, 2021

61 Statistics ABo. National Health Survey SF-36 Population Norms Australia. *Australia, Australian Bureau of Statistics*. 1995.

62 Irvine JE. Quality of life of patients with ulcerative colitis: Past, present, and future. *Inflammatory Bowel Diseases*. 2008;14(4):554-565.

63 Higgins PDR, Schwartz M, Mapili J, Krokos I, Leung J, Zimmermann EM. Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis. *Gut*. 2005;54(6):782-788.

64 CADTH Common Drug Reviews. In: *Clinical Review Report: Tofacinitib (Xeljanz): (Pfizer Canada Inc): Indication: For the treatment of adult patients with moderately to severely active ulcerative colitis (UC) with an inadequate response, loss of response, or intolerance to either conventional UC therapy or a tumour necrosis factor alpha inhibitor*. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health

65 Erol Doğan Ö, Karaca Çelik KE, Baş M, Alan EH, Çağın YF. Effects of Mediterranean Diet, Curcumin, and Resveratrol on Mild-to-Moderate Active Ulcerative Colitis: A Multicenter Randomized Clinical Trial. *Nutrients*. 2024;16(10).

66 Sánchez-Fidalgo S, Sánchez de Ibargüen L, Cárdeno A, Alarcón de la Lastra C. Influence of extra virgin olive oil diet enriched with hydroxytyrosol in a chronic DSS colitis model. *Eur J Nutr*. 2012;51(4):497-506.

67 Takashima T, Sakata Y, Iwakiri R, et al. Feeding with olive oil attenuates inflammation in dextran sulfate sodium-induced colitis in rat. *J Nutr Biochem*. 2014;25(2):186-192.

68 Hamam GG, Raafat MH, Shoukry Y. Possible protective effect of dietary extra-virgin olive oil on experimentally induced acute colitis in adult male albino rats: a histological and immunohistochemical study. *Egyptian Journal of Histology*. 2014;37(2).

69 Hegazi RAF, Saad RS, Mady H, Matarese LE, O'Keefe S, Kandil HM. Dietary fatty acids modulate chronic colitis, colitis-associated colon neoplasia and COX-2 expression in IL-10 knockout mice. *Nutrition*. 2006;22(3):275-282.

70 Giner E, Recio MC, Ríos JL, Giner RM. Oleuropein protects against dextran sodium sulfate-induced chronic colitis in mice. *J Nat Prod*. 2013;76(6):1113-1120.

71 Sánchez-Fidalgo S, Cárdeno A, Sánchez-Hidalgo M, et al. Dietary unsaponifiable fraction from extra virgin olive oil supplementation attenuates acute ulcerative colitis in mice. *Eur J Pharm Sci*. 2013;48(3):572-581.

72 Sánchez-Fidalgo S, Villegas I, Aparicio-Soto M, et al. Effects of dietary virgin olive oil polyphenols: hydroxytyrosyl acetate and 3, 4-dihydroxyphenylglycol on DSS-induced acute colitis in mice. *J Nutr Biochem*. 2015;26(5):513-520.

73 Cariello M, Contursi A, Gadaleta RM, et al. Extra-Virgin Olive Oil from Apulian Cultivars and Intestinal Inflammation. *Nutrients*. 2020;12(4).

74 Giner E, Andújar I, Recio MC, Ríos JL, Cerdá-Nicolás JM, Giner RM. Oleuropein Ameliorates Acute Colitis in Mice. *Journal of Agricultural and Food Chemistry*. 2011;59(24):12882-12892.

75 Güvenç M, Cellat M, Özkan H, et al. Protective Effects of Tyrosol Against DSS-Induced Ulcerative Colitis in Rats. *Inflammation*. 2019;42(5):1680-1691.

76 Sánchez-Fidalgo S, Cárdeno A, Sánchez-Hidalgo M, Aparicio-Soto M, de la Lastra CA. Dietary extra virgin olive oil polyphenols supplementation modulates DSS-induced chronic colitis in mice. *J Nutr Biochem*. 2013;24(7):1401-1413.

77 Naegeli AN, Hunter T, Dong Y, et al. Full, Partial, and Modified Permutations of the Mayo Score: Characterizing Clinical and Patient-Reported Outcomes in Ulcerative Colitis Patients. *Crohn's & Colitis 360*. 2021;3(1):otab007.

78 Turner D, Seow CH, Greenberg GR, Griffiths AM, Silverberg MS, Steinhart AH. A Systematic Prospective Comparison of Noninvasive Disease Activity Indices in Ulcerative Colitis. *Clinical Gastroenterology and Hepatology*. 2009;7(10):1081-1088.

79 D'Haens G, Sandborn WJ, Feagan BG, et al. A Review of Activity Indices and Efficacy End Points for Clinical Trials of Medical Therapy in Adults With Ulcerative Colitis. *Gastroenterology*. 2007;132(2):763-786.

80 Cooney RM, Warren BF, Altman DG, Abreu MT, Travis SP. Outcome measurement in clinical trials for Ulcerative Colitis: towards standardisation. *Trials*. 2007;8:17.

81 Han SW, McColl E, Barton JR, James P, Steen IN, Welfare MR. Predictors of Quality of Life in Ulcerative Colitis.: The Importance of Symptoms and Illness Representations. *Inflammatory Bowel Diseases*. 2005;11(1):24-34.

82 McColl E, Han SW, Barton JR, Welfare MR. A comparison of the discriminatory power of the Inflammatory Bowel Disease Questionnaire and the SF-36 in people with ulcerative colitis. *Qual Life Res*. 2004;13(4):805-811.

83 Irvine EJ. Quality of Life in Inflammatory Bowel Disease: Biases and Other Factors Affecting Scores. *Scandinavian Journal of Gastroenterology*. 1995;30(sup208):136-140.

84 Knowles SR, Keefer L, Wilding H, Hewitt C, Graff LA, Mikocka-Walus A. Quality of Life in Inflammatory Bowel Disease: A Systematic Review and Meta-analyses—Part II. *Inflammatory Bowel Diseases*. 2018;24(5):966-976.

85 Dubinsky M, Rice A, Yarlas A, et al. Systematic Literature Review: Ability of the IBDQ-32 to Detect Meaningful Change in Ulcerative Colitis Health Indicators. *Inflammatory Bowel Diseases*. 2023:izad282.

86 Yarlas A, Maher S, Bayliss M, et al. The Inflammatory Bowel Disease Questionnaire in Randomized Controlled Trials of Treatment for Ulcerative Colitis: Systematic Review and Meta-Analysis. *J Patient Cent Res Rev*. 2020;7(2):189-205.

87 Packer N, Hoffman-Goetz L, Ward G. Does physical activity affect quality of life, disease symptoms and immune measures in patients with inflammatory bowel disease? A systematic review. *Journal of Sports Medicine and Physical Fitness*. 2010;50(1):1-18.

88 Leeming ER, Johnson AJ, Spector TD, Le Roy CI. Effect of Diet on the Gut Microbiota: Rethinking Intervention Duration. *Nutrients*. 2019;11(12):2862.

89 Fosså SD, Dahl AA. Short Form 36 and Hospital Anxiety and Depression Scale: A comparison based on patients with testicular cancer. *Journal of Psychosomatic Research*. 2002;52(2):79-87.

90 LoMartire R, Äng BO, Gerdle B, Vixner L. Psychometric properties of Short Form-36 Health Survey, EuroQol 5-dimensions, and Hospital Anxiety and Depression Scale in patients with chronic pain. *PAIN*. 2020;161(1).

91 Mulvaney-Day N, Marshall T, Downey Piscopo K, et al. Screening for Behavioral Health Conditions in Primary Care Settings: A Systematic Review of the Literature. *J Gen Intern Med*. 2018;33(3):335-346.

92 Chan W, Shim HH, Lim MS, et al. Symptoms of anxiety and depression are independently associated with inflammatory bowel disease-related disability. *Digestive and Liver Disease*. 2017;49(12):1314-1319.

93 Bernstein CN, Zhang L, Lix LM, et al. The Validity and Reliability of Screening Measures for Depression and Anxiety Disorders in Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2018;24(9):1867-1875.

94 Keightley P, Reay RE, Pavli P, Looi JCL. Inflammatory bowel disease-related fatigue is correlated with depression and gender. *Australasian Psychiatry*. 2018;26(5):508-513.
95 Van Langenberg DR, Gibson PR. Systematic review: fatigue in inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*. 2010;32(2):131-143.
96 D'Silva A, Fox DE, Nasser Y, et al. Prevalence and Risk Factors for Fatigue in Adults With Inflammatory Bowel Disease: A Systematic Review With Meta-Analysis. *Clin Gastroenterol Hepatol*. 2022;20(5):995-1009.e1007.
97 Borren NZ, van der Woude CJ, Ananthakrishnan AN. Fatigue in IBD: epidemiology, pathophysiology and management. *Nature Reviews Gastroenterology & Hepatology*. 2019;16(4):247-259.
98 Haß U, Herpich C, Norman K. Anti-Inflammatory Diets and Fatigue. *Nutrients*. 2019;11(10):2315.
99 Holt DQ, Strauss BJ, Moore GT. Patients with inflammatory bowel disease and their treating clinicians have different views regarding diet. *J Hum Nutr Diet*. 2017;30(1):66-72.
100 Sigall-Boneh R, Levine A, Lomer M, et al. Research Gaps in Diet and Nutrition in Inflammatory Bowel Disease. A Topical Review by D-ECCO Working Group [Dietitians of ECCO]. *Journal of Crohn's and Colitis*. 2017;11(12):1407-1419.
101 Lomer MCE, Wilson B, Wall CL. British Dietetic Association consensus guidelines on the nutritional assessment and dietary management of patients with inflammatory bowel disease. *Journal of Human Nutrition and Dietetics*. 2023;36(1):336-377.
102 Durchschein F, Petritsch W, Hammer HF. Diet therapy for inflammatory bowel diseases: The established and the new. *World J Gastroenterol*. 2016;22(7):2179-2194.
103 Serrano-Moreno C, Brox-Torrecilla N, Arhip L, et al. Diets for inflammatory bowel disease: What do we know so far? *European Journal of Clinical Nutrition*. 2022;76(9):1222-1233.
104 Vissers MN, Zock PL, Katan MB. Bioavailability and antioxidant effects of olive oil phenols in humans: a review. *European Journal of Clinical Nutrition*. 2004;58(6):955-965.
105 Salvini S, Sera F, Caruso D, et al. Daily consumption of a high-phenol extra-virgin olive oil reduces oxidative DNA damage in postmenopausal women. *Br J Nutr*. 2006;95(4):742-751.
106 Derakhshandeh-Rishehri SM, Kazemi A, Shim SR, et al. Effect of olive oil phenols on oxidative stress biomarkers: A systematic review and dose-response meta-analysis of randomized clinical trials. *Food Sci Nutr*. 2023;11(5):2393-2402.
107 Schwingshackl L, Christoph M, Hoffmann G. Effects of Olive Oil on Markers of Inflammation and Endothelial Function-A Systematic Review and Meta-Analysis. *Nutrients*. 2015;7(9):7651-7675.
108 Fernandes J, Fialho M, Santos R, et al. Is olive oil good for you? A systematic review and meta-analysis on anti-inflammatory benefits from regular dietary intake. *Nutrition*. 2020;69:110559.

109 Wang Q, Liu R, Chang M, Zhang H, Jin Q, Wang X. Dietary oleic acid supplementation and blood inflammatory markers: a systematic review and meta-analysis of randomized controlled trials. *Critical Reviews in Food Science and Nutrition*. 2022;62(9):2508-2525.

110 Pastor R, Bouzas C, Tur JA. Beneficial effects of dietary supplementation with olive oil, oleic acid, or hydroxytyrosol in metabolic syndrome: Systematic review and meta-analysis. *Free Radical Biology and Medicine*. 2021;172:372-385.

111 Morvaridzadeh M, Cohen AA, Heshmati J, et al. Effect of Extra Virgin Olive Oil on Anthropometric Indices, Inflammatory and Cardiometabolic Markers: a Systematic Review and Meta-Analysis of Randomized Clinical Trials. *The Journal of Nutrition*. 2024;154(1):95-120.

112 Pourrajab B, Fotros D, Asghari P, Shidfar F. Effect of the Mediterranean Diet Supplemented With Olive Oil Versus the Low-Fat Diet on Serum Inflammatory and Endothelial Indexes Among Adults: A Systematic Review and Meta-analysis of Clinical Controlled Trials. *Nutrition Reviews*. 2024:nuae166.

113 Navajas-Porras B, Pérez-Burillo S, Morales-Pérez J, Rufián-Henares JA, Pastoriza S. Relationship of quality parameters, antioxidant capacity and total phenolic content of EVOO with ripening state and olive variety. *Food Chemistry*. 2020;325:126926.

114 Vissers MN, Zock PL, Roodenburg AJ, Leenen R, Katan MB. Olive oil phenols are absorbed in humans. *J Nutr*. 2002;132(3):409-417.

115 Hohmann CD, Cramer H, Michalsen A, et al. Effects of high phenolic olive oil on cardiovascular risk factors: A systematic review and meta-analysis. *Phytomedicine*. 2015;22(6):631-640.

116 Tuck KL, Freeman MP, Hayball PJ, Stretch GL, Stupans I. The In Vivo Fate of Hydroxytyrosol and Tyrosol, Antioxidant Phenolic Constituents of Olive Oil, after Intravenous and Oral Dosing of Labeled Compounds to Rats. *The Journal of Nutrition*. 2001;131(7):1993-1996.

117 Corona G, Tzounis X, Assunta DessÌ M, et al. The fate of olive oil polyphenols in the gastrointestinal tract: Implications of gastric and colonic microflora-dependent biotransformation. *Free Radical Research*. 2006;40(6):647-658.

118 Markopoulos C, Vertzoni M, Agalias A, Magiatis P, Reppas C. Stability of oleuropein in the human proximal gut. *Journal of Pharmacy and Pharmacology*. 2009;61(2):143-149.

119 Mosele JI, Martín-Peláez S, Macià A, et al. Faecal microbial metabolism of olive oil phenolic compounds: In vitro and in vivo approaches. *Molecular Nutrition & Food Research*. 2014;58(9):1809-1819.

120 Korukluoglu M, Sahan Y, Yigit A. Antifungal Properties of Olive Leaf Extracts and their Phenolic Compounds. *Journal of Food Safety*. 2008;28(1):76-87.

121 Bisignano G, Tomaino A, Cascio RL, Crisafi G, Uccella N, Saija A. On the In-vitro Antimicrobial Activity of Oleuropein and Hydroxytyrosol. *Journal of Pharmacy and Pharmacology*. 1999;51(8):971-974.

122 Juven B, Henis Y, Jacoby B. Studies on the Mechanism of the Antimicrobial Action of Oleuropein. *Journal of Applied Bacteriology*. 1972;35(4):559-567.
123 Guo L, Sun Q, Gong S, et al. Antimicrobial Activity and Action Approach of the Olive Oil Polyphenol Extract Against Listeria monocytogenes. *Front Microbiol*. 2019;10:1586.
124 Tripoli E, Giammanco M, Tabacchi G, Di Majo D, Giammanco S, La Guardia M. The phenolic compounds of olive oil: structure, biological activity and beneficial effects on human health. *Nutrition Research Reviews*. 2005;18(1):98-112.
125 Hirschman SZ. Inactivation of DNA Polymerases of Murine Leukaemia Viruses by Calcium Elenolate. *Nature New Biology*. 1972;238(87):277-279.
126 Pennisi R, Ben Amor I, Gargouri B, et al. Analysis of Antioxidant and Antiviral Effects of Olive (Olea europaea L.) Leaf Extracts and Pure Compound Using Cancer Cell Model. *Biomolecules*. 2023;13(2):238.
127 Micol V, Caturla N, Pérez-Fons L, Más V, Pérez L, Estepa A. The olive leaf extract exhibits antiviral activity against viral haemorrhagic septicaemia rhabdovirus (VHSV). *Antiviral Research*. 2005;66(2):129-136.
128 Vezza T, Rodríguez-Nogales A, Algieri F, et al. The metabolic and vascular protective effects of olive (Olea europaea L.) leaf extract in diet-induced obesity in mice are related to the amelioration of gut microbiota dysbiosis and to its immunomodulatory properties. *Pharmacological Research*. 2019;150:104487.
129 Martínez N, Prieto I, Hidalgo M, et al. Refined versus Extra Virgin Olive Oil High-Fat Diet Impact on Intestinal Microbiota of Mice and Its Relation to Different Physiological Variables. *Microorganisms*. 2019;7(2):61.
130 Hidalgo M, Prieto I, Abriouel H, et al. Changes in Gut Microbiota Linked to a Reduction in Systolic Blood Pressure in Spontaneously Hypertensive Rats Fed an Extra Virgin Olive Oil-Enriched Diet. *Plant Foods Hum Nutr*. 2018;73(1):1-6.
131 Nemoto H, Kataoka K, Ishikawa H, et al. Reduced Diversity and Imbalance of Fecal Microbiota in Patients with Ulcerative Colitis. *Digestive Diseases and Sciences*. 2012;57(11):2955-2964.
132 Shen ZH, Zhu CX, Quan YS, et al. Relationship between intestinal microbiota and ulcerative colitis: Mechanisms and clinical application of probiotics and fecal microbiota transplantation. *World J Gastroenterol*. 2018;24(1):5-14.
133 Basha OM, Hafez RA, Salem SM, Anis RH, Hanafy AS. Impact of gut Microbiome alteration in Ulcerative Colitis patients on disease severity and outcome. *Clinical and Experimental Medicine*. 2023;23(5):1763-1772.
134 Cárdeno A, Sánchez-Hidalgo M, Aparicio-Soto M, Sánchez-Fidalgo S, Alarcón-de-la-Lastra C. Extra virgin olive oil polyphenolic extracts downregulate inflammatory responses in LPS-activated

murine peritoneal macrophages suppressing NFκB and MAPK signalling pathways. *Food Funct*. 2014;5(6):1270-1277.

135 Fernández-Tomé S, Ortega Moreno L, Chaparro M, Gisbert JP. Gut Microbiota and Dietary Factors as Modulators of the Mucus Layer in Inflammatory Bowel Disease. *Int J Mol Sci*. 2021;22(19).

136 Hildebrandt MA, Hoffmann C, Sherrill–Mix SA, et al. High-Fat Diet Determines the Composition of the Murine Gut Microbiome Independently of Obesity. *Gastroenterology*. 2009;137(5):1716-1724.e1712.

137 Daniel H, Gholami AM, Berry D, et al. High-fat diet alters gut microbiota physiology in mice. *The ISME Journal*. 2014;8(2):295-308.

138 Morrison KE, Jašarević E, Howard CD, Bale TL. It's the fiber, not the fat: significant effects of dietary challenge on the gut microbiome. *Microbiome*. 2020;8(1):15.

139 Schoonakker MP, van Peet PG, van den Burg EL, et al. Impact of dietary carbohydrate, fat or protein restriction on the human gut microbiome: a systematic review. *Nutrition Research Reviews*. 2024:1-18.

140 Yubero-Serrano EM, Lopez-Moreno J, Gomez-Delgado F, Lopez-Miranda J. Extra virgin olive oil: More than a healthy fat. *European Journal of Clinical Nutrition*. 2019;72(1):8-17.

141 de Silva PSA, Luben R, Shrestha SS, Khaw KT, Hart AR. Dietary arachidonic and oleic acid intake in ulcerative colitis etiology: a prospective cohort study using 7-day food diaries. *European Journal of Gastroenterology & Hepatology*. 2014;26(1).

142 Nishida T, Miwa H, Shigematsu A, Yamamoto M, Iida M, Fujishima M. Increased arachidonic acid composition of phospholipids in colonic mucosa from patients with active ulcerative colitis. *Gut*. 1987;28(8):1002-1007.

143 Wiese DM, Horst SN, Brown CT, et al. Serum Fatty Acids Are Correlated with Inflammatory Cytokines in Ulcerative Colitis. *PLOS ONE*. 2016;11(5):e0156387.

144 Sharon P, Ligumsky M, Rachmilewitz D, Zor U. Role of Prostaglandins in Ulcerative Colitis: Enhanced production during active disease and inhibition by sulfasalazine. *Gastroenterology*. 1978;75(4):638-640.

145 Sharon P, Stenson WF. Enhanced Synthesis of Leukotriene B4 by Colonic Mucosa in Inflammatory Bowel Disease. *Gastroenterology*. 1984;86(3):453-460.

146 Wang F, Lin X, Zhao Q, Li J. Fat intake and risk of ulcerative colitis: Systematic review and dose–response meta-analysis of epidemiological studies. *Journal of Gastroenterology and Hepatology*. 2017;32(1):19-27.

147 Ananthakrishnan AN, Khalili H, Konijeti GG, et al. Long-term intake of dietary fat and risk of ulcerative colitis and Crohn's disease. *Gut*. 2014;63(5):776.

148 Turner D, Shah PS, Steinhart AH, Zlotkin S, Griffiths AM. Maintenance of remission in inflammatory bowel disease using omega-3 fatty acids (fish oil): A systematic review and meta-analyses. *Inflammatory Bowel Diseases*. 2011;17(1):336-345.
149 Cabré E, Mañosa M, Gassull MA. Omega-3 fatty acids and inflammatory bowel diseases – a systematic review. *British Journal of Nutrition*. 2012;107(S2):S240-S252.
150 Marion-Letellier R, Savoye G, Beck PL, Panaccione R, Ghosh S. Polyunsaturated Fatty Acids in Inflammatory Bowel Diseases: A Reappraisal of Effects and Therapeutic Approaches. *Inflammatory Bowel Diseases*. 2013;19(3):650-661.
151 John S, Luben R, Shrestha SS, Welch A, Khaw K-T, Hart AR. Dietary n-3 polyunsaturated fatty acids and the aetiology of ulcerative colitis: a UK prospective cohort study. *European Journal of Gastroenterology & Hepatology*. 2010;22(5).
152 Rashvand S, Somi MH, Rashidkhani B, Hekmatdoost A. Dietary fatty acid intakes are related to the risk of ulcerative colitis: a case–control study. *International Journal of Colorectal Disease*. 2015;30(9):1255-1260.
153 Fritsch J, Garces L, Quintero MA, et al. Low-Fat, High-Fiber Diet Reduces Markers of Inflammation and Dysbiosis and Improves Quality of Life in Patients With Ulcerative Colitis. *Clinical Gastroenterology and Hepatology*. 2021;19(6):1189-1199.e1130.
154 Wedlake L, Slack N, Andreyev HJN, Whelan K. Fiber in the Treatment and Maintenance of Inflammatory Bowel Disease: A Systematic Review of Randomized Controlled Trials. *Inflammatory Bowel Diseases*. 2014;20(3):576-586.
155 Soriguer F, Almaraz MC, García-Almeida JM, et al. Intake and home use of olive oil or mixed oils in relation to healthy lifestyles in a Mediterranean population. Findings from the prospective Pizarra study. *British Journal of Nutrition*. 2010;103(1):114-122.
156 Haskey N, Gibson DL. An Examination of Diet for the Maintenance of Remission in Inflammatory Bowel Disease. *Nutrients*. 2017;9(3):259.
157 Wilson NA, Villani A, Mantzioris E. Preferences for dietary oils and fats in cooking and food preparation methods: a cross-sectional analysis of Australian adults. *British Journal of Nutrition*. 2023;130(5):841-851.
158 Mili S, Bouhaddane M. Forecasting Global Developments and Challenges in Olive Oil Supply and Demand: A Delphi Survey from Spain. *Agriculture*. 2021;11(3):191.
159 Estruch R, Ros E, Salas-Salvadó J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med*. 2018;378(25):e34.
160 Papadaki A, Johnson L, Toumpakari Z, et al. Validation of the English Version of the 14-Item Mediterranean Diet Adherence Screener of the PREDIMED Study, in People at High Cardiovascular Risk in the UK. *Nutrients*. 2018;10(2).

161 Peters V, Tigchelaar-Feenstra EF, Imhann F, et al. Habitual dietary intake of IBD patients differs from population controls: a case–control study. *European Journal of Nutrition*. 2021;60(1):345-356.
162 Opstelten JL, de Vries JHM, Wools A, Siersema PD, Oldenburg B, Witteman BJM. Dietary intake of patients with inflammatory bowel disease: A comparison with individuals from a general population and associations with relapse. *Clinical Nutrition*. 2019;38(4):1892-1898.
163 Marsh A, Kinneally J, Robertson T, Lord A, Young A, Radford –Smith G. Food avoidance in outpatients with Inflammatory Bowel Disease – Who, what and why. *Clinical Nutrition ESPEN*. 2019;31:10-16.
164 Casanova MJ, Chaparro M, Molina B, et al. Prevalence of Malnutrition and Nutritional Characteristics of Patients With Inflammatory Bowel Disease. *Journal of Crohn's and Colitis*. 2017;11(12):1430-1439.
165 Magkiosi A, Strongylou DE, Gkikas K, Gerasimidis K, Androutsos O, Svolos V. P757 Patient attitudes, perceptions, and beliefs on the role of diet and nutrition in inflammatory bowel diseases. A scoping review. *Journal of Crohn's and Colitis*. 2024;18(Supplement_1):i1411-i1413.
166 Brown AC, Rampertab SD, Mullin GE. Existing dietary guidelines for Crohn's disease and ulcerative colitis. *Expert Review of Gastroenterology & Hepatology*. 2011;5(3):411-425.
167 Vagianos K, Clara I, Carr R, et al. What Are Adults With Inflammatory Bowel Disease (IBD) Eating? A Closer Look at the Dietary Habits of a Population-Based Canadian IBD Cohort. *Journal of Parenteral and Enteral Nutrition*. 2016;40(3):405-411.
168 Palsson OS, Whitehead WE, van Tilburg MAL, et al. Development and Validation of the Rome IV Diagnostic Questionnaire for Adults. *Gastroenterology*. 2016;150(6):1481-1491.
169 Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. *Aliment Pharmacol Ther*. 1997;11(2):395-402.
170 Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. *Pharmacoeconomics*. 1999;15(2):141-155.
171 Irvine EJ. Development and Subsequent Refinement of the Inflammatory Bowel Disease Questionnaire: A Quality-of-Life Instrument for Adult Patients with Inflammatory Bowel Disease. *Journal of Pediatric Gastroenterology and Nutrition*. 1999;28(S4):S23-S27.
172 Lemay KR, Tulloch HE, Pipe AL, Reed JL. Establishing the Minimal Clinically Important Difference for the Hospital Anxiety and Depression Scale in Patients With Cardiovascular Disease. *J Cardiopulm Rehabil Prev*. 2019;39(6):E6-e11.
173 Puhan MA, Frey M, Büchi S, Schünemann HJ. The minimal important difference of the hospital anxiety and depression scale in patients with chronic obstructive pulmonary disease. *Health and Quality of Life Outcomes*. 2008;6(1):46.

174 Longo UG, Berton A, De Salvatore S, et al. Minimal Clinically Important Difference and Patient Acceptable Symptom State for the Pittsburgh Sleep Quality Index in Patients Who Underwent Rotator Cuff Tear Repair. *Int J Environ Res Public Health*. 2021;18(16).

175 McCarthy C, Tinsley GM, Bosy-Westphal A, et al. Total and regional appendicular skeletal muscle mass prediction from dual-energy X-ray absorptiometry body composition models. *Scientific Reports*. 2023;13(1):2590.

176 Yu S, Appleton S, Chapman I, et al. An Anthropometric Prediction Equation for Appendicular Skeletal Muscle Mass in Combination With a Measure of Muscle Function to Screen for Sarcopenia in Primary and Aged Care. *Journal of the American Medical Directors Association*. 2015;16(1):25-30.

177 Steptoe A, Pollard TM, Wardle J. Development of a measure of the motives underlying the selection of food: the food choice questionnaire. *Appetite*. 1995;25(3):267-284.

Figure 5.1. **COLONiC Participant Recruitment Flowchart**

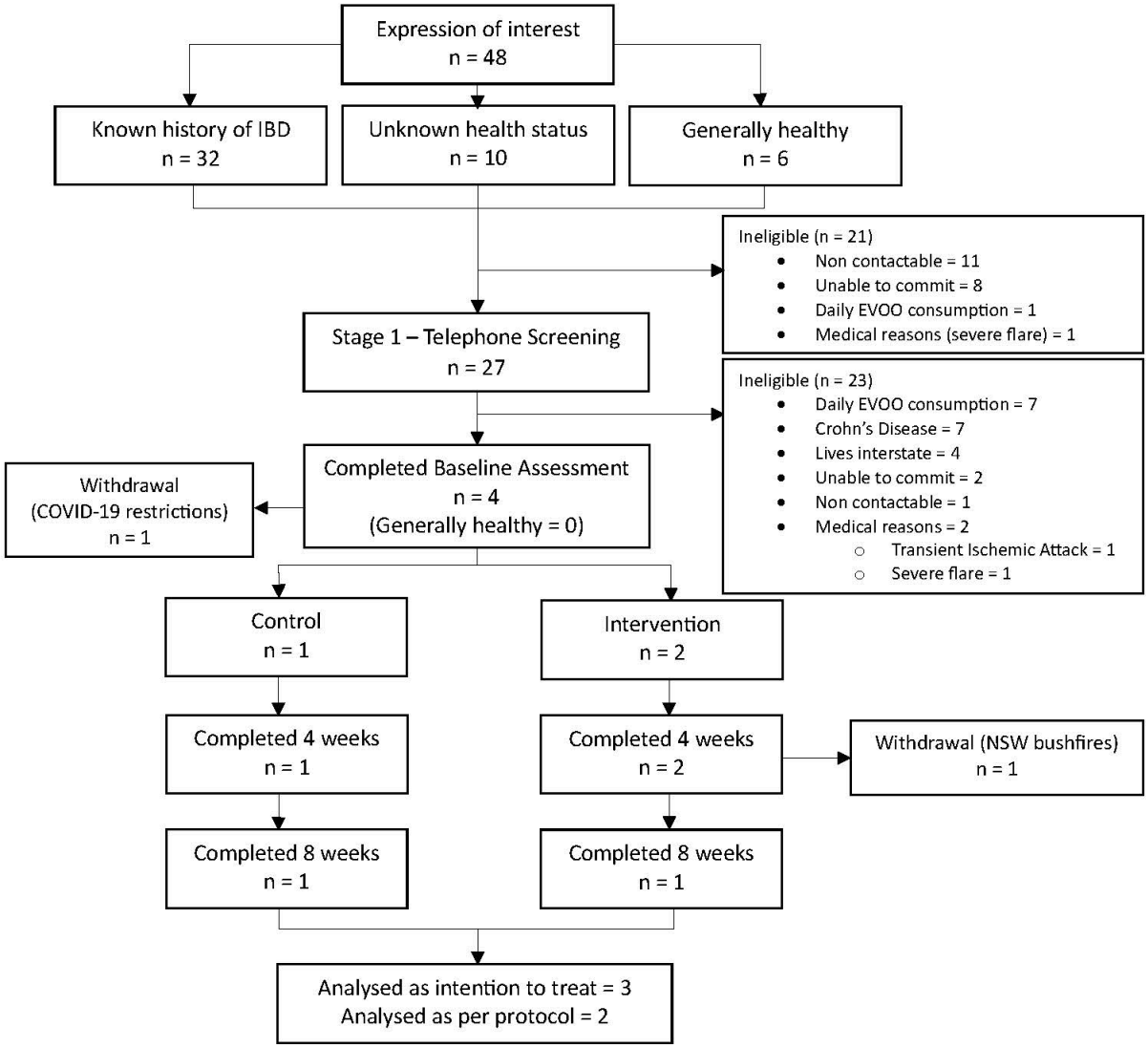


Figure 5.2. **Partial Mayo Score change at 4 weeks and 8 weeks**

Figure 5.2.1. Partial Mayo Score change at 4 weeks

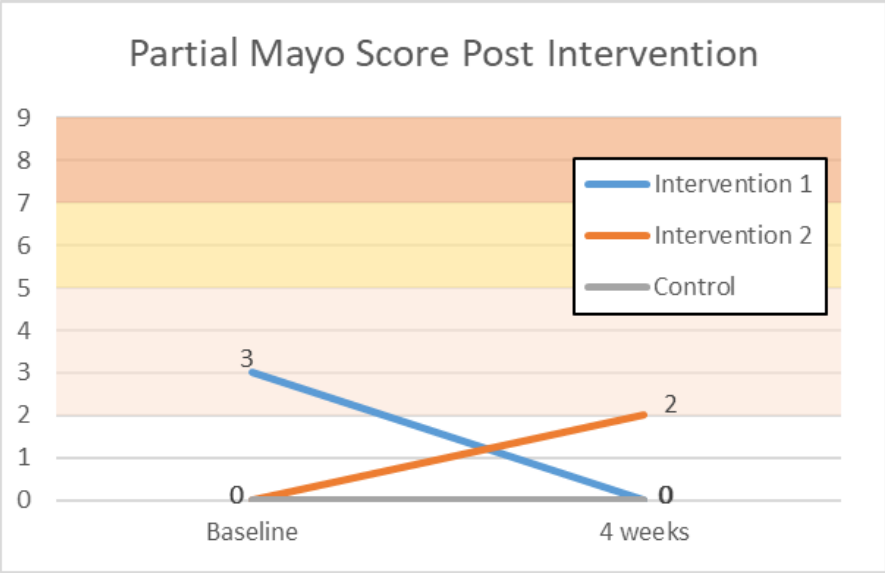
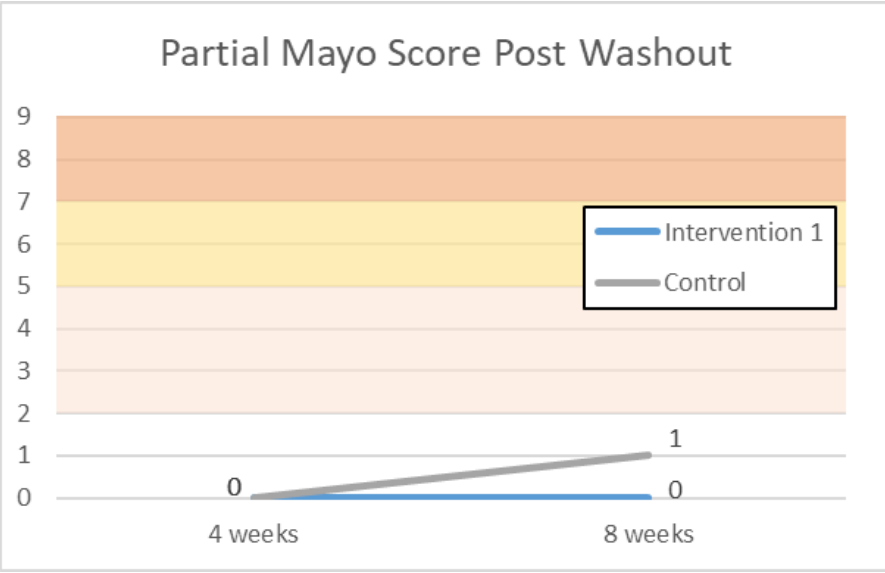


Figure 5.2.2. Partial Mayo Score change at 8 weeks)



Partial Mayo Score is an index of disease activity for Ulcerative Colitis. The 9-point tool comprises sub-scores for self-reported stool frequency (3), rectal bleeding (3), and a global physician assessment (3) over the past 3-days. Increases in the score are suggestive of worsening disease and graded according to disease severity. Clinically meaningful changes are defined as a score change of ≥ 3 [47]

***Figure 5.3*. SF-36 score change at 4 weeks and 8 weeks**

Figure 5.3.1. Physical Component Summary (PCS) score

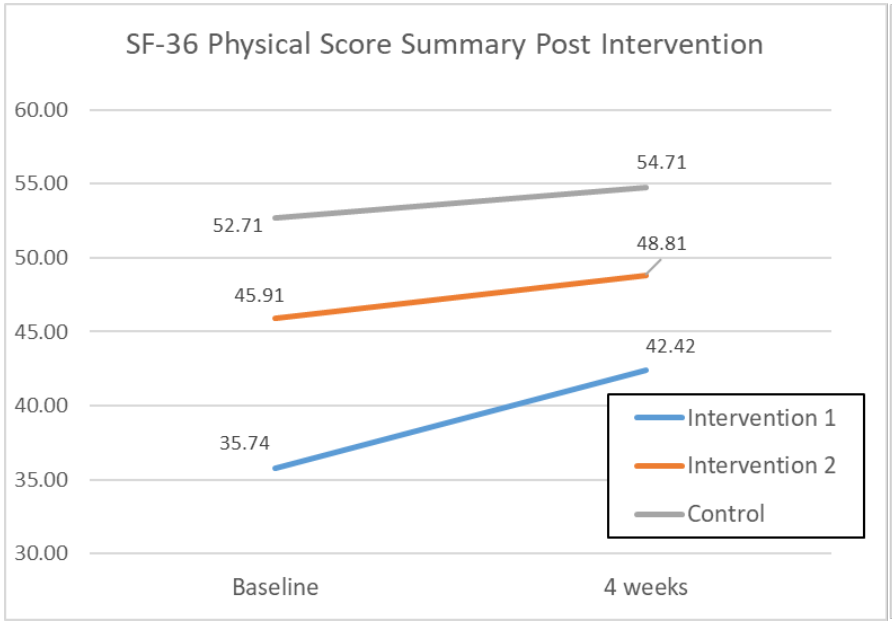
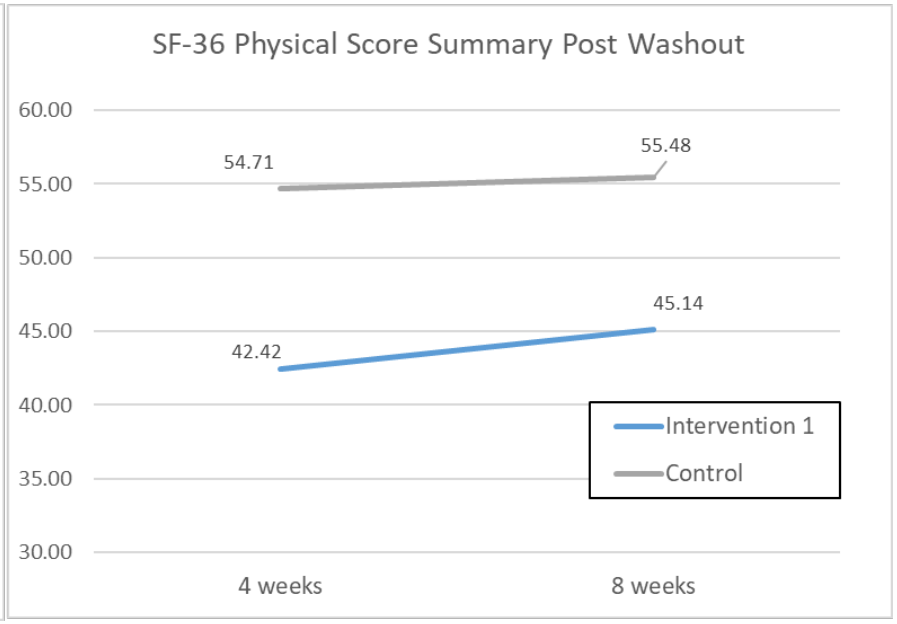


Figure 5.3.2. Physical Component Summary (PCS) score



Physical Component Summary (PCS) from the SF-36 v2 was compared against a general Australian population with a mean score of 50 ± 10. Scores scale from 0 (worst) to 100 (best). Absolute score changes of 3 to 5 points in the PCS Score is clinically significant. [63, 170]

Figure 5.3.3. Mental Component Summary (MCS) Score

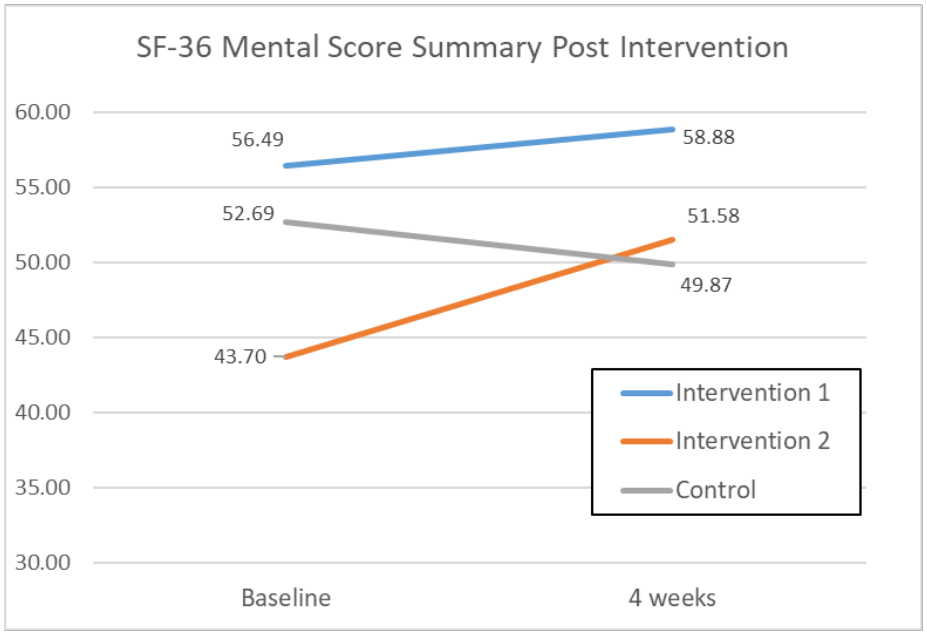
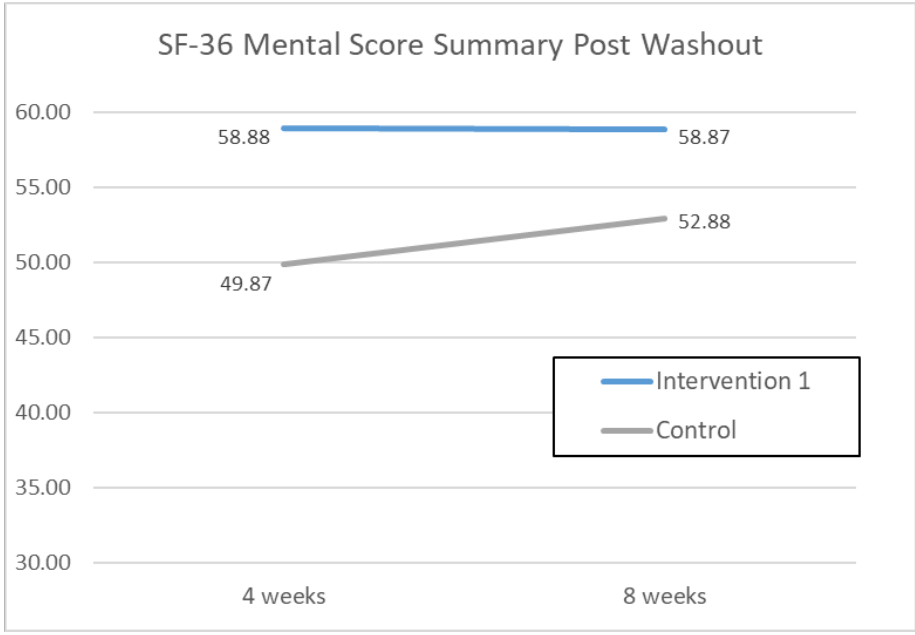


Figure 5.3.4. Mental Component Summary (MCS) Score



Mental Component Summary (MCS) from the SF-36 v2 was compared against a general Australian population with a mean score of 50 ± 10. Scores scale from 0 (worst) to 100 (best). Absolute score changes of 3 to 5 points is the MCS Score is clinically significant. [63, 170]

***Figure 5.4*. Food-related Quality of Life (FRQoL-29) scores at 4 and 8 weeks**

Figure 5.4.1. Food-related Quality of Life scores at 4 weeks

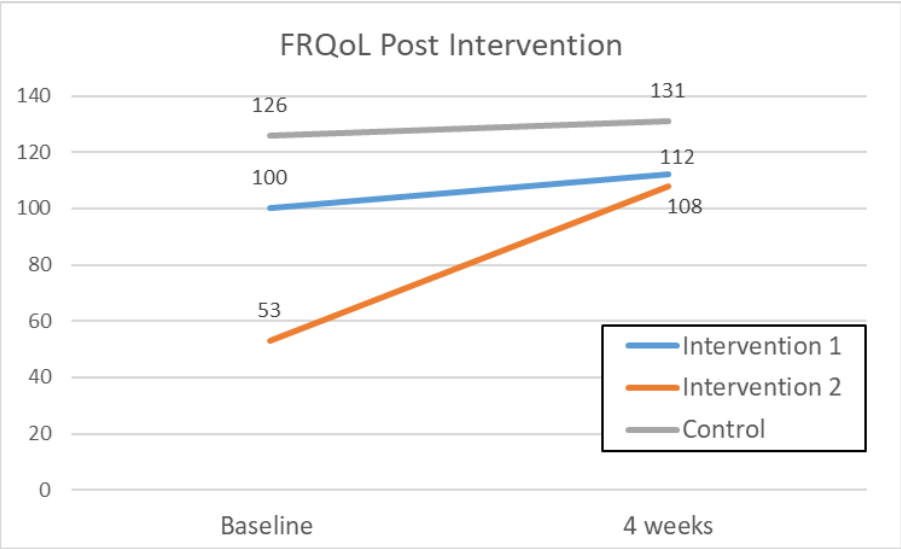
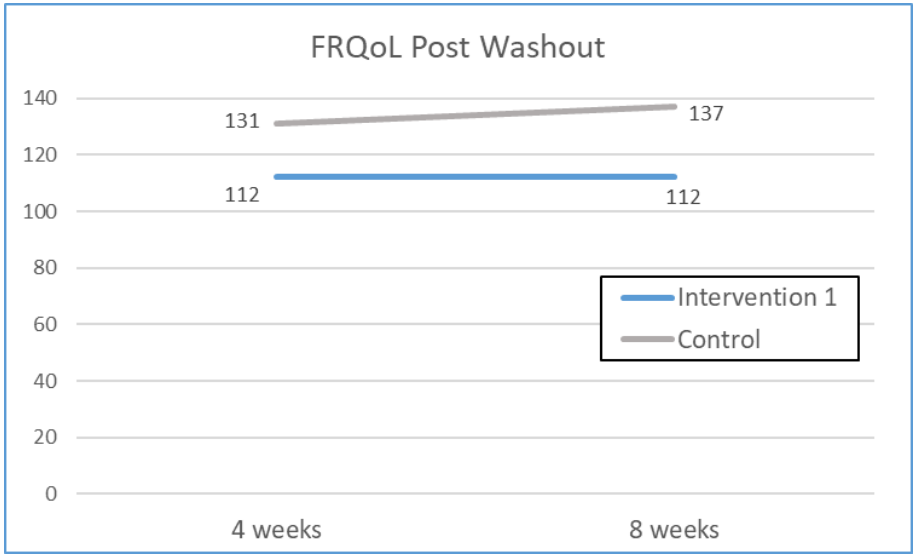


Figure 5.4.2. Food Related Quality of Life Score at 8 weeks



Food Related Quality of Life (FR-QoL-29) is a 29-item self-reported questionnaire comprising of a 5-point Likert scale delivered through a semi structured interview. The tool examines psychosocial aspect of eating and drinking in IBD. Total scores range from 29 to 145, with higher scores reflecting better food related quality of life. [53] *Minimal clinically important difference (MCID) has yet to be established for this tool.*

Figure 5.5. **Inflammatory Bowel Disease questionnaire (IBDQ-32) scores at 4 weeks and 8 weeks**

Figure 5.5.1. IBDQ-32 Total Score Post Intervention

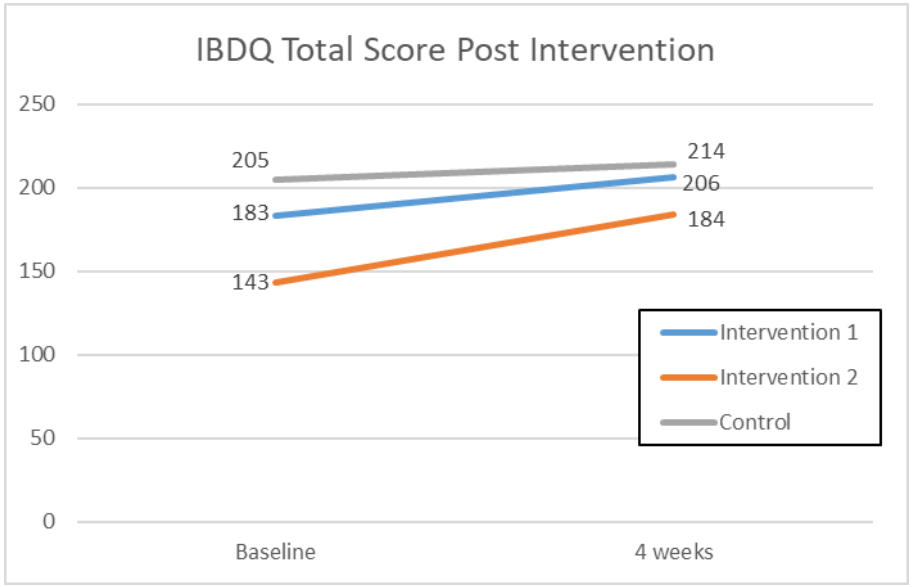
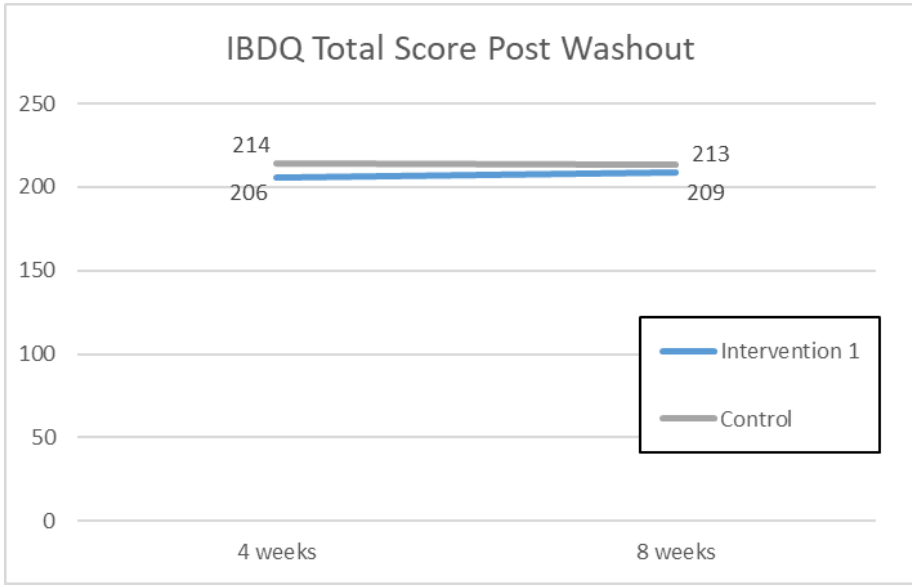


Figure 5.5.2. IBDQ-32 Total Score Post Wash-out



Inflammatory Bowel Disease Questionnaire (IBDQ-32) is a 32-item questionnaire comprising of a 7-point likert scale examining 4-domains (Bowel Score, Systemic Symptoms, Emotional Function, and Social Function) in the past 2-weeks. Total scores are reported, which range from 32 to 224. Higher scores reflect better quality of life,[52] *,*[52] *and absolute change to the total score above 30 points is clinically significant.* [62-64] *A total score above 170 is generally suggestive of stable disease* [62, 171]

Figure 5.6. **Patient Health Questionnaire 9 (PHQ-9) scores at 4 weeks and 8 weeks**

Figure 5.6.1. PHQ-9 score at 4 weeks.

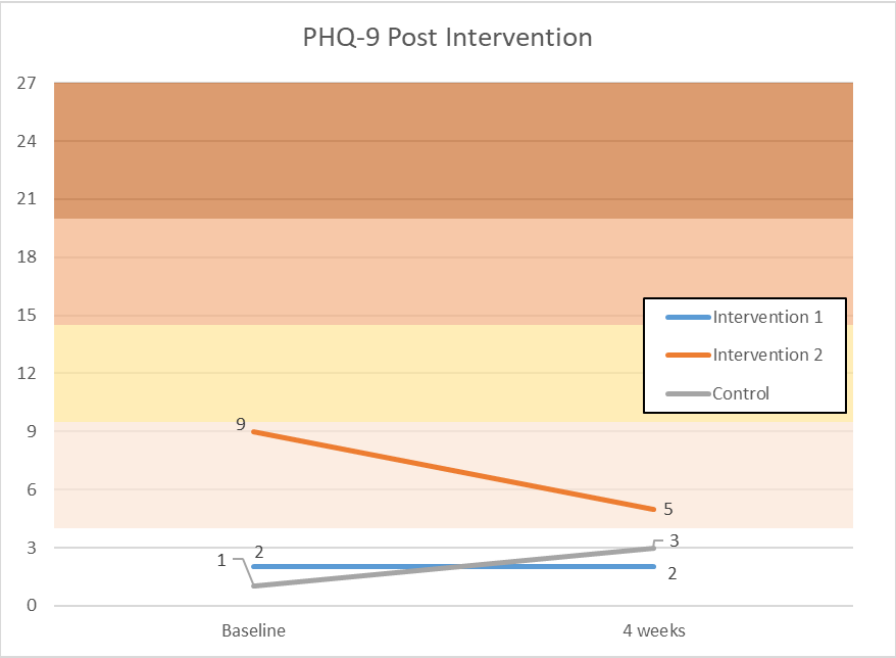
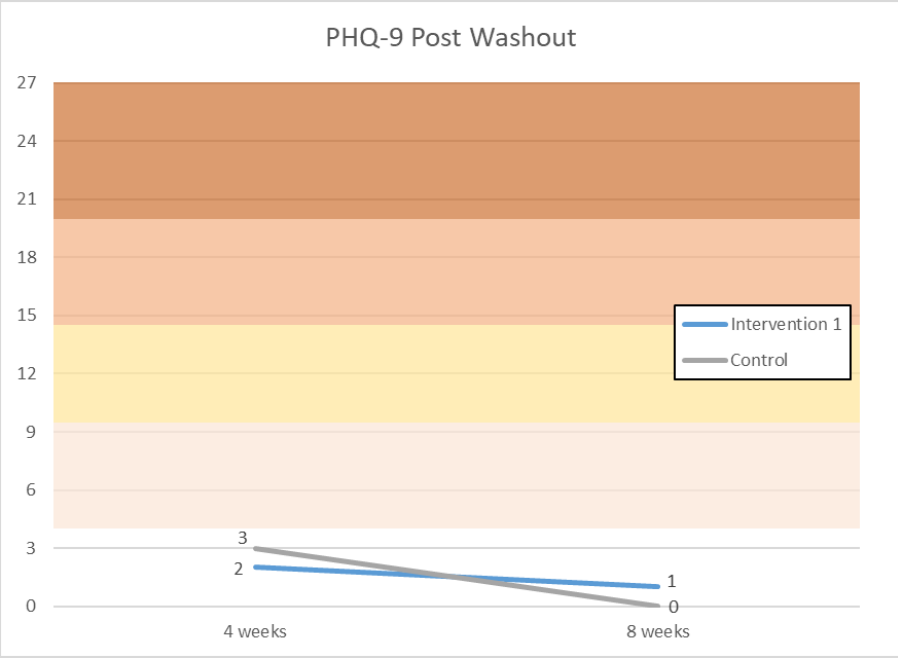


Figure 5.6.2. PHQ-9 score at 8 weeks.



Patient Health Questionnaire 9 (PHQ-9) is a self-reported, 9-item questionnaire assessing depression severity over the past 2 weeks. Each item is scaled based on frequency, ranging from not at all (0) to nearly every day (3). Scores range from 0 to 27, with higher scores correlated with greater depression symptoms and severity.

Figure 5.7. **Hospital Anxiety and Depression scale (HADS)scores at 4 weeks and 8 weeks**

Figure 5.7.1. HADS-A score at 4 weeks

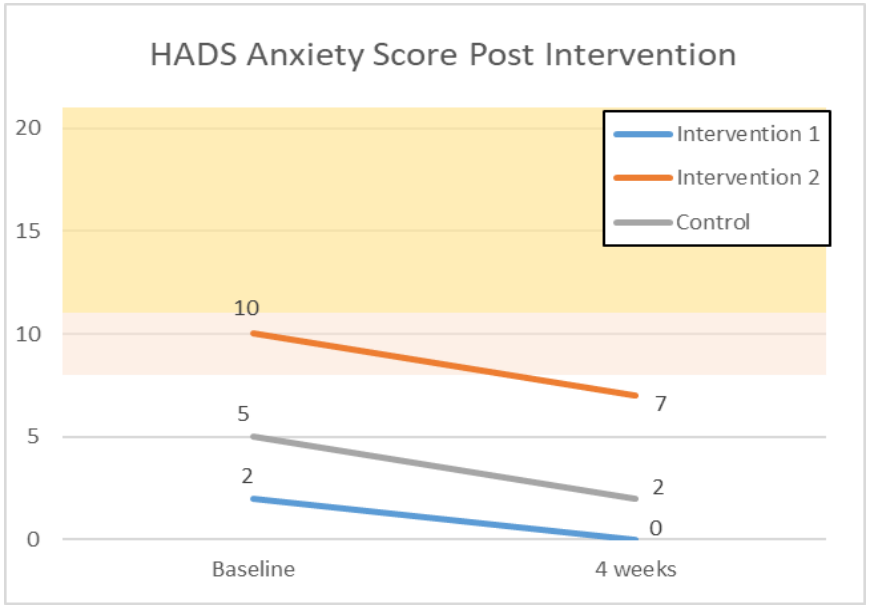
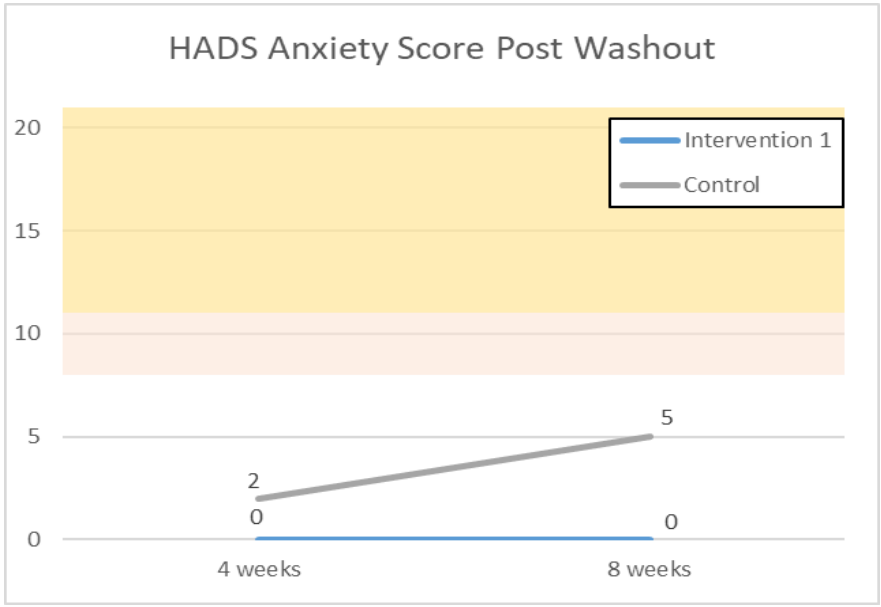


Figure 5.7.2. HADS-A score at 8 weeks



The Hospital Anxiety and Depression Scale (HADS) is a self-reported 14-item questionnaire to screen for anxiety and depression symptoms in the past week. The tool was administered in the form of a semi-structured clinical interview. The anxiety subscale (HADS-A) is comprised of 7 questions scored on a 4-point Likert scale (range 0 to 3), with a total score out of 21. Higher scores represent worse anxiety symptoms, with scores greater than 8 defined as"possible" cases while scores greater than 11 defined as "probable" cases. No minimal clinically important difference (MCID) for the HADS in IBD have been defined,however a change score of 1-2 points for each subscale have been determined to be clinically significant in outpatients with cardiovascular disease [172] and chronic obstructive pulmonary disease. [173]

Figure 5.7.3. HADS-D score at 4 weeks

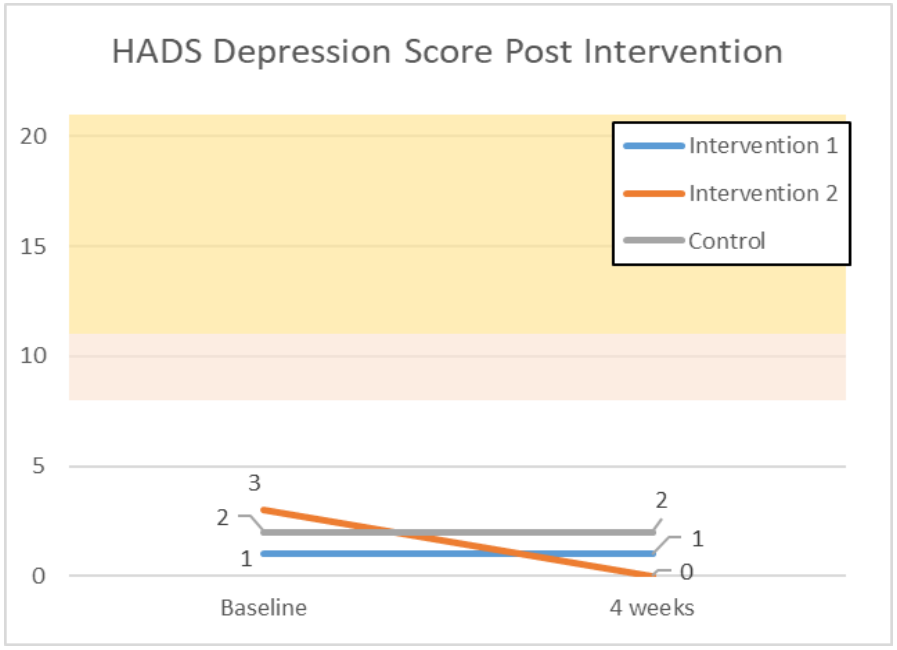
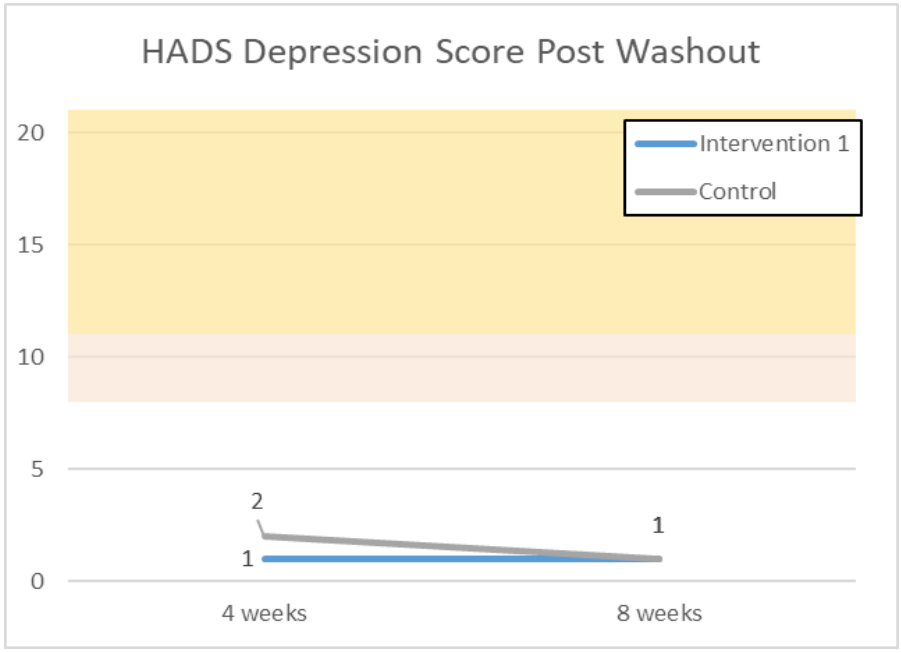


Figure 5.7.4. HADS-D score at 8 weeks



The Hospital Anxiety and Depression Scale (HADS) is a self-reported 14-item questionnaire to screen for anxiety and depression symptoms in the past week. The tool was administered in the form of a semi-structured clinical interview. The depression subscale (HADS-D) is comprised of 7 questions scored on a 4-point Likert scale (range 0 to 3), with a total score out of 21. Higher scores represent worse depression symptoms, with scores greater than 8 defined as"possible" cases while scores greater than 11 defined as "probable" cases. No minimal clinically important difference (MCID) for the HADS in IBD have been defined, however a change score of 1-2 points for each subscale have been determined to be clinically significant in outpatients with cardiovascular disease [172] and chronic obstructive pulmonary disease. [173]

***Figure 5.8*. Inflammatory Bowel Disease fatigue self-assessment scale (IBD-F) at 4 weeks and 8 weeks**

Figure 5.8.1. IBD-F total score at 4 weeks

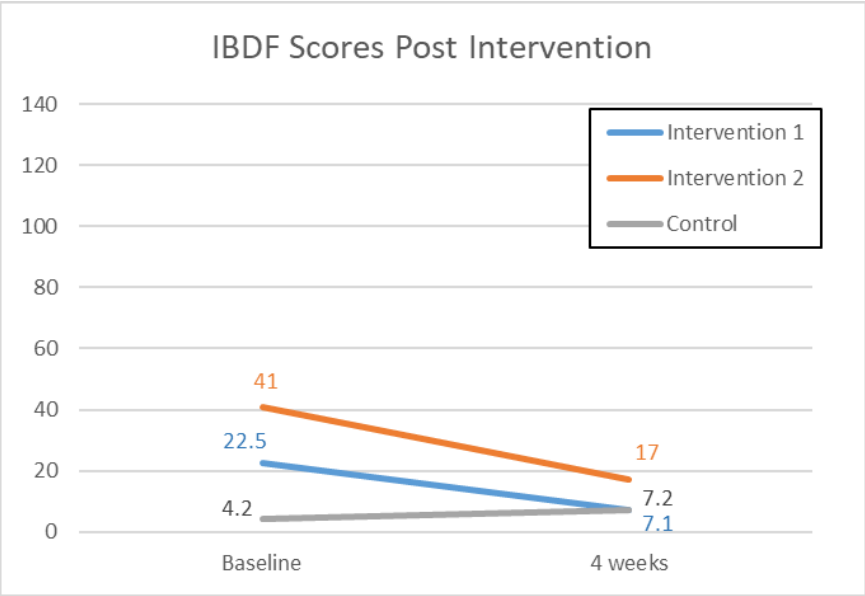
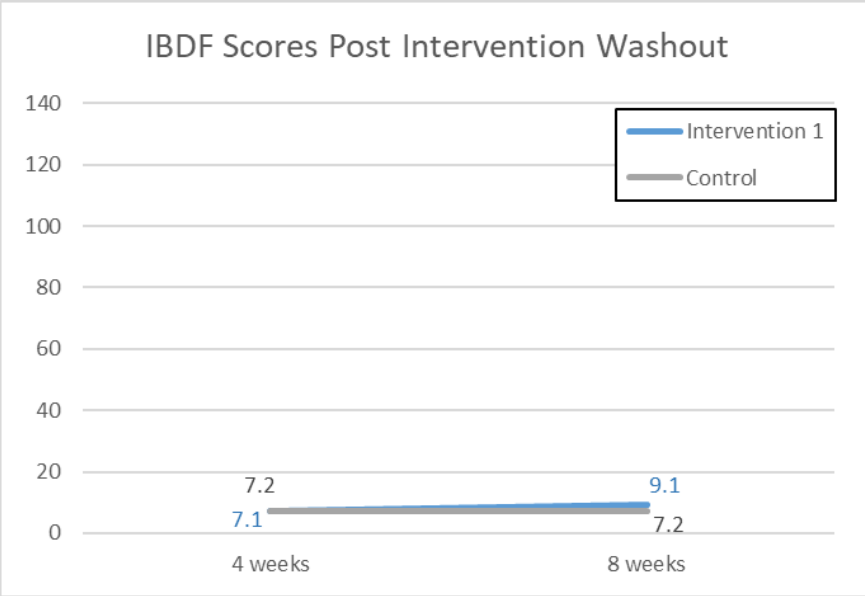


Figure 5.8.2. IBD-F total score at 8 weeks



The Inflammatory Bowel Disease Fatigue (IBD-F) self-assessment scale is a questionnaire which is used to examine and monitor fatigue severity, frequency, and duration over the past 2-week period. It comprises of 3 sections; level and duration of fatigue (Section 1, 5 questions), impact of fatigue on daily activities (Section 2, 30 question), and other factors related to fatigue (Section 3, 5 questions). Questions in sections 1 and 2 are scored on a 5-point Likert scale from 0 to 4, with a total score of 140. Section 3 is not scored but used to describe circumstances associated with fatigue. Higher scores represent worse fatigue symptoms. [57]

***Figure 5.9*. Patient Sleep Quality Index (PSQI) at 4 weeks and 8 weeks**

Figure 5.9.1. PSQI global score at 4 weeks

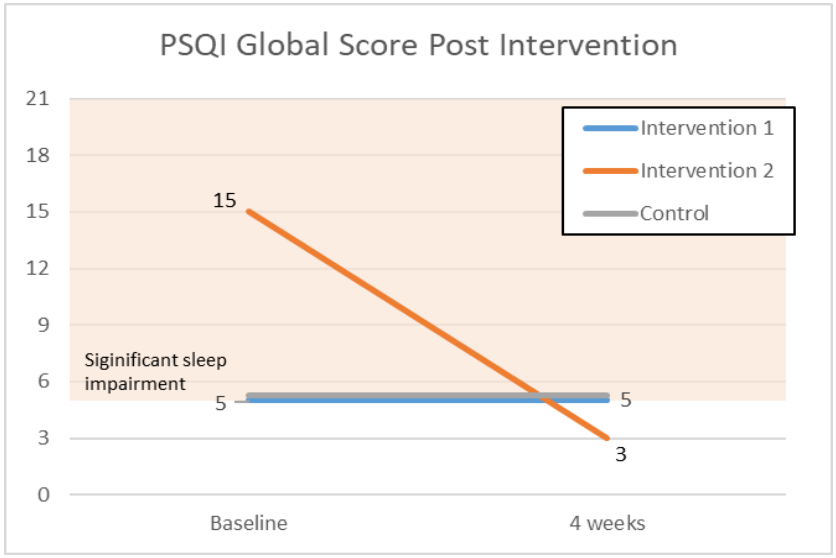
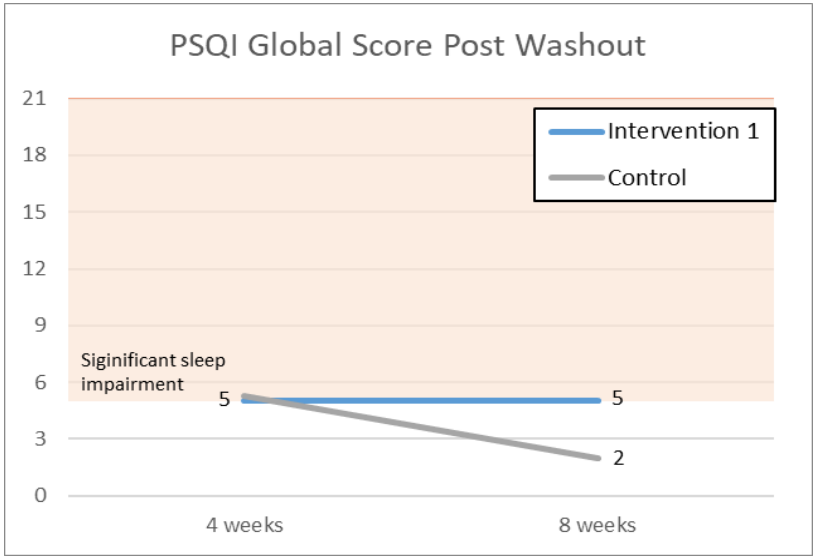


Figure 5.9.2. PSQI global score at 8 weeks



The Pittsburgh Sleep Quality Index (PSQI) examines overall sleep quality by assessing 7 components; subjective sleep quality, sleep latency, duration, habitual sleep efficiency, sleep disturbances, use of medication for sleep and daytime dysfunction over a 1 month retrospective priod. The tool is administered in the form of a semi-structured interview. Each component is scored on a range of 0 to 3, with a global score achieved by summing all the components for a maximum score of 21. Higher scores are indicative of more impairment, with a cut-off score of ≥ 5 used for poor sleep quality. [56] *Miinimal clinically important difference (MCID) in Inflammatory Bowel Disease cohorts have not been defined previously, however a change score of 5.5 points have been suggested as significant in patients undergoing rotator cuff repair.* [174].

Table 5.1. Participant characteristics at baseline

	Intervention 1	Intervention 2	Control
Age (years)	62	43	52
Sex	F	F	F
Ethnicity	Caucasian	Caucasian	Asian
Years since diagnosis	2	18	7
Comorbidities	Obesity PCOS Osteoarthritis Knee replacement (2013)	Anxiety (2018) Appendectomy (1991)	Anxiety (2011) Osteopenia (2017) Rosacea
Medications	Mesavant 1.2 g x 4 daily Methoblastin 2.5 mg weekly Methoblastin 10 mg weekly Megafol 5 mg x 6 weekly Multivitamin daily Magnesium PRN	Loxalate 20 mg daily Quetiapine XR 50 mg daily Gaviscon 10 mL PRN	Pentasa (oral) 2 g x 2 daily Imuran 125 mg daily Pentasa (suppository) 1 g x 2 weekly Caltrate 600mg daily

Notes. PRN, pro re nata or "as needed"; PCOS, Polycystic Ovarian Syndrome

Table 5.2.1 Baseline body composition

	Intervention 1	Intervention 2	Control
Height (cm)	154.1	150.7	168
Weight (kg)	98.7	59.7	73.2
Body mass index (kg/m^2)	41.6	26.3	25.9
Fat mass (kg)	53.477	19.841	28.463
Android / gynoid ratio	1.08	1.01	1.30
Android (% fat)	64.3	48.2	48.0
Gynoid (% fat)	59.3	47.8	36.8
Fat free mass (kg)	43.068	39.892	44.718
Whole body lean mass (g)	40453	37432	41751
Arms lean mass (g)	4306	3972	4693
Legs lean mass (g)	11512	11995	14436
ALM (g)	15818	15967	19129
Total SM (kg)	17.086	17.253	20.794
Arm SM (kg)	2.647	2.454	2.872
Leg SM (kg)	7.909	8.286	10.190
ASM (kg)	10.557	10.740	13.062
ASMI (kg/m^2)	4.4	4.7	4.6

Notes. ALM, Appendicular Lean Mass. SM, Skeletal Muscle. ASM, Appendicular Skeletal Musle, ASMI, Appendicular Skeletal Muscle Index. Body mass index was calculated using weight (in kg) divided by the squared height (in m). Total SM, Arm SM, and Leg SM was calculated using previously published prediction equations [175]. ASMI was calculated using ASM (in kg) divided by the squared height (in m). [175, 176]

Table 5.2.1 Baseline body composition

	Intervention 1	Intervention 2	Control
Height (cm)	154.1	150.7	168
Weight (kg)	98.7	59.7	73.2
Body mass index (kg/m^2)	41.6	26.3	25.9
Fat mass (kg)	53.477	19.841	28.463
Android / gynoid ratio	1.08	1.01	1.30
Android (% fat)	64.3	48.2	48.0
Gynoid (% fat)	59.3	47.8	36.8
Fat free mass (kg)	43.068	39.892	44.718
Whole body lean mass (g)	40453	37432	41751
Arms lean mass (g)	4306	3972	4693
Legs lean mass (g)	11512	11995	14436
ALM (g)	15818	15967	19129
Total SM (kg)	17.086	17.253	20.794
Arm SM (kg)	2.647	2.454	2.872
Leg SM (kg)	7.909	8.286	10.190
ASM (kg)	10.557	10.740	13.062
ASMI (kg/m^2)	4.4	4.7	4.6

Notes. ALM, Appendicular Lean Mass. SM, Skeletal Muscle. ASM, Appendicular Skeletal Musle, ASMI, Appendicular Skeletal Muscle Index. Body mass index was calculated using weight (in kg) divided by the squared height (in m). Total SM, Arm SM, and Leg SM was calculated using previously published prediction equations [175]. ASMI was calculated using ASM (in kg) divided by the squared height (in m). [175, 176]

Table 5.2.2 Baseline bone mineral densitometry measures

	Intervention 1	Intervention 2	Control
Total body BMC (g)	2615	2967	2459
Total body BMD (g/cm^2)	1.212	1.254	1.236
T-score	1.2	1.6	1.4
Z-score	0.8	1.3	2.0
Spine BMC L2 – L4 (g)	55.08	55.04	61.59
L2	14.95	15.92	17.12
L3	17.90	18.18	19.68
L4	22.23	20.94	24.79
Spine BMD L2- L4 (g/cm^2)	1.450	1.302	1.421
T-score	1.6	0.5	1.4
Z-score	1.6	0.3	1.9
Bilateral Total Femur BMC (g)	35.94	27.17	35.56
Bilateral Total Femur BMD (Mean, g/cm^2)	1.171	1.181	0.935
T-score	0.9	1.0	-0.9
Z-score	0.3	0.8	-0.3
Left Femur Total BMD (g/cm^2)	1.214	1.211	0.917
T-score	1.2	1.2	-1.0
Z-score	0.6	1.0	-0.5
Right Femur Total BMD (g/cm^2)	1.129	1.150	0.954
T-score	0.6	0.7	-0.7

Z-score	0	0.6	-0.2
Bilateral Femur Neck BMD (Mean, g/cm^2)	1.077	1.131	0.869
T-score	0.5	0.9	-1.2
Z-score	0.5	1.0	-0.4
Left Femur Neck BMD (g/cm^2)	1.104	1.176	0.830
T-score	0.7	1.2	-1.5
Z-score	0.7	1.3	-0.7
Right Femur Neck BMD (g/cm^2)	1.051	1.086	0.908
T-score	0.3	0.5	-0.9
Z-score	0.3	0.6	-0.1

Notes. BMC, Bone Mineral Content. BMD, Bone Mineral Density. L2, Lumbar Spine Vertebrae 2. L3, Lumbar Spine Vertebrae 3. L4, Lumbar Spine Vertebrae 4. Total femur include measurements for the femur neck, greater trochanter and lesser trochanter. Normal bone mineral density is defined as T-score ≥-1.0 SD, Osteopenia T-score between -1.0 and -2.5 SD, Osteoporosis T-score ≤ 2.5. Young healthy Caucasian women reference database was used to determine T-scores. [59] Z-scores are compared against reference populations of the same age, weight, sex, and ethnicity.

Table 5.3. Self-reported habitual physical activity 7 days at baseline, post intervention (4 weeks), and post wash-out (8 weeks)

Intervention 1

	Day 1			Day 2			Day 3			Day 4			Day 5			Day 6			Day 7		
	Activity	Duration (mins)	RPE (10)	Activity	Duration (mins)	RPE (10)	Activity	Duration (mins)	RPE (10)	Activity	Duration (mins)	RPE (10)	Activity	Duration (mins)	RPE (10)	Activity	Duration (mins)	RPE (10)	Activity	Duration (mins)	RPE (10)
Baseline	Walk	30	3	Walk	30	3	Walk	30	3	Walk	30	3	Walk	30	3	Walk	30	3	Walk	30	3
	Pilates	20	3										Curves	30	3	Curves	30	3	Curves	30	3
4-Weeks	Curves	30	3	Walk	30	3	Walk	30	3	Walk	40	4	Walk	40	3	Walk	55	3	Walk	55	3
	Walk	45	3	Curves	45	3	Curves	45	3							Curves	30	3	Curves	30	3
8-Weeks	Walk	30	4	Walk	55	4	Walk	45	3	Walk	40	3	Walk	30	3	Walk	45	3	Walk	40	3
				Curves	30	4	Curves	30	4							Curves	30	3			

Self-reported physical activity was completed 7-days prior to the 2nd in person health assessment (Assessment 2) at baseline, 4 weeks and 8 weeks. The record was completed alongside a 7-day self-reported sleep diary which accompanied an AX3 3-axis accelerometer and 3-day weighted food diary. Samples for fasting measures (stools, bloods) are provided on day 8.

Control

	Day 1			Day 2			Day 3			Day 4			Day 5			Day 6			Day 7		
	Activity	Duration (mins)	RPE (10)	Activity	Duration (mins)	RPE (10)	Activity	Duration (mins)	RPE (10)	Activity	Duration (mins)	RPE (10)	Activity	Duration (mins)	RPE (10)	Activity	Duration (mins)	RPE (10)	Activity	Duration (mins)	RPE (10)
Baseline	Walk Tai Chi	20 30	3-4 2	Walk Tai Chi	20 30	3-4	Stretching	5	2	Stretching Tai Chi	5 60	2 2	Stretching	5	2	-	-	-	Walk	50	3
4-Weeks	Walk Tai Chi	20 30	3 2	Walk Tai Chi	20 30	3 2	Stretching	5	2	Stretching Tai Chi	5 60	2 2	Stretching	5	2	Tai Chi	10	2	-	-	-
8-Weeks	Stretching Walk	5 20	3 3	Walk	20	2	Tai Chi Walk	20 20	2 3	-	-	-	Stretching Tai Chi	5 60	2 2	-	-	-	-	-	-

Self-reported physical activity was completed 7-days prior to the 2nd in person health assessment (Assessment 2) at baseline, 4 weeks and 8 weeks. The record was completed alongside a 7-day self-reported sleep diary which accompanied an AX3 3-axis accelerometer and 3-day weighted food diary. Samples for fasting measures (stools, bloods) are provided on day 8.

Table 5.4. Analysis of 3-day weighed food diaries at baseline, 4 weeks and 8 weeks.

	Intervention 1			Intervention 2	Control		
	Baseline	4 weeks	8 weeks	Baseline	Baseline	4 weeks	8 weeks
Energy Intake (kJ)	6788.5	7975.8	8296.9	8794.6	7628.7	6267.3	6167.8
Protein (g)	94.7	101.8	96.1	97.7	99.5	86.8	83.9
Carbohydrates (g)	142.9	161.7	183.5	186.9	212.4	156.3	165.5
Sugars (g)	69.0	59.2	83.3	72.4	53.2	58.0	55.6
Starch (g)	72.6	102.5	100.1	114.5	157.1	98.0	109.0
Dietary fibre (g)	16.1	24.3	17.2	20.9	21.7	19.9	16.9
Total fat (g)	55.4	74.4	75.9	96.7	58.9	53.9	49.1
Monounsaturated fat (g)	20.2	31.3	27.9	35.1	25.9	24.1	20.2
Polyunsaturated fat (g)	7.4	11.2	7.8	13.0	8.8	9.8	9.2
Saturated fat (g)	23.0	25.7	33.5	39.4	18.5	15.5	14.8
Trans fatty acids (g)	0.7	0.7	0.9	2.1	0.7	0.7	0.3
Cholesterol (mg)	378.1	397.0	654.5	406.6	314.2	208.8	431.3
Omega-3 fatty acids (g)	0.23	0.53	0.28	0.02	0.14	0.37	0.12
Linoleic acid (g)	5.55	7.59	6.39	4.53	7.29	7.92	6.95
Alpha linoleic acid (g)	0.78	1.64	1.03	0.61	0.68	0.73	1.35
Eicosapentaenoic acid (g)	0.10	0.16	0.10	0.00	0.05	0.13	0.02
Docosapentaenoic acid (g)	0.07	0.11	0.08	0.01	0.05	0.09	0.03
Docosahexaenoic (g)	0.07	0.26	0.09	0.02	0.05	0.15	0.08
% monounsaturated fat	39.9	45.9	40.4	35.0	48.6	48.8	45.7

% polyunsaturated fat	14.6	16.4	11.2	27.8	16.5	20.0	20.8
% saturated fat	45.5	37.7	48.4	37.2	34.9	31.3	33.5
Ash (g)	16.2	21.1	18.1	16.5	15.6	15.3	12.6
Alcohol (g)	20.7	19.6	22.9	8.6	0.0	0.0	0.0
Water (g)	1295.3	4086.8	1062.7	1816.0	3020.1	2683.8	2829.3

Based on daily averages from 3-day weighed food diaries analysed via FoodWorks 9 Professional (Xyris Pty Ltd, Australia). Diaries comprised of 2 weekdays and 1 weekend within a 7-day period. All participants completed a food diary 24 hours prior to collection of a fasting blood and stool sample.

Table 5.5. Weekly status check and reported adverse events during study participation

Table 5.5.1. Weekly status check for Intervention 1 participant

	Primary fat	EVOO consumption in past week	Abdominal Pain	Nausea	Bloating	Reduced appetite	Fatigue	Joint pain	Illness	Other	Notes	Stool frequency past 7 days	Rectal bleeding past 7 days
Week 1 intervention	EVOO	6 days				Yes	Yes			Yes	Reduced toileting	Normal	None
Week 2 intervention	EVOO	Daily					Yes			Yes	Increased cravings	Normal	None
Week 3 intervention	EVOO	5 days										Normal	None
Week 4 intervention	EVOO	5 days									Reduced toileting	Normal	None
Mid-point 1	EVOO	6 days										Normal	None
Mid-point 2	EVOO	5 days								Yes	Loose stools	Normal	None
Mid-point 2 repeat	EVOO	4 days					Yes					Normal	None
Week 5 usual care	Butter & LOO	none										Normal	None

Week 6 usual care	Butter & LOO	none									Softer stools	Normal	None
Week 7 usual care	Butter & LOO	none								Yes	Bowel discomfort	Normal	None
Week 8 usual care	Butter & LOO	none										Normal	None
Final assessment 1	Butter & LOO	none										Normal	None
Final assessment 2	Butter & LOO	none					Yes					Normal	None

Notes. EVOO, Extra Virgin Olive Oil. LOO, Light Olive Oil.

Table 5.5.2. Weekly status check for Intervention 2 participant

Intervention 2	Primary fat	EVOO consumption in past week	Abdominal Pain	Nausea	Bloating	Reduced appetite	Fatigue	Joint pain	Illness	Other	Notes	Stool frequency past 7 days	Rectal bleeding past 7 days
Week 1 intervention	EVOO	Daily										Normal	None
Week 2 intervention	EVOO	6 days										Normal	None
Week 3 intervention	EVOO	Daily										Normal	None
Week 4 intervention	EVOO	Daily										Normal	None
Mid-point 1	EVOO	Daily		Yes						Yes	Mild concussion	Normal	None
Mid-point 2	EVOO	Daily	Yes	Yes		Yes			Yes		Suspected food poisoning	3-4 more than normal	None

Notes. EVOO, Extra Virgin Olive Oil.

Table 5.5.3. Weekly status check for Control participant

	Primary fat	EVOO consumption in past week	Abdominal Pain	Nausea	Bloating	Reduced appetite	Fatigue	Joint pain	Illness	Other	Notes	Stool frequency past 7 days	Rectal bleeding past 7 days
Week 1 usual care	LOO	none			Yes				Yes	Yes	Sore throat	1-2 more than normal	Visible with stool less than half the time
Week 2 usual care	LOO	none					Yes	Yes	Yes		Cold/flu	Normal	None
Week 3 usual care	LOO	none					Yes	Yes	Yes		Cold/flu	Normal	None
Week 4 usual care	LOO	none										Normal	None
Mid-point 1	LOO	none										Normal	None
Mid-point 2	LOO	none									Back pain	Normal	None
Week 5 usual care	LOO	none						Yes				Normal	None
Week 6 usual care	LOO	none										Normal	None
Week 7 usual care	LOO	none										Normal	None

Week 8 usual care	LOO	none										Normal	None
Final assessment 1	LOO	none										Normal	None
Final assessment 2	LOO	none	Yes			Yes		Yes		Yes	Mild abdominal pain	1-2 more than normal	Visible with stool less than half the time

Notes. LOO, Light Olive Oil.

Table 5.6. Food Choice Questionnaire (FCQ) at baseline

	Intervention 1		Intervention 2		Control	
Domain	Mean (/4)	SD	Mean (/4)	SD	Mean (/4)	SD
Health	3.50	0.55	3.67	0.52	2.83	0.41
Mood	2.50	1.05	2.67	1.37	1.33	0.82
Convenience	3.40	0.55	3.20	0.84	3.80	0.45
Sensory appeal	4.00	0.00	3.75	0.50	3.00	0.00
Natural content	3.67	0.58	4.00	0.00	1.67	1.15
Price	1.33	0.58	2.00	1.00	3.00	0.00
Weight control	2.67	0.58	3.33	0.58	2.67	0.58
Familiarity	1.33	0.58	1.00	0.00	2.23	1.15
Ethics	4.00	0.00	3.67	0.58	1.00	0.00

Food Choice Questionnaire (FCQ) is a 36-item questionnaire examining 9 factors which influence food selection and rates them based on level of importance (from 1, not important at all, to 4, very important).[177] *No reference timeframe is assigned on how participants rate these individual items. Each domain is an average of individual questions, with higher scores reflecting greater importance assigned by the participant.*

Table 5.7. SF-36 8 domains and summary scores at baseline, post intervention (4 weeks), and post wash-out (8 weeks)

	Intervention 1			Intervention 2			Control		
SF-36 Health Concepts	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks
Physical Function	42.05	42.05	48.51	50.66	52.81		57.12	54.97	57.12
Role Function	46.69	52.07	52.07	46.69	52.07		55.66	53.87	55.66
Bodily Pain	43.98	52.84	52.84	39.96	48.82		52.84	59.28	59.28
General health	27.00	36.82	39.28	44.19	44.19		41.74	44.19	44.19
Vitality	49.00	52.16	52.16	36.36	45.84		49.00	49.00	52.16
Social Function	51.09	56.70	56.70	45.49	51.09		56.70	51.09	56.70
Emotional Role Function	47.45	55.23	55.23	47.45	52.64		55.23	55.23	55.23
Mental Health	61.21	58.27	61.21	46.48	55.32		55.32	52.37	55.32
Summary Score									
Physical Component Score	35.74	42.42	45.14	45.91	48.81		52.71	54.71	55.48
Mental Component Score	56.49	58.88	58.87	43.70	51.58		52.69	49.87	52.88

Physical component score and mental component score have been calculated using the factor score coefficient of the Australian population from the 1995 Australian National Health Survey [61]

Table 5.8. Inflammatory Bowel Disease questionnaire (BDQ-32) 4-domains and summary scores at baseline, post intervention (4 weeks), and post wash-out (8 weeks)

	Intervention 1			Intervention 2			Control		
	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks
Bowel Score (70)	60	66	69	45	55		68	70	68
Systemic symptoms (35)	19	27	27	12	25		29	33	33
Emotional function (84)	74	79	79	54	69		73	76	78
Social function (35)	30	34	34	32	35		35	35	34
Total Score (224)	183	206	209	143	184		205	214	213

Inflammatory Bowel Disease Questionnaire (IBDQ-32) is a 32-item questionnaire comprising of a 7-point likert scale examining 4-domains (Bowel Score, Systemic Symptoms, Emotional Function, and Social Function) in the past 2-weeks. Total scores are reported, which range from 32 to 224. Higher scores reflect better quality of life[52] and absolute change to the total score above 30 points is clinically significant. [62-64]

Table 5.9. Inflammatory Bowel Disease fatigue self-assessment scale (IBD-F) at baseline, post intervention (4 weeks), and post wash-out (8 weeks)

Table 5.9.1. IBD-F Section 1, Section 2, and Total Score

	Intervention 1			**Intervention 2**			**Control**		
	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks
Section 1 score (20)	6	3	7	12	4		1	4	4
Section 2 score (120)	16.5	4.1	2.1	29	13		3.2	3.2	3.2
Total Score (140)	22.5	7.1	9.1	41	17		4.2	7.2	7.2

The Inflammatory Bowel Disease Fatigue (IBD-F) self-assessment scale is a questionnaire which is used to examine and monitor fatigue severity, frequency, and duration over the past 2-week period. It comprises of 3 sections; level and duration of fatigue (Section 1, 5 questions), impact of fatigue on daily activities (Section 2, 30 question), and other factors related to fatigue (Section 3, 5 questions). Questions in sections 1 and 2 are scored on a 5-point Likert scale from 0 to 4, with a total score of 140. Section 3 is not scored but used to describe circumstances associated with fatigue. Higher scores represent worse fatigue symptoms, with Section 1 indicating worsening levels of fatigue and Section 2 greater impact on the individual. [57]. Adjusted scores were used to calculate Section 2 scores to account for "N/A' in the provided responses using the formula $adjusted\ score = \frac{Section\ 2\ score}{120-(number\ of\ "NA"s\ x\ 4)} \times 120$. *Cut-offs and minimal clinically important difference (MCID) have yet to be defined for this tool.*

Table 5.9.2. IBD-F Section 3 responses

	Intervention 1			Intervention 2			Control		
	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks
What do you think is the main cause of your fatigue apart from IBD?	Weight	Not eating enough	None	Trying to do too much	Trying to do too much		Ageing	Ageing	Ageing
What do you think are the other causes of your fatigue?	N/A	N/A	N/A	Inability to shut off my mind	Stress and anxiety		N/A	N/A	N/A
Have you found anything that helps with your fatigue?	Rest or nap	Rest or nap	Sleep, meditation	GP prescribed medication	None		Rest or nap	Rest or nap	Rest or nap
How long have you experienced fatigue? (years and/or months)	2 years	2 years	2 years	10 years	10 years		10 years	10 years	10 years
What is the frequency of your fatigue during this period?	Intermittent	Intermittent	Intermittent	Intermittent	Intermittent		intermittent	intermittent	intermittent

Section 3 of the Inflammatory Bowel Disease Fatigue (IBD-F) self-assessment scale is a set of 5 open ended questions administered as a semi-structured interview asking participants to describe other factors relating to their fatigue in the past 2 weeks.

Table 5.10. Pittsburgh Sleep Quality Index (PSQI) component and summary scores at baseline, post intervention (4 weeks), and post wash-out (8 weeks)

	Intervention 1			Intervention 2			Control		
	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks
Subjective quality (3)	1	1	1	2	0		1	1	1
Sleep latency (3)	1	1	1	2	1		1	1	0
Sleep duration (3)	1	1	1	1	0		1	1	0
Habitual sleep efficiency	0	0	0	2	0		0	0	0
Sleep disturbance (3)	1	1	1	2	1		1	1	1
Sleep medications (3)	0	0	0	3	0		0	0	0
Daytime dysfunction (3)	1	1	1	3	1		1	1	0
Global PSQI Score (21)	5	5	5	15	3		5	5	2

The Pittsburgh Sleep Quality Index (PSQI) examines overall sleep quality by assessing 7 components; subjective sleep quality, sleep latency, duration, habitual sleep efficiency, sleep disturbances, use of medication for sleep and daytime dysfunction over a 1 month retrospective priod.

The tool is administered in the form of a semi-structured interview. Each component is scored on a range of 0 to 3, with a global score achieved by summing all the components for a maximum score of 21. Higher scores are indicative of more impairment, with a cut-off score of ≥ 5 used for poor sleep quality. [56] *Miinimal clinically important difference (MCID) in Inflammatory Bowel Disease cohorts have not been defined previously, however a change score of 5.5 points have been suggested as significant in patients undergoing rotator cuff repair.*[174]

CHAPTER 6: DISCUSSION AND CONCLUSION

6.1. The Purpose of this Thesis

Diet remains a key area of interest for both patients and clinicians managing Inflammatory Bowel Disease (IBD), with a range of dietary strategies proposed in literature. Dietary advice and nutrition research often apply a uniform approach to IBD management, despite the variability of food-related risk factors and therapeutic responses between IBD phenotypes. It is increasingly clear that a one-size-fits-all dietary approach is not effective, highlighting the need for more flexible and individualised strategies. Additionally, significant gaps remain in the evidence regarding the underlying mechanisms of food-related sensitivity in IBD, the efficacy and safety of dietary interventions, and the role of individual food ingredients in shaping the overall nutritional value and impact of a diet. As such, the primary aim of this thesis was to bridge these gaps in the evidence by investigating the relationships among dietary factors, health status, and lifestyle in individuals with IBD, as well as systematically review the pre-clinical literature and conduct a pilot intervention study of the effects of a theoretically-grounded, novel single food- extra virgin olive oil (EVOO), to define its impact on health outcomes in ulcerative colitis (UC).

Six chapters were written to address the overarching aims of this manuscript. In **Chapter 1**, we provided a background and overview of the relationship between diet and IBD, with a particular focus on ulcerative colitis. We highlighted the gaps in existing literature and opportunities for robust nutrition investigations in this cohort. In **Chapter 2**, we presented a protocol for two concurrent studies which involved comprehensive examination of the health status, body composition, habitual diet, physical activity, psychosocial wellbeing, and experience with nutrition support in individuals living with IBD. The first study was a cross-sectional study assessing individuals diagnosed with CD or UC investigating the relationships

among physical fitness, quality of life and disease activity in people with Inflammatory Bowel Disease (XIBD). Through this study, we aimed to examine patient attitudes and management strategies adopted by individuals living with UC and contrast these findings with individuals with CD to highlight similarities and differences between these two cohorts. The second project was: the Consequences of OLive Oil replacemenNt on Ulcerative Colitis (COLONiC) study. This novel randomised controlled trial aimed to investigate the effects of replacing fats and oils used in meal preparation with EVOO and it's impacts on health outcomes in UC as well as the broader diet. A washout phase was incorporated into COLONiC to assess residual effects of the intervention, and as part of the initial study design, we also aimed to compare the impact of these intervention in generally healthy populations and assess the gut microbiome of all participants. In **Chapter 3**, we examined findings from XIBD, in which we had hypothesised the symptomatic presentation between CD and UC would be reflected in differing patient attitudes and management strategies, presenting an opportunity to explore and develop more targeted support strategies in each population. **Chapter 4** was a published systematic literature review of randomised controlled trials examining the impact of one specific targeted nutritional approach to IBD: the effect of olive oil-based interventions on disease presentation in UC, incorporating findings from both human and animal trials. In **Chapter 5**, we examined findings from the COLONiC pilot study.

6.2. Key Findings

In **Chapter One** we introduced the complex interplay between genetic host factors, lifestyle, and environmental factors on the development of IBD from epidemiological data, and potential intervention strategies derived from those observations. Several consensus statements on the topic of nutrition in IBD highlight both recent advancements to IBD care and the increasing

recognition of evidence-based dietary approaches in improving health outcomes in this population. Despite ongoing interest on this topic, several barriers exist both within literature and the unpredictability associated with managing IBD, which may preclude the development of IBD-specific diets in favour of more conservative guidelines.

Considering these gaps in the literature, cross sectional studies highlight the significant unmet needs of individuals living with IBD, particularly on the topic of diet. A range of IBD-specific and non-specific diets have been described in literature, with variable levels of quality regarding their efficacy. Unfortunately, challenges in adopting these strategies are commonly reported, and as such individuals living with IBD often adopt multiple sequential diets through trial and error.

Most recent advancements highlight the strong evidence supporting the use of partial enteral nutrition in facilitating remission in CD, while strategies in UC remains elusive. Evidence points towards variability in response to therapy between CD and UC, as evidenced by differing risk factors between the two conditions. These variances likely extend to dietary response as well, thus the need for more targeted approaches in this cohort is evident.

6.2.1. Findings from the IBD Cross Sectional Study

To better understand the lived experience on the topic of food and nutrition management strategies of individuals living with ulcerative colitis (UC) and compare their experiences with Crohn's disease (CD), we developed a protocol (**Chapter 2**) for a comprehensive cross-sectional study examining a range of health, lifestyle, and psychosocial parameters in both UC

and CD (**Chapter 3**). Thirty-eight participants enrolled into this study, 17 participants with UC and 21 participants with CD (50% women). From this study, we found significant gaps in nutrition support as evidenced by 6/38 (16%) participants reporting prior dietetic intervention, while 21/38 (55%) reported having attempted a specialised diet for the management of IBD. The highest number of diets attempted by a single person since their diagnosis was 9, while another participant reported following 4 diets concurrently during the study. Most participants reported being unsure of the efficacy of the diets attempted previously and would have appreciated dietetic support, while 4/38 participants (all with UC) reported never receiving a dietetic referral despite their interest. One participant voiced their scepticism of dietitians based on poor past experience, highlighting variability in the perceived quality of care in this cohort.

Concerningly, we also noted that all participants in the study were eating below their estimated energy requirements, 23/38 (61%) of participants reported either food restriction or food avoidance for symptom control with a range of foods implicated. More than half (55%) of participants reported musculoskeletal impairments in their medical history, while body composition results indicated 9/36 (25%) of participants completing a bone mineral density scan had scores consistent with osteopenia or osteoporosis in the hip and/or spine. Very concerningly, several participant had low skeletal muscle mass based on published thresholds,[1] despite the average age being 34.7±10.6 years (range 19-62 years). These results suggests a markedly increased risk for sarcopenia later in life in this cohort. Significant comorbidities were also identified in this cohort, with questionnaires indicating high rates of depressive symptoms (18-52%), anxiety (19-41%), fatigue (97%) and impaired sleep quality (57-65%), most of which were correlated with each other, highlighting the substantial physical and psychological burden in this population, concordant with existing literature.[2-4]

Interestingly we observed limited statistical difference between nutrient intake and reported food habits between IBD classifications, however greater Food Choice Questionnaire scores (indicating greater selectivity of food options) were observed in participants with UC. Likewise, although significantly poorer sleep efficiency (p<0.001) and higher prevalence of anxiety symptoms were identified in UC, we observed comparable outcomes for most health-related quality of life outcomes between IBD phenotypes. This similarity is significant, as disease burden in UC is at times underestimated compared to CD.[4] Considering the small sample size within each participant group, these findings should be interpreted with caution. What is quite clear however, is the significant need for robust, targeted evidence-based interventions in both UC and CD due to the lack of dietary support and impairments described.

6.2.2. Olive-Based Interventions in Intestinal Inflammation

As part of the central theme of this thesis in its initial conception, a systematic literature review of randomised controlled trials (**Chapter 4**) was conducted to evaluate the effects of olive oil and its components on the clinical presentation and health outcomes in ulcerative colitis. From 10,624 unique papers, we included 19 randomised controlled studies in this systematic review. Notably, at the time of publication we found no eligible human trials. Use of combined interventions in which olives or its components formed part of a comprehensive dietary prescription, and uncontrolled trials severely limited our ability to independently verify the effects of on disease outcomes. Extra virgin olive oil and/or regular olive oil were used in 14 of the 19 animal trials, with the remaining studies using polyphenols found in olives. The 19 animal trials were heterogeneous in nature which precluded a meta-analysis; however, a broad range of outcomes were identified.

Olive-based interventions imparted protective effects against the development and progression of chemically-induced colitis in murine models of disease. We summarised reduced disease activity scores with moderate-to-large effect sizes (ESs) of -0.66 (95% CIs -1.56, 0.24) to -12.70 (95% CIs -16.8, -8.7), reduced mortality rates, weight preservation, and lower concentration of inflammatory markers particularly, Tumour Necrosis Factor alpha (TNF-α) and Interleukin-6 (IL-6), favouring the interventions. Examination of colon morphology similarly resulted in lower histology scores, reduced weight/length ratios and preservation of mucosal architecture particularly in the middle and distal colon in the intervention. Greater alpha diversity of commensal gut bacteria following olive oil intervention was also noted, which was theorised by the investigators to have contributed to these observations.

Despite the promising results, translating these findings into human cohorts should be approached with extreme caution. Firstly, the lack of randomised human trials from the initial review highlights a clear gap in the evidence which requires further investigation. Search alerts for new publications were maintained until the 3rd of January 2025, in which no new eligible human trials were identified highlighting a gap in the evidence. Secondly, significant heterogeneity was observed between studies, including the animal model selected, method of inducing colitis, the type and dose of the intervention, and mode of administration. The use of high doses of olive polyphenols may also raise concerns for polypharmacy and toxicity which should be considered. Finally, we identified significant variability on the reporting of experimental parameters in using the SYRCLE's Risk of Bias tool for animal studies [5] highlighting the need for caution in translating animal studies and more transparent reporting practices.

6.2.3. Findings from the COLONiC Randomised Controlled Trial

Chapter 5 describes the results of the COLONiC study examining the effects of a 4-week dietary intervention using EVOO in place of usual cooking oils or fats in culinary preparation towards UC disease activity. The secondary aim of this investigation was to examine residual effects of dietary change, and broader impacts to dietary patterns. Due to paucity of participants, we present a pilot study involving 3 participants diagnosed with UC (all women), with two completing the full study duration (1 intervention, 1 control) while another participant in the intervention withdrew at completion of the 4-week intervention due to circumstances unrelated to the study. No adverse events attributable to the intervention were reported throughout the study duration, and all participants in the intervention group complied with incorporating the intervention into habitual intake. No specific consumption targets were provided in this study in the interest of maintaining habitual intake, with an average 15 mL of EVOO consumed daily by both intervention participants.

We observed clinically meaningful improvements to disease activity as indicated by a 3-point reduction on the Partial Mayo Score [6] following 4 weeks of EVOO consumption in one intervention participant. These changes were accompanied by improvements to Food-related Quality of Life (FRQoL-29), Improvements to the anxiety sub domain of the Hospital Anxiety and Depression Scale (HADS-A), and improvements to Inflammatory Bowel Disease Fatigue scale (IBD-F). Notably, changes were sustained during the 4-week washout period following cessation of the intervention. which may indicate some residual effects, although without examination of gut microbiome outcomes the mechanism for this observation remains uncertain. Furthermore, considering the small participant numbers these findings should be interpreted with caution.

Findings from the 2nd intervention participant were less clear. We observed a 2-pont increase to the Partial Mayo Score attributed to food poisoning which resolved the following week. No other IBD symptoms nor adverse events were reported throughout the intervention, thus it is unlikely to be related to IBD. However, it should be acknowledged that the lack of endoscopic results limits our ability to confirm this with certainty. Beyond disease severity scores, we observed significant changes in a range of health-related quality of life outcomes including clinically meaningful improvements in the Patient Health Questionnaire 9 (PHQ-9), both sub domains of the HADS, and the Pittsburgh Sleep Quality Index (PSQI). Due to this participant's withdrawal, it is unclear if the changes reported were sustained in the washout phase.

Findings from the usual care participant indicated that disease activity, health-related quality of life, fatigue, sleep, and diet remained largely stable throughout the study period. However, notable improvements were observed in responses to the FRQoL, the Inflammatory Bowel Disease Questionnaire (IBDQ-32), and the PSQI, with these benefits sustained between weeks 4 and 8.

Beyond evaluations of disease outcomes and health-related quality of life measures, the changes to habitual diet following EVOO intervention demonstrated some interesting results. Compared to the usual care participant, the intervention participant increased their energy intake, fibre intake, monounsaturated fatty acids, polyunsaturated fatty acids, and omega-3 fatty acids by week 4 of the intervention. These changes returned to baseline levels following the cessation of the intervention at 8 weeks, while the results from the usual care participant remained stable.

As described in **Chapter 1,** single dietary modifications are likely to impact other aspects of the diet, regardless of intent, potentially influencing food choice, dietary composition and behaviour. It is interesting that the nutrients which increased during week 4 predominantly consist of anti-inflammatory components of the diet which we described in **Chapter 3**. Although day-to-day variability of dietary intake may introduce bias and explain some of these differences, the change of dietary intakes which coincided with the intervention presents an interesting area of further exploration. It should be acknowledged that evaluation of usual dietary patterns remains a challenge in research, particularly in investigations such as the COLONiC study involving free-living individuals in a community setting. Recall bias, misreporting of foods, intentional or unintentional changes to habit during the recording period and participant burden associated with recording food intakes are significant sources of error in evaluating habitual diet [7] which should be acknowledged. Although food records were verified in this study, the accuracy of the information presented is dependent on individual participants while the activity present additional participant burden. Objective measures such as inflammatory cytokines concentrations [8] and urinary hydroxytyrosol [9] were considered to assess EVOO intake, however the cost and resources associated with evaluating these outcomes should also be considered.

Finally, score changes observed across all participants highlight the importance of randomised controlled trials in this population, as noted in the heterogenous responses between intervention participants and the improvements to health outcomes in the usual care participant. As highlighted in **Chapter 4**, the COLONiC study is to our knowledge the first randomised controlled trial examining dietary intervention using EVOO in community dwelling participants living with UC. Considering the high level of need and significant gaps in research

described in this manuscript, and the very small number of participants enrolled, further research is critical.

6.3. Limitations

There were several limitations to this thesis that are summarised below:

- For the systematic literature review, significant heterogeneity between included studies were noted including different animal models, mode of inducing colitis, type of intervention, duration of the intervention, mode of administering the intervention, and outcome measures selected precluding a meta-analysis of the findings.

- Considering the timing of the publication of the systematic literature review and submission of this manuscript, new randomised controlled trials examining the role of olive-based interventions in IBD may have been published. Alerts for new publication meeting the inclusion criteria of the systematic literature review were maintained until the 3rd of January 2025, and grey searches during the writing process of this manuscript have yet to identify any new evidence in humans. We did identify several studies which used olive oil as a comparator rather than an intervention, which would not have met our inclusion criteria. Because these search alerts may not sufficiently present all new publications, a systematic approach should be considered to ensure these studies are appropriately identified.

- The primary challenge of this thesis was the inability to meet the estimated sample size for the COLONiC study due to extenuating circumstances during the recruitment process, challenges in recruiting participants who met our inclusion criteria, and the number of assessments which were both resource intensive for the investigators and presented a potential barrier for participation. As such, findings from **Chapter 5** are not generalisable with more extensive investigations warranted. It was notable that many prospective participants expressing interest were ineligible due to pre-existing habitual consumption of EVOO, however amounts varied between these participants and the variety of EVOO consumed wasn't quite clear. Future studies could consider higher doses of EVOO to align with findings from Mediterranean diet studies and animal trials or consider the use of supplementation using polyphenols found in EVOO to minimise confounding from diet changes. Future studies could also consider case-control trials examining differences between individuals living with IBD who regularly consume EVOO and those who do not to provide additional insight on its potential role in shaping dietary composition and eating patterns.

- Recruitment of generally healthy controls was unsuccessful in this study due to both external circumstances, and frequency of assessments which forms part of the COLONiC study which meant many prospective participants were unable to commit to the required study duration.

- Funding constraint was a limiting factor in analysing gut microbiome outcomes, stool and blood markers of inflammation, as well as habitual activity and sleep patterns as captured by the Axivity AX3 3-axis accelerometer. Inclusion of these parameters would

have provided additional insight into the interactions among diet, host microbiome, and disease expression in IBD in both the XIBD and COLONiC studies.

- Evaluations of dietary intake through 3-day weighed food diaries remains a challenge due to the significant burden placed on participants. We incorporated some guardrails to ensure that the dietary data provided was accurate and representative of habitual intake, however some variability is likely.

- Estimation of energy requirements using prediction equations rather than measuring resting metabolic rate through indirect calorimetry or doubly labelled water limited our ability to examine more accurate estimations for daily energy needs.

6.4. Concluding Remarks

The overarching aim of this thesis was to address a significant gap in literature on the role of dietary components and their impact on disease presentation and health outcomes in IBD. Rather than a comprehensive dietary approach, we nominated a single food interventions strategy and aimed to comprehensively evaluate its effects on ulcerative colitis, with the view that this manuscript provides a strong case for future novel dietary approaches in IBD. To address the main aim of the written manuscript, we developed a study protocol evaluating the health status, body composition, habitual diet and physical activity, lived experience with dietary interventions, psychological health, fatigue and sleep quality of individuals living with IBD to examine the current landscape of lifestyle approaches in IBD. We systematically examined the evidence on the role of olive-based interventions on IBD outcomes, which revealed strong support from pre-clinical studies in animal models but highlighted the need for

further research considering the lack of robustly designed studies in human cohorts. Finally, we conducted a randomised controlled trial to evaluate the impact of an EVOO intervention on the disease activity and quality of life of individuals living with UC, which examined many variables influencing health outcomes in this cohort, although conclusions could not be drawn due to limited sample size In the discussion of this chapter, we reflected on our findings including some of the difficulties in conducting randomised controlled trials in this cohort and propose modifications for future trials.

In our approach to this topic, we utilised a broad range of evidence-based approaches and scientific methodologies including a cross-sectional study, a systematic literature review, a novel randomised controlled trial, and statistical analysis of our findings where warranted. Although there were several key limitations due to difficulties in recruiting sufficient participant numbers in the randomised controlled trial, we identified several key findings which would inform future trials investigating novel nutritional strategies to optimally support individuals living with this condition.

6.5. References

1 Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age and Ageing*. 2019;48(1):16-31.

2 Yarlas A, Rubin DT, Panés J, et al. Burden of Ulcerative Colitis on Functioning and Well-being: A Systematic Literature Review of the SF-36® Health Survey. *Journal of Crohn's and Colitis*. 2018;12(5):600-609.

3 Bernstein CN, Nugent Z, Shaffer S, Singh H, Marrie RA. Comorbidity before and after a diagnosis of inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*. 2021;54(5):637-651.

4 Le Berre C, Ananthakrishnan AN, Danese S, Singh S, Peyrin-Biroulet L. Ulcerative Colitis and Crohn's Disease Have Similar Burden and Goals for Treatment. *Clinical Gastroenterology and Hepatology*. 2020;18(1):14-23.

5 Hooijmans CR, Rovers MM, de Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC Medical Research Methodology*. 2014;14(1):43.

6 Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis*. 2008;14(12):1660-1666.

7 Gavrieli A, Trichopoulou A, Valsta LM, et al. Identifying sources of measurement error in assessing dietary intakes – Results of a multi-country ring-trial. *Nutrition, Metabolism and Cardiovascular Diseases*. 2019;29(2):127-134.

8 Patti AM, Carruba G, Cicero AFG, et al. Daily Use of Extra Virgin Olive Oil with High Oleocanthal Concentration Reduced Body Weight, Waist Circumference, Alanine Transaminase, Inflammatory Cytokines and Hepatic Steatosis in Subjects with the Metabolic Syndrome: A 2-Month Intervention Study. *Metabolites*. 2020;10(10):392.

9 Almanza-Aguilera E, Davila-Cordova E, Guiñón-Fort D, et al. Correlation Analysis between Dietary Intake of Tyrosols and Their Food Sources and Urinary Excretion of Tyrosol and Hydroxytyrosol in a European Population. *Antioxidants*. 2023;12(3):715.

British Journal of Nutrition (2022), 127, 1153–1171 doi:10.1017/S0007114521001999

Effects of olives and their constituents on the expression of ulcerative colitis: a systematic review of randomised controlled trials

Kenneth Daniel[1]*, Luis Vitetta[2] and Maria A. Fiatarone Singh[1,2,3]

[1]*Sydney School of Health Sciences, Faculty of Medicine and Health, The University of Sydney, NSW 2006, Australia*
[2]*Sydney Medical School, Faculty of Medicine and Health, The University of Sydney, NSW 2006, Australia*
[3]*The Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife, Boston, MA 02131, USA*

(Submitted 12 January 2021 – Final revision received 5 May 2021 – Accepted 1 June 2021 – First published online 8 June 2021)

Abstract

Extra virgin olive oil is often associated with anti-inflammatory and antioxidant properties. Its effects on inflammatory conditions such as ulcerative colitis (UC), however, have yet to be defined. As such, we aimed to conduct a systematic review and meta-analysis of studies investigating olive-based interventions in UC. A comprehensive database search for randomised controlled trials was performed between 9 July 2018 and 16 August 2018. Studies identified from search alerts were included up to 22 June 2020. Both individuals living with UC at any disease stage and murine models of UC were included in this review. No human trials meeting the eligibility criteria were identified, while nineteen animal studies comprised 849 murine models of UC were included in this review. Pooling of the data could not be performed due to heterogeneous outcomes; however, general trends favouring olive-based interventions were identified. Milder disease expression including weight maintenance, reduced rectal bleeding and well-formed stools favouring olive-based interventions was statistically significant in 16/19 studies, with moderate-to-large effect sizes (−0·66 (95 % CI −1·56, 0·24) to −12·70 (95 % CI −16·8, −8·7)). Olive-based interventions did not prevent the development of colitis-like pathologies in any study. In conclusion, effects of olive-based interventions on murine models of UC appear promising, with milder disease outcomes favouring the intervention in most trials and effect sizes suggesting potential clinical relevance. However, the lack of published randomised controlled human trials warrants further investigation to determine if these effects would translate to individuals living with UC.

Key words: **Ulcerative colitis: Olive oil: Inflammatory bowel disease: Systematic review**

Ulcerative colitis (UC) is a chronic condition characterised by inflammation and ulcerations along the colonic mucosa. The disease predominantly affects the large bowel and develops from the rectum to other parts of the colon in a progressive fashion. Symptoms occur intermittently, cycling between active disease and periods of remission. These range from gastrointestinal issues, such as loose stools, urgency, frequency and bleeding, to systemic issues such as fatigue, joint pain, malnutrition and the development of colon cancer. As such, those living with this condition often report a significant impact on quality of life, although overall lifespan is not reduced[1]. Along with other inflammatory bowel diseases (IBD), the prevalence of UC is increasing globally[2]. The reason for this trend is not well understood; however, a combination of environmental[3], lifestyle[4] and genetic risk factors[3,5] has been proposed.

Diet has been a key lifestyle focus for both clinicians and patients. Its role in modifying disease risk factors, disease severity and symptoms has previously been reported in prospective studies and small trials[5,6]. In contrast to medical therapy, dietary approaches are often viewed as an attractive option due to the side effects of conventional treatment such as immunosuppressive therapy and monoclonal antibodies[7]. As such, patients often report a range of self-prescribed dietary behaviours and restrictions with potentially negative implications for health outcomes and quality of life[8]. Unfortunately, the efficacy of such practices remains unclear due to the lack of robust evidence[9].

Amongst the various dietary strategies proposed, the Mediterranean diet is one approach that has gained interest in recent years. Early findings suggest that dietary patterns which emulate the Mediterranean diet were associated with reduced faecal calprotectin[10,11], reduced inflammatory markers and improvements to anthropometric measures and quality of life measures[12]. Definitions of the diet tend to vary and may extend to include social aspects of food consumption and lifestyle; thus, it can be challenging to identify how specific elements of the diet impact health outcomes.

Abbreviations: DAI, Disease Activity Index; DSS, dextran sulphate sodium; ES, effect size; IBD, inflammatory bowel diseases; RCT, randomised controlled trial; UC, ulcerative colitis.

* **Corresponding author:** Kenneth Daniel, email Kenneth.daniel@sydney.edu.au

Amongst the various elements of the diet, extra virgin olive oil consumption is one aspect of the diet which is often credited with positive health outcomes[13]. Epidemiological studies have shown associations between higher olive oil consumption with lower UC prevalence[14–16]. However, it is unknown whether such observational associations indicate any causal relationships between olive oil and disease risk[15,16]. By contrast, one uncontrolled trial in eight adults with UC using 1 g olive oil capsules demonstrated no effects on UC disease activity scores after a 12-month period[17]. However, higher doses have yet to be investigated; no randomised controlled trials or systematic review of human or animal trials has been published to our knowledge.

Aim

We aimed to systematically review and, if appropriate, perform a meta-analysis of interventions using extra virgin olive oil from table olives (*Olea europaea*) or their constituents on disease outcomes of individuals living with UC and murine models of UC at any stage of the disease.

Methods

Searches for eligible articles for the systematic literature review commenced on 9 July 2018 and concluded on 16 August 2018. Inclusion of hand-searched literature and new trials identified through alerts and the Cochrane central registry of clinical trials concluded on 22 June 2020. This systematic literature review adhered to PRISMA guidelines[18] and was prospectively registered with the international prospective register of systematic reviews (PROSPERO) under CRD42018103754 on 9 August 2018.

Search strategy

A systematic literature search was conducted using the following databases: MEDLINE (1946 to August 2018), AMED (1985 to August 2018), CINAHL (1981 to August 2018), Embase (1947 to August 2018), Web of Science (1900 to August 2018), Google Scholar (first 100 results from 2008 to August 2018) and Cochrane central registry of clinical trials (1955 to 22 June 2020). Alerts were established for MEDLINE, AMED, CINAHL, Embase, Web of Science and Google Scholar, and additional references found were included up until 22 June 2020. Search strategy included a combination of 'Population' (UC) AND 'Intervention'(olives/constituents) terms. 'Comparison intervention' or 'Outcome' terms were not used, to optimise sensitivity. Searches using the following terms: ('ulcerative colitis' or 'colitis' or 'colitis, ischemic' or 'colitis, microscopic' or 'colitis, ulcerative' or 'proctocolitis' or 'inflammatory bowel diseases' or 'inflammatory bowel disease' or 'IBD' or 'Crohn disease' or 'proctitis' or 'enterocolitis') AND ('dietary fats' or 'dietary fat' or 'olive oil' or 'olive' or 'virgin olive oil' or 'fatty acid' or 'monounsaturated' or 'diet' or 'monounsaturated fat' or 'phenols' or 'polyphenols' or 'flavonoids' or 'phenyl ethyl alcohol' or 'antioxidant' or 'olea' or 'Tyrosol' or 'Hydroxytyrosol' or 'Oleocanthal' or 'plant oils' or 'plant extracts' or 'fatty acids' or 'fatty acids, unsaturated' or 'fatty acids, monounsaturated' or 'dietary fats, unsaturated'). Due to the range of phenols present in olives, we explicitly searched for phenols specific to olives which have been examined in previous clinical trials[19] in addition to broad search terms such as 'phenols' and 'plant extracts' (see online, Supplementary Material). Reference list of articles meeting the inclusion criteria was also examined to identify studies which may be eligible. No limitations were set for publication year, language or study location. Both human and animal studies were included. Potentially eligible abstracts not in English were translated to determine eligibility.

Selection of eligible studies

Inclusion criteria for both human and animal studies were as follows:

1) randomised experimental trials including a control arm,
2) peer-reviewed publication, either full-length articles or chapters,
3) clinical validation of UC in humans at any stage of disease or comparative pathology in animals,
4) ability to assess UC as an independent study arm,
5) *in vivo* intervention,
6) interventions using the olive fruit (*O. europaea*) and its products including olive oil, paste, freeze-dried powdered products and capsules, or phenolic compounds (Hydroxytyrosol, Tyrosol, Oleuropein and Oleocanthal). Studies using olives or its constituents as part of a broader dietary intervention were also included,
7) administration of the intervention either orally or rectally,
8) ability to isolate the effects of the olive fruit or its components as an intervention,
9) disease activity outcomes via disease activity score, weight loss, mortality, histology or inflammatory markers.

No limitations were set on disease severity or duration. Other conditions not meeting the definition of UC[20] such as Crohn's disease, Inflammatory Bowel Disease Unclassified and indeterminate colitis were excluded. Animal studies fulfilling the selection criteria were further screened for (1) mammalian models of the disease and (2) equivalent condition matching UC pathologies comprising both experimental and sporadic disease[21–23]. Mammalian models were selected due to the relative similarity of intestinal function and morphology to humans[21]. Other transient forms of colitis such as acute or episodic colitis, allergic colitis and stress colitis were excluded from this review. Studies which include olive-based interventions as part of a broader dietary intervention were considered.

The reference management software Endnote X9.3.3 was used for this review. The primary author (K.D.) was responsible for database searches, collation of studies and removal of duplicates and screening of eligible studies. Full text of remaining articles was assessed by K. D. and M. A. F. S. When agreement could not be reached, L.V. was consulted. All eligible articles were included in this systematic review.

Data extraction and analysis

Data extraction of eligible studies was completed by the first author (K. D.). A second reviewer (M. A. F. S.) verified extracted data and discrepancies for review. Summary of data extracted at each study level (aggregate) was reported. A meta-analysis for each outcome was considered if appropriate. Human and animal studies were analysed separately.

Data extraction included the following: (1) Publication metrics (first author surname, publication year, volume and number of publication), (2) population characteristics (sex, age, number recruited/studied, covariates), (3) disease & co-morbidities, (4) description of intervention, (5) duration and dose and (6) study outcomes and statistical analysis.

Outcome assessment

Due to the breadth of outcomes, assessment tools identified were in accordance with what was described in the literature, with some general trends identified. For both Disease Activity Index (DAI) scores and histology scores, an increase in the scores correspond to greater damage to colon tissue. Specific outcomes and assigned sub-scores varied between tools and are outlined accordingly in the results.

Similarly, colon shortening and increased colon weight are hallmarks of inflammation and indicators for disease progression in experimental colitis in animal models[23]. As such, increased colon weight:length ratios compared with non-colitis animals are typically considered a hallmark of disease severity. Negative effect sizes for DAI, histology score and colon weight:length ratio are indicative of milder disease expression favouring the intervention, with the reverse true for controls. Colon lengths and weight outcomes independent from colon weight:length ratios reported were included in the analysis.

Quantification of inflammatory cytokines and gut microbiome outcomes may vary between studies dependent on the techniques used and the measures selected. Outcomes extracted in the results were dependent on what was described in text, with no assumptions made in the event that no measurement value was described.

WebPlotDigitizer version 4.1 was used to extract graphical data in the absence of raw values. All results are expressed as mean and standard deviation unless stated otherwise. Post-study outcomes were analysed in all studies due to incomplete baseline data. Standard deviations between groups were assumed to be the same if data were not available, and when such assumptions were made, this was identified within tables. Mean values were used for studies expressing population numbers as ranges. An effect size calculator published by the Centre of Evaluation & Monitoring was used to calculate Hedge's bias-corrected effect sizes (ES) and 95 % CI using values extracted from the literature[24]. Interpretation of ES was determined based on the benchmark proposed by Cohen[25] with effects categorised as small ($d = 0{\cdot}2$), medium ($d = 0{\cdot}5$) and large ($d = 0{\cdot}8$).

Quality assessment

Two review authors K. D. and M. A. F. S. performed the risk of bias assessment independently. Human studies were evaluated using the Cochrane Collaboration Risk of Bias tool[26] which examines six types of bias comprising selection, performance, detection, attrition, reporting and other bias. The tool assigns each aspects of the trial with high, low or unclear risk of bias. Animal trials were evaluated using the SYRCLE's Risk of Bias Tool which was developed based on the Cochrane Collaboration Risk of Bias tool. The tool is composed of ten questions which are assigned high, low or unclear risk of bias on aspects of the study pertinent to animal interventions[27]. No final score is assigned for the studies assessed, and outcomes are summarised in the form of tables. Inter-observer variability was evaluated using Kappa statistics based on evaluations by authors K. D. and M. A. F. S.

Results

Thirty-two potentially eligible studies were identified through electronic searches and search alerts (Fig. 1). All human trials identified were excluded due to uncontrolled study design (n 1) and dietary interventions in which the effects of olives could not be isolated (n 2). Ten murine studies were excluded due to non-olive interventions (n 6), interventions bypassing the gastrointestinal tract (n 2) and combined interventions in which the effects of olive components could not be isolated (n 2). This resulted in a total of nineteen eligible animal studies, with no eligible human trials. Studies were heterogeneous which precluded a meta-analysis; however, effect sizes were calculated to demonstrate the magnitude of effect of olive-based intervention in each study.

Risk of bias

The overall study quality for eligible studies was deemed to be low. An average of 6/10 items in the risk of bias tool was not reported across all studies. Two of nineteen studies described allocation sequences through simple randomisation[28] or by weight[29] with no additional description. Eight of nineteen studies reported assessing representative histology specimens within each study arm; however, the sampling process was not described in any text (Table 1).

Study characteristics

Characteristics of animals. Twelve mouse studies and seven rat studies, representing more than 849 animals, were identified. The most common strains used were 6-to-8-week-old C57BL/6 mice and Wistar rats, and 10/19 studies used female animals. In all studies reporting age at baseline, all animals had reached sexual maturity but none could be considered old[30]. Study populations could not be assessed in three studies[31–33] (Table 2).

Environmental and control conditions. Husbandry conditions were poorly reported, with only 3/19 studies adequately describing number of animals per cage[34–36]. The American Institute of Nutrition-purified rodent diet[37,38] with modified fat content was the most common food used (7/19 studies), while remaining studies reported various commercial or non-specific diets. Energy content of the diet was described in 4/19 studies and ranged between 2900 and 3970 kcal/kg[28,31,32,34], while fat

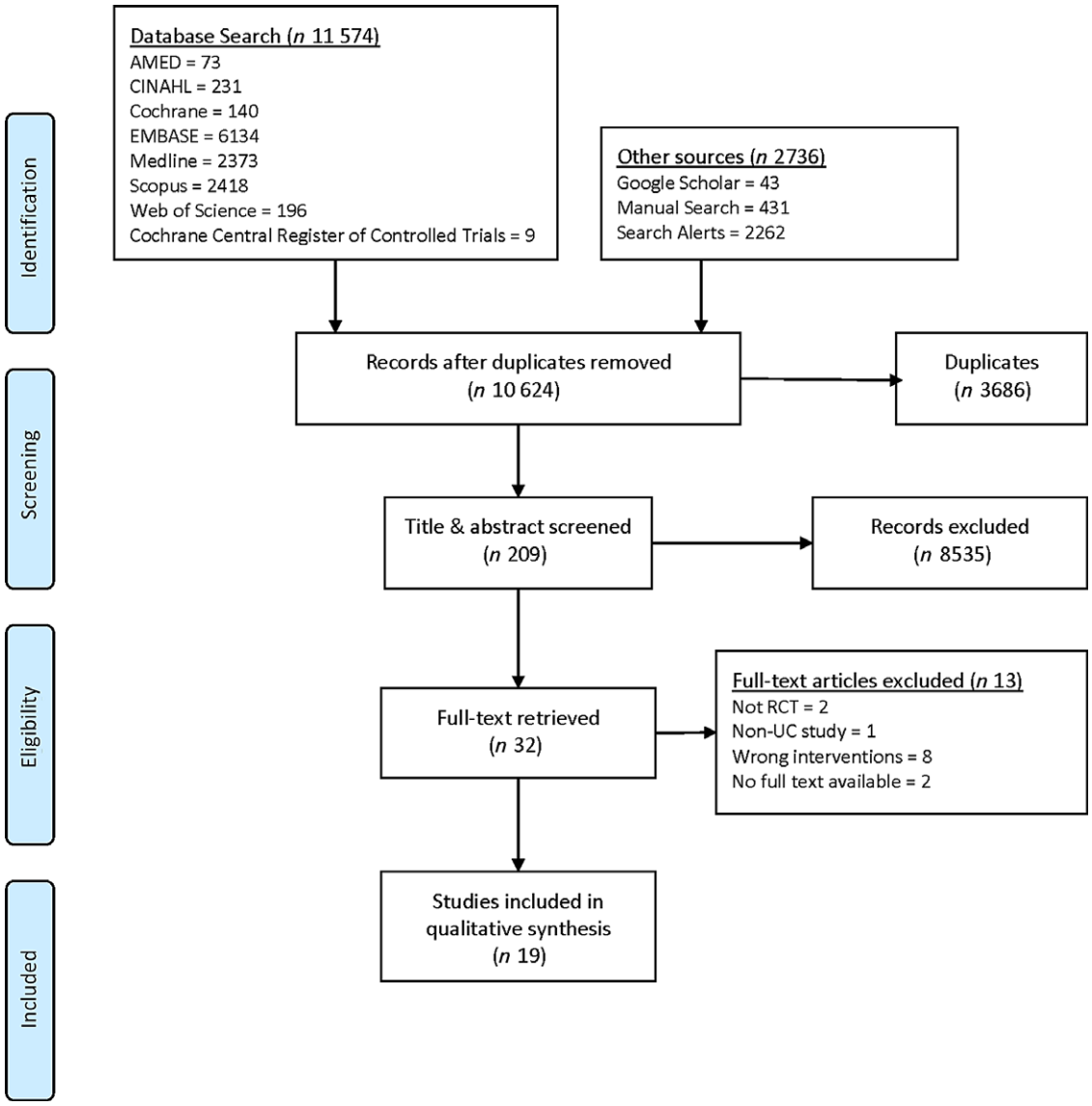


Fig. 1. Flow diagram of the literature search and selection of eligible studies.

content ranged from 4 to 10 % by weight (Table 2). Energy-matched diets between study groups were reported in only 1/19 study[34], while 5/19 studies[35,39–42] described matched fat, protein and carbohydrate content between diets. Sunflower oil was the most commonly used fat source in control diets[35,36,39–41], while maize oil[42] or soyabean oil[34] were used in the remaining studies.

Induction of colitis. Chemically induced colitis models were the most common method of simulating UC (17/19 studies), which was achieved predominantly using dextran sulphate sodium (DSS) (14/19 studies). Despite variances between study protocols, the overall procedures were similar. Briefly, DSS solution was prepared daily to the desired concentration (wt./vol.) using distilled water. This solution was provided in place of drinking water which could be consumed *ad libitum*. Duration of DSS exposure and concentration used varied between studies; acute models were induced between 3 and 15 d with a DSS concentration of 2–5 %, while chronic colitis models were induced between 28 and 259 d using 0·7–2 %. The remaining studies used either 2,4,6-trinitrobenzenesulfonic acid[28] or rectal administrations of acetic acid[43,44]. Two studies reported using transgenic HLA-B27 rats[42] or IL-10 knockout mice[45] predisposed to inflammation (Table 3).

Intervention. Interventions comprised olive oil (virgin and refined oils), Oleuropein, Hydroxytyrosol acetate and Tyrosol administered between 5 and 273 d, with a median of 30 d. Most studies combined olive-based intervention into dietary preparations, with 9/19 having enough information to estimate doses. These included 0·2–2·25 ml/d olive oil[28,42,46], 10–40 mg/d Oleuropein[31,32,47], 1·2–4·0 mg/d Hydroxytyrosol acetate[33,39]

Table 1. SYRCLE's risk of bias assessment

Study	Allocation sequence	Baseline similarity	Concealed allocation	Random housing	Caregiver blinding	Random assessment	Blinded assessment	Incomplete outcomes addressed	Reporting bias addressed	Other bias
Camuesco *et al.*[34]	NR	✓	✓	NR	✓	NR	✓	✓	X	✓
Hegazi *et al.*[45]	NR	NR	NR	NR	NR	NR	✓	✓	NR	✓
Sánchez-Fidalgo *et al.*[35]	NR	✓	NR	NR	NR	NR	NR	X	NR	✓
Giner *et al.*[31]	NR	✓	NR	NR	NR	NR	NR	X	✓	✓
Sánchez-Fidalgo *et al.*[39]	NR	✓	NR	NR	NR	NR	NR	X	NR	NR
Sánchez-Fidalgo *et al.*[40]	NR	✓	✓	NR	✓	NR	✓	X	X	✓
Sánchez-Fidalgo *et al.*[41]	NR	✓	✓	NR	✓	NR	✓	X	X	✓
Giner *et al.*[32]	NR	✓	NR	NR	NR	NR	NR	X	X	NR
Takashima *et al.*[49]	NR	✓	NR	NR	NR	NR	NR	X	X	X
Hamam *et al.*[43]	NR	✓	NR	NR	NR	NR	NR	X	X	X
Sánchez-Fidalgo *et al.*[33]	NR	✓	✓	NR	✓	NR	✓	✓	✓	X
Voltes *et al.*[28]	NR	✓	NR	NR	NR	NR	✓	✓	X	✓
Bigagli *et al.*[42]	NR	✓	NR	NR	NR	NR	✓	✓	✓	✓
Park *et al.*[46]	NR	✓	NR	NR	NR	NR	✓	✓	NR	✓
Güvenç *et al.*[48]	NR	NR	NR	NR	NR	NR	NR	✓	NR	✓
Wu *et al.*[44]	NR	NR	NR	NR	X	NR	NR	✓	✓	✓
Cariello *et al.*[29]	NR	✓	NR	NR	NR	NR	NR	✓	✓	✓
de Paula do Nascimento *et al.*[36]	NR	✓	NR	NR	✓	NR	✓	X	X	✓
Huguet-Casquero *et al.*[47]	NR	NR	NR	NR	NR	NR	NR	X	X	✓

NR, not reported in text, variables could not be assessed; ✓, Satisfied; X, Not satisfied.

and 3·6–5·0 mg/d Tyorosol[48]. Doses in eight studies could not be calculated due to unreported food consumption, one study due to unreported animal weights[44] and one study in which the olive oil was combined with a reagent prior to administration[28]. Voltes *et al.*[28] was the only study to intervene post-colitis, while all remaining studies administered the intervention either prior to, or concurrent with, colitis induction (Table 4).

Five studies reported food consumption, with mice consuming 3–4 g/d[31,34,35,49], and HLA-B27 rats 15 g/d[42]. One study[42] described the method of evaluating food consumption. Lower food intake in untreated animals was reported in one study[49], while four studies reported no difference between groups[31,34,35,42]. None of the studies intervening via oral gavage[29,43,44,46–48] or rectal administration[28] of an olive-based therapy described matching for potential energy contributions of the intervention.

Study outcomes

Mortality. Mortality was reported in 7/19 studies[31,32,39,42,43,45,49] and ranged from 0 to 40 %. Animals in the olive-based interventions had lower mortality rates (2·9 ± 6·6 %) compared with controls (13·9 ± 16·9 %), with three studies reporting no mortality in either group (Table 5). Deceased animals were included in the DAI analysis in one study[39], while two studies did not report if deceased animals were included in any outcome analyses[43,49]. None of the studies documented cause of death.

Disease activity. All experimental models of colitis in this review demonstrated intestinal inflammation and mucosal damage and symptoms consistent with UC, including rectal bleeding, loose stools, weight changes, altered colon morphology, altered histology and up-regulation of inflammatory markers[23,50]. Disease severity was reported in 11/19 studies[31–36,39–41,47,49] as DAI, comprised sub-scores for rectal bleeding, weight loss and stool consistency. One study reported rectal bleeding scores and weight loss to characterise disease activity without using a scoring index[29].

Colitis induction increased the DAI in all studies, while cessation of reagents used improved DAI outcomes, although they did not return to non-colitis levels in any study. Inclusion of an olive-based intervention reduced disease activity scores (between –0·07 and –2·1 points) compared with control–colitis animals, indicating milder symptoms, in ten of twelve studies[29,31–35,40,41,47,49] reporting this outcome. The differences between groups were statistically significant in nine studies[29,31–35,40,41,49], with all but one of these[35] reporting moderate-to-large effects (ES –0·66 (95 % CI –1·56, 0·24) to –12·70 (95 % CI –16·8, –8·7)). Disease activity improvements were not seen in transgenic HLA-B-27 rats, however[42] (Table 6). Improvements to stool consistency[31] and reduced rectal bleeding[32] were the greatest contributors to the differences in DAI; however, only three studies reported these sub-scores[31,32,35]. Comparing studies using the same intervention, higher intervention doses for Hydroxytyrosol[33,39,51] and Oleuropein[31,32,47] were associated with greater DAI differences between groups.

Weight changes post-study. Ten of nineteen studies[28,29,33,36,40–42,45,46,49] reported weight changes as an outcome independent of the DAI score. Seven of ten studies showed benefit in the intervention group indicated by reduced weight loss (–19 ± 21·3 % from baseline measures in the intervention group, −28 ± 25·3 % from baseline measures in controls)[29,33,40,41,45,46] or greater weight gain at study completion (246 ± 18·4 g in the intervention group, 184 ± 18·4 g in animals receiving control diets)[49].

Among the studies reporting outcomes favouring the intervention, four were statistically significant ($P < 0{\cdot}05$ - 0·001)[29,33,40,41] and six studies reported large ES between 0·97 (95 % CI 0·12, 1·82) and 8·73 (95 % CI 6·14, 11·33)[29,33,40,45,46,49]. Within the

Table 2. Design characteristics of eligible animal studies

Study	Location	Animal	Strain	Sex	Age	Baseline Wt (g)	*n*	Housing	Cages	Temperature (°C)	Humidity (%)	Day–night cycle	Base diet	% Fat (by wt)
Camuesco *et al.*[34]	Spain	Rats	Wistar	F	NR	180–200	40	Individual	Makrolon® cages	'AC atmos-phere'	'AC atmos-phere'	12D–12N	Semi-synthetic diet	4
Hegazi *et al.*[45]	USA	Mice	IL-10 knockout	NR	8 week	NR	92	NR	NR	NR	NR	NR	Defatted regular mouse chow (Bio-Serv)	7
Sánchez-Fidalgo *et al.*[35]	Spain	Mice	C57BL/6	F	6 weeks	NR	84	5–6 per cage	NR	24–25	'constant'	12D–12N	Modified AIN-76A Diet	10
Giner *et al.*[31]	Spain	Mice	BALB/c	F	6–8 weeks	18–20	40*	NR	NR	22	60	12D–12N	'Standard Laboratory Rodent Diet'	NR
Sánchez-Fidalgo *et al.*[39]	Spain	Mice	C57BL/6	F	6 weeks	NR	75	NR	NR	24–25	70–75	12D–12N	AIN standard reference diet	10
Sánchez-Fidalgo, *et al.*[40]	Spain	Mice	C57BL/6	F	6 weeks	NR	80	NR	NR	24–25	70–75	12D–12N	AIN standard reference diet	10
Sánchez-Fidalgo *et al.*[41]	Spain	Mice	C57BL/6	F	6 weeks	NR	60	NR	NR	24–25	70–75	12D–12N	AIN standard reference diet	10
Giner *et al.*[32]	Spain	Mice	C57BL/6	F	6–8 weeks	18–20	40*	NR	NR	22	60	12D–12N	'Standard Laboratory Rodent Diet'	NR
Takashima *et al.*[49]	Japan	Rats	Sprague–Dawley	M	6 weeks	NR	41	NR	NR	24–25	'constant'	12D–12N	Modified AIN-76A Diet	5
Hamam *et al.*[43]	Egypt	Rats	Albino	M	3–5 months	200–225	35	NR	'standard cages'	NR	NR	NR	'Standard diet'	NR
Sánchez-Fidalgo *et al.*[33]	Spain	Mice	C57BL/6	F	6 weeks	NR	36*	NR	NR	24–25	70–75	12D–12N	'Standard diet'	NR
Voltes *et al.*[28]	Spain	Rats	Wistar	F	NR	205–294	40	NR	NR	NR	NR	NR	'Standard labora-tory feed'	NR
Bigagli *et al.*[42]	Italy	Rats	HLA-B27	M	6–8 weeks	200–230	26	NR	NR	NR	NR	NR	Modified AIN76 diet	10
Park *et al.*[46]	Korea	Mice	C57BL/6	M	8 weeks	22–25	27	NR	NR	21–22	NR	12D–12N	'Standard mouse chow'	NR
Güvenç *et al.*[48]	Turkey	Rats	Wistar-Albino	M	NR	180–250	35	NR	NR	20–22	NR	12D–12N	'Standard com-mercial feed'	NR
Wu *et al.*[44]	Taiwan	Rats	Sprague–Dawley	M	6 weeks	NR	36	NR	NR	NR	NR	NR	NR	NR
Cariello *et al.*[29]	Italy	Mice	C57BL/6	M	8 weeks	NR	50	NR	NR	23	NR	12D–12N	NR	NR
de Paula do Nascimento *et al.*[36]	Brazil	Mice	C57BL/6	F	8–9 weeks	NR	80	2 per cage	NR	23–27	60–70	12D–12N	AIN-93M diet	10
Huguet-Casquero *et al.*[47]	Belgium	Mice	C57BL/6	M	8 weeks	21–26	48	NR	NR	NR	NR	NR	'Standard labora-tory feed'	NR

F, Female; NR, not reported in text; AIN, American Institute of Nutrition; M, male; 12D–12N, 12-h daylight and 12-h night cycles.
* Total number of animals quantified from study results with the assumption of no mortality.

Table 3. Method of inducing colitis

Study	Reagent	Dose (wt/v)	Route	Colitis model	Duration of induction
Camuesco *et al.*[34]	DSS	5 % and 2 % cycles	Drinking water	Acute	15 d (5/10 d cycles)
Hegazi *et al.*[45]	N/A	N/A	N/A	NR	N/A
Sánchez-Fidalgo *et al.*[35]	DSS	0·7 %	Drinking water	Chronic	259 d
Giner *et al.*[31]	DSS	5 %	Drinking water	Acute	7 d
Sánchez-Fidalgo *et al.*[39]	DSS	3 %	Drinking water	Acute	5 d
Sánchez-Fidalgo *et al.*[40]	DSS	3 %	Drinking water	Chronic	5 d
Sánchez-Fidalgo *et al.*[41]	DSS	3 %	Drinking water	Acute	5 d
Giner *et al.*[32]	DSS	1 % and 2 % cycles	Drinking water	Chronic	28 d (14/14 d cycles)
Takashima *et al.*[49]	DSS	4 %	Drinking water	Chronic	35 d
Hamam *et al.*[43]	Acetic acid	2 %	Intra-rectal	Acute	3 d
Sánchez-Fidalgo *et al.*[33]	DSS	3 %	Drinking water	Acute	5 d
Voltes *et al.*[28]	TNBS	0·5 ml	Intra-rectal	Acute	3 d
Bigagli *et al.*[42]	N/A	N/A	N/A	Chronic	N/A
Park *et al.*[46]	DSS	3 %	Drinking water	Acute	4 d
Güvenç *et al.*[48]	DSS	4 %	Drinking water	Acute	7 d
Wu *et al.*[44]	Acetic acid	4 %	Intra-rectal	Acute	21 d
Cariello *et al.*[29]	DSS	5 %	Drinking water	NR	10 d
de Paula do Nascimento *et al.*[36]	DSS	3 %	Drinking water	Acute	5 d
Huguet-Casquero *et al.*[47]	DSS	3 %	Drinking water	Acute	5 d

wt/v, weight/volume; DSS, dextran sulphate sodium; N/A, not applicable; NR, not reported in text; TNBS, 2,4,6-trinitrobenzene sulfonic acid.

remaining studies, one study using DSS mouse models[36] and HLA-B27 rats[42] reported greater weight gain in controls, while a study using 2,4,6-trinitrobenzenesulfonic acid colitis models reported non-significant outcomes with no examinable data[28]. No differences were observed between studies using acute[28,33,36,41,42,46] *v.* chronic[40,49] models of colitis (Table 7). None of the studies investigated the source of weight loss; thus, it is unknown if weight changes were attributed to anorexia, secondary effects of inflammation, altered fluid balance or other physiological changes.

Colon morphology

Histology score. Sixteen of nineteen studies[28,29,31,33–36,39–42,44–46,48,49] reported histology outcomes using parameters of colonic damage[52,53]. Grading methods varied between studies, with scores ranging between 4 and 120. Fourteen studies reported blinded assessments[28,31,33–36,39–42,45,46,48,49].

Improved histology outcomes favouring the intervention group were demonstrated in fourteen of sixteen studies[28,29,31,33–35,39–41,44–46,48,49], with nine studies[29,31,33,39,40,44,46,48,49] showing large ES between –0·81 (95 % CI –1·64, 0·02) and –4·51 (95 % CI –6·16, –2·86). Microscopic outcomes were reported in one study[48], with statistically significant improvements in mucosal architecture, cell infiltration, crypt abscess formation and preservation of goblet cells (ES –0·5 (95 % CI –0·78, 1·98) to –1·15 (95 % CI –0·01, 2·89), $P < 0·001$). Five studies using DSS-colitis models reported sub-scores for proximal, middle and distal colon sections with the greatest difference noted in middle[40] and distal[33,39,41,49] colon sections. (Table 8).

Colon weight:length ratio. Nine of nineteen studies[31,32,34–36,39–41,47] reported colon weight:length ratios which were expressed as either mg/cm in five studies[31,32,34,36,39], g/cm[35] or percentages compared with non-colitis animals in two studies[40,41]. Favourable weight:length ratios in intervention animals were reported in six studies, with a mean difference of –11·9 ± 3·1 mg/cm[31,32,34,39] and –67·5 ± 10·6 %[40,41] compared with controls. Four studies showed large effects with an ES between –1·31 (95 % CI –2·27, –0·34) and –2·41 (95 % CI –3·56, –1·26)[31,32,40,41]. Results were omitted in one paper reporting no statistically significant differences between groups[47] (Table 9).

Colon length. Colon length was reported by 6/19 studies, comprised four mouse studies[31,33,36,46] and two rat studies[44,49]. Average colon length of non-colitis animals was 7·9 ± 0·7 cm for mice and 17·3 ± 2·8 cm for rats, which was shortened in all animals induced with colitis, a sign of inflammation and colonic injury. Olive-based interventions attenuated this change, with longer colon lengths reported in intervention animals (mean 6·3 ± 0·6 cm in mice, 13·1 ± 1·4 cm in rats) compared with controls (mean 5·9 ± 0·6 cm in mice, 11·2 ± 1·3 cm in rats). One of six studies reported statistical significance favouring the intervention[44], while 4/6 studies[31,33,44,49] reported large ES between +0·88 (95 % CI 0·04, 1·72) and +2·36 (95 % CI 1·22, 3·50) (Table 10).

Inflammatory cytokines

TNF-α. Fourteen studies reported TNF-α outcomes post-kill[31,34–36,39–44,46–49]; nine studies reported concentrations in colon tissue[31,34–36,43,44,47–49], three studies quantified TNF-α mRNA in tissue samples[40–42], one study expressed TNF-α in percentages compared with non-colitis animals[39] and one study reported number of cells expressing antibodies[46]. Twelve of fourteen studies[31,34,35,39–44,46–48] reported lower TNF-α expression in the intervention group compared with controls, with nine studies statistically significant ($P < 0·001$ to 0·05)[31,39,41–44,46–48]. ES ranged from –0·34 (95 % CI –1·15, 0·48) to –4·63 (95 % CI –6·31, –2·95), with nine of fourteen moderate-to-large favouring the intervention[31,34,41–44,46–48]. One study reported outcomes favouring controls[36] which was not statistically significant but had a large ES (+0·95, 95 % CI 0·00, 1·89). (Table 11).

Table 4. Characteristics of the intervention and comparator study arms

Study	Control	*n*	Intervention	*n*	Time point intervention	Route	Consumption	Estimated dose	Treatment duration
Camuesco *et al.*[34]	SD + SBO	10	SD + EVOO (4 %)	10	Pre UC & Concurrent	Diet	NR	Unable to calculate	29 d
Hegazi *et al.*[45]	SD + CO	28	SD + OO (7 %)	29	Concurrent	Diet	NR	Unable to calculate	84 d
Sánchez-Fidalgo *et al.*[35]	SD + SFO	20	SD + EVOO (10 %)	20	Pre UC & Concurrent	Diet	NR	Unable to calculate	273 d
Giner *et al.*[31]	SD	NR	SD + Oleuropein (1 %)	NR	Concurrent	Diet	4 g food/d	40 mg Oleuropein/d	7 d
Sánchez-Fidalgo *et al.*[39]	SD + SFO	17	SD + EVOO (0·04 % Hty-Ac)	17	Pre UC & Concurrent	Diet	3 g food/d	1·2 mg Hty-Ac/d	51 d
Sánchez-Fidalgo *et al.*[40]	SD + SFO	12	SD + EVOO (10 %)	12	Pre UC & Concurrent	Diet	NR	Unable to calculate	30 d
Sánchez-Fidalgo *et al.*[41]	SD + SFO	12	SD + EVOO (10 %)	12	Pre UC & Concurrent	Diet	NR	Unable to calculate	39 d
Giner *et al.*[32]	SD	Between 7 and 10	SD + Oleuropein (0·25 %)	Between 7 and 10	Concurrent	Diet	4 g food/d	10 mg Oleuropein/d	56 d
Takashima *et al.*[49]	SD	17	SD + EVOO (5 %)	12	Pre UC & Concurrent	Diet	NR	Unable to calculate	35 d
Hamam *et al.*[43]	None	10	EVOO	10	Pre UC & Concurrent	Oral Gavage	1 ml/100 g body weight	2·00–2·25 ml EVOO/d	10 d
Sánchez-Fidalgo *et al.*[33]	SD	NR	SD + Hty-Ac (0·10 %)	12	Pre UC & Concurrent	Diet	4 g food/d	4 mg Hty-Ac/d	28 d + 10 d*
Voltes *et al.*[28]	Pectin/ alginate	10	Pectin/alginate + EVOO	10	Post UC	Rectal	2 ml solution/d	Unable to calculate	5 d
Bigagli *et al.*[42]	SD + CO	6	SD + EVOO (10 %)	7	Concurrent	Diet	15 g food/d	1·5 g EVOO/d (4·3 mg/kg polyphenols/d)	84 d
Park *et al.*[46]	None	5	OO	5	Concurrent	Oral gavage	0·2 ml/d	0·2 ml/d	10 d
Güvenç *et al.*[48]	None	7	Saline solution + Tyrosol	7	Pre UC & Concurrent	Oral gavage	20 mg/kg body weight	3·6–5·0 mg /d	21 d
Wu *et al.*[44]	SBO	6	OO	6	Pre UC	Oral gavage	2 ml/kg body weight	Unable to calculate	21 d
Cariello *et al.*[29]	0·9 % NaCl solution	10	OO (Monocultivar Coratina)	10	Pre UC & Concurrent	Oral gavage	NR	Unable to calculate	11 d
de Paula do Nascimento *et al.*[36]	SD + SFO	Between 10 and 12	SD + EVOO	Between 10 and 12	Pre UC	Diet	NR	Unable to calculate	30 d
Huguet-Casquero *et al.*[47]	Deionized water	8	Oleuropein + deionised water	8	Concurrent	Oral gavage	0·5 g/kg body weight	10·5–13 mg/d	5 d

SD, standard diet; SBO, soyabean oil; EVOO, extra virgin olive oil; Pre UC, prior to induction of experimental colitis; NR, not reported in text; CO, Maize Oil; OO, olive oil; SFO, sunflower oil; Hty-Ac, hydroxytyrosol acetate; NaCl, sodium chloride. Concurrent, intervention and induction of colitis occurring at the same time points.

Table 5. Animal mortality at study completion (Percentages)

Study	Control colitis	%	Intervention colitis	%
Camuesco *et al.*[34]	NR		NR	
Hegazi *et al.*[45]	1/27	4	1/29	3
Sánchez-Fidalgo *et al.*[35]	NR		NR	
Giner *et al.*[31]	0/10	0	0/10	0
Sánchez-Fidalgo *et al.*[39]	7/17	40	3/17	17·6
Sánchez-Fidalgo *et al.*[40]	NR		NR	
Sánchez-Fidalgo *et al.*[41]	NR		NR	
Giner *et al.*[32]	0/10	0	0/10	0
Takashima *et al.*[49]	4/17	23·5	0/12	0
Hamam *et al.*[43]	3/10	30	0/10	0
Sánchez-Fidalgo *et al.*[33]	NR		NR	
Voltes *et al.*[28]	NR		NR	
Bigagli *et al.*[42]	0/6	0	0/7	0
Park *et al.*[46]	NR		NR	
Güvenç *et al.*[48]	NR		NR	
Wu *et al.*[44]	NR		NR	
Cariello *et al.*[29]	NR		NR	
de Paula do Nascimento *et al.*[36]	NR		NR	
Huguet-Casquero *et al.*[47]	NR		NR	

NR, not reported in text.

IL. Four families were identified in this systematic review: IL-1*β*, IL-6, IL-10 and IL-17.

IL-1β. Nine studies assessed pro-inflammatory IL-1*β* expressed as quantities in tissue[31,32,36,44], relative gene expression[29,42], percentages compared with non-colitis animals[39] and number of stained cells in sampled colon tissue[46]. Induction of experimental colitis resulted in higher IL-1*β* expression compared with non-colitis animals in all studies. Animals receiving an olive-based intervention showed a lower expression of IL-1*β* in 6/9 studies (ES −0·54 (95 % CI − 1·61, 0·52) to −3·57 (95 % CI − 5·40, −1·75)[29,31,32,42,44,46]. Statistical significance ($P < 0·05$) was reported in 3/9 studies[29,31,44], all favouring the intervention. Results were omitted in one paper reporting no statistically significant differences between groups[49]. (Table 12).

IL-6. Ten studies examined pro-inflammatory IL-6 expressed as tissue concentration[31,32,35,36,44,47,48], number of stained cells in colon samples[46] or relative gene expression[29]. Nine of ten studies[29,31,32,35,36,44,46–48] reported lower IL-6 favouring the intervention group, with 6/10 statistically significant ($P < 0·01$ to $P < 0·001$)[29,31,32,44,47,48]. Seven of ten studies had large ES between −0·84 (95 %CI −1·76, 0·07) and −2·81 (95 % CI −4·29, −1·33)[29,31,32,44,46–48]. Results were omitted in one paper reporting no statistically significant differences between groups[49] (Table 13).

IL-10. Three studies reported anti-inflammatory IL-10 outcomes which were expressed using varying units of measure[32,36,39]. Colitis induction reduced IL-10 expression in all the animals, which was attenuated by olive-based interventions in 2/3 studies[32,39]. Measures of IL-10 were 34–43 % greater in intervention animals compared with controls at kill. Outcomes from two studies were statistically significant, with large ES of +0·99 (95 % CI 0·13, 1·85)[39] and +10·33 (95 % CI 6·30, 14·17)[32]. Results were

Table 6. Post-Study disease activity index (DAI) score
(Numbers; mean values and standard deviations; 95 % confidence intervals)

Study	Scoring method	Max score	Control			Intervention			Mean difference‡	Effect size†‡	95 % CI‡	Reported *P*-value
			Mean	SD	*n*	Mean	SD	*n*				
Camuesco *et al.*[34]	Cooper *et al.*[94]	4	3·1	1·58	10	1·9	1·9	10	−1·2	−0·66	−1·56, −0·24	$P < 0·05$
Sánchez-Fidalgo *et al.*[35]	Gommeaux *et al.*[95]	3	0·29	0·13	20	0·22	0·18	20	−0·07	−0·43	−1·06, 0·19	$P < 0·05$
Giner *et al.*[31]	Unknown	4	2·6	0·32	10	1·5	0·63	10	−1·1	−2·11	−3·20, −1·02	$P < 0·01$
Sánchez-Fidalgo *et al.*[39]	Melgar *et al.*[96]	3	0·53	1·07	17	0·63	0·7	25	0·1	0·18	−0·44, 0·79	NS
Sánchez-Fidalgo *et al.*[40]	Melgar *et al.*[97] modified	3	0·77	0·35	12	0	0·35*	12	−0·77	−2·12	−3·12, −1·12	$P < 0·001$
Sánchez-Fidalgo *et al.*[41]	Melgar *et al.*[97] modified	3	1·8	0·69	12	1·1	0·69	12	−0·7	−0·98	−1·83, 0·13	$P < 0·001$
Giner *et al.*[32]	Unknown	4	1	0·41	10	0·47	0·25	10	−0·53	−1·49	−2·49, −0·50	$P < 0·01$
Takashima *et al.*[49]	Gommeaux *et al.*[95]	3	1·8	0·36	13	0·8	0·69	12	−1	−1·78	−2·71, −0·85	$P < 0·01$
Sánchez-Fidalgo *et al.*[33]	Melgar *et al.*[97] modified	3	2	0·69	12	0·9	0·35	12	−1·1	−5·30	−6·99, −3·60	$P < 0·001$
Cariello *et al.*[29]	Unknown	4	3·8	0·1	10	1·7	0·2	10	−2·1	−12·7	−16·8, −8·7	$P < 0·05$
de Paula do Nascimento *et al.*[36]	Gommeaux *et al.*[95]	3	1·16	0·33	11	1·38	0·46	11	0·22	0·49	−0·36, 1·34	NS
Huguet-Casquero *et al.*[47]	Melgar *et al.*[97]	3	1·46	0·62	8	1·36	0·76	8	−0·1	0·14	−1·12, 0·85	NS

* SD values unavailable in the intervention group, assumed to be same with controls.
† Negative effect size indicates lower disease activity scores and reduced severity.
‡ Mean difference, Hedges' *g* Effect Size, and CI for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at kill divided by pooled Standard Deviation.

British Journal of Nutrition

Table 7. Post-study weight changes
(Numbers, mean values and standard deviations; 95 % confidence intervals)

		Control colitis			Intervention colitis			Mean difference‡				
Author	Measure	Mean	SD	*n*	Mean	SD	*n*	Raw weight (g)	Weight change (%)	Effect size†‡	95 % CI‡	Reported *P*-value
Hegazi *et al.*[45]	Weight loss (g)	−0·46	0·36	26	0	0·16	27	0·46	Unable to calculate	1·76	1·13, 2·40	NS
Sánchez-Fidalgo *et al.*[40]	% Weight Change*	−7·6	2·1	12	11·2	2·1	12	Unable to calculate	18·8	8·73	6·14, 11·33	$P < 0·001$
Sánchez-Fidalgo *et al.*[41]	% Weight Change*	−23·7	NR	12	−17·6	NR	12	Unable to calculate	6·1	Unable to calculate		$P < 0·001$
Takashima *et al.*[49]	Post Weight (g)	329	39	17	376	25	12	47	62	3·28	2·16, 4·40	NS
Sánchez-Fidalgo *et al.*[33]	% Weight Change*	−26	11·4	12	−18	8·7	12	Unable to calculate	8	0·97	0·12, 1·82	$P < 0·001$
Voltes *et al.*[28]	Weight loss (g)	NR	NR	NR	NR	NR	NR	Unable to calculate	Unable to calculate	Unable to calculate		0·91
Bigagli *et al.*[42]	Post Weight (g)	319	NR	6	306	NR	7	−13	Unable to calculate	NR		NS
	Net Weight Gain (g)	99	93	6	95	116	7	−4	Unable to calculate	−0·03	−1·13, 1·06	NS
Park *et al.*[46]	Post Weight (g)	17·0	0·6	5	17·9	1·4	5	0·9	Unable to calculate	1·79	0·32, 3·25	NS
	% From Baseline Weight*	74	1·5	5	80	4·0	5	Unable to calculate	6	5·42	2·74, 8·09	NS
Cariello *et al.*[29]	% From Baseline Weight*	18·9	6·6	10	40	6·9	10	Unable to calculate	20·7	2·94	1·67, 4·20	$P < 0·05$
de Paula do Nascimento *et al.*[36]	Post Weight (g)	20·3	1·3	11	19·5	2·3	11	−0·8	Unable to calculate	−0·79	−1·66, 0·07	NS

NR, not reported in text.
* Studies reporting '% From Baseline Weight' and '% Weight Change' assumes animals are 100 % at baseline.
† Positive effect sizes indicate higher weights in the study intervention.
‡ Mean difference, Hedges' *g* Effect Size, and CI for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at kill divided by pooled Standard Deviation.

omitted in one paper reporting no statistically significant differences between groups[36].

IL-17. Park *et al.* was the only study reporting pro-inflammatory IL-17 outcome, expressed as number of positive cells[46]. Mean cell count expressing IL-17 in non-colitis animals was 10·5 ± 5·4 cells, while induction of colitis resulted in a marked increase in IL-17 expression. This increase was milder in intervention animals (55·9 ± 12·0 cells) compared with controls (71·2 ± 5·0 cells). This outcome was not statistically significant; however, calculated ES was −1·49 (95 % CI −2·89, −0·09).

Other outcomes

Microbiome outcomes were reported in only 1/19 studies[44], expressed as colony forming units of three bacteria families. Experimental colitis reduced *Lactobacillus* spp. and *Bifidobacterium* spp. counts in all study arms, while *Clostridium perfringens* counts remained stable. Animals supplemented with olive oil maintained greater *Lactobacillus* spp. counts compared with controls post induction of colitis, while *Bifidobacterium* spp. counts were not impacted by the intervention.

Outcomes not discussed due to word limits include myeloperoxidase activity, cyclo-oxygenase-2, monocyte chemoattractant protein-1, PPAR-γ, inducible nitric oxide synthase, p38 mitogen-activated protein kinases, interferon gamma, alkaline phosphatase activity, glutathione concentration, leukotriene B4, proliferating cell nuclear antigen, erythropoietin activity, N-acetyl-B-D-glucosaminidase activity, IκB kinase activity, pJNK, proteins p53, p65, STAT3, prostaglandin E synthase, pERK1/2 activation, caspase 3, NF-κB, b-catenin staining pattern, matrix metalloproteinase-9, Foxp3 expression and A1 mRNA expression.

Discussion

To our knowledge, this is the first systematic review investigating the effects of olive-based interventions on the expression of UC in both humans and animal models. A significant body of work has been done in murine models of colitis, while no randomised controlled trials in humans have been published at the time of writing. Studies were heterogeneous, which precluded a meta-analysis; however, general trends were identified, as discussed below.

Overall effects of olive-based interventions

Animals receiving olive-based interventions had milder UC severity in most studies, as shown by lower disease activity scores and favourable inflammatory markers compared with controls at kill. Interestingly, such findings were not replicated in HLA-B27 rats[42] and one study using C57BL/6 mice[36]. All remaining studies using C57BL/6 mice models demonstrated outcomes favouring the intervention[29,32,33,35,36,39–41,46,47], while no other study used HLA-B27 models. Other rat models however demonstrated outcomes favouring olive-based interventions[28,34,43,44,48,49]; thus, it is unclear if the use of HLA-B27 rat models or other experimental variables influenced these outcomes.

Table 8. Histology score from colon samples
(Numbers; mean values and standard deviations; 95 % confidence intervals)

Study	Colon site	Score method*	Max score	Control			Intervention			Mean Difference‡	Effect Size†‡	95 % CI‡	Reported *P*-value
				Mean	SD	*n*	Mean	SD	*n*				
Camuesco *et al.*[34]	Full length	Modified Histology Score[98]	27	15·1	3·5	10	10·3	24	10	–4·8	–0·27	–1·15, 0·61	NS
Hegazi *et al.*[45]	Full length	Colitis Score[99]	4	2·0	1·0	26	2·3	1·6	27	0·3	0·22	–0·32, 0·76	NS
		% Animals with dysplasia	100	15	NR	26	4	NR	27	–11	Unable to calculate		$P < 0·05$
		ACF	4	1·4	1·0	26	1·3	1·0	27	–0·1	–0·10	–0·63, 0·44	NS
		Crypt Index	Unknown	127·7	76·5	26	121·6	50·4	27	–6·1	–0·09	–0·63, 0·45	NS
Giner *et al.*[31]	Full length	Histology Score	10	8·5	4·7	10	2·5	4·7	10	–6	–1·21	–2·16, –0·26	$P < 0·01$
Sánchez-Fidalgo *et al.*[39]	Proximal	Modified Histology Score[96]	4	1	1·73	3	0·33	0·57	3	–0·7	–0·41	–2·03, 1·20	NS
	Distal		4	1·67	1·16	3	0·67	0·57	3	–1	–0·87	–2·55, 0·80	NS
	Rectum		4	3·67	0·57	3	1·33	0·57	3	–2·3	–3·27	–5·71, –0·82	NS
Sánchez-Fidalgo *et al.*[40]	Proximal	Colitis Score[100]	40	9·5	12·5	12	2·1	0·07	12	–7·4	–0·81	–1·64, 0·02	$P < 0·001$
	Distal		40	36·5	2·08	12	18·4	23·6	12	–18·1	–1·05	–1·90, –0·19	$P < 0·001$
	Rectum		40	16	6·24	12	15·5	17·7	12	–0·5	–0·04	–0·84, 0·76	NS
Sánchez-Fidalgo *et al.*[41]	Proximal	Histology Score[100]	40	2·6	0·69	12	1·9	2·08	12	–0·7	–0·44	–1·25, 0·37	NS
	Distal		40	35·7	1·73	12	23·6	26·7	12	–12·1	–0·62	–1·44, 0·20	$P < 0·05$
	Rectum		40	34·2	6·24	12	20·1	35·3	12	–14·1	–0·54	–1·35, 0·28	$P < 0·001$
Takashima *et al.*[49]	Proximal	Histology Score[96]	6	3·2	0·45	5	3	0·11	5	–0·2	–0·55	–1·82, 0·71	$P < 0·05$
	Distal		6	3·3	0·45	5	3	0·11	5	–0·3	–0·83	–2·12, 0,46	NS
	Rectum		6	5·3	0·67	5	3·9	0·67	5	–1·4	–1·88	–3·37, –0·39	$P < 0·05$
Sánchez-Fidalgo *et al.*[33]	Distal colon	Histology Score[100]	40	27·5	19·9	12	8·6	5·2	12	–18·9	–1·25	–2·13, –0·38	$P < 0·01$
Voltes *et al.*[28]	Full length	Modified Hunter Score[101]	8	3·4	2·63	10	2·6	1·36	10	–0·8	–0·37	–1·25, 0·52	NS
Bigagli *et al.*[42]	Full length	Colitis Score[102]	7	1·83	0·91	6	2	0·9	7	0·2	0·18	–0·92, 1·27	NS
Park *et al.*[46]	Full length	Modified Histology Score[103]	12	11·7	0·3	5	11	1	5	–0·7	–0·86	–2·15, 0·44	NS
Güvenç *et al.*[48]	Full length	Macroscopic damage[104]	5	4·26	0·85	7	1·97	1·22	7	–2·29	–2·03	–3·32, –0·74	$P < 0·001$
Wu *et al.*[44]	NR	Focal Haemorrhage	Unknown	3·67	1·37	6	2·17	1·18	6	–1·5	–1·08	–2·30, 0·13	$P < 0·05$
	NR	Injury Score[105]	Unknown	25	5·44	6	20·17	6·25	6	–4·83	–0·76	–1·93, 0·41	NS
Cariello *et al.*[29]	Distal colon	Histology Score[96]	6	4·6	0·3	10	3·4	0·2	10	–1·2	–4·51	–6·16, –2·86	$P < 0·05$
de Paula do Nascimento *et al.*[36]	Distal colon	Histology Score[100]	Unknown	1·01	0·79	10	1·94	0·85	10	0·93	1·08	0·14, 2·02	NS
	Distal colon	Histology Score[98]	Unknown	10·7	6·83	10	16·55	7·65	10	5·85	0·77	–0·14, 1·68	NS
Sánchez-Fidalgo *et al.*[35]	Low Grade Dysplasia	Dysplasia[106]	100	100	NR	20	100	NR	20	0	Unable to calculate		NS
	High Grade Dysplasia		100	85	NR	20	55·55	NR	20	–29	Unable to calculate		NS
	Adeno-carcinoma		100	55	NR	20	22·2	NR	20	–33	Unable to calculate		NS
	Tumour		100	30	NR	20	0	NR	20	–30	Unable to calculate		NS

ACF, Aberrant Crypt Foci.
*For all scoring methods, lower scores indicate less damage on the colon samples.
† Negative effect size indicates lower histology scores and less tissue damage.
‡ Mean difference, Hedges' *g* Effect Size, and CI for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at kill divided by pooled Standard Deviation.

Table 9. Colon weight/length ratio
(Numbers; mean values and standard deviations; 95 % confidence intervals)

		Control colitis			Intervention colitis						
Study	Unit	Mean	SD	*n*	Mean	SD	*n*	Mean difference‡	Effect size†‡	95 % CI‡	Reported *P*-value
Camuesco *et al.*[34]	mg/cm	100·6	19	10	84·2	18	10	–16·4	–0·85	–1·76, 0·07	$P < 0·05$
Hegazi *et al.*[45]	NR	NR	NR	26	NR	NR	27	Unable to calculate	Unable to calculate		NS
Sánchez-Fidalgo *et al.*[35]	g/cm	105·9	37·1	20	107·1	18·3	20	1·2	0·04	–0·72, 0·80	NS
Giner *et al.*[31]	mg/cm	40·5	6·01	10	29·1	2·21	10	–11·4	–2·41	–3·56, –1·26	NS
Sánchez-Fidalgo *et al.*[39]	mg/cm	118·3	47·4	10	108	33·7	14	–10·32	–0·25	–1·06, 0·56	NS
Sánchez-Fidalgo *et al.*[40]	%*	215	52	12	140	34·6	12	–75	–1·64	–2·56, –0·71	$P < 0·001$
Sánchez-Fidalgo *et al.*[41]	%*	147	52	12	87	24·3	12	–60	–1·43	–2·33, –0·53	$P < 0·001$
Giner *et al.*[32]	mg/cm	53·7	0·95	10	44·2	9·8	10	–9·5	–1·31	–2·27, –0·34	$P < 0·05$
de Paula do Nascimento *et al.*[36]	mg/cm	26·1	4·3	11	26·8	4	11	0·7	0·16	–0·67, 1·00	NS

NR, not reported in text.
* Percentage of colon weight:length ratios compared with non-colitis control animals at kill; control animals were assumed to be 100 %.
† Negative effect size indicates lower weight/length ratio in the intervention.
‡ Mean difference, Hedges' *g* Effect Size, and CI for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at kill divided by pooled Standard Deviation.

Table 10. Colon length between study arms
(Numbers; mean values and standard deviations; 95 % confidence intervals)

			Control			Intervention						
Author	Animal	Group	Mean (cm)	SD	*n*	Mean (cm)	SD	*n*	Mean difference‡	Effect size†‡	95 % CI‡	Reported *P*-value
Giner *et al.*[31]	Mice	Non-colitis	8·86	0·95	10	NR*	NR*	NR*	Unable to calculate	2·36	1·22, 3·50	NS
		Colitis	5·35	0·16	10	6·65	0·73	10	1·3			
Takashima *et al.*[49]	Rat	Non-colitis	18·0	3·12	12	NR*	NR*	NR*	Unable to calculate	1·28	0·41, 2·14	NS
		Colitis	11·2	0·61	13	12·65	1·46	12	1·45			
Sánchez-Fidalgo *et al.*[33]	Mice	Non-colitis	7·5	0·7	12	7·3	0·7	12	–0·2	0·88	0·04, 1·72	NS
		Colitis	6·5	0·7	12	7	0·4	12	0·5			
Park et al.[46]	Mice	Non-colitis	6·20	0·10	2	NR*	NR*	NR*	Unable to calculate	–0·55	–1·81, 0·72	NS
		Colitis	4·24	0·38	5	4·01	0·38	5	–0·23			
Wu *et al.*[44]	Rats	Non-colitis	159·1	22·1	6	NR*	NR*	NR*	Unable to calculate	1·20	–0·03, 2·42	$P < 0·05$
		Colitis	112·1	22·5	6	141·3	11·8	6	29·2			
de Paula do Nascimento *et al.*[36]	Mice	Non-colitis	7·6	0·3	10	NR*	NR*	NR*	Unable to calculate	–0·29	–1·13, 0·55	NS
		Colitis	6·5	0·7	10–12	6·3	0·7	10 – 12	–0·2			

NR, not reported in text.
*In studies not reporting colon lengths of non-colitis intervention animals (NR), Mean and Standard Deviation values assumed to be the same as non-colitis controls.
† Positive effect sizes indicate greater colon lengths favouring the intervention arm.
‡ Mean difference, Hedges' *g* Effect Size, and CI for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at kill divided by pooled Standard Deviation.

Table 11. TNF-α in colon tissue post kill
(Numbers; mean values and standard deviations; 95 % confidence intervals)

		Control colitis			Intervention colitis						
Author	Units of measurement	Mean	SD	*n*	Mean	SD	*n*	Mean difference‡	Effect size†‡	95 % CI‡	Reported *P*-value
Camuesco *et al.*[34]	pmol/g tissue	846·1	295·7	10	596·9	235·0	10	–249·2	–0·89	–1·81, 0·03	NS
Sánchez-Fidalgo *et al.*[35]	pg/mg tissue	4	2·2	20	3·2	1·8	20	–0·8	–0·39	–1·02, 0·23	NS
Giner *et al.*[31]	pg/ml	37·1	4·8	7	22	9·5	7	–15·1	–1·86	–3·12, –0·61	$P<0·01$
Sánchez-Fidalgo *et al.*[39]	% compared to non-UC controls	170·4	34·5	10	149·6	71·8	14	–20·8	–0·34	–1·15, 0·48	$P<0·05$
Sánchez-Fidalgo *et al.*[40]	NR	8·1	5·0	4	6·3	3·4	4	–1·8	–0·37	–1·76, 1·03	NS
Sánchez-Fidalgo *et al.*[41]	NR	13·95	9·84	4	4·78	0·74	4	–9·17	–1·14	–2·64, 0·35	$P<0·001$
Takashima *et al.*[49]	NR	NR	NR	NR	NR	NR	NR	Unable to calculate	Unable to calculate		NS
Hamam *et al.*[43]	% area expressing TNF-α	31·45	6·18	10	7·65	3·22	10	–23·8	–4·63	–6·31, –2·95	$P<0·05$
Bigagli *et al.*[42]	NR	1·33	0·15	6	1·19	0·08	7	–0·14	–1·11	–2·28, 0·06	$P<0·05$
Park *et al.*[46]	*n* cells	227·71	28·29	5	139·16	65·99	5	–88·55	–1·57	–2·99, –0·16	$P<0·05$
Güvenç *et al.*[48]	pg/ml	2·77	0·95	7	1·32	0·053	7	–1·446	–1·99	–3·28, –0·71	$P<0·05$
Wu *et al.*[44]	pg/mg tissue	55·1	35·5	6	11·2	8·1	6	–43·9	–1·57	–2·87, –0·28	$P<0·05$
de Paula do Nascimento *et al.*[36]	pg/mg tissue	0·5	0·3	7–12	1·1	0·7	7–12	0·57	0·95	0·00, 1·89	NS
Huguet-Casquero *et al.*[47]	pg/g protein	2650	876	7–8	1340	356	7–8	–1310	–1·84	–3·05, –0·63	$P<0·05$

NR, not reported in text.
† Negative effect size indicates lower colon TNF-α expression in the intervention group.
‡ Mean difference, Hedges' *g* Effect Size, and CI for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at kill divided by pooled Standard Deviation.

Table 12. IL-1β in colon tissue post kill
(Numbers; mean values and standard deviations; 95 % confidence intervals)

		Control colitis			Intervention colitis						
Author	Units of measurement	Mean	SD	*n*	Mean	SD	*n*	Mean difference‡	Effect size†‡	95 % CI‡	Reported *P*-value
Giner *et al.*[31]	pg/ml	175·1	15·9	7	133·9	23·6	7	–41·2	–1·91	–3·17, –0·64	$P<0·05$
Sánchez-Fidalgo *et al.*[39]	%*	162·4	35·1	10	180·8	55·0	14	18·90	0·37	–0·45, 1·19	NS
Giner *et al.*[32]	pg/ml	34·5	27·5	7	23·1	2·4	7	–13·70	–0·54	–1·61, 0·52	NS
Takashima *et al.*[49]	NR	NR	NR	NR	NR	NR	NR	Unable to calculate	Unable to calculate		NS
Bigagli *et al.*[42]	NR	3·53	0·3	6	2·95	0·5	7	–0·58	–1·34	–2·54, –0·13	NS
Park *et al.*[46]	*n* cells	125	6·7	5	94·4	17·9	5	–30·5	–2·06	–3·59, –0·52	NS
Wu *et al.*[44]	pg/mg tissue	175·9	24·5	6	60	34·5	6	–115·9	–3·57	–5·40, –1·75	$P<0·05$
Cariello *et al.*[29]	Relative gene expression	1·62	1·96	10	0·31	0·51	10	–1·31	–0·88	–1·79, 0·04	$P<0·05$
de Paula do Nascimento *et al.*[36]	pg/mg tissue	12·7	11·4	7–12	37	35·1	7–12	24·3	0·89	–0·05, 1·83	NS

NR, not reported in text.
* Expressions in % refer to proportions compared with non-colitis control animals at time of kill.
† Negative effect size indicates lower expression of IL-1β in the intervention group.
‡ Mean difference, Hedges' *g* Effect Size, and CI for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at kill divided by pooled Standard Deviation.

British Journal of Nutrition

Table 13. Interleukin-6 post kill
(Numbers; mean values and standard deviations; 95 % confidence intervals)

Author	Units of measurement	Control colitis			Intervention colitis			Mean difference‡	Effect size†‡	95 % CI‡	Reported *P*-value
		Mean	SD	*n*	Mean	SD	*n*				
Sánchez-Fidalgo *et al.*[35]	pg/mg tissue	2·2	2·24	20	2	1·79	20	−0·20	−0·10	−0·72, 0·52	NS
Giner *et al.*[31]	pg/ml	101·0	16·67	7	57·4	17·46	7	−43·60	−2·38	−3·74, −1·01	$P < 0·01$
Giner *et al.*[32]	pg/ml	121·4	30·43	7	76·5	16·40	7	−44·90	−1·71	−2·93, −0·48	$P < 0·05$
Takashima *et al.*[49]	NR	NR	NR	NR	NR	NR	NR	Unable to calculate	Unable to calculate		NS
Park *et al.*[46]	*n* cells	51·04	4·63	5	33·13	9·85	5	−17·91	−2·10	−3·64, −0·56	NS
Güvenç *et al.*[48]	pg/ml	1·841	0·317	7	1·142	0·079	7	−0·70	−2·81	−4·29, −1·33	$P < 0·001$
Wu *et al.*[44]	pg/mg tissue	69·7	37·2	6	37·1	20·8	6	−32·60	−1·00	−2·20, 0·20	$P < 0·05$
Cariello *et al.*[29]	gene expression	1·65	2·53	10	0·07	0·22	10	−1·58	−0·84	−1·76, 0·07	$P < 0·05$
de Paula do Nascimento *et al.*[36]	pg/mg tissue	34·8	31·1	7–12	23·9	24·7	7–12	−10·90	−0·37	−1·28, 0·54	NS
Huguet-Casquero *et al.*[47]	pg/g protein	1840	301	7–8	920	411	7–8	−920	−2·41	−3·74, −1·08	$P < 0·01$

NR, not reported in text.
† Negative effect size indicates lower expression of IL-6 in the intervention group.
‡ Mean difference, Hedges' *g* Effect Size, and CI for Effect Sizes are all post-study outcomes comparing colitis animals between study arms. Effect Sizes calculated using post-test measures at kill divided by pooled Standard Deviation.

Insufficient intervention doses may have contributed to this discrepancy. Polyphenol content was not described in one study[36], while Bigagli *et al.* reported hydroxytyrosol concentration of 15 mg/kg olive oil, equivalent to a daily dose of 90 µg/kg body weight in HLA-B27 rats[42]. By contrast, findings from other studies in this review suggest clinically significant outcomes were associated with polyphenol concentrations above 0·4 mg/kg body weight[39,40]. Similarly, in this review, we identified greater attenuation of disease scores at higher concentration of Hydroxytyrosol[33,39,51] and Oleuropein[31,32]. It should be noted that adverse effects may occur at higher doses[54]; however, this was not evident in any study in this review. Furthermore, a dose–response relationship cannot yet be established due to the small sample sizes, heterogeneity of studies and variable reporting of experimental methods.

Effects on body weight

Weight loss and malnutrition are known complications associated with colitis in both animal models[55,56] and human cohorts[9,57]. Anorexia, malabsorption, dietary restrictions and gut microbiome disturbances are some of the contributors to this phenomenon[58–60]. In this systematic review, olive-based interventions improved weight outcomes concordant with milder disease activity, as indicated by weight maintenance or increased weight gain. Energy density of control and intervention diets was matched in most studies; however, such precautions were not evident in studies intervening through oral gavage or rectal administration. As such, it is unknown if these interventions influenced daily energy intake and subsequent weight outcomes. Similarly, housing conditions and husbandry were poorly described in most studies and potential confounders for feeding behaviour and subsequent weight outcomes[61,62].

Interestingly, olive oil supplementation increased oral intake in one study[49]. Although exact mechanisms are unclear, associations between gastrointestinal dysfunction and feeding behaviours are plausible[60], as milder symptoms may promote feeding behaviour. In conjunction with these changes, mucosal healing as indicated by stool consistency and histology outcomes may offer greater opportunity for fluid and nutrient absorption along the gastrointestinal tract. In combination, these changes may ultimately contribute towards favourable weight outcomes in intervention animals. This relationship remains speculative as few studies quantified oral intake, further complicated by multiple animals per cage and *ad libitum* feeding.

Finally, gut microbiome favourable shifts mediated by olive interventions may have contributed to the outcomes observed. Reduced gut bacterial diversity and abundance of commensal species have been associated with disease severity in both UC and experimental colitis[63]. Such changes are significant considering the microbiome's role in supporting gut barrier integrity, gut inflammatory tone and intestinal immunity through the production of SCFA (e.g., butyrate) and other host interactions. By contrast, previous studies have shown that olive oil supplementation promotes α-diversity of commensal bacterial species and accumulation of lean muscle mass in healthy C57BL/6J mice[64], a finding which was replicated in this review[44]. No other study assessed microbiome outcomes; thus, any conclusions are premature.

Colon morphology

Chemically induced colitis results in several features which differ depending on the reagent and dosage used. DSS-colitis models exhibit loss of surface epithelium which subsequently increases mucosal permeability, predominantly impacting the distal colon. Administration of 2,4,6-trinitrobenzenesulfonic acid results in thickening of the proximal colon accompanied by loss of haustration, while intra-rectal administration of acetic acid solution results in necrosis of intestinal mucosa and submucosa[23]. Despite the variability of these changes, several shared features such as oedema, ulcerations, granulocyte infiltration and dysplasia can be used to ascertain severity of experimental colitis.

Findings from this review suggest that olive-based interventions may have a role in preserving colonic architecture and metabolic-immunological function in experimental UC. This was evident through milder microscopic and macroscopic outcomes, histology scores and normalised weight:length ratios favouring intervention animals. It should be noted that olive-based interventions did not *prevent* intestinal injury in any study; however, the degree of damage was considerably lower compared with animals in the control arm.

Comparing sub-sections of the colon, middle and distal sections are known to be most affected by colitis[65,66]. Importantly, these sub-sections showed the greatest improvements in response to olive-based interventions, suggesting specific protection on these sites. Promotion of wound healing and protection against oxidative damage of intestinal cells mediated by olive polyphenols have previously been demonstrated[32] which may explain how olive-based interventions protect against chemically induced colitis.

Beneficial alterations to the microbiome mediated by olive polyphenols may have conferred additional protective effects against experimental colitis. Consumption of olive oil and olive polyphenols has been demonstrated to facilitate growth of butyrate producing bacteria such as *Lactobacillus and Bifidobacterium*[67], increase mucosal concentrations of SCFA[67] and inhibit growth of pathogenic species associated with inflammation[68]. SCFA such as butyrate play a vital role in preserving intestinal epithelial barrier and serve as fuel for colonocytes[69,70]. Furthermore, SCFA have been demonstrated to exert anti-inflammatory effects in the intestinal mucosa[69]. Metabolism of SCFA is impaired in UC and has been correlated with poorer histology and endoscopy outcomes[71]. As such, strategies targeting both the microbiome and SCFA production may assist in maintaining colon homoeostasis; however, current evidence remains inconsistent, and further investigations are warranted.

Inflammatory markers

Many health outcomes of olive-based interventions have been ascribed to component effects on inflammatory responses. Olive oil is predominantly composed of the MUFA oleic acid, which has been shown to protect against oxidative stress, regulate immune function in intestinal smooth muscle cells and disrupt arachidonic acid and NF-κB signalling pathways associated with chronic inflammation[29,72]. Prospective studies in healthy cohorts suggest an inverse association between oleic acid consumption and risk of developing UC[16], although such findings have yet to be replicated in larger studies[73]. Similarly, associations between dietary oleic acid and disease severity in individuals living with UC remain inconclusive despite promising findings in pre-clinical and clinical data[74].

Consumption of olive oil may confer additional benefits through displacing less desirable fatty acids in the diet. Specific fatty acids such as *n*-6 PUFA, saturated fats, trans fats and high fat diets have been associated with increased markers of pro-inflammatory cytokines[75], increased risk of developing UC[16] and worsening symptoms in individuals living with UC and animal models[75,76]. Similarly, inclusion of *n*-3 fatty acids have been demonstrated to exert protective effects against experimental colitis[77,78]; however, its role in prevention and treatment of UC remains controversial[79–81]. Finally, although dietary fat manipulation through olive oil consumption may confer some benefits on inflammatory markers and disease outcomes, it is unlikely that the effects observed in this review could be attributed to the fatty acid profile alone.

Previous experiments have highlighted the bioavailability and anti-inflammatory properties of olive oil polyphenols such as Oleuropein, Hydroxytyrosol and Oleocanthal in the gut[82]. In this review, we identified dose-dependent associations between Hydroxytyrosol and Oleuropein interventions with lower cytokine expression in concert with improved disease outcomes in murine models of UC. These findings further support previous *in vitro* studies on colonic biopsies of UC cohorts[83] and healthy cohorts[84,85], in which cytokine expression was reduced by olive polyphenols such as Hydroxytyrosol and Oleuropein.

Regulation of inflammatory markers has been identified as a potential therapeutic target in IBD, as increased secretion of pro-inflammatory (TNF-α, IL-1β, IL-6) and reduction of anti-inflammatory cytokines (IL-10) are associated with chronic inflammation and symptoms[86–88]. However, limited evidence is available on the specific markers associated with UC outcomes and their response to olive-based interventions, with several inconsistencies identified in the literature. Moraes *et al.* found minimal differences in cytokine expression between a cross-sectional study of UC cohorts with and without gastrointestinal symptoms[89]. Similarly, an uncontrolled study comparing 50 ml/d extra virgin olive oil and rapeseed oil interventions in UC cohorts reported alleviation of gastrointestinal symptoms and reduction of hs-CRP without alterations to serum TNF-α favouring extra virgin olive oil, although no other markers were quantified[90]. Finally, a meta-analysis in non-IBD populations similarly reported no changes to TNF-α despite favourable CRP and IL-6 outcomes with olive oil interventions[91]. The discrepancies between animal data in this review and human studies highlight the limitations of translating our findings to human cohorts and current gaps in the evidence. As such, although olive-based interventions appear to influence disease activity and symptoms as well as attenuation of pro-inflammatory cytokine expression in experimental UC models, it is unknown if findings would be replicated in human trials. Therefore, further investigations are warranted.

Limitations of this review methodology

The search strategy for this review was comprehensive, although no unpublished studies were sought, and no non-English language databases were searched, which could have limited the number of trials available for review. In addition, only one author (K. D.) performed the search and initial selection of eligible articles. However, the final selection was agreed upon by all authors.

Limitations of the literature to date

The studies identified were heterogeneous, with variations between experimental models, outcome measures and methods of evaluating disease severity. Chemically induced colitis models formed the majority of the evidence, which may limit the translation of our findings to other models of UC and human cohorts. Scaling up of olive oil doses described in this review for individuals living with UC should consider the feasibility and safety of implementing these interventions. Furthermore, quality of the evidence through the SYRCLE's Risk of Bias tool was sub-optimal due to limited reporting of key domains such as animal characteristics and husbandry; factors known to influence disease severity and experimental outcomes (such as individual animal stool volumes), as well as determine actual individual animal consumption of both food and olive-based product[92,93]. Moreover, strength to murine models of IBD would be further enhanced if researchers conducting the histology studies were unsighted to the collected colon samples.

Most of the studies intervened prior to, or during induction of, experimental colitis, limiting our ability to determine the efficacy of such strategies post-colitis. It does lend support to epidemiological data on consumption patterns and risk of developing disease[14–16]. However, translation to therapeutic interventions in cohorts who have established UC or similar conditions require explicit human studies with robust experimental designs.

Conclusion

Olive-based interventions exerted protective effects against chemically induced colitis in murine models. Despite these promising outcomes, conclusions are limited by the overall low quality of existing animal trials due to sub-optimal reporting of key parameters. Future investigations should include well-defined baseline characteristics, greater transparency regarding randomisation, blinding and husbandry as well as mortality. Most importantly, translation of these basic studies to human trials is warranted given the absence of robustly designed trials investigating the relationship between olive-based interventions and outcomes in UC cohorts.

Acknowledgements

The authors would like to acknowledge the contributions of Associate Professor Helen O'Connor during the conception and design phase of this manuscript, as well as supervision of author K. D.

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

All authors contributed equally towards the study conception and design. K. D. was responsible for data extraction and analysis. Data integrity and accuracy were confirmed by K. D. and M. A. F. S. and K. D. drafted the manuscript, which was revised by L. V. and M. A. F. S. All authors read and approved the final manuscript.

There are no conflicts of interest.

Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114521001999

References

1. Winther KV, Jess T, Langholz E, *et al.* (2003) Survival and cause-specific mortality in ulcerative colitis: follow-up of a population-based cohort in Copenhagen County. *Gastroenterology* **125**, 1576–1582.
2. Bernstein CN (2010) Epidemiologic clues to inflammatory bowel disease. *Curr Gastroenterol Rep* **12**, 495–501.
3. Abegunde AT, Muhammad BH, Bhatti O, *et al.* (2016) Environmental risk factors for inflammatory bowel diseases: evidence based literature review. *World J Gastroenterol* **22**, 6296–6317.
4. Chapman-Kiddell CA, Davies PSW, Gillen L, *et al.* (2010) Role of diet in the development of inflammatory bowel disease. *Inflammatory Bowel Dis* **16**, 137–151.
5. Aleksandrova K, Romero-Mosquera B & Hernandez V (2017) Diet, gut microbiome and epigenetics: emerging links with inflammatory bowel diseases and prospects for management and prevention. *Nutrients* **9**, 30.
6. Haskey N & Gibson DL (2017) An examination of diet for the maintenance of remission in inflammatory bowel disease. *Nutrients* **9**, 259.
7. Carter MJ, Lobo AJ & Travis SPL (2004) Guidelines for the management of inflammatory bowel disease in adults. *Gut* **53**, v1.
8. Casanova M, Chaparro M, Molina B, *et al.* (2016) Prevalence of malnutrition and nutritional characteristics of patients with inflammatory bowel disease. *J Crohn's Colitis* **10**, S208–S209.
9. Alastair F, Emma G & Emma P (2011) Nutrition in inflammatory bowel disease. *J Parenteral Enteral Nutr* **35**, 571–580.
10. Godny L, Reshef L, Pfeffer-Gik T, *et al.* (2020) Adherence to the Mediterranean diet is associated with decreased fecal calprotectin in patients with ulcerative colitis after pouch surgery. *Eur J Nutr* **59**, 3183–3190.
11. Strisciuglio C, Cenni S, Serra MR, *et al.* (2020) Effectiveness of Mediterranean diet's adherence in children with inflammatory bowel diseases. *Nutrients* **12**, 3206.
12. Chicco F, Magrì S, Cingolani A, *et al.* (2021) Multidimensional impact of mediterranean Diet on IBD patients. *Inflammatory Bowel Diseases* **27**, 1–9.
13. Santangelo C, Varì R, Scazzocchio B, *et al.* (2018) Anti-inflammatory activity of extra virgin olive oil polyphenols: which role in the prevention and treatment of immune-mediated inflammatory diseases? *Endocr Metab Immune Disord - Drug Targets* **18**, 36–50.
14. Triantafillidis JK, Emmanouilidis A, Manousos ON, *et al.* (1998) Ulcerative colitis in Greece: clinicoepidemiological data, course, and prognostic factors in 413 consecutive patients. *J Clin Gastroenterol* **27**, 204–210.
15. Shivananda S, Lennard-Jones J, Logan R, *et al.* (1996) Incidence of inflammatory bowel disease across Europe: is

there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut* **39**, 690–697.
16. De Silva P, Luben R, Mc Taggart A, *et al.* (2011) Dietary arachidonic acid and the aetiology of ulcerative colitis: data from a UK prospective cohort study, using 7-day food diaries. *Gut* **60**, A140.
17. Greenfield SM, Green AT, Teare JP, *et al.* (1993) A randomized controlled study of evening primrose oil and fish oil in ulcerative colitis. *Aliment Pharmacol Therapeut* **7**, 159–166.
18. Moher D, Liberati A, Tetzlaff J, *et al.* (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* **6**, e1000097.
19. Cicerale S, Lucas LJ & Keast RSJ (2012) Antimicrobial, antioxidant and anti-inflammatory phenolic activities in extra virgin olive oil. *Curr Opin Biotechnol* **23**, 129–135.
20. Geboes K, Dewit O, Moreels TG, *et al.* (2018) Inflammatory bowel diseases. In *Colitis: a Practical Approach to Colon and Ileum Biopsy Interpretation*, pp. 107–140 [A Jouret-Mourin, G Faa & K Geboes, editors]. Cham: Springer International Publishing.
21. Jiminez JA, Uwiera TC, Douglas Inglis G, *et al.* (2015) Animal models to study acute and chronic intestinal inflammation in mammals. *Gut Pathogens* **7**, 29–29.
22. Mizoguchi A (2012) Animal models of inflammatory bowel disease. *Prog Mol Biol Transl Sci* **105**, 263–320.
23. Randhawa PK, Singh K, Singh N, *et al.* (2014) A review on chemical-induced inflammatory bowel disease models in rodents. *Korean J Physiol Pharmacol* **18**, 279–288.
24. Centre for Evaluation & Monitoring (2020) Effect Size Calculator. https://www.cem.org/effect-size-calculator (accessed July 2019).
25. Cohen J (2013) *Statistical Power Analysis for the Behavioral Sciences*. New York: Academic press.
26. Higgins JPT, Altman DG, Gøtzsche PC, *et al.* (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **343**, d5928.
27. Hooijmans CR, Rovers MM, de Vries RBM, *et al.* (2014) SYRCLE's risk of bias tool for animal studies. *BMC Med Res Method* **14**, 43.
28. Voltes A, Bermúdez A, Rodríguez-Gutiérrez G, *et al.* (2018) Anti-Inflammatory local effect of hydroxytyrosol combined with pectin-alginate and olive oil on trinitrobenzene sulfonic acid-induced colitis in wistar rats. *J Invest Surg* 1–7.
29. Cariello M, Contursi A, Gadaleta RM, *et al.* (2020) Extra-Virgin olive oil from apulian cultivars and intestinal inflammation. *Nutrients* **12**, 1084.
30. Dutta S & Sengupta P (2016) Men and mice: relating their ages. *Life Sci* **152**, 244–248.
31. Giner E, Andújar I, Recio MC, *et al.* (2011) Oleuropein ameliorates acute colitis in mice. *J Agric Food Chem* **59**, 12882–12892.
32. Giner E, Recio MC, Ríos JL, *et al.* (2013) Oleuropein protects against dextran sodium sulfate-induced chronic colitis in mice. *J Nat Prod* **76**, 1113–1120.
33. Sánchez-Fidalgo S, Villegas I, Aparicio-Soto M, *et al.* (2015) Effects of dietary virgin olive oil polyphenols: hydroxytyrosyl acetate and 3, 4-dihydroxyphenylglycol on DSS-induced acute colitis in mice. *J Nutr Biochem* **26**, 513–520.
34. Camuesco D, Gálvez J, Nieto A, *et al.* (2005) Dietary olive oil supplemented with fish oil, rich in EPA and DHA (*n*-3) polyunsaturated fatty acids, attenuates colonic inflammation in rats with DSS-induced colitis. *J Nutr* **135**, 687–694.
35. Sánchez-Fidalgo S, Villegas I, Cárdeno A, *et al.* (2010) Extra-virgin olive oil-enriched diet modulates DSS-colitis-associated colon carcinogenesis in mice. *Clin Nutr* **29**, 663–673.
36. de Paula do Nascimento R, Lima AV, Oyama LM, *et al.* (2020) Extra virgin olive oil and flaxseed oil have no preventive effects on DSS-induced acute ulcerative colitis. *Nutrition* **74**, 110731.
37. Nutrition AIo (1977) Report of the American Institute of Nutrition. Committee on standards for nutritional studies. *J Nutr* **107**, 1340–1348.
38. Bieri JG (1980) Second report of the committee on standards for nutritional studies. *J Nutr* **110**, 1726–1726.
39. Sánchez-Fidalgo S, Sánchez De Ibargüen L, Cárdeno A, *et al.* (2012) Influence of extra virgin olive oil diet enriched with hydroxytyrosol in a chronic DSS colitis model. *Eur J Nutr* **51**, 497–506.
40. Sánchez-Fidalgo S, Cárdeno A, Sánchez-Hidalgo M, *et al.* (2013) Dietary extra virgin olive oil polyphenols supplementation modulates DSS-induced chronic colitis in mice. *J Nutr Biochem* **24**, 1401–1413.
41. Sánchez-Fidalgo S, Cárdeno A, Sánchez-Hidalgo M, *et al.* (2013) Dietary unsaponifiable fraction from extra virgin olive oil supplementation attenuates acute ulcerative colitis in mice. *Eur J Pharm Sci* **48**, 572–581.
42. Bigagli E, Toti S, Lodovici M, *et al.* (2019) Dietary extra-virgin olive oil polyphenols do not attenuate colon inflammation in Transgenic HLAB-27 rats but exert hypocholesterolemic effects through the modulation of HMGCR and PPAR-α gene expression in the liver. *Lifestyle Genomics* 1–10.
43. Hamam GG, Raafat MH & Shoukry Y (2014) Possible protective effect of dietary extra-virgin olive oil on experimentally induced acute colitis in adult male albino rats: a histological and immunohistochemical study. *Egypt J Histol* **37**, 373–385.
44. Wu C-C, Tung Y-T, Chen S-Y, *et al.* (2020) Anti-Inflammatory, antioxidant, and microbiota-modulating effects of camellia oil from camellia brevistyla on acetic acid-induced colitis in rats. *Antioxidants* **9**, 58.
45. Hegazi RAF, Saad RS, Mady H, *et al.* (2006) Dietary fatty acids modulate chronic colitis, colitis-associated colon neoplasia and COX-2 expression in IL-10 knockout mice. *Nutrition* **22**, 275–282.
46. Park JS, Choi J, Hwang SH, *et al.* (2019) Cottonseed oil protects against intestinal inflammation in dextran sodium sulfate-induced inflammatory bowel disease. *J Med Food* **22**, 672–679.
47. Huguet-Casquero A, Xu Y, Gainza E, *et al.* (2020) Oral delivery of oleuropein-loaded lipid nanocarriers alleviates inflammation and oxidative stress in acute colitis. *Int J Pharm* **586**, 119515.
48. Guvenc M, Cellat M, Ozkan H, *et al.* (2019) Protective effects of tyrosol against DSS-induced ulcerative colitis in rats. *Inflammation* **42**, 1680–1691.
49. Takashima T, Sakata Y, Iwakiri R, *et al.* (2014) Feeding with olive oil attenuates inflammation in dextran sulfate sodium-induced colitis in rat. *J Nutr Biochem* **25**, 186–192.
50. Waldner MJ & Neurath MF (2009) Chemically induced mouse models of colitis. *Curr Protocol Pharmacol* **46**, 5–55.
51. Rosillo MA, Sánchez-Hidalgo M, González-Benjumea A, *et al.* (2015) Preventive effects of dietary hydroxytyrosol acetate, an extra virgin olive oil polyphenol in murine collagen-induced arthritis. *Mol Nutr Food Res* **59**, 2537–2546.
52. Solomon L, Mansor S, Mallon P, *et al.* (2010) The Dextran Sulphate Sodium (DSS) model of colitis: an overview. *Comparative Clin Pathol* **19**, 235–239.
53. Brenna O, Furnes MW, Drozdov I, *et al.* (2013) Relevance of TNBS-colitis in rats: a methodological study with endoscopic, histologic and Transcriptomic [corrected] characterization and correlation to IBD. *PLoS One* **8**, e54543.

54. Kouka P, Tekos F, Papoutsaki Z, *et al.* (2020) Olive oil with high polyphenolic content induces both beneficial and harmful alterations on rat redox status depending on the tissue. *Toxicol Rep* **7**, 421–432.
55. Goyal N, Rana A, Ahlawat A, *et al.* (2014) Animal models of inflammatory bowel disease: a review. *Inflammo pharmacology* **22**, 219–233.
56. Antoniou E, Margonis GA, Angelou A, *et al.* (2016) The TNBS-induced colitis animal model: an overview. *Ann Med Surg* **11**, 9–15.
57. Cabré E & Gassull MA (2001) Nutrition in inflammatory bowel disease: impact on disease and therapy. *Curr Opin Gastroenterol* **17**, 342–349.
58. Scaldaferri F, Pizzoferrato M, Lopetuso LR, *et al.* (2017) Nutrition and IBD: malnutrition and/or Sarcopenia? A practical guide. *Gastroenterol Res Pract* **2017**, 8646495.
59. Mija DD, Janković GLJ, Jorga J, *et al.* (2010) Nutritional status in patients with active inflammatory bowel disease: prevalence of malnutrition and methods for routine nutritional assessment. *Eur J Intern Med* **21**, 315–319.
60. Tuzun A, Uygun A, Yesiolva Z, *et al.* (2004) Leptin levels in the acute stage of ulcerative colitis. *J Gastroenterol Hepatol* **19**, 429–432.
61. Yamauchi C, Fujita S, Obara T, *et al.* (1983) Effects of room temperature on reproduction, body and organ weights, food and water intakes, and hematology in mice. *Exp Anim* **32**, 1–11.
62. Nicholson A, Malcolm RD, Russ PL, *et al.* (2009) The response of C57BL/6J and BALB/cJ mice to increased housing density. *J Am Assoc Lab Anim Sci* **48**, 740–753.
63. Fabia R, Ar'Rajab A, Johansson ML, *et al.* (1993) Impairment of bacterial flora in human ulcerative colitis and experimental colitis in the rat. *Digestion* **54**, 248–255.
64. Patterson E, O' Doherty RM, Murphy EF, *et al.* (2014) Impact of dietary fatty acids on metabolic activity and host intestinal microbiota composition in C57BL/6J mice. *Br J Nutr* **111**, 1905–1917.
65. Diaz-Granados N, Howe K, Lu J, *et al.* (2000) Dextran sulfate sodium-induced colonic histopathology, but not altered epithelial ion transport, is reduced by inhibition of phosphodiesterase activity. *Am J Pathol* **156**, 2169–2177.
66. Chassaing B, Aitken JD, Malleshappa M, *et al.* (2014) Dextran sulfate sodium (DSS)-induced colitis in mice. *Curr Protocol Immunol* **104**, 15–25.
67. Farràs M, Martinez-Gili L, Portune K, *et al.* (2020) Modulation of the gut microbiota by olive oil phenolic compounds: implications for lipid metabolism, immune system, and obesity. *Nutrients* **12**, 2200.
68. Rodríguez-García C, Sánchez-Quesada C, Algarra I, *et al.* (2020) The high-fat diet based on extra-virgin olive oil causes dysbiosis linked to colorectal cancer prevention. *Nutrients* **12**, 1705.
69. Parada Venegas D, De la Fuente MK, Landskron G, *et al.* (2019) Short chain fatty acids (SCFAs)-Mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. *Front Immunol* **10**, 277–277.
70. Rivière A, Selak M, Lantin D, *et al.* (2016) Bifidobacteria and Butyrate-Producing Colon Bacteria: importance and Strategies for Their Stimulation in the Human Gut. *Front Microbiol* **7**, 979–979.
71. De Preter V, Arijs I, Windey K, *et al.* (2012) Impaired butyrate oxidation in ulcerative colitis is due to decreased butyrate uptake and a defect in the oxidation pathway. *Inflammatory Bowel Dis* **18**, 1127–1136.
72. Gálvez J, Camuesco D, Rodríguez-Cabezas ME, *et al.* (2010) Intestinal anti-inflammatory activity of dietary olive oil. In *Olives and Olive Oil in Health and Disease Prevention*, pp. 1049–1055 [VR Preedy & RR Watson, editors]. San Diego: Academic Press.
73. Hart AR, Luben R, Olsen A, *et al.* (2008) Diet in the aetiology of ulcerative colitis: a European prospective cohort study. *Digestion* **77**, 57–64.
74. Barnes EL, Nestor M, Onyewadume L, *et al.* (2017) High dietary intake of specific fatty acids increases risk of flares in patients with ulcerative colitis in remission during treatment with aminosalicylates. *Clin Gastroenterol Hepatol* **15**, 1390–1396.
75. Wiese DM, Horst SN, Brown CT, *et al.* (2016) Serum fatty acids are correlated with inflammatory cytokines in ulcerative colitis. *PLoS One* **11**, e0156387.
76. Nishida T, Miwa H & Shigematsu A (1987) Increased arachidonic acid composition of phopsholipids in colonic mucosa from patients with active ulcerative colitis. *Gut* **28**, 1002–1007.
77. Dennis EA & Norris PC (2015) Eicosanoid storm in infection and inflammation. *Nat Rev Immunol* **15**, 511–523.
78. Bosco N, Brahmbhatt V, Oliveira M, *et al.* (2013) Effects of increase in fish oil intake on intestinal eicosanoids and inflammation in a mouse model of colitis. *Lipids Health Dis* **12**, 1–13.
79. Barbalho SM, Goulart RDA, Quesada K, *et al.* (2016) Inflammatory bowel disease: can *n*-3 fatty acids really help? *Ann Gastroenterol* **29**, 37–43.
80. Cabré E, Mañosa M & Gassull MA (2012) *n*-3 fatty acids and inflammatory bowel diseases-a systematic review. *Br J Nutr* **107**, S240–S252.
81. Turner D, Shah PS, Steinhart AH, *et al.* (2011) Maintenance of remission in inflammatory bowel disease using *n*-3 fatty acids (fish oil): a systematic review and meta-analyses. *Inflammatory Bowel Dis* **17**, 336–345.
82. Corona G, Tzounis X, Assunta Dessì M, *et al.* (2006) The fate of olive oil polyphenols in the gastrointestinal tract: implications of gastric and colonic microflora-dependent biotransformation. *Free Radic Res* **40**, 647–658.
83. Larussa T, Oliverio M, Suraci E, *et al.* (2017) Oleuropein decreases interleukin-17 and attenuates inflammatory damage in colonic mucosa from ulcerative colitis patients. *J Crohn's Colitis* **11**, S130.
84. Martin-Pelaez S, Castaner O, Sola R, *et al.* (2016) Influence of phenol-enriched olive oils on human intestinal immune function. *Nutrients* **8**, 213.
85. Papageorgiou N, Tousoulis D, Psaltopoulou T, *et al.* (2011) Divergent anti-inflammatory effects of different oil acute consumption on healthy individuals. *Eur J Clin Nutr* **65**, 514–519.
86. Cioffi M, Rosa AD, Serao R, *et al.* (2015) Laboratory markers in ulcerative colitis: current insights and future advances. *World J Gastrointest Pathophysiol* **6**, 13–22.
87. Pearl DS, Shah K, Whittaker MA, *et al.* (2013) Cytokine mucosal expression in ulcerative colitis, the relationship between cytokine release and disease activity. *J Crohn's Colitis* **7**, 481–489.
88. Reimund JM, Wittersheim C, Dumont S, *et al.* (1996) Mucosal inflammatory cytokine production by intestinal biopsies in patients with ulcerative colitis and Crohn's disease. *J Clin Immunol* **16**, 144–150.
89. Moraes L, Magnusson MK, Mavroudis G, *et al.* (2020) Systemic inflammatory protein profiles distinguish Irritable Bowel Syndrome (IBS) and ulcerative colitis, irrespective of inflammation or IBS-Like symptoms. *Inflammatory Bowel Dis* **26**, 874–884.
90. Morvaridi M, Jafarirad S, Seyedian SS, *et al.* (2020) The effects of extra virgin olive oil and canola oil on inflammatory markers and gastrointestinal symptoms in patients with ulcerative colitis. *Eur J Clin Nutr* **74**, 891–899.

91. Schwingshackl L, Christoph M & Hoffmann G (2015) Effects of olive oil on markers of inflammation and endothelial function-a systematic review and meta-analysis. *Nutrients* **7**, 7651–7675.
92. Mähler M, Bristol IJ, Leiter EH, *et al.* (1998) Differential susceptibility of inbred mouse strains to dextran sulfate sodium-induced colitis. *Am J Physiology-Gastrointestinal Liver Physiol* **274**, G544–G551.
93. Bramhall M, Flórez-Vargas O, Stevens R, *et al.* (2015) Quality of methods reporting in animal models of colitis. *Inflammatory Bowel Dis* **21**, 1248–1259.
94. Cooper HS, Murthy SN, Shah RS, *et al.* (1993) Clinicopathologic study of dextran sulfate sodium experimental murine colitis. *Lab Investig J Tech Meth Pathol* **69**, 238–249.
95. Gommeaux J, Cano C, Garcia S, *et al.* (2007) Colitis and colitis-associated cancer are exacerbated in mice deficient for tumor protein 53-induced nuclear protein 1. *Mol Cell Biol* **27**, 2215–2228.
96. Melgar S, Karlsson L, Rehnstrom E, *et al.* (2008) Validation of murine dextran sulfate sodium-induced colitis using four therapeutic agents for human inflammatory bowel disease. *Int Immunopharmacol* **8**, 836–844.
97. Melgar S, Karlsson A & Michaëlsson E (2005) Acute colitis induced by dextran sulfate sodium progresses to chronicity in C57BL/6 but not in BALB/c mice: correlation between symptoms and inflammation. *Am J Physiology-Gastrointestinal Liver Physiol* **288**, G1328–G1338.
98. Stucchi AF, Shofer S, Leeman S, *et al.* (2000) NK-1 antagonist reduces colonic inflammation and oxidative stress in dextran sulfate-induced colitis in rats. *Am J Physiol Gastrointest Liver Physiol* **279**, G1298–G1306.
99. Berg DJ, Davidson N, Kühn R, *et al.* (1996) Enterocolitis and colon cancer in interleukin-10-deficient mice are associated with aberrant cytokine production and CD4(+) TH1-like responses. *J Clin Invest* **98**, 1010–1020.
100. Dieleman LA, Palmen MJ, Akol H, *et al.* (1998) Chronic experimental colitis induced by dextran sulphate sodium (DSS) is characterized by Th1 and Th2 cytokines. *Clin Exp Immunol* **114**, 385–391.
101. Hunter MM, Wang A, Hirota CL, *et al.* (2005) Neutralizing anti-IL-10 antibody blocks the protective effect of tapeworm infection in a murine model of chemically induced colitis. *J Immunol* **174**, 7368–7375.
102. Castagnini C, Luceri C, Toti S, *et al.* (2009) Reduction of colonic inflammation in HLA-B27 transgenic rats by feeding Marie Menard apples, rich in polyphenols. *Br J Nutr* **102**, 1620–1628.
103. Han ES, Oh JY & Park HJ (2011) Cordyceps militaris extract suppresses dextran sodium sulfate-induced acute colitis in mice and production of inflammatory mediators from macrophages and mast cells. *J Ethnopharmacol* **134**, 703–710.
104. Morris GP, Beck PL, Herridge MS, *et al.* (1989) Hapten-induced model of chronic inflammation and ulceration in the rat colon. *Gastroenterology* **96**, 795–803.
105. Lee C-P, Shih P-H, Hsu C-L, *et al.* (2007) Hepatoprotection of tea seed oil (Camellia oleifera Abel.) against CCl4-induced oxidative damage in rats. *Food Chem Toxicol* **45**, 888–895.
106. Riddell RH, Goldman H, Ransohoff DF, *et al.* (1983) Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Pathol* **14**, 931–968.