

The role of the Dutch dietary and physical activity guidelines in Inflammatory Bowel Disease: implications for clinical practice

Thesis committee

Promotor

Prof. Dr. B.J.M. Witteman Special professor Nutrition and Intestinal Health in Transitional Care Wageningen University & Research

Co-promotor

Dr. N.M. de Roos Assistant professor, Division of Human Nutrition & Health Wageningen University & Research

Other members

Prof. Dr. E.J.M. Feskens, Wageningen University & Research

Prof. Dr. G. Dijkstra, University Medical Center Groningen

Prof. Dr. D.M.A.E. Jonkers, Maastricht University

Prof. Dr. J. Zwerver, University Medical Center Groningen

This research was conducted under the auspices of the Graduate School VLAG (Advanced studies in Food Technology, Agrobiotechnology, Nutrition and Health Sciences)

The role of the Dutch dietary and physical activity guidelines in Inflammatory Bowel Disease: implications for clinical practice

Carlijn R. Lamers

Thesis

submitted in fulfilment of the requirements for the degree of doctor at Wageningen University by the authority of the Rector Magnificus,
Prof. Dr. A.P.J. Mol,
in the presence of the
Thesis Committee appointed by the Academic Board to be defended in public on Wednesday 8 June 2022 at 1.30 p.m. in the Omnia Auditorium.

Carlijn R. Lamers

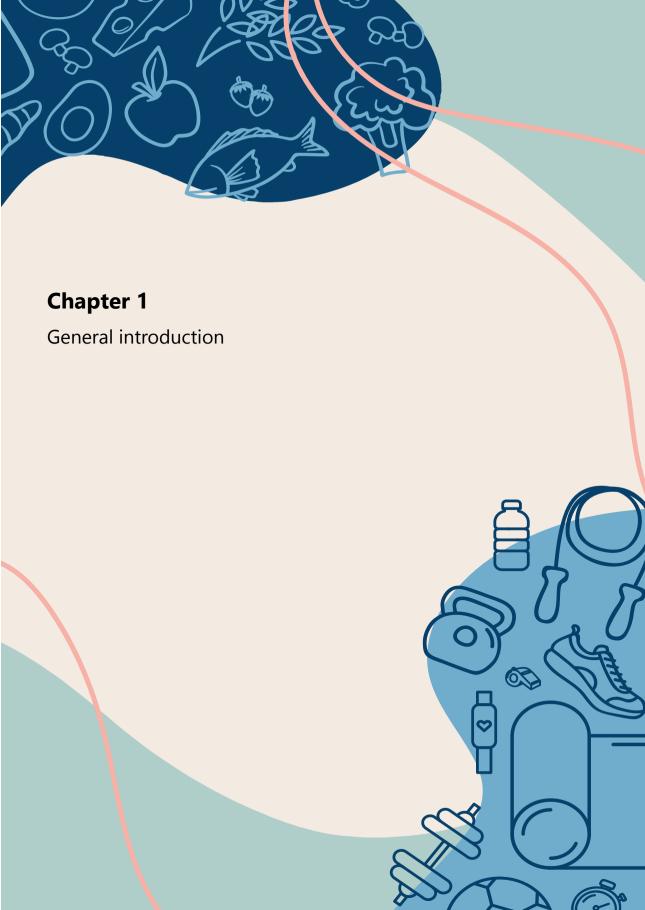
The role of the Dutch dietary and physical activity guidelines in Inflammatory Bowel Disease: implications for clinical practice
196 pages

PhD thesis, Wageningen University, Wageningen, the Netherlands (2022) With references, with summaries in English and Dutch

ISBN: 978-94-6447-140-3 DOI: 10.18174/566410

Table of contents

Chapter 1	General introduction	7
Chapter 2	The association between inflammatory potential of diet and disease activity: results from a cross-sectional study in patients with inflammatory bowel disease	25
Chapter 3	Patient experiences with the role of physical activity in inflammatory bowel disease: results from a survey and interviews	47
Chapter 4	Repeated prolonged moderate-intensity walking exercise does not appear to have harmful effects on inflammatory markers in patients with inflammatory bowel disease	75
Chapter 5	Lower impact of disease on daily life and less fatigue in patients with Inflammatory Bowel Disease following a lifestyle intervention	101
Chapter 6	Web-based dietary assessment and advice helps inflammatory bowel disease patients to improve their diet quality	129
Chapter 7	General discussion	155
	Summary Nederlandse samenvatting Dankwoord About the author List of publications	173 179 185 189 190
	Overview of completed training activities	193

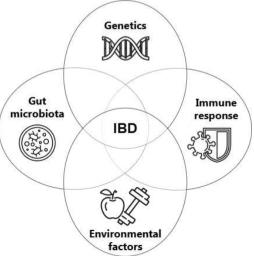


Inflammatory bowel disease (IBD)

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract of which Crohn's disease (CD) and ulcerative colitis (UC) are the main subtypes. CD is characterized by transmural inflammation often in a non-continuous manner that can affect the entire gastrointestinal tract, although the terminal ileum and colon are most often involved. On the contrary, inflammation in UC is superficial, continuous and restricted to the colon [1, 2]. Both are characterized by a variable and unpredictable disease course with periods of active disease alternating with periods of remission. Symptoms usually include diarrhoea, abdominal pain, passage of blood or mucus in the stool, fatigue and weight loss [1]. Besides gastrointestinal symptoms, extra-intestinal manifestations may also occur, with joints, skin and eyes being affected most frequently [3]. IBD has a significant impact on quality of life and this impact is even bigger during active disease [4, 5].

Although the exact pathogenesis of IBD is unclear, multiple factors seem to play a role (Figure 1). It seems to be a interaction complex between alterations in the gut microbiota, dysregulated immune responses and environmental factors in genetically susceptible individuals [2, 6]. The gut microbiota contributes to defence, immune system development and supply of nutrients and energy. In IBD, the diversity of the gut microbiota is reduced. A lower number of Firmicutes and short-chain fatty acid

Figure 1. Factors in pathogenesis of IBD



(SCFA)-producing bacteria is present resulting in dysbiosis which affects the immune system and gut barrier integrity [7, 8]. The dysregulated immune response in IBD is caused by an altered innate and adaptive immune system [9]. The altered innate immune system induces production of pro-inflammatory cytokines such as tumour necrosis factor α (TNF- α), interleukin (IL)-1 β , IL-6, and IL-18, while the altered adaptive immune system results in an increased presence of B-cells and activated effector T-cells, of which T helper 17 (Th17) cells play a key role in IBD [9, 10]. This

inappropriate inflammatory response, together with reduced regulatory mechanisms and anti-inflammatory cytokines such as IL-10 and transforming growth factor β (TGF- β), leads to chronic intestinal inflammation [9].

Besides gut microbiota and immune responses, environmental factors seem to have a major role in IBD [11]. In this respect, diet and lifestyle have been identified as important factors. IBD mainly used to be a disease of westernised countries in Europe, North America, and Oceania, with currently over 2 million people in Europe suffering from IBD [12]. However, over the past decades the incidence has risen in newly industrialized countries whose societies have adopted a westernized lifestyle characterized by unhealthy dietary habits and a decreased level of physical activity [12, 13]. Besides contribution to the development of IBD, lifestyle factors also seem to significantly impact the disease course and clinical outcomes in patients with established IBD [14, 15].

IBD is mainly treated with medication. In addition to medication, many IBD patients look for supportive and adjunctive or even alternative therapies [16, 17]. Diet and physical activity are modifiable lifestyle factors in which IBD patients seem to be interested. Surveys performed on dietary beliefs and behaviour showed that 57-92% of patients believe that diet could trigger a flare up and up to 89% of patients reported avoidance of particular foods to prevent or treat a flare [18]. This nutritional knowledge is mainly based on their own experiences [19]. Surveys performed on physical activity showed that around 41% of patients believe that physical activity reduces relapse rates and up to 79% of patients reported that physical activity improves their general well-being [20, 21]. These patient experiences are supported by several studies that suggest influence of various lifestyle factors on the course of disease [14, 15, 22, 23]. However, evidence-based dietary and physical activity quidelines for clinical IBD practice are lacking, mainly because the number of randomized interventional studies and prospective cohort studies is limited. Nonetheless, it is important to be aware of the current available evidence to support patients in their needs [16].

Diet and IBD

Food avoidance and restrictive dietary behaviour are very common among IBD patients as a result of the belief that avoiding certain foods would prevent a relapse

or exacerbation of symptoms [18]. However, this can result in a poorer food-related quality of life which is associated with lower intakes of nutrients that are important for general health and in particular gut health, like fibre, vitamin C, calcium and magnesium [24]. For example, a lower intake of dietary fibre is associated with an increased risk of exacerbation and worsening of disease activity [25, 26]. Besides an impaired intake of important nutrients, the intake of animal-based protein and omega-6 fatty acids is generally high which is also associated with an increased relapse risk [27, 28].

Several mechanisms have been proposed via which diet may influence the disease course of IBD via the gut microbiota [29, 30]. First, some dietary components influence microbiota structure and function which results in beneficial effects on immune activity. Dietary fibre, for example from vegetables, fruits, legumes and nuts, is an important component in this respect. Fermentation of dietary fibre by colonic bacteria results in the production of short-chain fatty acids (SCFAs) of which acetate, propionate and butyrate are the main ones. These SCFAs support the immune system by improving the mucosal barrier, interacting with immune cells, and decreasing the production of pro-inflammatory cytokines resulting in a reduced immune response [29, 30]. Second, some components can change the structure and permeability of the mucosal barrier. Sugar, for example from sweetened beverages and fruit juices, and alcohol can increase gut permeability, and emulsifiers, used in processed foods to improve texture and quality, can erode the mucus barrier both increasing bacterial translocation resulting in intestinal inflammation [29, 31]. In contrast, vitamin D, for example from fatty fish, can strengthen the epithelial barrier via promoting the expression of tight junction proteins [29]. Third, some dietary components can directly interact with aspects of the immune response. Animal-based protein, fat and salt, for example from meat and processed foods, can all activate inflammatory pathways. Saturated fat and omega-6 fatty acids promote a pro-inflammatory T-cell response, while omega-3 fatty acids can reduce the level of pro-inflammatory cytokines and suppress inflammation [29, 30]. Combining all these mechanisms, a diet rich in vegetables, fruits, legumes and nuts, with more plant-based instead of animal-based products, and avoidance of alcoholic beverages, high-fat processed meat and soft drinks might have the potential to prevent intestinal inflammatory processes via the gut microbiota [32].

Since cumulative evidence suggests that dietary components can have anti- or proinflammatory properties [30, 33], it might be useful to classify a diet according to these properties. For this purpose, the Dietary Inflammatory Index (DII) has been developed by reviewing the effects of dietary components on inflammatory markers like CRP and cytokines [34-36]. This index consists of 45 dietary components including energy, protein, carbohydrate, fat, fibre, vitamins and minerals, but also alcohol, flavonoids, herbs and spices. With this DII, diets can be categorized from maximally anti-inflammatory to maximally pro-inflammatory. Dietary assessment based on the inflammatory potential takes into account that foods can contain both anti- and pro-inflammatory components. Therefore, it might reflect the overall influence of a diet on inflammation. So far, the DII has been used in several types of cancer, cardiovascular diseases and chronic inflammatory diseases, including UC, to predict the risk for development of disease related to the inflammatory potential of diet [37-40]. Studies using the DII in patients with an established IBD diagnosis are lacking.

In line with the inflammatory potential of diet, exclusion of certain pro-inflammatory food components, such as industrialized, processed foods, animal fat and red and processed meat, seems to benefit IBD patients by reducing inflammatory processes [27, 28, 30]. In this respect, many different types of exclusion diets have been proposed in the treatment of IBD, such as the Specific Carbohydrate Diet (SCD), IgG4 quided exclusion diet, and CD-TREAT [41-43]. However, adherence can be a challenge and controlled trials are lacking, thus it is too soon to conclude if these restrictive diets benefit IBD patients [14]. The general Dutch dietary guidelines are based on the best available evidence regarding a healthy diet. In those guidelines, the general recommendation is to follow a more plant-based and less animal-based dietary pattern (Figure 2) [44]. It is recommended to daily consume at least 200 g of vegetables and 200 g of fruit, at least 90 g of wholegrain products, at least 15 g of unsalted nuts, a few portions of dairy, and three cups of tea. Moreover, it is recommended to weekly consume legumes and one serving of (oily) fish. Besides, it is recommended to limit the intake of red meat, particularly processed meat, salt, sugar-containing beverages and alcohol. Furthermore, it is recommended to replace refined cereal products by wholegrain products, and butter, hard margarines and cooking fats by soft margarines, liquid cooking fats and vegetable oils [44]. Since these general guidelines support the intake of foods with anti-inflammatory

properties and limit the intake of pro-inflammatory components, they might also apply to IBD patients, resulting in a non-restrictive diet with beneficial effects on inflammation. However, application of these general guidelines in IBD patients has not been investigated yet.

Physical activity and IBD

IBD patients are less physically active after their IBD diagnosis than before [20]. They experience barriers be physically active due to IBDrelated limitations such as fatigue, lack of toilet access, abdominal and joint pain, and weakness [21, 45. 461. Moreover, they are afraid of disease exacerbation as a result of physical activity [21].

Figure 2. Dutch dietary guidelines

General recommendations



More plant-based, less animal-based



Limit intake of red and processed meat



Limit intake of sugar-containing beverages and alcohol

Daily intake recommendations



At least 200 g of vegetables and 200 g of fruit



At least 90 g of wholegrain products



Few portions of dairy



At least 15 g of unsalted nuts



Use soft margarines, liquid cooking fats and vegetable oils



Sufficient intake of fluids, at least three cups of tea

Weekly intake recommendations



Weekly consume legumes and one serving of (oily) fish

However, positive effects of physical activity have also been mentioned. Physical activity makes IBD patients feel better in general, improves their quality of life and helps in symptom control [20, 21].

Studies performed so far showed that low to moderate intensity physical activity appears to be safe and well tolerated with minimal risk of symptom exacerbation in patients in remission or with mildly active disease [23, 47]. A large prospective study found that patients with CD in remission who had higher levels of physical activity were significantly less likely to develop active disease at six months [48]. The same tendency was found in patients with UC, but this was not significant. The safety of

high-intensity physical activity and physical activity in patients with severely active disease is currently not clear [23].

Besides the positive effects on disease activity, physical activity also has beneficial effects on bone mineral density, muscle mass and strength, and functional capacity [23, 48-50]. This is important since patients with IBD, either in remission or during active disease, already have a reduced muscle mass compared with healthy controls, which might negatively affect physical fitness and functional capacity [51-53]. Moreover, physical activity has psychological benefits, helps to maintain a normal weight and it has been associated with improvement in the perception of pain and sleep [47-50]. Physical activity can reduce fatigue and increase health-related quality of life [23, 47].

The exact mechanism via which physical activity might benefit IBD patients is unknown, but two possible routes of action have been proposed. The first route is via the release of cytokines and the second route is via changes in the gut microbiota. Several cytokines are released into the circulation as a result of physical activity [50]. These cytokines can either have anti- or pro-inflammatory effects depending on the type of cytokine and the intensity and duration of the activity. Low to moderate intensity physical activity can exert anti-inflammatory effects possibly via the release of protective myokines from working skeletal muscles [50, 54]. In this respect, mainly IL-6 is released into the circulation from contracting muscle fibres. This muscle derived IL-6 release appears to be responsible for an increase in circulating levels of anti-inflammatory cytokines IL-10 and IL-1. Moreover, IL-10 inhibits the expression of several pro-inflammatory cytokines, further promoting an anti-inflammatory state [54]. However, physical activity can also evoke transient mild systemic inflammation enhance pro-inflammatory cytokine release, which can exacerbate gastrointestinal symptoms [50]. Especially acute, very high-intensity bouts of exercise could lead to release of pro-inflammatory cytokines like TNF- α and IL-1 β and trigger systemic inflammation followed by a subsequent immunodepression [50].

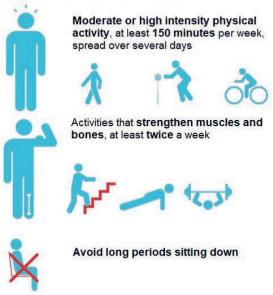
Regarding the gut microbiota, regular physical activity can enrich the microbiota diversity with higher numbers of *Firmicutes* and short-chain fatty acid (SCFA)-producing bacteria, and can stimulate proliferation of bacteria that modulate mucosal immunity and improve barrier functions [55]. These effects of physical

activity might be the result of a bidirectional crosstalk between skeletal muscles and the gut via the muscle-gut axis [56, 57], and can result in rebalance of dysbiosis which can improve health status [55]. However, physical activity can also have negative effects on the gut microbiota. High-intensity physical activity is accompanied by a decrease in intestinal blood flow which can induce ischemic events leading to dysfunction of the intestinal mucosa with detrimental consequences for the gut microbiota [57]. Moreover, ischemic events are associated with an increased intestinal permeability allowing bacteria to enter the circulation and activate systemic inflammation [57].

Studies indicate that IBD patients seem to prefer low-intensity types of physical activity, such as walking, over high-intensity types, such as running [45, 46]. This preference corresponds to what seems to be the preferred type of physical activity based on the beforementioned effect mechanisms. Moreover, low to moderate intensity physical activity is in line with the recommendations of the general Dutch physical activity guidelines [58]. In those guidelines, it is recommended to perform moderate-intensity physical activity at least 150 minutes every week spread over several days (*Figure 3*). Health will benefit more from being physically active longer

and more frequent. Additionally, it is recommended to perform activities that strengthen muscles and bones at least twice a week. and to avoid sitting down for long periods ſ581. Since these guidelines focus on regular low to moderate intensity activities. which have been shown to be safe and not to exaggerate inflammation, these general guidelines might also apply to IBD patients. However, application of these general guidelines in IBD patients has not been investigated yet.

Figure 3. Dutch physical activity guidelines



Most physical activity interventions examined the effect of controlled, supervised physical activity which is important to determine modes, frequencies, intensities and timing of physical activity. However, for regular and sustained physical activity it is also important to look at the effects of home-based activities supported by for example printed information, online platforms, and telephone consultations [59].

Web-based dietary guidance

During a regular consult at the outpatient clinic, time is often lacking to pay attention to lifestyle. To properly advice patients about lifestyle, it is important to first identify the aspects that require improvement. Regarding diet, a web-based screening tool might be useful for this purpose. The *Eetscore* is such a tool that can be used to assess diet quality [60, 61]. Based on this assessment, it provides personalised dietary advice to eat healthier and more in line with the Dutch dietary guidelines. Patients can complete the dietary assessment at home and read the dietary advice. Hereafter, the physician only has to support and guide the patients in which steps to take first. So far, this web-based dietary tool has only been used in healthy populations and in patients with cardiovascular diseases. IBD patients make up an interesting population to use the *Eetscore*, since it meets patients' need for dietary guidance and physicians' need for easy support of a healthy diet in IBD patients.

Aim and outline of this thesis

Besides medication, diet and physical activity can be complementary therapies in the treatment of IBD [62]. However, implementing these lifestyle factors in a patient's daily routine requires sustained changes in habits which may not be easy. Moreover, diets and physical activity programs can deviate greatly from the usual, especially when special foods or supplements are advised, making integration in social life and adherence in the long-term difficult. With sustainable and feasible recommendations based on the Dutch dietary and physical activity guidelines, adherence should be easier. Besides, special guidelines can make patients feel isolated whereas following general guidelines might make them feel less like a patient. Moreover, following these recommendations might also lead to an improved well-being of IBD patients, exert positive effects on the disease course and decrease their risk of other (chronic) diseases.

All currently available evidence regarding beneficial effects of nutrients and physical activity in IBD is in line with the Dutch guidelines for a healthy diet and physical activity, suggesting that disease-specific guidelines might not be necessary. However, these Dutch guidelines have not been investigated in IBD yet. Therefore, the aim of this thesis was to investigate the health effects of the Dutch dietary and physical activity guidelines as part of treatment in IBD patients.

First, we wanted to investigate the habitual diet and level of physical activity of IBD patients. For diet, we used the Dietary Inflammatory Index (DII) to determine the inflammatory potential of the diet. In **Chapter 2**, associations between the inflammatory potential of the diet and clinical disease activity are described. In **Chapter 3**, we investigated associations between level of physical activity and clinical disease activity. This survey study was combined with interviews to further elucidate associations since experiences of IBD patients regarding physical activity have been studied sparsely.

Most previous research on physical activity focused on short or low-intensity physical activity and subjective outcomes. Since moderate-intensity physical activity is an important part of the Dutch physical activity guidelines, we wanted to assess whether this is safe for IBD patients. Therefore, in **Chapter 4**, we performed a study on repeated prolonged moderate-intensity walking exercise and its effects on objective inflammatory markers.

Application of the Dutch dietary and physical activity guidelines was performed in a combined lifestyle intervention study of which the results are described in **Chapter 5**. We provided personal dietary and physical activity advice to improve the lifestyle of IBD patients and we investigated the effects of this 6-month intervention on the impact of disease on daily life, clinical disease activity, health-related quality of life, fatigue and faecal calprotectin.

Finally, since a combined lifestyle intervention is costly and time consuming, we also used a web-based tool, the *Eetscore*, to assess diet quality and provide personalised dietary advice to IBD patients, again based on the Dutch dietary guidelines. In **Chapter 6**, assessment of diet quality by the *Eetscore* is described as well as the effects of web-based dietary advice on diet quality in IBD patients over time.

In **Chapter 7**, the general discussion, the main findings of this thesis will be summarized and placed into perspective, and implications for future studies will be discussed.

References

- 1. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet. 2007;369(9573):1641-57.
- 2. Chang JT. Pathophysiology of Inflammatory Bowel Diseases. N Engl J Med. 2020;383(27):2652-64.
- 3. Vavricka SR, Schoepfer A, Scharl M, et al. Extraintestinal Manifestations of Inflammatory Bowel Disease. Inflamm Bowel Dis. 2015;21(8):1982-92.
- 4. Knowles SR, Graff LA, Wilding H, et al. Quality of Life in Inflammatory Bowel Disease: A Systematic Review and Meta-analyses-Part I. Inflamm Bowel Dis. 2018;24(4):742-51.
- 5. Knowles SR, Keefer L, Wilding H, et al. Quality of Life in Inflammatory Bowel Disease: A Systematic Review and Meta-analyses-Part II. Inflamm Bowel Dis. 2018;24(5):966-76.
- 6. Zhang YZ, Li YY. Inflammatory bowel disease: pathogenesis. World J Gastroenterol. 2014;20(1):91-9.
- 7. Nishida A, Inoue R, Inatomi O, et al. Gut microbiota in the pathogenesis of inflammatory bowel disease. Clin J Gastroenterol. 2018;11(1):1-10.
- 8. Mentella MC, Scaldaferri F, Pizzoferrato M, et al. Nutrition, IBD and Gut Microbiota: A Review. Nutrients. 2020;12(4).
- 9. Ahluwalia B, Moraes L, Magnusson MK, Öhman L. Immunopathogenesis of inflammatory bowel disease and mechanisms of biological therapies. Scand J Gastroenterol. 2018;53(4):379-89.
- 10. Lee SH, Kwon JE, Cho ML. Immunological pathogenesis of inflammatory bowel disease. Intest Res. 2018;16(1):26-42.
- 11. Ananthakrishnan AN, Bernstein CN, Iliopoulos D, et al. Environmental triggers in IBD: a review of progress and evidence. Nat Rev Gastroenterol Hepatol. 2018;15(1):39-49.
- 12. 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):2769-78.
- 13. 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; quiz e30.
- 14. Pigneur B, Ruemmele FM. Nutritional interventions for the treatment of IBD: current evidence and controversies. Therap Adv Gastroenterol. 2019;12:1756284819890534.
- 15. Rozich JJ, Holmer A, Singh S. Effect of Lifestyle Factors on Outcomes in Patients With Inflammatory Bowel Diseases. Am J Gastroenterol. 2020;115(6):832-40.
- 16. Torres J, Ellul P, Langhorst J, et al. European Crohn's and Colitis Organisation Topical Review on Complementary Medicine and Psychotherapy in Inflammatory Bowel Disease. J Crohns Colitis. 2019;13(6):673-85e.

- 17. Duff W, Haskey N, Potter G, et al. Non-pharmacological therapies for inflammatory bowel disease: Recommendations for self-care and physician guidance. World J Gastroenterol. 2018;24(28):3055-70.
- 18. Day AS, Yao CK, Costello SP, et al. 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.
- 19. de Vries JHM, Dijkhuizen M, Tap P, Witteman BJM. Patient's Dietary Beliefs and Behaviours in Inflammatory Bowel Disease. Dig Dis. 2019;37(2):131-9.
- 20. 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. J Crohns Colitis. 2019;13(6):686-92.
- 21. Chan D, Robbins H, Rogers S, et al. Inflammatory bowel disease and exercise: results of a Crohn's and Colitis UK survey. Frontline Gastroenterol. 2014;5(1):44-8.
- 22. Charlebois A, Rosenfeld G, Bressler B. The Impact of Dietary Interventions on the Symptoms of Inflammatory Bowel Disease: A Systematic Review. Crit Rev Food Sci Nutr. 2016;56(8):1370-8.
- 23. Engels M, Cross RK, Long MD. Exercise in patients with inflammatory bowel diseases: current perspectives. Clin Exp Gastroenterol. 2018;11:1-11.
- 24. Whelan K, Murrells T, Morgan M, et al. Food-related quality of life is impaired in inflammatory bowel disease and associated with reduced intake of key nutrients. Am J Clin Nutr. 2021;113(4):832-44.
- 25. Brotherton CS, Martin CA, Long MD, et al. Avoidance of Fiber Is Associated With Greater Risk of Crohn's Disease Flare in a 6-Month Period. Clin Gastroenterol Hepatol. 2016;14(8):1130-6.
- 26. Wedlake L, Slack N, Andreyev HJ, Whelan K. Fiber in the treatment and maintenance of inflammatory bowel disease: a systematic review of randomized controlled trials. Inflamm Bowel Dis. 2014;20(3):576-86.
- 27. Lewis JD, Abreu MT. Diet as a Trigger or Therapy for Inflammatory Bowel Diseases. Gastroenterology. 2017;152(2):398-414.e6.
- 28. Jowett SL, Seal CJ, Pearce MS, et al. Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study. Gut. 2004;53(10):1479-84.
- 29. Wark G, Samocha-Bonet D, Ghaly S, Danta M. The Role of Diet in the Pathogenesis and Management of Inflammatory Bowel Disease: A Review. Nutrients. 2020;13(1).
- 30. Tilg H, Moschen AR. Food, immunity, and the microbiome. Gastroenterology. 2015;148(6):1107-19.
- 31. Keshavarzian A, Fields JZ, Vaeth J, Holmes EW. The differing effects of acute and chronic alcohol on gastric and intestinal permeability. Am J Gastroenterol. 1994;89(12):2205-11.

- 32. Bolte LA, Vich Vila A, Imhann F, et al. Long-term dietary patterns are associated with pro-inflammatory and anti-inflammatory features of the gut microbiome. Gut. 2021;70(7):1287-98.
- 33. Lee D, Albenberg L, Compher C, et al. Diet in the pathogenesis and treatment of inflammatory bowel diseases. Gastroenterology. 2015;148(6):1087-106.
- 34. Cavicchia PP, Steck SE, Hurley TG, et al. A new dietary inflammatory index predicts interval changes in serum high-sensitivity C-reactive protein. J Nutr. 2009;139(12):2365-72.
- 35. Shivappa N, Steck SE, Hurley TG, et al. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutrition. 2014;17(8):1689-96.
- 36. Hébert JR, Shivappa N, Wirth MD, et al. Perspective: The Dietary Inflammatory Index (DII)-Lessons Learned, Improvements Made, and Future Directions. Adv Nutr. 2019;10(2):185-95.
- 37. Rafiee P, Shivappa N, Hébert JR, et al. Dietary Inflammatory Index and Odds of Colorectal Cancer and Colorectal Adenomatous Polyps in A Case-Control Study from Iran. Nutrients. 2019;11(6).
- 38. Bodén S, Wennberg M, Van Guelpen B, et al. Dietary inflammatory index and risk of first myocardial infarction; a prospective population-based study. Nutr J. 2017;16(1):21.
- 39. Shivappa N, Hebert JR, Behrooz M, Rashidkhani B. Dietary Inflammatory Index and Risk of Multiple Sclerosis in a Case-Control Study from Iran. Neuroepidemiology. 2016;47(1):26-31.
- 40. Shivappa N, Hébert JR, Rashvand S, et al. Inflammatory Potential of Diet and Risk of Ulcerative Colitis in a Case-Control Study from Iran. Nutr Cancer. 2016;68(3):404-9.
- 41. 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).
- 42. Gunasekeera V, Mendall MA, Chan D, Kumar D. Treatment of Crohn's Disease with an IgG4-Guided Exclusion Diet: A Randomized Controlled Trial. Dig Dis Sci. 2016;61(4):1148-57.
- 43. 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):1354-67.e6.
- 44. Kromhout D, Spaaij CJ, de Goede J, Weggemans RM. The 2015 Dutch food-based dietary guidelines. Eur J Clin Nutr. 2016;70(8):869-78.
- 45. DeFilippis EM, Tabani S, Warren RU, et al. Exercise and Self-Reported Limitations in Patients with Inflammatory Bowel Disease. Dig Dis Sci. 2016;61(1):215-20.
- 46. Tew GA, Jones K, Mikocka-Walus A. Physical Activity Habits, Limitations, and Predictors in People with Inflammatory Bowel Disease: A Large Cross-sectional Online Survey. Inflamm Bowel Dis. 2016;22(12):2933-42.

- 47. Hashash JG, Binion DG. Exercise and Inflammatory Bowel Disease: Insights into Etiopathogenesis and Modification of Clinical Course. Gastroenterol Clin North Am. 2017;46(4):895-905.
- 48. Jones PD, Kappelman MD, Martin CF, et al. Exercise decreases risk of future active disease in patients with inflammatory bowel disease in remission. Inflamm Bowel Dis. 2015;21(5):1063-71.
- 49. Narula N, Fedorak RN. Exercise and inflammatory bowel disease. Can J Gastroenterol. 2008;22(5):497-504.
- 50. Bilski J, Mazur-Bialy A, Brzozowski B, et al. Can exercise affect the course of inflammatory bowel disease? Experimental and clinical evidence. Pharmacol Rep. 2016;68(4):827-36.
- 51. Pizzoferrato M, de Sire R, Ingravalle F, et al. Characterization of Sarcopenia in an IBD Population Attending an Italian Gastroenterology Tertiary Center. Nutrients. 2019;11(10).
- 52. Rocha R, Santana GO, Almeida N, Lyra AC. Analysis of fat and muscle mass in patients with inflammatory bowel disease during remission and active phase. Br J Nutr. 2009;101(5):676-9.
- 53. Bryant RV, Trott MJ, Bartholomeusz FD, Andrews JM. Systematic review: body composition in adults with inflammatory bowel disease. Aliment Pharmacol Ther. 2013;38(3):213-25.
- 54. Gleeson M, Bishop NC, Stensel DJ, et al. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol. 2011;11(9):607-15.
- 55. Monda V, Villano I, Messina A, et al. Exercise Modifies the Gut Microbiota with Positive Health Effects. Oxid Med Cell Longev. 2017;2017:3831972.
- 56. Codella R, Luzi L, Terruzzi I. Exercise has the guts: How physical activity may positively modulate gut microbiota in chronic and immune-based diseases. Dig Liver Dis. 2018;50(4):331-41.
- 57. Ticinesi A, Lauretani F, Tana C, et al. Exercise and immune system as modulators of intestinal microbiome: implications for the gut-muscle axis hypothesis. Exerc Immunol Rev. 2019:25:84-95.
- 58. Weggemans RM, Backx FJG, Borghouts L, et al. The 2017 Dutch Physical Activity Guidelines. Int J Behav Nutr Phys Act. 2018;15(1):58.
- 59. Raman M, Rajagopalan V, Kaur S, et al. Physical Activity in Patients With Inflammatory Bowel Disease: A Narrative Review. Inflammatory Bowel Diseases. 2021.
- 60. van Lee L, Feskens EJ, Meijboom S, et al. Evaluation of a screener to assess diet quality in the Netherlands. Br J Nutr. 2016;115(3):517-26.
- 61. Looman M, Feskens EJ, de Rijk M, et al. Development and evaluation of the Dutch Healthy Diet index 2015. Public Health Nutr. 2017;20(13):2289-99.

62. Bernstein CN. Treatment of IBD: where we are and where we are going. Am J Gastroenterol. 2015;110(1):114-26.



Chapter 2

The association between inflammatory potential of diet and disease activity: results from a cross-sectional study in patients with inflammatory bowel disease

Lamers CR, de Roos NM, Witteman BJM

Published in BMC Gastroenterology, 2020;20:316. doi: 10.1186/s12876-020-01435-4.

.

Abstract

Background Diet may play a role in disease status in patients with inflammatory bowel disease. We tested whether the inflammatory potential of diet, based on a summation of pro- and anti-inflammatory nutrients, is associated with disease activity in patients with Crohn's disease and ulcerative colitis.

Methods Participants completed a disease activity questionnaire (short Crohn's Disease Activity (sCDAI) or Patient Simple Clinical Colitis Activity Index (P-SCCAI)) and a Food Frequency Questionnaire (FFQ). FFQ data were used to calculate the Dietary Inflammatory Index (DII) which enables categorization of individuals' diets according to their inflammatory potential on a continuum from pro- to anti-inflammatory. Associations with disease activity were investigated by multiple linear regression.

Results The analysis included 329 participants; 168 with Crohn's disease (median sCDAI score 93 [IQR 47-156]), and 161 with ulcerative colitis (median P-SCCAI score 1 [IQR 1-3]). Mean DII was 0.71 ± 1.33 , suggesting a slightly pro-inflammatory diet. In Crohn's disease, the DII was positively associated with disease activity, even after adjustment for confounders (p = 0.008). The mean DII was significantly different between participants in remission and with mild and moderately active disease (0.64, 0.97 and 1.52 respectively, p = 0.027). In ulcerative colitis, the association was not significant.

Conclusions Disease activity was higher in IBD participants with a more proinflammatory diet with statistical significance in Crohn's disease. Although the direction of causality is not clear, this association strengthens the role for diet in medical treatment, which should be tested in an intervention study.

Background

Dietary intake seems to play a role in the development of Crohn's disease (CD) and ulcerative colitis (UC), and possibly also in maintenance of remission and improvement of quality of life in patients with one of these inflammatory bowel diseases (IBD) [1, 2]. The exact mechanism is unknown, but modification of the gut microbiota and influence on immunological processes seem to be important [3, 4].

Diet is a modifiable lifestyle factor in which IBD patients seem to be interested and that may have beneficial effects on the course of IBD. Surveys performed on dietary beliefs and behaviour showed that around sixty percent of patients believe that diet influences their disease course and up to 77% of patients reported avoidance of particular foods to prevent or treat a flare [5-7]. There is cumulative evidence that certain components of a diet have anti- or pro-inflammatory properties and may therefore influence the course of disease [3, 8]. This has led to the development of the Dietary Inflammatory Index (DII). With this DII, diets can be categorized from maximally anti-inflammatory to maximally pro-inflammatory. Assessment of the inflammatory potential of a diet takes into account that some foods contain both beneficial and unhealthy nutrients. Therefore, it is likely that the DII better reflects the influence of diet on inflammation and thus on the course of disease than analyses with single foods [9-11]. The DII has been used in several other patient groups to predict the dietary inflammatory potential related risk for development of disease or the influence on clinical course of disease [12-14].

Therefore, the aim of this study was to assess the association between the inflammatory potential of diet and disease activity in patients with inflammatory bowel disease, separated into CD and UC patients. We also investigated participants' self-perceived impact of diet on disease and whether they had made dietary modifications.

Methods

Study design and study population

In this cross-sectional study, IBD patients aged 18 years or older, diagnosed with either CD or UC, were included. Participants were recruited between July and October 2018. A total of 1035 patients received a personal invitation: 940 IBD patients of a local regional hospital in the Netherlands received a letter and 95 IBD patients from the Nijmegen Exercise Study - a longitudinal study to examine the impact of a physically active lifestyle on health, quality of life, development and progression of various (chronic) diseases - received an email with an invitation to participate. Furthermore, an unknown number of patients responded to an invitation via digital newsletters and the website of the Dutch IBD patient association. In total, 397 patients sent us an e-mail to show interest in the study and received access to our online questionnaire. Unfortunately, we did not register the source each participant originated from. Participation comprised an online questionnaire composed of questions regarding participants characteristics, a disease activity questionnaire (short Crohn's Disease Activity (sCDAI) or Patient Simple Clinical Colitis Activity Index (P-SCCAI)) and a Food Frequency Questionnaire (FFQ) [15-17]. It took participants about 40 minutes to complete the whole questionnaire. Participants were excluded in case of indeterminate colitis or unknown IBD type, missing or incomplete FFO data or an implausible energy intake (<800 or >4000 kcal per day for men and <500 or >3500 kcal per day for women) to limit errors due to misreporting [18].

The medical ethical committee of Wageningen University decided that no formal ethical approval was needed, due to the low burden and risk of the study. All participants provided digital informed consent.

Data collection

Participant characteristics

Information on age, gender, height and weight, level of education, type of IBD, age at diagnosis, current medication and supplement use, previous IBD-related surgeries, food allergies and smoking was retrieved from the online questionnaire.

Disease activity

Disease activity was evaluated using the short Crohn's Disease Activity Index (sCDAI) for CD and the Patient Simple Clinical Colitis Activity Index (P-SCCAI) for UC [15, 16].

Disease activity scores were used as a continuous outcome measure and classified using previously validated cut-off points: remission (sCDAI <150 or P-SCCAI \leq 2), mildly active disease (sCDAI 150-219 or P-SCCAI 3-5), moderately active disease (sCDAI 220-450 or P-SCCAI 6-11) and severely active disease (sCDAI >450 or P-SCCAI \geq 12) [15, 19].

Dietary intake

Dietary intake was assessed using a 179-item validated Food Frequency Questionnaire (FFQ) designed to assess the intake of the Dutch population by capturing the foods consumed during the previous month [17]. Macronutrient intake was calculated and the FFQ was used to calculate the inflammatory potential of their habitual diet by using the DII. The DII is an index consisting of 45 food parameters developed by reviewing and scoring scientific articles on diet and inflammatory markers to be able to determine the inflammatory potential of a diet [9, 10]. A DII score above zero represents a pro-inflammatory diet and a DII score below zero represents an anti-inflammatory diet. Several papers described the development of inflammatory indices and calculation of the DII [9-11]. In short, DII scores of each food parameter were calculated by subtraction of the standard global mean of a representative world database from the amount of the food parameter eaten estimated from an FFO and dividing this value by its standard deviation [10]. This Zvalue was converted to a centred percentile score to minimize the effect of skewing and to achieve a symmetrical distribution. This centred percentile score was multiplied by the food parameter specific inflammatory effect score. All food parameter DII scores were summed to create an overall DII score. When calculated from all 45 parameters, the DII could theoretically range from -8.87 (maximally antiinflammatory) to +7.98 (maximally pro-inflammatory) [20]. In our study, data on 28 of the 45 parameters were available for inclusion in the overall DII score, namely: energy, protein, carbohydrate, total fat, saturated fat, cholesterol, trans fat, monoand polyunsaturated fat, n-3 and n-6 fatty acids, fibre, thiamine, riboflavin, niacin, vitamins A, B6, B12, C, D and E, zinc, iron, magnesium, selenium, folic acid, betacarotene and alcohol. The remaining 17 parameters, mainly flavonoids, herbs and spices, were not available because not all food parameters could be assessed reliably with the FFQ we used or were not available in the food composition database.

Patient reported impact and modification of diet

Information on participants' self-perceived impact of diet on disease and whether they had made dietary modifications since their diagnosis was retrieved from the online questionnaire.

Statistical analysis

Normally distributed data are presented as mean \pm standard deviation (SD), skewed data as median with interquartile range (IQR) and categorical data as frequencies with proportions. To compare baseline characteristics and DII between CD and UC and between disease activity groups, Chi-square tests were performed for categorical data, and independent samples t-test and one-way analysis of variance (ANOVA) (or Kruskall-Wallis when not normally distributed) were performed for continuous variables. Post-hoc analyses for disease activity groups were performed using the Bonferroni multiple comparisons test. Multiple linear regression was used to determine associations between inflammatory potential of diet and disease activity. Results were reported as β -coefficients with 95% confidence intervals (CI). A p-value of <0.05 was considered statistically significant. Statistical analysis was carried out using IBM SPSS Statistics version 24.

Results

Participants characteristics

In total, 329 participants were included in the analysis (*Figure 1*). Of these 329 participants, 168 participants (51%) had CD and 161 participants (49%) had UC. The majority of participants was female, well-educated and had experienced two or less flare-ups in the last year. The number of participants classified as having severely active disease was too small to analyse as a separate group (UC, n=2), so they were included in the moderately active disease group. About two-thirds of participants were in remission. Participants with CD were slightly younger at the time of this study and at diagnosis, they used more immunosuppressants and biologicals, and had more IBD-related surgeries than patients with UC. Supplement use was comparable in CD and UC (*Table 1*).

Figure 1. Flowchart of individuals included in analysis

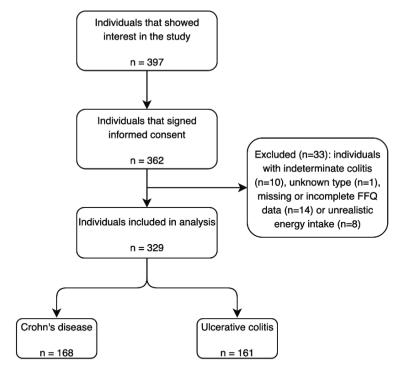


Table 1. Characteristics of the study population consisting of 168 CD and 161 UC participants

			Dis	Disease activity CD	CD	Dis	Disease activity UC	on.
	0	Ŋ	Remission	Mild	Moderate	Remission	Mild	Moderate
Subjects, n (%)	168 (51)	161 (49)	123 (73)	27 (16)	18 (11)	108 (67)	38 (24)	15 (9)
Gender, n (%)								
Female	117 (70)	(09) 26	84 (68)	17 (63)	16 (89)	(95) 09	27 (71)	10 (67)
Age (years)	47 ± 16*	51 ± 15*	48 ± 16	46 ± 17	47 ± 14	50 ± 14	54 ± 16	45 ± 16
Age at diagnosis (years)	32 ± 15*	36 ± 15*	33 ± 16	30 ± 14	33 ± 9	35 ± 14	41 ± 17	32 ± 15
BMI (kg/m²)	24.8 ± 4.7	24.9 ± 3.8	24.8 ± 4.4	24.9 ± 5.1	25.0 ± 6.6	24.7 ± 3.6	25.4 ± 3.9	24.8 ± 4.9
Smoking, n (%)								
Never	123 (73)	124 (77)	e(6 <i>L</i>) 26	17 (63) ^{a,b}	_q (05) 6	80 (74)	31 (82)	13 (87)
Current	16 (10)	7 (4)	e(7) 8	6 (22) ^b	2 (11) a,b	5 (5)	1 (3)	1 (7)
Former	29 (17)	30 (19)	$18 (15)^a$	4 (15) ^{a,b}	7 (39) ^b	23 (21)	6 (16)	1 (7)
Education level#, n (%)								
Low	37 (22)	34 (21)	25 (20)	7 (26)	5 (28)	21 (19)	10 (26)	3 (20)
Middle	52 (31)	48 (30)	38 (31)	5 (19)	6 (50)	33 (31)	8 (21)	7 (47)
High	79 (47)	79 (49)	(46)	15 (56)	4 (22)	54 (50)	20 (53)	5 (33)

Table 1. Continued

			Dise	Disease activity CD	ē	Dise	Disease activity UC	nc
	CD	nc	Remission	Mild	Moderate	Remission	Mild	Moderate
Medication use, n (%)								
Mesalazines	28 (17)**	**(09) 76	21 (17)	4 (15)	3 (17)	(09) 59	21 (55)	11 (73)
Corticosteroids	22 (13)	24 (15)	13 (11)	6 (22)	3 (17)	e(8) 6	10 (26) ^b	5 (33) ^b
Immunosuppressants	70 (42)**	33 (21)**	52 (42)	11 (41)	7 (39)	20 (19)	9 (24)	4 (27)
Biologicals	58 (35)**	27 (17)**	36 (29)	12 (44)	10 (56)	11 (10) ^a	9 (24)a,b	7 (47) ^b
Other	24 (14)*	11 (7)*	14 (11)	6 (22)	4 (22)	4 (4) ^a	4 (11)ab	3 (20) ^b
No medication use	34 (20)	30 (19)	29 (24)	4 (15)	1 (6)	24 (22)	6 (16)	0 (0)
Flare-ups in past year, n (%)								
None	92 (55)*	61 (38)*	$80 (65)^a$	7 (26) ^b	5 (28) ^b	50 (46) ^a	10 (26) ^{a,b}	1 (7) ^b
1-2 flare-ups	55 (33)*	70 (44)*	35 (29)	14 (52)	6 (33)	45 (42)	20 (53)	5 (33)
3-4 flare-ups	8 (5)*	19 (12)*	2 (2) ^a	4 (15) ^b	$2(11)^{a,b}$	8 (7)a	4 (11) ^a	7 (47) ^b
More than 4 flare-ups	13 (7)	11 (7)	6 (5)a	2 (7) a,b	5 (28) ^b	5 (5)	4 (11)	2 (13)
Supplement use, n (%)	74 (44)	68 (42)	54 (44)	11 (41)	6 (50)	39 (36)	21 (55)	8 (53)
Surgery, n (%)	57 (34)**	13 (8)**	40 (33)	8 (30)	6 (50)	(9) 9	6 (16)	1 (7)
Intolerances/allergies, n (%)	62 (37)	44 (27)	40 (33)	13 (48)	6 (50)	23 (21) ^a	16 (42) ^b	5 (33)a,b
Data are presented as mean ± SD	SD for normally distributed data. Categorical data is presented as n (%). * p $< 0.05 ** p < 0.001$	tributed data. C	ategorical data i	s presented a	ıs n (%). * p <0.	05 ** p<0.001		

Abbreviations: CD: Crohn's disease, UC: ulcerative colitis, BMI: body mass index

[#] Education level: no education, primary or lower vocational education and lower general secondary education (low); secondary vocational education ab groups with the same superscript letters do not differ significantly after post-hoc analyses using the Bonferroni test (p>0.05) and higher general secondary education (middle); higher vocational education and university (high).

Dietary intake and inflammatory potential

The total energy intake and intakes of protein, carbohydrates and fat were not significantly different between CD and UC. In the total population, the DII ranged from -2.32 to 4.10 with a mean of 0.71 ± 1.33, suggesting a slightly pro-inflammatory diet. No significant differences were found between CD and UC (0.79 ± 1.37 vs 0.62 \pm 1.28, p = 0.245) (*Table 2*). Multiple linear regression showed a positive association for CD disease activity scores and the DII in the crude model ($\beta = 12.96$; p = 0.002), suggesting that CD participants with a higher disease activity consumed a more proinflammatory diet. After adjustment for age, age at diagnosis, gender, BMI and education level, this association remained ($\beta = 11.86$; p = 0.008). No significant association was found between UC disease activity scores and the DII (p = 0.307) (Table 3). Across CD and UC disease activity groups, no significant differences were found regarding total energy, protein, carbohydrates and fat intake. In CD, the mean DII was significantly more pro-inflammatory when disease activity was higher (p = 0.027), with a significant difference between the remission and moderately active disease group after post-hoc analyses (p = 0.030) (Table 2/Figure 2). The parameters that contributed to differences in the DII were alcohol, mono- and polyunsaturated fatty acids, n-3 and n-6 fatty acids, magnesium, selenium, vitamin A, vitamin D and niacin, all having anti-inflammatory effect scores. Lower intakes of these parameters led to a less anti-inflammatory, so a more pro-inflammatory diet, in participants with a higher disease activity.

Table 2. Disease activity and inflammatory potential of diet of CD and UC participants and stratified for disease activity

		·		Disease activity CD	0	Dis	Disease activity UC	C
	CD	nc	Remission	Mild	Moderate	Remission	Mild	Moderate
Disease activity								
sCDAI score	93 [47-156]	1	79 [44-103]ª	171 [165-191] ^b	269 [233-326] ^c	1	1	1
Range	44-357	1	44-146	150-218	220-357	1	-	-
P-SCCAI score	ı	1 [1-3]	ı	I	ı	1 [1-1]a	3 [3-4] ^b	7 [6-9] ^c
Range	1	0-13	ı	I	I	0-2	3-5	6-13
Dietary intake								
Nutrient intake								
Energy (kcal)	1912 ± 618	2011 ± 565	1958 ± 601	1789 ± 602	1780 ± 738	2050 ± 587	1919 ± 496	1958 ± 577
Protein, EN%	15.0 ± 2.5	15.3 ± 2.7	15.1 ± 2.4	15.0 ± 2.2	14.6 ± 3.1	15.2 ± 2.8	15.4 ± 2.6	15.2 ± 2.6
Carbohydrates, EN%	43.4 ± 7.3	42.5 ± 6.4	42.9 ± 7.4	45.6 ± 6.6	43.9 ± 7.2	42.2 ± 6.8	43.1 ± 5.7	43.1 ± 4.6
Fat, EN%	36.4 ± 6.2	36.5 ± 5.5	36.7 ± 6.1	34.4 ± 6.1	37.3 ± 6.8	36.6 ± 5.8	36.1 ± 5.2	37.3 ± 4.4
DII	0.79 ± 1.37	0.62 ± 1.28	0.64 ± 1.29ª	0.97 ± 1.51a,b	1.52 ± 1.42 ^b	0.51 ± 1.28	0.78 ± 1.13	0.98 ± 1.61
Range	-2.22 - 3.99	-2.32 - 4.10	-2.22 - 3.94	-1.53 - 3.61	-1.06 - 3.99	-2.32 - 3.46	-1.04 - 2.64	-0.86 - 4.10

Abbreviations: CD: Crohn's disease, UC: ulcerative colitis, sCDAI: short Crohn's Disease Activity Index, P-SCCAI: Patient Simple Clinical Colitis Activity Index, Data are presented as mean ± SD for normally distributed data or median [interquartile range] when skewed. Categorical data is presented as n (%). ab groups with the same superscript letters do not differ significantly after post-hoc analyses using the Bonferroni test (p>0.05) EN%: energy percent, DII: dietary inflammatory index

Remission Mild Moderate

Figure 2. Mean DII of CD (n=168) and UC (n=161) participants stratified for disease activity

Abbreviations: CD: Crohn's disease, UC: ulcerative colitis, DII: dietary inflammatory index. Error bars represent standard error. * indicates significant difference between groups (p=0.03)

UC

Table 3. Results of multiple linear regression of the association between DII and disease activity as continuous variables, for CD and UC

	,	CD (n=168)		UC (n=161)	
		β-coefficient (95% CI)	p-value	β-coefficient (95% CI)	p-value
DII	Crude	12.96 (4.74 – 21.18)	0.002	0.145 (-0.134 – 0.424)	0.307
	Adjusted*	11.86 (3.14 – 20.58)	0.008	0.062 (-0.236 – 0.361)	0.681

Abbreviations: CD: Crohn's disease, UC: ulcerative colitis, DII: dietary inflammatory index, CI: confidence interval. CD disease activity scores can range from 0 to >450 and UC disease activity scores can range from 0 to 19. Bold values are significant.

Patient reported impact and modification of diet

CD

Of the 329 participants, 216 participants (66%) reported that diet had an impact on the course of their disease (73% CD vs 58% UC; p = 0.007). Since their diagnosis, 216 participants (66%) have adjusted their dietary intake. Generally, they reported avoidance of certain food products instead of a higher intake of beneficial foods. Lactose-containing products were mostly mentioned to be avoided (37%) followed by spicy foods (23%). Furthermore, participants reported that they reduced their intake of fat (20%), meat (18%), sugar (12%) and onions (11%). No differences were found between CD and UC or disease activity groups. Of the 329 participants, 194 participants (59%) adjust their diet during a flare-up.

^{*}Adjusted model: adjusted for age (years), age at diagnosis (years), gender (m/f), BMI (kg/m²) and education level (low/middle/high)

Discussion

In this study, disease activity was associated with the inflammatory potential of diet in participants with Crohn's disease. Participants with a more pro-inflammatory diet seem to have a higher disease activity. Whether this association is causal remains unclear. In participants with ulcerative colitis, the association was not significant. The majority of participants reported impact of diet on their disease. Modification of diet since diagnosis and during flare-ups was common in both patient groups and all disease activity groups.

To our knowledge, this is the first study to investigate the association between the inflammatory potential of diet and disease activity in patients with IBD in such a large sample. The DII has been calculated previously in a case control study including 62 UC patients and 124 controls to predict the risk of UC based on the inflammatory potential of diet. In that cross-sectional study, participants with higher DII scores seemed to have a higher risk of UC [21]. An analysis of three large prospective cohorts showed that dietary patterns with high inflammatory potential were associated with an increased risk of developing CD, but not UC, though they used a slightly different inflammatory index [2]. In contrast to our results, a recently published cross-sectional study in Iranian patients with an established IBD diagnosis did not find an association between the inflammatory potential of diet and disease activity [22]. The null finding in the Iranian patients might be due to the small sample size (n=143), especially the small number of participants with CD (n=32), as compared to 178 CD patients in the present study.

The DII consists of 45 food parameters that all have their own inflammatory effect score. The inflammatory effect scores we used varied from -0.663 for fibre to +0.373 for saturated fat. The contribution of a food parameter to the total DII score depends on the individuals' intake and the deviation of the inflammatory effect score from 0. Of the food parameters available in this study, fibre, vitamin A, B6, C, D, E, magnesium, zinc, poly-unsaturated fatty acids and n-3 fatty acids had the largest anti-inflammatory impact. Total fat and saturated fat had the largest pro-inflammatory impact. These anti- and pro-inflammatory effects are all based on general inflammation, but seem to be in line with IBD specific nutrient studies. The anti-inflammatory potential of fibre is in line with a prospective study in which they found that high consumption of dietary fibre reduces the risk of relapse among CD

patients [23]. By bacterial fermentation of dietary fibre, the production of short-chain fatty acids increases which has anti-inflammatory effects [24]. However, in both the abovementioned study and the DII, no distinction is made between the fermentability, solubility and viscosity of fibres, factors that influence the therapeutic effects of consumption [25]. Regarding the before mentioned vitamins and minerals, several reviews have described the effect of deficiencies on IBD [26-28]. For example, clinical disease activity increases and quality of life decreases significantly with lower levels of vitamin D, and zinc deficiency was shown to be correlated with inflammation in IBD by increasing the number of pro-inflammatory cells [26-28]. Poly-unsaturated and especially n-3 fatty acids have mostly been investigated in the context of supplementation with controversial results [29]. Beneficial effects have been shown. although a clear protective effect in preventing clinical relapse is not demonstrated [29]. A prospective study in patients with CD showed that a diet higher in total fat, saturated fat and a higher ratio of n-6:n-3 fatty acids was associated with disease relapses, which is in line with the inflammatory effect scores of the DII [30]. It seems reasonable to increase dietary intake of n-3 fatty acids for anti-inflammatory effects taking into account the involvement of n-3 fatty acids in immunological and inflammatory responses and an imbalance in n-6:n-3 fatty acid ratio to be a powerful pro-inflammatory stimulus [31]. All before mentioned studies combined, it is likely that the DII reflects influence of diet not only on general inflammation, but also on inflammation in IBD.

The differences in associations of inflammatory potential of diet with disease activity between CD and UC found in this study, are in line with previous studies. Regarding dietary intake, trends are observed in CD as well as in UC, but significant effects are more commonly found in CD [32]. Although we had to use a different disease activity questionnaire for each type of IBD, there is a similar distribution of disease activity groups in CD and UC. This distribution makes it unlikely that the different questionnaires account for the differences in associations between CD and UC. We did not assess the affected part of the gastrointestinal tract. Therefore, it is not possible to correct the associations for this aspect, although the affected part of the gastrointestinal tract may explain differences in associations between CD and UC.

Dietary beliefs of the participants in our study are in line with previous surveys. A similar percentage (58-62%) reported that diet influences their disease course and

that avoidance of certain food products is preferred over a higher intake of beneficial foods [5-7].

Strengths of this study include the large number of participants, which enabled us to perform analyses for CD and UC separately, and the use of validated questionnaires to determine disease activity and dietary intake. However, some limitations should be mentioned. This was a cross-sectional study and any association could therefore be a result of reverse causality. Participants who experience more pain or discomfort because of their disease may have changed their diet to relieve symptoms. Besides that, our sample included mainly participants in remission. A sample with an equal number of participants in each disease activity category would have increased the power to find stronger associations. Next to this, some extent of bias possibly occurred. More women than men responded, and the education level in our sample was high. In a large German study that compared responders to non-responders, women (up to 50 years old) were more likely to respond than men, as were nonsmokers and those with a high education level [33]. As diet quality is related to gender, education level, and various other lifestyle factors [34], this could mean that on average, our study sample had a more healthy diet than that of the average IBD patient, corresponding with a lower DII (more anti-inflammatory). Although, the range in DII was wide enough to find associations with disease activity, putting more effort into recruiting patients with more active disease or an unhealthy diet would be recommendable for the future. However, we do not think that selection bias negatively affected our study results. Another limitation is that we could not perform the complete calculation of the DII, because not all food parameters could be assessed with the FFO or were not available in the food composition database. Those food parameters, mainly flavonoids, herbs and spices, all had anti-inflammatory effect scores. Therefore, our results were probably more directed towards proinflammatory scores. Using less food parameters generally also results in a lower variation in DII [11]. However, all other studies that calculated the DII also were unable to include all 45 food parameters and used a number of food parameters that was comparable to our study [12-14, 20, 21]. The DII only consists of food parameters, supplement use is not included. In our study, more than 40% of the participants used a food supplement, including vitamin supplements. Most vitamins and minerals do have anti-inflammatory effect scores, which might have led to an underestimation of the DII in our study. As we did not have information about brands and dosages of

the supplements, it was not possible to incorporate these in the calculation of the DII. However, supplement use was equal in CD and UC participants as well as all disease activity groups, which makes it less likely that supplement use affected the association between DII and disease activity. Finally, for the outcome disease activity, we did not use an objective marker, but based it on a questionnaire, which was filled in by the participant instead of a physician. However, previous studies have validated the sCDAI and P-SCCAI and concluded that both are reliable and feasible for disease activity measurement. For both participant-based disease activity questionnaires, significant correlations were found with the physician-based questionnaires as well as biomarkers such as CRP [15, 16].

Conclusions

In conclusion, we found an association between the inflammatory potential of diet and disease activity in Crohn's disease, but not in ulcerative colitis. Although this association does not prove a causal relationship, for daily practice it suggests that a diet high in anti-inflammatory nutrients such as fibre, n-3 fatty acids, vitamins and minerals, which is a diet in line with current nutritional guidelines for healthy adults, seems to be equally prudent in IBD patients, especially Crohn's disease. Longitudinal studies are needed to further investigate the effect of diet on the course of disease.

Acknowledgements

We would like to thank all the participants that filled in our survey and the Crohn en Colitis Ulcerosa Vereniging (CCUVN) and Nijmegen Exercise Study for their support in participant recruitment.

Funding

This work was supported by a grant from the Province of Gelderland as part of the EAT2MOVE project (proposal PS2014-49). This grant was used to pay the salary of the corresponding author and the use of the FFQ.

References

- 1. Charlebois A, Rosenfeld G, Bressler B. The Impact of Dietary Interventions on the Symptoms of Inflammatory Bowel Disease: A Systematic Review. Crit Rev Food Sci Nutr. 2016;56(8):1370-8.
- 2. Lo CH, Lochhead P, Khalili H, et al. Dietary Inflammatory Potential and Risk of Crohn's Disease and Ulcerative Colitis. Gastroenterology. 2020.
- 3. Lee D, Albenberg L, Compher C, et al. Diet in the pathogenesis and treatment of inflammatory bowel diseases. Gastroenterology. 2015;148(6):1087-106.
- 4. Llewellyn SR, Britton GJ, Contijoch EJ, et al. Interactions Between Diet and the Intestinal Microbiota Alter Intestinal Permeability and Colitis Severity in Mice. Gastroenterology. 2018;154(4):1037-46.e2.
- 5. Zallot C, Quilliot D, Chevaux JB, et al. Dietary beliefs and behavior among inflammatory bowel disease patients. Inflamm Bowel Dis. 2013;19(1):66-72.
- 6. Limdi JK, Aggarwal D, McLaughlin JT. Dietary Practices and Beliefs in Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2016;22(1):164-70.
- 7. de Vries JHM, Dijkhuizen M, Tap P, Witteman BJM. Patient's Dietary Beliefs and Behaviours in Inflammatory Bowel Disease. Dig Dis. 2019;37(2):131-9.
- 8. Tilg H, Moschen AR. Food, immunity, and the microbiome. Gastroenterology. 2015;148(6):1107-19.
- 9. Cavicchia PP, Steck SE, Hurley TG, et al. A new dietary inflammatory index predicts interval changes in serum high-sensitivity C-reactive protein. J Nutr. 2009;139(12):2365-72.
- 10. Shivappa N, Steck SE, Hurley TG, et al. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr. 2014;17(8):1689-96.
- 11. Hébert JR, Shivappa N, Wirth MD, et al. Perspective: The Dietary Inflammatory Index (DII)-Lessons Learned, Improvements Made, and Future Directions. Adv Nutr. 2019;10(2):185-95.
- 12. Shivappa N, Godos J, Hebert JR, et al. Dietary Inflammatory Index and Colorectal Cancer Risk-A Meta-Analysis. Nutrients. 2017;9(9).
- 13. Boden S, Wennberg M, Van Guelpen B, et al. Dietary inflammatory index and risk of first myocardial infarction; a prospective population-based study. Nutr J. 2017;16(1):21.
- 14. da Costa Silva BY, de Carvalho Sampaio HA, Shivappa N, et al. Dietary Inflammatory Index and clinical course of multiple sclerosis. Eur J Clin Nutr. 2019;73(7):979-88.
- 15. Thia K, Faubion WA, Jr., Loftus EV, Jr., et al. Short CDAI: development and validation of a shortened and simplified Crohn's disease activity index. Inflamm Bowel Dis. 2011;17(1):105-11.
- 16. Bennebroek Evertsz F, Nieuwkerk PT, Stokkers PC, et al. The patient simple clinical colitis activity index (P-SCCAI) can detect ulcerative colitis (UC) disease activity in remission: a comparison of the P-SCCAI with clinician-based SCCAI and biological markers. J Crohns Colitis. 2013;7(11):890-900.

- 17. Streppel MT, de Vries JH, Meijboom S, et al. Relative validity of the food frequency questionnaire used to assess dietary intake in the Leiden Longevity Study. Nutr J. 2013;12:75.
- Willett W. Nutritional epidemiology. Oxford: New York: Oxford University Press; 2013.
- 19. Walsh AJ, Ghosh A, Brain AO, et al. Comparing disease activity indices in ulcerative colitis. J Crohns Colitis. 2014;8(4):318-25.
- 20. Shivappa N, Hebert JR, Kivimaki M, Akbaraly T. Alternative Healthy Eating Index 2010, Dietary Inflammatory Index and risk of mortality: results from the Whitehall II cohort study and meta-analysis of previous Dietary Inflammatory Index and mortality studies. Br J Nutr. 2017;118(3):210-21.
- 21. Shivappa N, Hébert JR, Rashvand S, et al. Inflammatory Potential of Diet and Risk of Ulcerative Colitis in a Case-Control Study from Iran. Nutr Cancer. 2016;68(3):404-9.
- 22. Mirmiran P, Moslehi N, Morshedzadeh N, et al. Does the inflammatory potential of diet affect disease activity in patients with inflammatory bowel disease? Nutr J. 2019;18(1):65.
- 23. Brotherton CS, Martin CA, Long MD, et al. Avoidance of Fiber Is Associated With Greater Risk of Crohn's Disease Flare in a 6-Month Period. Clin Gastroenterol Hepatol. 2016;14(8):1130-6.
- 24. Wong C, Harris PJ, Ferguson LR. Potential Benefits of Dietary Fibre Intervention in Inflammatory Bowel Disease. Int J Mol Sci. 2016;17(6).
- 25. Holscher HD. Dietary fiber and prebiotics and the gastrointestinal microbiota. Gut Microbes. 2017;8(2):172-84.
- 26. Weisshof R, Chermesh I. Micronutrient deficiencies in inflammatory bowel disease. Curr Opin Clin Nutr Metab Care. 2015;18(6):576-81.
- 27. Reich KM, Fedorak RN, Madsen K, Kroeker KI. Vitamin D improves inflammatory bowel disease outcomes: basic science and clinical review. World J Gastroenterol. 2014;20(17):4934-47.
- 28. Rossi RE, Whyand T, Murray CD, et al. The role of dietary supplements in inflammatory bowel disease: a systematic review. Eur J Gastroenterol Hepatol. 2016;28(12):1357-64.
- 29. Scaioli E, Liverani E, Belluzzi A. The Imbalance between n-6/n-3 Polyunsaturated Fatty Acids and Inflammatory Bowel Disease: A Comprehensive Review and Future Therapeutic Perspectives. Int J Mol Sci. 2017;18(12).
- 30. Tanaka M, Iwao Y, Sasaki S, et al. Moderate dietary temperance effectively prevents relapse of Crohn disease: a prospective study of patients in remission. Gastroenterol Nurs. 2007;30(3):202-10.
- 31. Cabré E, Mañosa M, Gassull MA. Omega-3 fatty acids and inflammatory bowel diseases a systematic review. Br J Nutr. 2012;107 Suppl 2:S240-52.
- 32. Richman E, Rhodes JM. Review article: evidence-based dietary advice for patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2013;38(10):1156-71.

- 33. Enzenbach C, Wicklein B, Wirkner K, Loeffler M. Evaluating selection bias in a population-based cohort study with low baseline participation: the LIFE-Adult-Study. BMC Med Res Methodol. 2019;19(1):135.
- 34. Looman M, Feskens EJ, de Rijk M, et al. Development and evaluation of the Dutch Healthy Diet index 2015. Public Health Nutr. 2017;20(13):2289-99.

Chapter 3

Patient experiences with the role of physical activity in inflammatory bowel disease: results from a survey and interviews

Lamers CR, de Roos NM, Koppelman LJM, Hopman MTE, Witteman BJM

Published in BMC Gastroenterology, 2021;21:172. doi: 10.1186/s12876-021-01739-z.



Abstract

Background Physical activity may affect disease activity in patients with inflammatory bowel disease. We used a survey to investigate this association and performed interviews to get a better understanding of patient experiences, and therefore the nature of this association.

Methods Patients with Crohn's disease (CD, n=176) and ulcerative colitis (UC, n=162) completed the short Crohn's Disease Activity (sCDAI) or Patient Simple Clinical Colitis Activity Index (P-SCCAI) and the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH). Associations were investigated by multiple linear regression. Semi-structured interviews (7 CD, 7 UC) were conducted to assess patient experiences with the role of physical activity in their disease.

Results The majority of survey participants were in remission (70%) and adhered to the Dutch physical activity guidelines (61%). In Crohn's disease, the total physical activity score was inversely associated with disease activity, even after adjustment for confounders (β = -0.375; p=0.013). No association between physical activity and disease activity was found in ulcerative colitis. Of the interviewees, 86% experienced beneficial effects of physical activity, such as improved general fitness, quality of life and self-image. However, during periods of active disease they struggled to find the motivation and perseverance to be physically active due to physical barriers.

Conclusions Crohn's disease participants with a higher physical activity level had a lower disease activity. This inverse association was not found in ulcerative colitis. Interviews revealed that IBD patients generally experience beneficial effects from physical activity, although the barriers caused by active disease may put them off to be physically active.

Background

Physical activity might have a protective role in the development of Crohn's disease (CD) and ulcerative colitis (UC), and possibly also supports maintenance of remission and improves quality of life in patients with one of these inflammatory bowel diseases (IBD) [1]. An increasing number of studies suggest that low to moderate intensity exercise might be beneficial for IBD patients by increasing health-related quality of life and reducing inflammation [2]. Although the exact mechanism is unknown, modification of the gut microbiota and influence of physical activity on immunological processes have been proposed as possible routes of action [3, 4]. Another way in which physical activity might be beneficial, is by reducing psychological stress. In a longitudinal study in sixty UC patients in remission, researchers found that stressful events were associated with higher chances of relapse [5]. Moreover, some studies suggest that physical activity might reduce fatigue levels in patients with IBD [6, 7].

Despite the potential beneficial effects of exercise, a recent cross-sectional study showed that patients were significantly less physically active after their IBD diagnosis than before. It is not clear whether this was due to discomforts from their disease or to a certain fear that exercise would worsen their disease progression or symptoms [8]. In surveys, patients report to experience barriers to exercise due to conditions related to their IBD such as fatigue, joint pain and weakness, and fear for symptom exacerbation [9]. They also report complaints during physical activity such as an increased urgency and abdominal pain, making it hard to complete the exercise [9, 10]. However, interviews explicitly addressing patient experiences are lacking.

Since IBD patients experience less complaints during remission than during active disease, it is vital to sustain remission as long as possible [11]. Although medication is the predominant form of treatment [12], physical activity could be a complementary therapy that can be implemented easily in a patient's daily routine. Consequently, it is valuable to understand the relation between physical activity and disease activity in IBD patients, and how this affects well-being. Therefore, the aim of this study was to assess the association between physical activity and disease activity in a large group of IBD patients including both CD and UC patients, and to explain the nature of this association by interviews.

Methods

Study design and study population

This study consisted of an online survey and interviews. The online survey was part of a larger survey about lifestyle factors and disease activity [13], which was conducted between July and October 2018. The survey was composed of questions regarding disease activity, physical activity and participants' characteristics. IBD patients aged 18 years or older, diagnosed with either CD or UC, were included. Details about recruitment can be found elsewhere [13]. In total, 397 patients showed interest in the study and received access to our online survey. We excluded participants with indeterminate colitis, unknown IBD type or incomplete physical activity data.

For the interviews, participants who had not taken part in the survey were recruited between December 2019 and July 2020 via the outpatient clinic of Hospital Gelderse Vallei, Ede, the Netherlands. The same in- and exclusion criteria as applied for the survey were used. The interviews focussed on effects of physical activity on disease activity, fatigue and quality of life, and vice versa. In total, fourteen interviews were conducted. This sample size was chosen because data saturation is typically reached between ten to fifteen semi-structured interviews [14, 15], which also applied to this study.

The medical ethical committee of Wageningen University decided that no formal ethical approval was needed, due to the low burden and risk of the study. All participants provided digital or written informed consent.

Data collection

Survey

The short Crohn's Disease Activity Index (sCDAI) and the Patient Simple Clinical Colitis Activity Index (P-SCCAI) were used to assess disease activity [16, 17]. Disease activity was used as a continuous outcome measure and classified into remission, mildly, moderately and severely active disease using previously validated cut-off points [16, 18].

Physical activity was assessed using the validated Short Questionnaire to Assess Health-enhancing physical activity (SQUASH). The SQUASH contains questions

regarding multiple activities during an average week in the past month, namely commuting activities, leisure time activities, household activities and activities at work or school. The number of days per week, average time per day and intensity of every activity was reported [19]. The total physical activity score was calculated by summing up the different activity scores which were calculated by the number of minutes per week of that activity times the corresponding metabolic equivalent of task (MET) [20]. The total physical activity score was used to investigate the association between physical activity and disease activity.

Besides, information was collected on age, gender, height and weight, level of education, type of IBD, age at diagnosis, current medication, previous IBD-related surgeries and smoking.

Interviews

Interviews were explorative and semi-structured according to an interview guide (*Appendix 1*), and were all performed by the same researcher. The interviews mainly consisted of open-ended questions about IBD-related complaints, physical activity in general, the link between physical activity and IBD, fatigue, and quality of life. These questions could lead to follow-up questions, which were impromptu. This semi-structured method is suitable for interpretation and exploration of wishes, attitudes, perceptions, and opinions of interviewees [21]. Nine interviews were held face-to-face and five interviews were conducted via telephone due to COVID-19. All interviews were recorded after which they were transcribed verbatim. Recordings were removed immediately after full transcription and were not shared with persons outside the research team. During transcription, names were coded to ensure anonymity. All interviews were conducted in Dutch. Quotes originating from the interviews were translated into English.

Data analysis

Survey

Data are presented as mean ± standard deviation (SD) for normally distributed continuous data or median with interquartile range (IQR) when skewed. Categorical data are presented as counts and percentages. To test for differences between CD and UC and between disease activity groups, independent samples t-test and one-way analysis of variance (ANOVA) were performed for continuous variables, or

Kruskall-Wallis test when not normally distributed. Post-hoc analyses for disease activity groups were performed using the Bonferroni multiple comparisons test. For categorical data, Chi-square tests were performed. Multiple linear regression was used to determine associations between total physical activity score and disease activity, and was adjusted for age, gender, BMI and education level in the first model, and also for age at diagnosis, medication use and previous IBD-related surgery in the second model. Results were reported as β -coefficients (per 100 point change in total physical activity score) with 95% confidence intervals (95% CI). A p-value of <0.05 was considered statistically significant. Statistical analysis was carried out using IBM SPSS Statistics version 24.

Interviews

Analysis of the transcripts was done by inductive coding with Atlas.ti 8. In vivo codes and codes assigned by the researcher were used to code the data. Four main themes emerged from the analysis. Within these themes, results were analysed on corresponding and contradicting answers.

Results

Participants' characteristics

For the survey, 338 participants were included in the analysis of which 176 participants (52%) had CD and 162 participants (48%) had UC (*Figure 1*). About two-thirds of participants were female and close to half of participants was highly educated and had experienced no flare-ups in the last year. As only two UC participants were classified as having severely active disease, they were included in the moderately active disease group. About two-thirds of participants were in remission. CD participants were slightly younger at diagnosis, used more immunosuppressants and biologicals, and had more IBD-related surgeries than UC participants (*Table 1*). Interviews were conducted with fourteen IBD patients of which seven had CD and seven had UC. The interviewees were 25 to 78 years of age (median 61 years), and the number of males and females was equal. Mean body mass index (BMI) of the interviewees was 26.3 ± 7.1 kg/m² and they were low (n=4), middle (n=5) and highly (n=5) educated (*Appendix 2 – Supplementary Table 1*).

Figure 1. Flowchart of individuals included in analysis

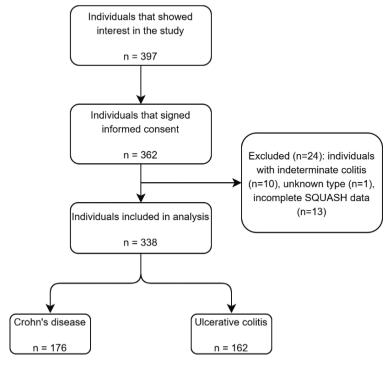


Table 1. Characteristics of the survey study population consisting of 176 CD and 162 UC participants

			Dis	Disease activity CD	8	Dis	Disease activity UC	C
	СО	nc	Remission	Mild	Moderate	Remission	Mild	Moderate
Subjects, n (%)	176 (52.1)	162 (47.9)	127 (72.2)	31 (17.6)	18 (10.2)	110 (67.9)	36 (22.2)	16 (9.9)
Gender, n (%)								
Female	124 (70.5)	101 (62.3)	89 (70.1)	19 (61.3)	16 (88.9)	65 (59.1)	26 (72.2)	10 (62.5)
Age (years)	47.6 ± 15.6	50.0 ± 14.5	47.8 ± 15.7	47.2 ± 16.6	46.7 ± 13.9	49.8 ± 14.0	52.5 ± 15.4	45.4 ± 15.5
Age at diagnosis (years)	32.3 ± 14.6*	35.4 ± 14.1*	32.6 ± 15.1	30.9 ± 14.8	32.6 ± 9.4	34.3 ± 13.3	39.7 ± 15.5	33.4 ± 15.5
BMI (kg/m²)	24.9 ± 4.7	24.9 ± 3.8	25.0 ± 4.4	24.6 ± 4.8	25.0 ± 6.6	24.6 ± 3.5	25.4 ± 3.9	25.6 ± 5.6
Smoking, n (%)								
Never	127 (72.2)	125 (77.2)	99 (78.0) ^a	19 (61.3) ^{a,b}	9 (50.0) ^b	83 (75.5)	28 (77.8)	14 (87.5)
Current	18 (10.2)	6 (3.7)	10 (7.9)	6 (19.4)	2 (11.1)	4 (3.6)	1 (2.8)	1 (6.3)
Former	31 (17.6)	31 (19.1)	18 (14.2) ^a	6 (19.4) _{a,b}	7 (38.9) ^b	23 (20.9)	7 (19.4)	1 (6.3)
Education level#, n (%)								
Low	40 (22.7)	32 (19.8)	27 (21.3)	8 (25.8)	5 (27.8)	21 (19.1)	8 (22.2)	3 (18.8)
Middle	53 (30.1)	50 (30.9)	38 (29.9)	6 (19.4)	9 (50.0)	35 (31.8)	8 (22.2)	7 (43.8)
High	83 (47.2)	80 (49.4)	62 (48.8)	17 (54.8)	4 (22.2)	54 (49.1)	20 (55.6)	6 (37.5)

Table 1. Continued

			Dis	Disease activity CD	8	Dis	Disease activity UC	nc
	СО	nc	Remission	Mild	Moderate	Remission	Mild	Moderate
Medication use, n (%)								
Mesalazines	29 (16.5)**	102 (63.0)**	22 (17.3)	4 (12.9)	3 (16.7)	(62.7)	20 (55.6)	13 (81.3)
Corticosteroids	24 (13.6)	23 (14.2)	14 (11.0)	7 (22.6)	3 (16.7)	10 (9.1) ^a	9 (25.0) ^b	4 (25.0) _{a,b}
Immunosuppressants	76 (43.2)**	33 (20.4)**	55 (43.3)	14 (45.2)	7 (38.9)	20 (18.2)	8 (22.2)	5 (31.3)
Biologicals	57 (32.4)**	28 (17.3)**	35 (27.6) ^a	12 (38.7) ^{a,b}	10 (55.6) ^b	11 (10.0) ^a	9 (25.0) _{a,b}	8 (50.0) ^b
Other	24 (13.6)	12 (7.4)	14 (11.0)	6 (19.4)	4 (22.2)	5 (4.5) ^a	3 (8.3)ab	4 (25.0) ^b
No medication use	36 (20.5)	29 (17.9)	30 (23.6)	5 (16.1)	1 (5.6)	23 (20.9)	6 (16.7)	0.0)
Flare-ups in past year, n (%)								
None	91 (51.7)*	63 (38.9)*	79 (62.2) ^a	7 (22.6) ^b	5 (27.8) ^b	51 (46.4) ^a	10 (27.8) a,b	2 (12.5) ^b
1-2 flare-ups	59 (33.5)	68 (42.0)	38 (29.9)	15 (48.4)	6 (33.3)	42 (38.2)	21 (58.3)	5 (31.3)
3-4 flare-ups	9 (5.1)*	18 (11.1)*	2 (1.6) ^a	5 (16.1) ^b	2 (11.1)a,b	9 (8.2) ^a	3 (8.3) ^a	6 (37.5) ^b
More than 4 flare-ups	17 (9.7)	13 (8.0)	8 (6.3) ^a	4 (12.9)a,b	5 (27.8) ^b	8 (7.3)	2 (5.6)	3 (18.8)
Surgery, n (%)	60 (34.1)**	13 (8.0)**	41 (32.3)	10 (32.3)	9 (50.0)	6 (5.5)	6 (16.7)	1 (6.3)
Data are presented as mean ± SD for normally distributed data. Categorical dat Abbreviations: CD: Crohn's disease, UC: ulcerative colitis, BMI: body mass index	SD for normally distributed data. Categorical data is presented as n (%). * p <0.05 ** p<0.01 ease, UC: ulcerative colitis, BMI: body mass index	tributed data. Ca	ategorical data y mass index	is presented a	s n (%). * p <0.	05 ** p<0.01		-
Education level: no education, primary or lower vocational education and lower general second higher general secondary education (middle); higher vocational education and university (high)	primary or lower vocational education and lower general secondary education (low), secondary v ocational education and ation (middle); higher vocational education and university (high).	ocationai educai ner vocational ed	tion and lower g ducation and ur	jenerai second iiversity (high)	iary education	(IOW); secondar	y v ocational e	ducation and
^{ab} groups with the same superscript letters do not differ significantly after post -hoc analyses using the Bonferroni test (p>0.05)	ript letters do not	differ significan	tly after post -ho	oc analyses us	ing the Bonferi	roni test (p>0.0	(5)	

Survey

Significant differences were found between CD and UC regarding total physical activity scores and total minutes per week, with UC participants being more physically active than CD participants (p = 0.035) and performing activities with a higher intensity resulting in a higher total physical activity score (p = 0.025) (Table 2). In CD participants, multiple linear regression showed an inverse association between the total physical activity score and disease activity scores in the crude model ($\beta = -0.406$; p = 0.007) (*Table 3*). This suggests that CD participants who are more physically active and probably perform activities with a higher intensity, have a lower disease activity. After adjustment for age, gender, BMI and education level, and additionally age at diagnosis, medication use and previous IBD-related surgery, this association remained ($\beta = -0.375$; p = 0.013) (*Table 3*). No significant association was found between the total physical activity score and UC disease activity scores (B = -0.006; p = 0.162) (Table 3). Across disease activity groups, the total physical activity score was significantly lower in CD when disease activity was higher (p = 0.035), with a significant difference between the remission and moderately active disease group after post-hoc analyses (p = 0.046) (Table 2/Figure 2). When disease activity is higher, the number of minutes per week spent on physical activity is the same as for the lower disease activity groups, but participants seem to choose activities with a lower intensity (Table 2/ Figure 2).

3

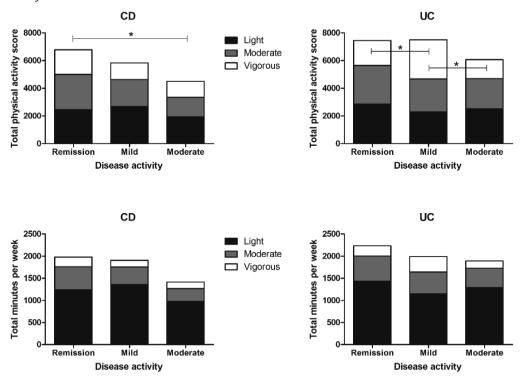
Table 2. Disease activity and physical activity scores of CD and UC participants and stratified for disease activity

				Disease activity CD	e	Ö	Disease activity UC	S S
	8	Ŋ	Remission	Mild	Moderate	Remission	Mild	Moderate
Disease activity								
sCDAI score	95 [48-158]	,	79 [44-107]ª	79 [44-107] ^a 175 [165-198] ^b 269 [233-326] ^c	269 [233-326] ^c	ı	,	,
Range	44-357	1	44-146	150-219	220-357	•	1	
P-SCCAI score	1	1 [1-3]		I	1	1 [1-2] ^a	3 [3-4] ^b	²[6-9] 7
Range	•	0-13	1	ı	1	0-2	3-5	6-13
Physical activity								

Abbreviations: CD: Crohn's disease, UC: ulcerative colitis, sCDAI: short Crohn's Disease Activity Index, P-SCCAI: Patient Simple Clinical Colitis Activity Index 7501 ± 4160 1989 ± 998 7457 ± 4052 2230 ± 1035 Data are presented as mean \pm SD for normally distributed data or median [interquartile range] when skewed. * p < 0.054501 ± 2858^b 1413 ± 895 $5834 \pm 2863^{a,b}$ 1903 ± 871 6782 ± 3963^{a} 1979 ± 1071 6382 ± 3747* 7329 ± 3989* 2143 ± 1016 * $1907 \pm 1031*$ Total physical activity score Total minutes per week

^{ab} groups with the same superscript letters do not differ significantly after post-hoc analyses using the Bonferroni test (p>0.05)

Figure 2. Total physical activity score (top) and total minutes per week (bottom) of CD and UC participants stratified for disease activity, divided into light, moderate and vigorous physical activity.



Total physical activity score was calculated by summing up the different activity scores which were calculated by the number of minutes per week of that activity times the corresponding metabolic equivalent of task (MET). * p<0.05. Abbreviations: CD: Crohn's disease, UC: ulcerative colitis

Table 3. Results of multiple linear regression of the association between physical activity with disease activity as continuous variables, for CD and UC

		CD (n=176)		UC (n=162)	
		β-coefficient (95% CI)§	p-value	β-coefficient (95% CI)§	p-value
Total physical activity score	Crude	-0.406 (-0.6980.114)	0.007	-0.006 (-0.015 – 0.003)	0.162
-	1	-0.395 (-0.6930.097)	0.010	-0.005 (-0.014 – 0.004)	0.293
	2	-0.375 (-0.6680.081)	0.013	-0.003 (-0.013 – 0.006)	0.490

Abbreviations: CD: Crohn's disease, UC: ulcerative colitis, CI: confidence interval

CD disease activity scores can range from 0 to >450 and UC disease activity scores can range from 0 to 19. Bold values are significant.

Model 1: adjusted for age (years), gender (m/f), BMI (kg/m²) and education level (low/middle/high)

Model 2: as model 1 plus age at diagnosis (years), medication use (yes/no) and previous surgery (yes/no)

[§] Per 100 point increase in total physical activity score

Interviews

Thirteen out of the fourteen interviewees reported to adhere to the Dutch physical activity guidelines of 150 minutes of moderate to high intensity exercise per week spread over several days. All in all, twelve out of the fourteen participants (86%) mentioned some kind of beneficial effect of physical activity. Regarding the role of physical activity in their disease, the difficulties experienced during physical activity were identified as one theme, whereas effects on disease activity, fatigue and quality of life were identified as three other themes. These four themes will be discussed in more detail below. Numbers do not always add up to fourteen, since interviewees could experience positive, negative or no effect of physical activity on disease activity, fatigue and quality of life, or sometimes they did not have an opinion about the effect.

Difficulties during physical activity

All interviewees reported to have experienced difficulties related to IBD that hindered their physical activity. Most commonly mentioned obstacles were frequent toilet use, pain and fatigue. Nine interviewees explained that the proximity of a toilet is important because they have unpredictable and urgent bowel movements.

"When I was a teen, the disease was such a burden I could not exercise at all. I was very dependent on the presence of a toilet. Physical activity affects my bowel movements. When someone asked me: "Do you want to come over and play soccer?", I could not join because I knew there were no toilets anywhere nearby. Things like that can really have an influence in times of active disease." (Interviewee 10)

Seven interviewees also mentioned that bowel movements can be induced by physical activity. One interviewee said that she would always bring some toilet paper with her when she would go for a run just in case, although her disease was not very active. Pain was also mentioned as a reason to not be physically active. Three interviewees were afraid of exercise-induced abdominal pain, and others already suffered from muscle pain and did not want to aggravate this. Six interviewees reported that they often are too fatigued to exercise. They said they could feel so tired they just wanted to lay down. In this case they found it very hard to gather enough motivation to exercise, so they would not do any physical activity.

Effects of physical activity on disease activity

Eight interviewees mentioned that physical activity can have positive effects on their disease activity, while five interviewees mentioned the opposite. Most commonly mentioned positive effects were that physical activity can help to improve overall fitness and muscle strength, making the body more resilient. Two interviewees also said that this resilience would help the body to recover quicker and better from flareups.

"I think it can have a positive effect in the sense that my body is always strong and fit, and I recover more quickly when I have a flare-up. The past six months my disease was very active. The doctors and I think that me being very physically active has prevented me from a colectomy and a stoma. We could keep trying different things without my body giving in, because it was strong." (Interviewee 2)

Four interviewees also mentioned positive effects of physical activity on mental health. The distraction by physical activity is very important, this would take their mind off the pain they experience. Another interviewee mentioned that physical activity helps him to get a better mindset to help him cope with the disease. He mentioned that mind-body exercises are very important for him and help him to be aware of his body.

Negative effects were that physical activity, especially when including movements of the abdomen, can induce abdominal pain and bowel movement. Sit-ups, bending over, and jogging were mentioned as being too painful as the abdomen would move too much. Exercise-induced bowel movements were also mentioned as a negative effect. One interviewee mentioned she had to go to the toilet immediately when she tried to exercise, making physical activity very uncomfortable.

"When I start exercising, I have to go to the toilet. I get cramps and need to sit on the toilet for half an hour. Afterwards, I am all sweaty and I do not feel like exercising anymore." (Interviewee 4)

Effects of physical activity on fatigue

Four interviewees were convinced physical activity could reduce fatigue. They mentioned it is harder to start exercising when they are fatigued, but they always feel more energetic after exercise than before.

"Sometimes when I come home from work, I feel like I cannot go any further. I am so extremely fatigued, something I do not recognise from before the diagnosis. Then I think, I have to train, and if I just do it, I always feel better afterwards. So, I think it is definitely good, even if you exercise on a lower level or speed. It requires a lot of discipline though. I totally understand that people with this disease do not feel like exercising anymore. It requires a lot of effort, it hurts, and you are tired. But I know it is good for me and if I do it, I feel better afterwards." (Interviewee 2)

One interviewee said that when he is too tired, he would not exercise which only worsens his fatigue. He called it a vicious cycle.

Effects of physical activity on quality of life

Twelve interviewees noticed positive effects of physical activity on their quality of life. Physical activity leads to the feeling of being in shape, that they are healthier and can handle more physical setbacks. When interviewees felt physically fit, this also had a positive effect on their mental health, and it reduced stress levels. The social aspect of physical activity was also mentioned to be important for quality of life. Two interviewees said that they enjoyed physical activity because of the friends they cycle with, or the cup of coffee after a workout in the gym. Lastly, one interviewee mentioned that physical activity can help to recover quicker from a flare-up and thereby can improve her quality of life dramatically, from a score of 1 during severely active disease, to an 8 during remission. All twelve interviewees that noticed positive effects of physical activity on their quality of life indicated that when they are not able to exercise because of their disease activity, their quality of life is lower.

"When I can be more physically active, this would definitely have a positive effect. It would make me feel stronger, more in shape. You walk a bit more upright and you dare to show that you are there." (Interviewee 7)

Discussion

In this study, the level of physical activity was inversely associated with disease activity in participants with Crohn's disease. This association was not found in participants with ulcerative colitis. Crohn's disease participants who are less physically active seem to have a higher disease activity. Whether this association is causal remained unclear from the survey. However, interviews to gain insight in the nature of this association showed that most interviewees (86%) experience some kind of beneficial effect of physical activity. They reported that physical activity is very important to improve general fitness, quality of life, and self-image. However, in periods of active disease they found it is hard to find the motivation and perseverance to be physically active, since there are many physical barriers limiting physical activity. The proximity of a toilet was mentioned as a necessity for being able to exercise, and pain and fatigue were mentioned as obstructing factors.

Our data confirm that disease activity is associated with physical activity. A comparable result was found in a prospective study of 1857 IBD patients in remission. Patients with higher physical activity levels, measured by the Godin leisure-time activity index, were less likely to develop active disease at 6 months [22]. We showed that physical activity has the same association with disease activity in a more diverse patient group of CD patients, not only patients in remission, as we used the same questionnaires and cut-off points for disease activity. When comparing the physical activity rates of participants in our study to those in other studies, we found that physical activity rates vary widely between IBD cohorts, which may be explained by the heterogeneity of physical activity quantification and risk of selection bias [1, 9, 10, 23, 241. Only one study used total activity scores and minutes per week to classify physical activity [24], just as in our study, whereas others only reported the times and degree of physical activity per week. The association found in CD, and the lack of an association in UC, is in line with previous studies: significant results are more commonly found in CD [22]. For each type of IBD a different disease activity questionnaire had to be used, which may induce bias. However, we found a similar distribution of disease activity groups in CD and UC, which makes it unlikely that the different questionnaires account for the difference in associations between CD and UC. The difference in associations might be explained by defective autophagy, which is only present in Crohn's disease. It has been well established that exercise can induce autophagy, thereby it might exert a positive effect on disease activity [25, 26].

When looking into the nature of the association between physical activity and disease activity, interviewees reported that IBD-related complaints limit their physical activity for various reasons. Most commonly mentioned barriers were fatigue, exercise-induced pain, irregular and unpredictable bowel movements, and no proximity to a toilet; barriers that were also mentioned in previous studies [9, 24]. Several interviewees also mentioned immediate effects of physical activity on their symptoms. Inducement of bowel movement was mentioned the most, which could also result in cramps and abdominal pain. Similar exercise-induced symptoms were described in other studies, although these studies specifically focussed on highintensity exercise [9, 27]. In the current study, not all interviewees defined the intensity of the exercise that caused symptom exacerbation but rather the mode of exercise. For example, running was mentioned to aggravate symptoms, whereas swimming was mentioned as an exercise mode that patients could endure for a long time without symptom aggravation. However, based on the MET scores, both are qualified as vigorous intensity exercise [20]. This indicates that not only the intensity of physical activity might influence symptoms, but the mode of exercise plays a crucial role. This is supported by, for example, runner's diarrhoea, which is a common phenomenon in the general population, and this type of diarrhoea can also be present in IBD patients [28].

Besides immediate aggravation of symptoms, interviewees also mentioned alleviation of symptoms as a result of physical activity. Alleviation of fatigue was mentioned as an immediate effect. Interviewees often felt fatigued, but at the same time energized after physical activity. This finding is in line with a review supplemented with a case series which aimed to explore issues that clinicians may need to consider when giving exercise advice to IBD patients [7]. This study also reported that physical activity improved the mood of IBD patients. Mood improvement was also mentioned in the current study, as were long-term positive effects for example improved overall fitness, resilience, and positive effects on mental health. All these long-term effects were reported to have a beneficial effect on the quality of life of the interviewees, which is in line with existing literature [29, 30]. Interviewees mentioned that their quality of life could be improved by physical activity, but only when disease activity was low enough. Although not mentioned by the interviewees in this study, literature suggests that stress could aggravate disease activity and high stress levels can lead to a flare-up [5, 31, 32]. In line with previous

studies, interviewees in the current study suggested that physical activity could reduce stress levels [33]. This could potentially mean that physical activity could reduce disease activity and the frequency of flare-ups by lowering stress levels and improving quality of life. However, more research on this topic is needed to confirm this hypothesis.

Strengths of this study include the combination of an online survey with interviews, with a large number of participants in the survey part, which enabled us to perform analyses for CD and UC separately, and the use of validated questionnaires to determine disease activity and physical activity. However, some limitations should be mentioned. Since the survey was cross-sectional any association could be due to reverse causality. In our case, it is probable that patients with more severe disease are less likely to be physically active, which was supported by the interviews, so we cannot conclude that lack of physical activity leads to higher disease activity. Next to this, our sample mainly included participants in remission. The power to find associations would have increased with an equal number of participants in each disease activity category. Another drawback is that we could not verify participants' physical activity compliance. However, compliance applies to all participants at all times, and this systematic bias would not affect the association. An advantage of interviews is that they allowed us to discuss effects of physical activity during every disease stage, in contrast to the surveys in which only current disease activity was discussed. Another limitation of the survey is that we based disease activity on a questionnaire instead of an objective marker. However, previous studies validated the sCDAI and P-SCCAI and concluded that both are reliable and feasible for disease activity measurement [16, 17]. Final limitation of the survey is the self-reported data on medication and previous IBD-related surgery which could not be verified with medical records. A limitation of the interviews is that the intercoder reliability is small because the interviews were coded by one researcher only. However, all interviews were also performed by one researcher, which increases the comparability of the interviews, and regular discussion of the analysis within the research team acted as a quality control measure. Finally, separate analysis of the interviews for CD and UC would have been better to support the survey findings, but this was not possible since data saturation was not reached in these separate groups. However, our interviewees form a representative group of IBD patients.

Conclusions

In conclusion, we found an inverse association between physical activity and disease activity in Crohn's disease, but not in ulcerative colitis. No causal relationship has been proven with this association, but interviews with IBD patients suggest that it is prudent to stimulate IBD patients to be more physically active, as they generally experience beneficial effects from physical activity. When disease activity does not hinder IBD patients to be physically active, they experience an improved quality of life, reduced stress levels, less fatigue and a general feeling of fitness. Intervention studies are needed to further investigate the effect of lifestyle factors like physical activity on the course of disease.

Acknowledgements

We would like to thank all participants that filled in our survey or were interviewed, and *Crohn & Colitis NL (previously CCUVN)* and Nijmegen Exercise Study for their support in participant recruitment.

Funding

This work was supported by a grant from the Province of Gelderland as part of the EAT2MOVE project (proposal PS2014-49). This grant was used to partly pay the salary of the corresponding author.

References

- 1. Engels M, Cross RK, Long MD. Exercise in patients with inflammatory bowel diseases: current perspectives. Clin Exp Gastroenterol. 2018;11:1-11.
- 2. 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. J Sports Med Phys Fitness. 2010;50(1):1-18.
- 3. Monda V, Villano I, Messina A, et al. Exercise Modifies the Gut Microbiota with Positive Health Effects. Oxid Med Cell Longev. 2017;2017:3831972.
- 4. Ball D. Metabolic and endocrine response to exercise: sympathoadrenal integration with skeletal muscle. J Endocrinol. 2015;224(2):R79-95.
- 5. Bitton A, Sewitch MJ, Peppercorn MA, et al. Psychosocial determinants of relapse in ulcerative colitis: a longitudinal study. Am J Gastroenterol. 2003;98(10):2203-8.
- 6. Vogelaar L, van't Spijker A, Timman R, et al. Fatigue management in patients with IBD: a randomised controlled trial. Gut. 2014;63(6):911-8.
- 7. Nathan I, Norton C, Czuber-Dochan W, Forbes A. Exercise in individuals with inflammatory bowel disease. Gastroenterol Nurs. 2013;36(6):437-42.
- 8. 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. J Crohns Colitis. 2019;13(6):686-92.
- 9. DeFilippis EM, Tabani S, Warren RU, et al. Exercise and Self-Reported Limitations in Patients with Inflammatory Bowel Disease. Dig Dis Sci. 2016;61(1):215-20.
- 10. Chan D, Robbins H, Rogers S, et al. Inflammatory bowel disease and exercise: results of a Crohn's and Colitis UK survey. Frontline Gastroenterol. 2014;5(1):44-8.
- 11. Simrén M, Axelsson J, Gillberg R, et al. Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors. Am J Gastroenterol. 2002;97(2):389-96.
- 12. Bernstein CN. Treatment of IBD: where we are and where we are going. Am J Gastroenterol. 2015;110(1):114-26.
- 13. 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.
- 14. Mikocka-Walus AA, Gordon AL, Stewart BJ, Andrews JM. A magic pill? A qualitative analysis of patients' views on the role of antidepressant therapy in inflammatory bowel disease (IBD). BMC Gastroenterol. 2012;12:93.
- 15. Hall NJ, Rubin GP, Dougall A, et al. The fight for 'health-related normality': a qualitative study of the experiences of individuals living with established inflammatory bowel disease (ibd). J Health Psychol. 2005;10(3):443-55.

- 16. Thia K, Faubion WA, Jr., Loftus EV, Jr., et al. Short CDAI: development and validation of a shortened and simplified Crohn's disease activity index. Inflamm Bowel Dis. 2011:17(1):105-11.
- 17. Bennebroek Evertsz F, Nieuwkerk PT, Stokkers PC, et al. The patient simple clinical colitis activity index (P-SCCAI) can detect ulcerative colitis (UC) disease activity in remission: a comparison of the P-SCCAI with clinician-based SCCAI and biological markers. J Crohns Colitis. 2013;7(11):890-900.
- 18. Walsh AJ, Ghosh A, Brain AO, et al. Comparing disease activity indices in ulcerative colitis. J Crohns Colitis. 2014;8(4):318-25.
- 19. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003;56(12):1163-9.
- 20. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011;43(8):1575-81.
- 21. Barriball KL, While A. Collecting data using a semi-structured interview: a discussion paper. J Adv Nurs. 1994:19(2):328-35.
- 22. Jones PD, Kappelman MD, Martin CF, et al. Exercise decreases risk of future active disease in patients with inflammatory bowel disease in remission. Inflamm Bowel Dis. 2015;21(5):1063-71.
- 23. D'Inca R, Garribba AT, Vettorato MG, et al. Use of alternative and complementary therapies by inflammatory bowel disease patients in an Italian tertiary referral centre. Dig Liver Dis. 2007;39(6):524-9.
- 24. Tew GA, Jones K, Mikocka-Walus A. Physical Activity Habits, Limitations, and Predictors in People with Inflammatory Bowel Disease: A Large Cross-sectional Online Survey. Inflamm Bowel Dis. 2016;22(12):2933-42.
- 25. Wang Q, Xu K-Q, Qin X-R, et al. Association between physical activity and inflammatory bowel disease risk: A meta-analysis. Digestive and Liver Disease. 2016;48(12):1425-31.
- 26. Nys K, Agostinis P, Vermeire S. Autophagy: a new target or an old strategy for the treatment of Crohn's disease? Nature Reviews Gastroenterology & Hepatology. 2013;10(7):395-401.
- 27. Bilski J, Brzozowski B, Mazur-Bialy A, et al. The role of physical exercise in inflammatory bowel disease. Biomed Res Int. 2014;2014:429031.
- 28. de Oliveira EP. Runner's diarrhea: what is it, what causes it, and how can it be prevented? Curr Opin Gastroenterol. 2017;33(1):41-6.
- 29. Ng V, Millard W, Lebrun C, Howard J. Low-intensity exercise improves quality of life in patients with Crohn's disease. Clin J Sport Med. 2007;17(5):384-8.

- 30. D'Incà R, Varnier M, Mestriner C, et al. Effect of moderate exercise on Crohn's disease patients in remission. Ital J Gastroenterol Hepatol. 1999;31(3):205-10.
- 31. Mawdsley JE, Rampton DS. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. Gut. 2005;54(10):1481-91.
- 32. Bernstein CN, Singh S, Graff LA, et al. A prospective population-based study of triggers of symptomatic flares in IBD. Am J Gastroenterol. 2010;105(9):1994-2002.
- 33. Hegberg NJ, Tone EB. Physical activity and stress resilience: Considering those at-risk for developing mental health problems. Mental Health and Physical Activity. 2015;8:1-7.

Appendix 1 - Interview guide

Introduction

This interview is part of a study that investigates the influence of physical activity on complaints related to Crohn's disease or ulcerative colitis. To get a good and complete picture of what physical activity does to people with one of these inflammatory bowel diseases, it is important to hear the experiences of these people. The interview will take about half an hour. During this time we will discuss a number of topics; IBD and experienced complaints, physical activity, the link between IBD and physical activity and lastly the relation between IBD, quality of life, fatigue and physical activity. The interview will be recorded with your approval, for the sole purpose of transcribing the interview. The recordings will not be shared with people outside the research team and will be deleted directly after transcribing.

If you have any questions or comments, you can always ask or report them during the interview

(Fill in informed consent form)
(Start voice recorder)

To begin with, I have a few questions to get a sense of the population I am interviewing

- What is your age?
- What is your highest level of education?

IBD and experienced complaints

- Do you have Crohn's disease or ulcerative colitis?
- Do you currently experience CD/UC related complaints?
- How do you notice IBD in your daily life?
 - O What causes this?

Physical activity in general

- How physically active are you on an average day?
- Do you meet the advised level of physical activity of 30 minutes moderately intensive physical activity per day for at least 5 days a week? (Examples could be cycling to work or walking briskly)

- What is your profession?
 - o Are you physically active at work?
 - o How many days a week do you work?
- Do you perform many household activities and chores in and/or around the house?
- If you exercise, what kind of sports do you do?
 - o Why?

Link between IBD and physical activity

- Do you feel that physical activity affects your IBD related disease burden?
 - o If so: What is specifically affected?
 - o Do you have a possible explanation for this?
- Are there things that prevent you from being physically active?
 - o Does IBD play a role in this?
- Do you feel that physical activity affects your disease activity or vice versa; that your disease activity affects the degree to which you are physically active?

Quality of life and fatigue

- From one to ten, how would you rate your quality of life right now?
 - Which factors do you take into account when determining this rating?
 - o What is the role of IBD in this rating?
 - Do you think physical activity plays a role in this rating?
- Do you suffer from fatigue?
 - o If so: Do you feel that physical activity can affect fatigue?
 - o If so: How does this work for you?
- Would you like to clarify or add something else?

Closing

This is the end of this interview. Is there anything you would like to explain further because you think I might be able to misinterpret it? Do you have any other questions? Or other things you would like to say?

Appendix 2

Supplementary Table 1. Characteristics of the interview study population consisting of 7 CD

and 7 UC participants

	Type of IBD CD / UC	Gender male / female	Age years	BMI kg/m²	Education # low / middle / high
Interviewee 1	UC	female	63	27,1	high
Interviewee 2	UC	female	35	20,0	high
Interviewee 3	UC	female	78	26,5	middle
Interviewee 4	CD	female	26	18,0	high
Interviewee 5	CD	male	64	21,4	low
Interviewee 6	CD	female	25	34,4	middle
Interviewee 7	CD	male	50	21,6	high
Interviewee 8	UC	male	70	46,7	low
Interviewee 9	CD	female	71	23,0	low
Interviewee 10	UC	male	29	26,1	middle
Interviewee 11	CD	male	74	27,8	high
Interviewee 12	UC	male	63	25,7	middle
Interviewee 13	CD	female	56	25,7	low
Interviewee 14	UC	male	58	23,4	middle

Abbreviations: CD: Crohn's disease, UC: ulcerative colitis, BMI: body mass index

[#] Education level: no education, primary or lower vocational education and lower general secondary education (low); secondary vocational education and higher general secondary education (middle); higher vocational education and university (high).

Chapter 4

Repeated prolonged moderate-intensity walking exercise does not appear to have harmful effects on inflammatory markers in patients with inflammatory bowel disease

Lamers CR, de Roos NM, Bongers CCWG, ten Haaf DSM, Hartman YAW, Witteman BJM, Hopman MTE



Abstract

Background and objectives The role of exercise in the management of inflammatory bowel disease (IBD) is inconclusive as most research focused on short or low-intensity exercise bouts and subjective outcomes. We assessed the effects of repeated prolonged moderate-intensity exercise on objective inflammatory markers in IBD patients.

Methods In this study, IBD patients (IBD walkers, n=18), and a control group (non-IBD walkers, n=19), completed a 30, 40 or 50 km walking exercise on four consecutive days. Blood samples were taken at baseline and every day post-exercise to test for the effect of disease on exercise-induced changes in cytokine concentrations. A second control group of IBD patients who did not take part in the exercise, IBD non-walkers (n=19), was used to test for the effect of exercise on faecal calprotectin. Both IBD groups also completed a clinical disease activity questionnaire.

Results Changes in cytokine concentrations were similar for IBD walkers and non-IBD walkers (IL-6 p=0.95; IL-8 p=0.07; IL-10 p=0.40; IL-1 β p=0.28; TNF- α p=0.45), with a temporary significant increase in IL-6 (p<0.001) and IL-10 (p=0.006) from baseline to post-exercise day 1. Faecal calprotectin was not affected by exercise (p=0.48). Clinical disease activity did not change in the IBD walkers with ulcerative colitis (p=0.92), but did increase in the IBD walkers with Crohn's disease (p=0.024).

Conclusion Repeated prolonged moderate-intensity walking exercise led to similar cytokine responses in participants with or without IBD, and it did not affect faecal calprotectin concentrations, suggesting that IBD patients can safely perform this type of exercise.

Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are characterized by a clinical course with periods of active disease alternating with periods of remission [1]. Environmental factors like exercise may influence the course of IBD [2]. A recent study showed that IBD patients were significantly less physically active after their IBD diagnosis than before [3]. Patients experience barriers to exercise due to IBD-related limitations such as fatigue, diarrhea, joint pain, weakness and fear for symptom exacerbation [4]. However, small prospective studies showed that low-intensity exercise appears to be safe and well tolerated with minimal risk of symptom exacerbation in patients in remission or with mildly active disease [2, 5, 6]. Moreover, a large observational study showed that patients in remission with higher exercise levels were significantly less likely to develop active disease after six months follow-up [7].

Exercise may have beneficial effects on IBD by changing the intestinal microbiota and by release of cytokines, but the exact mechanism is unknown [8, 9]. Exercise can enrich the microbiota diversity, stimulate proliferation of bacteria that modulate mucosal immunity and improve barrier functions of the gut, which all seem to be beneficial in an inflamed intestine [10]. By contraction of skeletal muscles, myokines such as IL-6 are released which are known to exert anti-inflammatory effects and inhibit the release of proinflammatory cytokines such as IL-1 β and TNF- α [9]. It is known that cytokine concentrations can increase directly after exercise [11-13]. In healthy individuals, this increase seems to depend on the intensity and duration of exercise [10, 14]. In a previous study during the Nijmegen Four Days Marches it was suggested that there is an adaptive response of the body to prolonged and repeated exercise, since they found a gradual decrease in cytokine concentration in healthy individuals after a peak on the first exercise day [15]. It is unknown whether this pattern is the same in IBD patients and to what extent an increase in cytokine concentrations is actually a sign of IBD activity or whether it is all related to exercise. Therefore, it is of interest to also study faecal calprotectin as a more specific measure of IBD activity to be able to differentiate between exercise and disease effects. Faecal calprotectin is a marker of intestinal inflammation and correlates significantly with endoscopic disease activity [16, 17]. So far, only a few studies on exercise in IBD patients assessed faecal calprotectin and they found no changes [18-21]. Based on these studies on cytokines and faecal calprotectin, we expected that repeated

prolonged exercise would not lead to a clinically relevant increase in inflammatory markers.

Previous studies on exercise in IBD mainly focused on short bouts of exercise or low-intensity exercise, while health enhancing effects of exercise are generally more noticeable after repeated bouts of exercise [2, 5]. In addition, studies often explore patient well-being and disease activity without objective markers of inflammation. Therefore, the aim of this study was to assess the effects of repeated bouts of prolonged moderate-intensity walking exercise on inflammatory markers (i.e. cytokines and faecal calprotectin) in patients with inflammatory bowel disease. Besides this, we investigated the effect of repeated prolonged moderate-intensity exercise on clinical disease activity.

Materials and methods

Study population

We included 19 IBD patients who participated in the 2019 edition of the Niimegen Four Days Marches, the IBD walkers, Additionally, we included two control groups; a control group of 19 Nijmegen Four Days Marches participants without a history of IBD, the non-IBD walkers, to test for the effect of disease, and a control group of 19 IBD patients who did not participate in the exercise event, the IBD non-walkers, to test for the effect of exercise. IBD walkers and non-IBD walkers were recruited via the Nijmegen Exercise Study database of Radboud University Medical Centre, Nijmegen, The Netherlands, via social media and via word-of-mouth promotion. IBD nonwalkers were recruited via the outpatient clinic of Hospital Gelderse Vallei, Ede, The Netherlands. Inclusion criteria for all IBD patients were age ≥18 years and diagnosis of Crohn's disease or ulcerative colitis made by a gastroenterologist. IBD patients were excluded when they used specific biologicals (infliximab, adalimumab, golimumab, ustekinumab) as these might reduce cytokine concentrations. Non-IBD walkers were included when they were ≥18 years of age and they were excluded when they had a history of IBD or other gastro-intestinal diseases. The non-IBD walkers and IBD non-walkers were comparable with the IBD walkers for age (± 5 years) and gender. This study was approved by the Medical Ethical Committee region Arnhem-Niimegen (CMO registration number: 2019-5375) and by the Medical Ethical Committee of Wageningen University. All participants provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki and was registered at trialregister.nl as NL7872.

Study design

Measurements were performed one or two days prior to the first exercise day (baseline) and within 30 minutes post-exercise at the four consecutive exercise days. At baseline, body weight and height were measured, participant characteristics were registered, and questionnaires regarding physical activity and, in case of IBD participants, clinical disease activity were completed. Blood samples from IBD walkers and non-IBD walkers were collected at baseline and every exercise day directly after finishing to determine cytokine concentrations. Besides that, faecal samples were collected by IBD walkers and IBD non-walkers at baseline, at day 2 or 3 and at the end of the exercise event to determine calprotectin. Non-IBD walkers did not collect faecal samples. IBD walkers and non-IBD walkers walked 30, 40 or 50 km at a self-

selected pace at four consecutive exercise days. Start and finish time were registered and used to calculate walking speed, without correction for breaks. Their heart rate was measured every 5 km during the first exercise day using a 2-channel ECG chest band system. Heart rate (HR) was used to estimate exercise intensity as a percentage of the maximum HR (exercise intensity = measured HR / expected maximal HR x 100%, where expected max HR = 208 - (0.7 x age)) [22]. Heart rate measurements and blood sampling were not performed in IBD non-walkers. At the end of the exercise event, IBD walkers and IBD non-walkers completed a clinical disease activity questionnaire for the second time.

Participant characteristics and physical activity questionnaires

All participants completed a general questionnaire on demographics, level of education, smoking and medication use, and the validated Short Questionnaire to Assess Health enhancing physical activity (SQUASH) [18]. IBD walkers and non-IBD walkers also completed a questionnaire on their preparations for the exercise event. IBD walkers and IBD non-walkers completed an extended general questionnaire with additional questions on type and extent of IBD, age of disease onset, number of flareups, previous IBD-related surgeries and their opinion on the influence of physical activity on their IBD.

Blood samples

Blood samples were taken at baseline and within 30 minutes post-exercise at the four consecutive exercise days. A venous blood sample was collected in a 10 mL EDTA vacutainer (Becton-Dickinson, New Jersey, USA). The vacutainer was put on melting ice water and centrifuged at 1200 rcf for fifteen minutes at 4°C. Plasma was then transferred to polypropylene tubes and stored at -80°C until analysis. IL-6, IL-8, IL-10, IL-1 β and TNF- α concentrations were determined using the MesoScale Discovery (MSD) MULTI-SPOT Assay System (Proinflammatory Panel 1 (human) Kits, K15049D) according to the manufacturers' instructions. The lower detection limits varied per plate and were 0.136-0.432 (IL-6), 0.052-0.138 (IL-8), 0.039-0.213 (IL-10), 0.013-0.080 (IL-1 β) and 0.066-0.229 (TNF- α) pg/ml. All values below these lower detection limits were considered as missing's. The percentages of missing values were 3.8% for IL-8 and TNF- α , 8.6% for IL-6 and IL-1 β and 20.5% for IL-10. These values were imputed during statistical analysis. All standards for the calibration curve, control samples, and 10% of the plasma samples from participants were measured

in duplicate. Accuracy and precision were evaluated by controls across multiple runs and multiple lots as described in the manufacturer's protocol.

Faecal samples

Faecal samples were collected at baseline, halfway and at the end of the exercise event. Participants were provided with materials and instructions to collect the samples at home. Samples were stored in a refrigerator before transfer to the study laboratory for analysis. Faecal calprotectin was determined using a sandwich enzyme-linked immunosorbent assay (ELISA). Faecal calprotectin concentrations for this assay ranged from 0 to 2500 μ g/q.

Clinical disease activity questionnaire

IBD walkers and IBD non-walkers completed a clinical disease activity questionnaire at baseline and at the end of the last exercise day. Depending on their type of IBD, this was the Patient Harvey Bradshaw Index (P-HBI) for Crohn's disease and the Patient Simple Clinical Colitis Activity Index (P-SCCAI) for ulcerative colitis [23, 24].

Statistical analysis

Normally distributed data are presented as mean ± standard deviation (SD), skewed data as median with interquartile range (IOR) and categorical data as frequency with proportion. Differences between groups for participant and exercise characteristics were analyzed with a chi-square test for categorical data, and an independent samples t-tests for continuous data. One-way analysis of variance (ANOVA) was used to examine differences in exercise characteristics over time within groups. Post-hoc analyses were performed using the Bonferroni multiple comparisons test. The main outcomes, cytokine responses and faecal calprotectin, were analysed using linear mixed models to account for missing values, after log10 transformation to obtain normality [25]. Participant was used as a random factor and sampling days, groups and their interaction were used as fixed factors. A random intercept was used with an unstructured covariance structure for cytokines and an identity covariance structure for faecal calprotectin for covariance of timepoints. Baseline values were used as reference. Changes in clinical disease activity scores were analyzed with a Wilcoxon signed-ranks test within groups and with an independent samples t-test and a Mann-Whitney U test between groups. A p-value of <0.05 was considered

statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 24.

Results

Participant and exercise characteristics

In total, 56 participants were included in the data analysis: 18 IBD walkers, 19 non-IBD walkers and 19 IBD non-walkers. One male IBD walker dropped out after the first exercise day, due to a fall, and was excluded from further analysis. Another IBD walker withdrew during the second exercise day due to abdominal pain and frequent loose stools. Since this might have been related to her IBD, she was included in further analysis. The mean age of the study population was 54 ± 12 years and the average BMI of all participants was $26.0 \pm 3.8 \text{ kg/m}^2$. In each group 11 participants were female. No significant differences were found between IBD walkers and non-IBD walkers or IBD non-walkers regarding participant characteristics, except for training distance during the last two weeks before the walking event (IBD walkers vs non-IBD walkers, p=0.03, Table 1a). The average heart rate during the first exercise day was 114 \pm 12 bpm, resulting in an average exercise intensity of 67 \pm 8%, which fulfills the definition of moderate-intensity exercise [26]. This is supported by the subjective rate of perceived exertion which was 5.0 [IQR 3.0 – 7.0], indicating that participants scored the prolonged walking exercise as a moderate activity [27]. No differences in heart rate and exercise intensity were found between IBD walkers and non-IBD walkers (p=0.96 and p=0.99, respectively). Walking distance did not differ between groups (p=0.35) and walking speed did also not differ between groups or between days (p=0.50 and p=0.15, respectively, *Table 1a*). IBD non-walkers were more often treated with immunosuppressants compared to IBD walkers (6% vs 47%, p=0.004). Furthermore, IBD non-walkers reported not to experience an effect of physical activity on their IBD, while IBD walkers were positive about the effect of physical activity (Table 1b).

Table 1a. Characteristics of the study population consisting of IBD walkers, compared to non-IBD walkers for effects of disease and to IBD non-walkers for effects of exercise

	IBD walkers	non-IBD walkers	IBD non-walkers
Subjects, n	18	19	19
Gender, n (%)			
Female	11 (61)	11 (58)	11 (58)
Age (years)	54 ± 11	54 ± 14	54 ± 13
BMI (kg/m²)	25.7 ± 3.8	26.0 ± 4.5	26.2 ± 3.2
Education#, n (%)			
Low	3 (17)	5 (26)	7 (37)
Middle	7 (39)	6 (32)	7 (37)
High	8 (44)	8 (42)	5 (26)
Smoking, n (%)			
Never	9 (50)	13 (68)	14 (74)
Current	1 (6)	0 (0.0)	2 (11)
Former	8 (44)	6 (32)	3 (16)
Walking distance per day, n (%)			
30 km	5 (28)	2 (11)	-
40 km	11 (61)	13 (68)	-
50 km	2 (11)	4 (21)	-
Average walking speed (km/h)¥	4.5 ± 0.8	4.4 ± 0.7	-
Physical activity			
Total activity score [§]	10147 ± 5030	9919 ± 4291	7559 ± 3918
Training distance last 2 weeks before walking event (km)	37 ± 34*	68 ± 49*	-

Continuous data are presented as mean \pm SD. Categorical data are presented as n (%). * p <0.05 Abbreviations: BMI: body mass index, IBD: inflammatory bowel disease

^{*} Education level: no education, primary or lower vocational education and lower general secondary education (low); secondary vocational education and higher general secondary education (middle); higher vocational education and university (high).

[¥] Number of kilometres (30, 40 or 50) divided by finish time minus start time, no correction for breaks.

[§] Total activity score represents intensity factors per activity (MET-scores) multiplied by the minutes per week spent on each activity as derived from the SQUASH

Table 1b. IBD specific characteristics, IBD walkers compared to IBD non-walkers

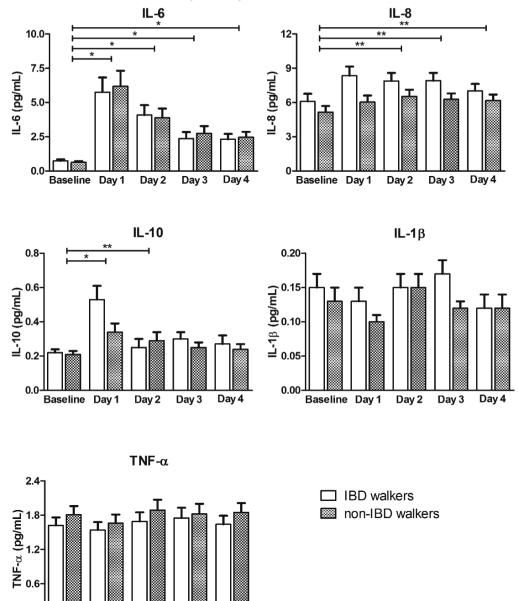
	IBD walkers	IBD non-walkers
Age at diagnosis (years)	33 ± 13	40 ± 15
CD disease location, n (%)	8	8
Ileum	2 (25)	0 (0)
Colon	2 (25)	4 (50)
Ileum and colon	2 (25)	4 (50)
Unknown	2 (25)	0 (0)
UC disease location, n (%)	10	11
Pancolitis	2 (20)	3 (27)
Left-sided colitis	3 (30)	2 (18)
Proctitis	5 (50)	6 (55)
Flare-ups in past 12 months, n (%)		
None	8 (44)	7 (37)
1-2 flare-ups	6 (33)	10 (53)
3-4 flare-ups	2 (11)	0 (0)
More than 4 flare-ups	2 (11)	2 (11)
Medication use, n (%)		
5-ASA, oral	9 (50)	6 (32)
5-ASA, rectal	4 (22)	1 (5)
Corticosteroids, oral	4 (22)	3 (16)
Corticosteroids, rectal	2 (11)	0 (0)
Immunosuppressants	1 (6)*	9 (47)*
No medication use	7 (39)	3 (16)
Surgery, n (%)	1 (6)	2 (11)
Perceived effect of physical activity on IBD, n (%)		
Very negative	0 (0)	0 (0)
Negative	1 (6)	0 (0)
No effect	3 (17)*	11 (58)*
Positive	12 (67)	7 (37)
Very positive	2 (11)	1 (5)

Continuous data are presented as mean \pm SD. Categorical data are presented as n (%). * p <0.05 Abbreviations: 5-ASA: 5-aminosalicylic acid, CD: Crohn's disease, IBD: inflammatory bowel disease, UC: ulcerative colitis

Cvtokines

No differences in cytokine concentrations were found between IBD walkers and non-IBD walkers (F-test: IL-6 p=0.95; IL-8 p=0.07; IL-10 p=0.40; IL-1 β p=0.28; TNF- α p=0.45) in the linear mixed model analysis. From baseline until post-exercise day 4. all IL-8 concentrations were higher in IBD walkers compared to non-IBD walkers. though not significant (p=0.07, Figure 1/Appendix 1 – Supplementary Table 1). When combining the two groups, differences between days were found (F-test: IL-6 p<0.001; IL-8 p=0.012; IL-10 p<0.001; IL-1 β p=0.008; TNF- α p=0.018). For IL-6 and IL-10, a significant increase was seen between baseline and post-exercise day 1 (p<0.001 and p=0.006, respectively). Hereafter, both concentrations decreased, and from day 3 onwards IL-10 did not significantly differ anymore from baseline (p=0.21), while IL-6 remained significantly higher throughout the days compared to baseline (p<0.001, Figure 1/Appendix 1 – Supplementary Table 1). IL-8 concentrations increased between baseline and post-exercise day 1 in both groups and further increased on exercise day 2 in non-IBD walkers. From post-exercise day 2 onwards, IL-8 concentrations remained quite stable and significantly higher compared to baseline (p=0.033, p=0.029 and p=0.040, respectively, Figure 1/Appendix 1 -Supplementary Table 1). Concentrations of IL-1 β and TNF- α stayed rather stable during the event and concentrations did not differ from baseline (all p-values ≥ 0.10 , Figure 1/Appendix 1 – Supplementary Table 1).

Figure 1. Estimated marginal mean cytokine concentrations (pg/mL) after back transformation, at baseline and day 1 to day 4, for IBD walkers and non-IBD walkers.



Cytokine concentrations are presented in picogram per millilitre. * p <0.01 ** p <0.05. Data are presented as mean \pm standard error and were derived from a linear mixed model analysis. All statistical tests were performed on the log10 scale. Hereafter, data were back transformed for presentation in this figure. Differences between groups were never statistically significant and therefore groups were combined to test for differences between days, using baseline as reference.

Abbreviations: IBD: inflammatory bowel disease, IL: interleukin, TNF: tumor necrosis factor

0.0

Baseline Day 1

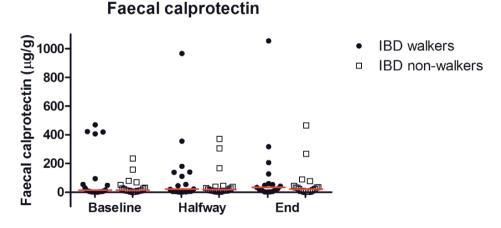
Day 2

Day 3

Faecal calprotectin

Faecal calprotectin concentrations showed a wide-range and skewed distribution, ranging from 0 to 1054 μ g/g (*Figure 2*). With use of linear mixed models, no differences were found between IBD walkers and IBD non-walkers (F-test: p=0.73) nor over time (F-test: p=0.48). A remarkable increase was observed in one IBD walker and in two IBD non-walkers. Faecal calprotectin concentrations of the IBD walker increased from 419 at baseline to 1054 μ g/g at the end of the exercise event. Despite this increase, the participant was able to complete the exercise event. Concentrations of the two IBD non-walkers increased from baseline to the end of the exercise event from 234 to 465 μ g/g and from 156 to 266 μ g/g (*Figure 2*).

Figure 2. Column scatter of faecal calprotectin concentrations (µg/g) at baseline, halfway (day 2 or 3) and at the end of the exercise event, for IBD walkers and IBD non-walkers



Faecal calprotectin concentrations are presented in microgram per millilitre. All statistical tests were performed on the log10 scale using baseline as a reference.

Red lines represent medians.

Abbreviations: IBD: inflammatory bowel disease

Clinical disease activity

P-SCCAI scores, ranging from 0 to 13, were not different between UC walkers and UC non-walkers at baseline and at the end of the exercise event (p=0.42 and p=0.20, respectively), nor did they change within groups (p=0.92 and p=0.75) or between groups (p=0.81, *Table 2*). P-HBI scores ranging from 0 to 15, were also not different between CD walkers and CD non-walkers at baseline and at the end of the exercise event (p=0.82 and p=0.10, respectively), nor did they change over time in CD non-walkers (p=0.50). Yet, P-HBI scores increased significant over time in CD walkers (p=0.024) and therefore became significantly different between CD walkers and CD non-walkers (p=0.046), indicating that clinical disease activity worsened during the exercise event in participants with CD (*Table 2*).

Table 2. Clinical disease activity scores at baseline and at the end of the exercise event, for IBD walkers and IBD non-walkers, UC and CD separately

	Baseline	End	Within group median change (end - baseline)	Within group P- value#	Mean change between groups (95% CI) (walkers - non-walkers)	Between groups P-value [¥]
UC - P-SCCAI score						
IBD walkers (n=10)	1.0 [1.0-2.0]	1.0 [1.0-2.0] 1.0 [0.8-3.3]	0.0 [-1.0-1.3]	0.92	-0.2 (-2.0-1.6)	0.81
IBD non-walkers (n=11)	1.0 [0.0-3.0]	0.0 [0.0-2.0]	0.0 [-1.0-0.0]	0.75		
P-value*	0.42	0.20				
CD - P-HBI score						
IBD walkers (n=7)§	3.0 [1.0-5.0]	5.0 [3.0-7.0]	1.0 [1.0-5.0]	0.024	3.5 (0.1-6.9)	0.046
IBD non-walkers (n=8)	3.0 [0.3-5.8]	4.0 [0.5-4.0]	0.0 [-1.8-0.8]	0.50		
P-value*	0.82	0.10				

Data are presented as median [interquartile range]. # P-values refer to a Wilcoxon signed-rank test. * P-values refer to an independent samples t-test. * P-values refer to a Mann-Whitney U test. Bold values are significant.

§ One CD walker was excluded from the analysis because of missing P-HBI end score

Abbreviations: CD: Crohn's disease, IBD: inflammatory bowel disease, P-HBI: Patient Harvey Bradshaw Index; P-SCCAI: Patient Simple Clinical Colitis Activity Index, UC: ulcerative colitis

Discussion

We found that repeated bouts of prolonged moderate-intensity exercise results in comparable changes in cytokine concentrations in IBD walkers and non-IBD walkers, suggesting that the cytokine response is only affected by exercise rather than disease activity. Furthermore, stable and comparable faecal calprotectin in IBD walkers and IBD non-walkers also suggests that repeated prolonged moderate-intensity exercise does not lead to disease exacerbation. These objective findings are supported by self-reported P-SCCAI scores, though not by P-HBI scores. Our results suggest that repeated prolonged moderate-intensity exercise does not appear to have harmful effects on disease activity in ulcerative colitis and probably not in Crohn's disease either. It seems that IBD patients can safely perform this type of exercise without significant exacerbation of inflammation.

To the best of our knowledge, this is the first study to investigate the effect of repeated prolonged moderate-intensity exercise on IBD patients. At the moment it is unknown which exercise type, intensity and duration is safe and beneficial in IBD patients. Our study revealed that cytokine responses to repeated prolonged moderate-intensity exercise in IBD patients were comparable to the responses in non-IBD controls and these responses are in line with literature. In two comparable studies, cytokine concentrations increased and decreased in a similar manner as cytokine concentrations in our study [15, 28]. In these studies and ours, a peak in IL-6 and IL-10 concentrations was seen post-exercise day 1 compared to the other exercise days despite rather similar durations of exercise on the four consecutive exercise days. This might be due to training adaptation of the body [29]. The strong increase of IL-6 and IL-10 between baseline and post-exercise day 1 indicates a substantial increase in production and secretion of myokines which is primarily regulated by skeletal muscles. Therefore, the increase in IL-6 and IL-10 might be explained by the walking exercise rather than other factors such as gender, fitness level or (type of) IBD [11, 29]. Contrary to IL-6, IL-8 and IL-10, there were barely any changes in IL-1 β and TNF- α between baseline and the four consecutive exercise days, which is also in line with literature. The majority of studies showed that the concentrations of IL-1 β and TNF- α remain unchanged following exercise [13, 30]. Two studies specifically investigated cytokine responses in IBD patients. A pilot study in 15 paediatric CD patients and 15 healthy controls showed that IL-6 increased significantly in both groups during 60 minutes of moderate-intensity cycling, but not after short bouts of high-intensity cycling. Within 60 minutes after exercise, IL-6 returned to baseline. No change was found in TNF- α comparable to our observations [30]. The fact that IL-6 only increased after moderate-intensity cycling could be explained by the production and secretion of myokines by skeletal muscles, which is predominantly influenced by the duration rather than the intensity or mode of exercise [29]. A randomized cross-over trial in 17 IBD patients found no changes in IL-6, IL-8, IL-10 and TNF- α after eight weeks of moderate-intensity aerobic and resistance training three times per week [31]. As cytokines seem to return to baseline within minutes to hours after exercise, changes might have been missed due to timing of blood sampling since they sampled before and after the eight week intervention period. Our study with a prolonged duration of exercise and blood sampling within 30 minutes post-exercise therefore adds new insights to the current literature on cytokines in IBD patients.

We found comparable faecal calprotectin concentrations in IBD walkers and IBD nonwalkers and no change over time. This is in line with the results of a randomized clinical trial on moderate-intensity running and two pilot studies on yoga classes and high-intensity interval training or moderate-intensity continuous training. In these studies, all types of exercise were performed three or four times per week during eight to twelve weeks and no significant changes in faecal calprotectin were found [19-21]. Even though repeated prolonged moderate-intensity exercise did not significantly change faecal calprotectin concentrations in our study, noticeable changes were observed in some participants. The observed increase in calprotectin concentrations in three participants (one IBD walker and two IBD non-walkers) may be a sign of disease exacerbation, since calprotectin is a sensitive biomarker of intestinal inflammation [16, 17]. However, as an increase was seen in both groups, it is not likely that the repeated bouts of prolonged moderate-intensity exercise caused this increase. It has been hypothesized that calprotectin concentrations depend on the amount of blood in stool and stool consistency, which varies widely between stools in IBD patients with active disease and causes natural day-to-day variation in faecal calprotectin [32-35]. Thus, the fact that a considerable number of participants had active disease is a likely explanation for the high variability of faecal calprotectin concentrations in our study.

To date, the majority of studies examined the effect of exercise on IBD by subjective measures such as self-perceived disease activity and quality of life. It was found that low-intensity exercise significantly improves self-perceived disease activity in IBD patients in remission or with mildly active disease [36, 37]. Regarding moderateintensity exercise, self-perceived disease activity did not change in the previously mentioned randomized controlled trial on moderate-intensity running or in the randomized cross-over trial on moderate-intensity aerobic and resistance training [19, 31]. Another randomized controlled trial also found no change in self-perceived disease activity after 10 weeks of mind-body therapy including moderate-intensity exercise in 30 UC patients in remission of with mildly active disease [38]. In the current study, we found that changes in P-HBI scores were higher in walking CD patients compared to the CD non-walkers, suggesting worsening of clinical disease activity during the exercise event. However, these changes were not reflected in faecal calprotectin. Therefore, the chance that clinical disease activity increased due to the exercise event is small, since faecal calprotectin better correlates with endoscopic disease activity than clinical disease activity questionnaires, especially in patients with colonic disease which applied to the majority of our patient group [39-411.

The strengths of this explorative study are the use of objective inflammatory markers on the systemic as well as the intestinal level combined with self-reported validated questionnaires, in comparable groups in terms of age, gender and disease type. Moreover, the inclusion of CD as well as UC with a variety of disease states widens the applicability of the results. However, some limitations should be taken into account. First, due to the explorative nature of this study no proper sample size calculation was performed and the sample size was relatively small. As a result, it was not possible to compare subgroups (CD vs UC or remission vs active disease) or to correct for confounders such as BMI or IBD specific medication. However, our sample size was large enough to detect a change in calprotectin of 40 µg/g as calculated in a post-hoc power analysis. Second, we excluded IBD patients that used specific biologicals which resulted in a select group of participants regarding medication use that does not accurately reflect the current IBD population. Though only a minority of the IBD population uses biologicals. Third, during the exercise event we only took post-exercise blood samples. Therefore, we do not know whether cytokine concentrations completely recovered overnight. Also, baseline blood samples were

not collected on the same day and same time of day across participants, which could have led to some variability due to normal daily variation in cytokine concentrations. However, these biases were equal for IBD walkers and non-IBD walkers and are therefore not likely to have affected cytokine responses. Fourth, we did not find harmful effects during the marches, though it would have been interesting to have follow-up data of the weeks or months after the marches to see whether harmful effects would appear at a later time.

In conclusion, we found a comparable change in cytokine concentrations after repeated prolonged moderate-intensity exercise in IBD walkers compared to non-IBD walkers, and stable and comparable faecal calprotectin in IBD walkers compared to IBD non-walkers. These results suggest that IBD patients can safely perform this type of exercise without significant exacerbation of inflammation. More studies, preferably with larger sample sizes and a follow-up period, are needed to further investigate the effects of this type of exercise.

Acknowledgements

We would like to thank all participants, and all student and faculty volunteers for their practical assistance in data collection. Special thanks to master students Vicky de Ruijter and Anne de Korte for their help with participant recruitment. We also would like to acknowledge laboratory technician Nhien Ly for analysing the cytokine concentrations and statistician dr. João Paulo for her help with the statistical analysis.

Funding

This work was supported by a grant from the Province of Gelderland as part of the EAT2MOVE project (proposal PS2014-49).

References

- 1. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet. 2007;369(9573):1641-57.
- 2. Engels M, Cross RK, Long MD. Exercise in patients with inflammatory bowel diseases: current perspectives. Clin Exp Gastroenterol. 2018;11:1-11.
- 3. 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. J Crohns Colitis. 2019;13(6):686-92.
- 4. DeFilippis EM, Tabani S, Warren RU, et al. Exercise and Self-Reported Limitations in Patients with Inflammatory Bowel Disease. Dig Dis Sci. 2016;61(1):215-20.
- 5. Narula N, Fedorak RN. Exercise and inflammatory bowel disease. Can J Gastroenterol. 2008;22(5):497-504.
- 6. Eckert KG, Abbasi-Neureither I, Koppel M, Huber G. Structured physical activity interventions as a complementary therapy for patients with inflammatory bowel disease a scoping review and practical implications. BMC Gastroenterol. 2019;19(1):115.
- 7. Jones PD, Kappelman MD, Martin CF, et al. Exercise decreases risk of future active disease in patients with inflammatory bowel disease in remission. Inflamm Bowel Dis. 2015;21(5):1063-71.
- 8. Codella R, Luzi L, Terruzzi I. Exercise has the guts: How physical activity may positively modulate gut microbiota in chronic and immune-based diseases. Dig Liver Dis. 2018;50(4):331-41.
- 9. Bilski J, Mazur-Bialy A, Brzozowski B, et al. Can exercise affect the course of inflammatory bowel disease? Experimental and clinical evidence. Pharmacol Rep. 2016;68(4):827-36.
- 10. Monda V, Villano I, Messina A, et al. Exercise Modifies the Gut Microbiota with Positive Health Effects. Oxid Med Cell Longev. 2017;2017:3831972.
- 11. Pedersen BK, Steensberg A, Fischer C, et al. Exercise and cytokines with particular focus on muscle-derived IL-6. Exerc Immunol Rev. 2001;7:18-31.
- 12. Brown M, McClean CM, Davison GW, et al. The acute effects of walking exercise intensity on systemic cytokines and oxidative stress. Eur J Appl Physiol. 2018;118(10):2111-20.
- 13. Suzuki K, Nakaji S, Yamada M, et al. Systemic inflammatory response to exhaustive exercise. Cytokine kinetics. Exerc Immunol Rev. 2002;8:6-48.
- 14. Pedersen BK. Special feature for the Olympics: effects of exercise on the immune system: exercise and cytokines. Immunol Cell Biol. 2000;78(5):532-5.
- 15. Terink R, Bongers CCWG, Witkamp RF, et al. Changes in cytokine levels after prolonged and repeated moderate intensity exercise in middle-aged men and women. Translational Sports Medicine. 2018;1(3):110-9.
- 16. D'Haens G, Ferrante M, Vermeire S, et al. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. Inflamm Bowel Dis. 2012;18(12):2218-24.

- 17. Kostas A, Siakavellas SI, Kosmidis C, et al. Fecal calprotectin measurement is a marker of short-term clinical outcome and presence of mucosal healing in patients with inflammatory bowel disease. World J Gastroenterol. 2017;23(41):7387-96.
- 18. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003;56(12):1163-9.
- 19. Klare P, Nigg J, Nold J, et al. The impact of a ten-week physical exercise program on health-related quality of life in patients with inflammatory bowel disease: a prospective randomized controlled trial. Digestion. 2015;91(3):239-47.
- 20. Arruda JM, Bogetz AL, Vellanki S, et al. Yoga as adjunct therapy for adolescents with inflammatory bowel disease: A pilot clinical trial. Complement Ther Med. 2018;41:99-104.
- 21. Tew GA, Leighton D, Carpenter R, et al. High-intensity interval training and moderate-intensity continuous training in adults with Crohn's disease: a pilot randomised controlled trial. BMC Gastroenterol. 2019;19(1):19.
- 22. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. J Am Coll Cardiol. 2001;37(1):153-6.
- 23. Bennebroek Evertsz F, Hoeks CC, Nieuwkerk PT, et al. Development of the patient Harvey Bradshaw index and a comparison with a clinician-based Harvey Bradshaw index assessment of Crohn's disease activity. J Clin Gastroenterol. 2013;47(10):850-6.
- 24. Bennebroek Evertsz F, Nieuwkerk PT, Stokkers PC, et al. The patient simple clinical colitis activity index (P-SCCAI) can detect ulcerative colitis (UC) disease activity in remission: a comparison of the P-SCCAI with clinician-based SCCAI and biological markers. J Crohns Colitis. 2013;7(11):890-900.
- 25. Molenberghs G, Bijnens L, Shaw D. Linear Mixed Models and Missing Data. In: Verbeke G MG, editor. Linear Mixed Models in Practice. New York: Springer; 1997. p. 191-274.
- 26. Riebe D, Ehrman JK, Liguori G, Magal M. ACSM's guidelines for exercise testing and prescription. Philadelphia: Wolters Kluwer; 2018. p. 143-79.
- 27. Scherr J, Wolfarth B, Christle JW, et al. Associations between Borg's rating of perceived exertion and physiological measures of exercise intensity. Eur J Appl Physiol. 2013;113(1):147-55.
- 28. Verheggen R, Eijsvogels TMH, Catoire M, et al. Cytokine responses to repeated, prolonged walking in lean versus overweight/obese individuals. J Sci Med Sport. 2019;22(2):196-200.
- 29. Fischer CP. Interleukin-6 in acute exercise and training: what is the biological relevance? Exerc Immunol Rev. 2006;12:6-33.
- 30. Ploeger H, Obeid J, Nguyen T, et al. Exercise and inflammation in pediatric Crohn's disease. Int J Sports Med. 2012;33(8):671-9.
- 31. Cronin O, Barton W, Moran C, et al. Moderate-intensity aerobic and resistance exercise is safe and favorably influences body composition in patients with quiescent

Inflammatory Bowel Disease: a randomized controlled cross-over trial. BMC Gastroenterol. 2019;19(1):29.

- 32. Cremer A, Ku J, Amininejad L, et al. Variability of Faecal Calprotectin in Inflammatory Bowel Disease Patients: An Observational Case-control Study. J Crohns Colitis. 2019;13(11):1372-9.
- 33. Du L, Foshaug R, Huang VW, et al. Within-Stool and Within-Day Sample Variability of Fecal Calprotectin in Patients With Inflammatory Bowel Disease: A Prospective Observational Study. J Clin Gastroenterol. 2018;52(3):235-40.
- 34. Calafat M, Cabre E, Manosa M, et al. High within-day variability of fecal calprotectin levels in patients with active ulcerative colitis: what is the best timing for stool sampling? Inflamm Bowel Dis. 2015;21(5):1072-6.
- 35. Lasson A, Stotzer PO, Ohman L, et al. The intra-individual variability of faecal calprotectin: a prospective study in patients with active ulcerative colitis. J Crohns Colitis. 2015;9(1):26-32.
- 36. Ng V, Millard W, Lebrun C, Howard J. Low-intensity exercise improves quality of life in patients with Crohn's disease. Clin J Sport Med. 2007;17(5):384-8.
- 37. Loudon CP, Corroll V, Butcher J, et al. The effects of physical exercise on patients with Crohn's disease. Am J Gastroenterol. 1999;94(3):697-703.
- 38. Elsenbruch S, Langhorst J, Popkirowa K, et al. Effects of mind-body therapy on quality of life and neuroendocrine and cellular immune functions in patients with ulcerative colitis. Psychother Psychosom. 2005;74(5):277-87.
- 39. Gracie DJ, Williams CJ, Sood R, et al. Poor Correlation Between Clinical Disease Activity and Mucosal Inflammation, and the Role of Psychological Comorbidity, in Inflammatory Bowel Disease. Am J Gastroenterol. 2016;111(4):541-51.
- 40. Walsh A, Kormilitzin A, Hinds C, et al. Defining Faecal Calprotectin Thresholds as a Surrogate for Endoscopic and Histological Disease Activity in Ulcerative Colitis-a Prospective Analysis. J Crohns Colitis. 2019;13(4):424-30.
- 41. Ricanek P, Brackmann S, Perminow G, et al. Evaluation of disease activity in IBD at the time of diagnosis by the use of clinical, biochemical, and fecal markers. Scand J Gastroenterol. 2011;46(9):1081-91.

Appendix 1

Supplementary Table 1. Estimated marginal mean cytokine concentrations (pg/mL) after back transformation, at baseline and day 1 to day 4, for IBD walkers and non-IBD walkers

	Baseline	Day 1	Day 2	Day 3	Day 4
IL-6					
IBD walkers	0.74 ± 0.11	5.75 ± 1.08	4.08 ± 0.72	2.37 ± 0.48	2.31 ± 0.40
Non-IBD walkers	0.63 ± 0.09	6.18 ± 1.13	3.88 ± 0.67	2.75 ± 0.53	2.46 ± 0.40
IL-8					
IBD walkers	6.09 ± 0.67	8.34 ± 0.80	7.88 ± 0.71	7.91 ± 0.68	7.01 ± 0.61
Non-IBD walkers	5.15 ± 0.54	6.03 ± 0.57	6.53 ± 0.58	6.28 ± 0.51	6.17 ± 0.51
IL-10					
IBD walkers	0.22 ± 0.02	0.53 ± 0.08	0.25 ± 0.05	0.30 ± 0.04	0.27 ± 0.05
Non-IBD walkers	0.21 ± 0.02	0.34 ± 0.05	0.29 ± 0.05	0.25 ± 0.03	0.24 ± 0.03
IL-1β					
IBD walkers	0.15 ± 0.02	0.13 ± 0.02	0.15 ± 0.02	0.17 ± 0.02	0.12 ± 0.02
Non-IBD walkers	0.13 ± 0.02	0.10 ± 0.01	0.15 ± 0.02	0.12 ± 0.01	0.12 ± 0.02
TNF-α					
IBD walkers	1.62 ± 0.14	1.54 ± 0.14	1.69 ± 0.16	1.75 ± 0.18	1.64 ± 0.15
Non-IBD walkers	1.81 ± 0.15	1.66 ± 0.15	1.89 ± 0.18	1.82 ± 0.18	1.85 ± 0.16

Cytokine concentrations are presented in picogram per millilitre. Data are presented as mean \pm standard error and were derived from a linear mixed model analysis. All statistical tests were performed on the log10 scale. Hereafter, data were back transformed for presentation in this table.

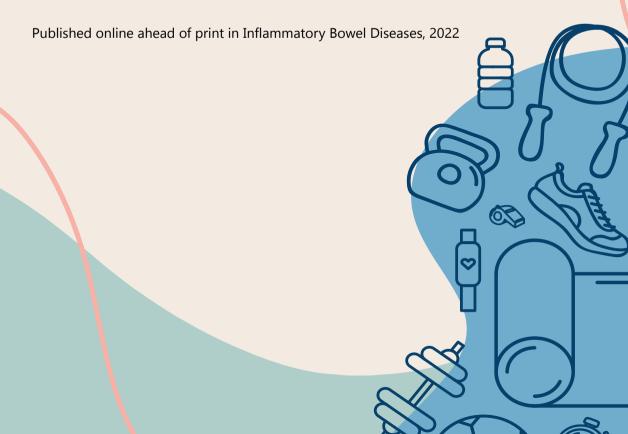
Abbreviations: IBD: inflammatory bowel disease, IL: interleukin, TNF: tumor necrosis factor



Chapter 5

Lower impact of disease on daily life and less fatigue in patients with Inflammatory Bowel Disease following a lifestyle intervention

Lamers CR, de Roos NM, Heerink HH, van de Worp - Kalter LA, Witteman BJM



Abstract

Background Despite the potential benefits of diet and physical activity, evidence for beneficial effects of a combined lifestyle intervention is lacking in patients with inflammatory bowel disease (IBD). We therefore assessed its effects on impact of disease on daily life, clinical disease activity, fatigue and health-related quality of life (HRQoL) in patients with IBD.

Methods A 6-month single-arm intervention study was performed in adult IBD patients in remission or with mildly active disease. Participants received personal dietary and physical activity advice from a dietician and a physiotherapist in six consults. At baseline and over time, questionnaires on diet quality, physical activity and disease-related outcomes were completed and faecal calprotectin was determined. Data were analysed by linear mixed models.

Results During the intervention, diet quality significantly increased (p<0.001), but level of physical activity remained the same. Over time, impact of disease on daily life reduced (p=0.009) and fatigue decreased (p=0.001), while clinical disease activity, HRQoL and faecal calprotectin did not change. Improvement in diet quality was significantly associated with a lower impact of disease on daily life (β =0.09, 95%CI 0.03; 0.15, p=0.003) and less fatigue (β =-0.13, 95%CI -0.20; -0.07, p<0.001), but not with clinical disease activity, HRQoL and faecal calprotectin. No associations were found with physical activity.

Conclusions This combined lifestyle intervention significantly improved diet quality and this improvement was associated with a reduction in the impact of disease on daily life and fatigue in patients with IBD in remission or with mildly active disease.

Introduction

Westernization of lifestyle, characterized by unhealthy dietary habits and decreased physical activity, not only has been linked to the increased incidence and prevalence of inflammatory bowel disease (IBD), but may also affect the disease course in patients with established IBD [1-3]. IBD is mainly treated with medication. In addition to medication, many IBD patients look for supportive and adjunctive therapies [4-6]. They frequently ask their physicians for advice on diet and lifestyle to improve or even cure their disease [7]. Several studies suggest influence of various lifestyle factors, including diet and physical activity, on the course of disease. A healthy lifestyle may support maintenance of remission and improve health-related quality of life (HRQoL) [2, 3], which is important since IBD is characterized by a clinical course with periods of active disease alternating with periods of remission and has a significant impact on daily life [8]. One study even found a healthy lifestyle, in terms of a healthy diet and weight and a sufficient level of physical activity, to be associated with reduced mortality in IBD patients [9].

Many different types of exclusion diets have been proposed in the treatment of IBD, such as the Specific Carbohydrate Diet (SCD) and CD-TREAT [7]. However, adherence can be a challenge and large controlled trials are lacking to conclude if these restrictive exclusion diets benefit IBD patients [7]. Furthermore, restrictive diets can also have potential adverse effects. For example, reducing fibre intake might have detrimental effects on the microbiota by less prebiotic actions, and there is a risk of undernutrition when insufficient attention is paid to nutritional adequacy [7]. However, some studies have shown that the exclusion of certain food components seems to benefit IBD patients, such as industrialized, processed foods, animal fat and red and processed meat [10, 11]. Excluding these foods may not only reduce proinflammatory processes but is also in line with the general dietary guidelines on healthy eating. These guidelines recommend a diet rich in vegetables, fruit and fibre which also appears to benefit IBD patients [4].

In addition to dietary interventions, several studies have evaluated different physical activity interventions and limited but promising evidence suggests that physical activity can benefit overall health, physical well-being and HRQoL [5]. Regular physical activity is associated with an increased biodiversity of the gut microbiome and release of protective myokines like IL-6 from working skeletal muscles, both

promoting an anti-inflammatory state [12, 13]. In a prospective cohort study, a higher level of physical activity was associated with a lower risk of relapse among IBD patients in remission [14]. In a review, it was recommended to maintain an active lifestyle consisting of endurance and resistance exercise [6]. Combining all evidence, regular physical activity of low-moderate intensity, including cardio and resistance exercise, may positively affect HRQoL and inflammation in IBD patients [4].

Although studies have been performed assessing the effects of diet or physical activity interventions, little information is available on combined lifestyle interventions in IBD patients. In other chronic conditions such as type 2 diabetes and obesity, interventions in which diet and physical activity are combined seem to be more effective than diet-only or physical-activity-only interventions [15]. So far, two combined lifestyle intervention studies have been performed in IBD patients by a research group from Germany. Their intervention focused on psychological aspects such as stress reduction and management, while diet and physical activity were secondary aspects of which changes were not reported, and their intervention lasted only 10 weeks [16, 17]. No studies to date have examined effects of a lifestyle intervention focusing on diet and physical activity in IBD patients. Therefore, we performed a 6-month combined lifestyle intervention study in which we provided personal dietary and physical activity advice to improve the lifestyle of IBD patients. The aim of this study was to investigate the effect of this 6-month lifestyle intervention primarily on the impact of disease on daily life and secondarily on clinical disease activity, HROoL and fatigue. In addition to these subjective measures, changes in faecal calprotectin were investigated. Patient experiences with the combined lifestyle intervention were also evaluated in this study.

Materials and methods

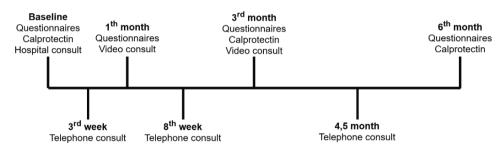
Study population

Participants were recruited between February 2020 and February 2021 via the outpatient clinic of Hospital Gelderse Vallei in Ede, the Netherlands. Inclusion criteria were a histologically proven diagnosis of Crohn's disease (CD) or ulcerative colitis (UC, total or left-sided) at least two years before recruitment, age 18-70 years, remission or mildly active disease that did not require immediate medication change and at least one flare-up in the past two years. Participants were excluded when they already adhered well to the Dutch dietary guidelines (*Eetscore*-FFQ >120 points), used prednisone, had a stoma or pouch, and when they already participated in another intervention study. This study was approved by the Medical Ethical Committee of Wageningen University (METC nr. 19/18) and conducted in accordance with the Declaration of Helsinki and registered at trialregister.nl (NL8267). All participants provided written informed consent.

Study design

A 6-month single-arm intervention study was performed. Participants were intensively supervised by a dietician and a physiotherapist for three months. During these first three months the focus was to change lifestyle. Five consults were scheduled for each participant of which three were planned to be performed at the hospital and two by telephone. Due to COVID-19 restrictions, two hospital consults were replaced by video consults for the majority of participants (*Figure 1*). After three months, participants were followed up for another three months. During these second three months the focus was to maintain lifestyle change; participants had one follow-up telephone consult to support them in maintaining their lifestyle change and to answer questions. Between consults, participants had the opportunity to email their dietician or physiotherapist with questions. Several measurements were performed at four time points (baseline and 1 month, 3 and 6 months after baseline) to assess the effects of the intervention.

Figure 1. Overview of study design



Lifestyle intervention

During the 6-month combined lifestyle intervention, participants adhered as well as possible to a healthy diet and physical activity level through intensive advice from a dietician and a physiotherapist. Dietary recommendations were based on the Dutch dietary quidelines with a few adjustments [18]. In short, the recommended diet was mainly plant-based rich in vegetables, fruits, wholegrains and nuts. Tea, coffee and water were the preferred drinks. Furthermore, participants were advised to limit their intake of red and processed meat, soft drinks and other processed foods. The recommended intake of vegetables (>300 grams per day) was higher than the Dutch dietary guidelines to achieve a higher fibre intake that is known for its beneficial effects on IBD symptoms and the gut microbiota [19]. Besides, there was a stricter limit on red meat intake (max. 100 grams per week) because red meat seems to be associated with disease relapse and detrimental effects on the gut microbiota [20]. Physical activity recommendations were based on the Dutch physical activity quidelines; exercise at moderate intensity for 30 minutes per day at least 5 days per week [21]. A combination of cardio (e.g. walking, running, cycling and swimming) and resistance exercise was advised and the statement "more exercise is better" applied. The exact dietary and physical activity adjustments were expected to vary per person since baseline diet quality and level of physical activity would differ per person, but the targets were the same. Therefore, a personalized approach was applied and discussed between participant, dietician and physiotherapist. By setting goals, giving feedback, shaping knowledge and repeating advice, the goal was to achieve a long-term behaviour change [22]. Throughout the study, participants were supported by a booklet with dietary and physical activity quidelines, an app with recipes and a booklet with examples of physical activity exercises.

Study assessments

Assessment of diet quality and level of physical activity

Diet quality was assessed using the *Eetscore* Food Frequency Questionnaire (*Eetscore*-FFQ). This is a short FFQ which is scored with the Dutch Healthy Diet 2015-index that is based on the Dutch dietary guidelines [23]. Dietary assessment by the *Eetscore*-FFQ is based on 16 food components (vegetables, fruit, wholegrain products, legumes, nuts, dairy, fish, tea, fats and oils, coffee, red meat, processed meat, sweetened beverages and fruit juices, alcohol, salt and unhealthy choices) with a score from 0 to 10 per component, resulting in a total score between 0 and 160. Higher scores indicate better adherence to the dietary guidelines.

Physical activity was assessed using the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) [24]. The SQUASH contains questions regarding multiple activities during an average week in the past month, namely commuting activities, leisure time activities, household activities and activities at work or school. Number of days per week, average time per day and intensity of every activity were reported. The total level of physical activity was calculated by summing up different activity scores which were calculated by the duration of an activity in minutes per week times the corresponding metabolic equivalent of the task (MET). Higher scores indicate a higher level of physical activity.

Assessment of clinical effects of lifestyle intervention

Several questionnaires were used to assess clinical effects of the lifestyle intervention. The primary outcome, impact of disease on daily life, was assessed using the inflammatory bowel disease disability index (IBD-DI), a 28-item questionnaire covering limitations across five domains: overall health, body functions (sleep, mood, abdominal pain, defecation, weight), body structures (blood in stool, arthralgia), activity participation (work/education, interpersonal activities) and environmental factors (effects of medication, food, family and health care) [25, 26]. The total score ranges from -80 (maximum degree of disability) to 22 (no disability), thus higher scores represent less impact of disease on daily life.

Clinical disease activity was assessed using the patient Harvey Bradshaw Index (P-HBI) for participants with CD and the patient Simple Clinical Colitis Activity Index (P-SCCAI) for participants with UC [27, 28]. Higher scores represent more active disease.

Health-related quality of life (HRQoL) was assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ), a 32-item questionnaire to assess disease specific HRQoL with a score range from 32 to 224 [29]. Higher scores represent better HRQoL. Fatigue was assessed using the inflammatory bowel disease fatigue (IBD-F) patient self-assessment scale which consists of two parts: 5 questions about the frequency, duration and severity of fatigue followed by 30 questions about the impact of fatigue on daily life [30]. Scores of the first part range from 0 to 20 and of the second part from 0 to 120. Higher scores represent more (impact of) fatigue.

Assessment of biochemical effects of lifestyle intervention

Inflammation was assessed by faecal calprotectin. Participants were provided with materials and instructions to collect faecal samples at home at baseline, and at 3 and 6 months. Samples were stored in participants' refrigerators before transfer to the study laboratory for analysis. Faecal calprotectin was determined using a sandwich enzyme-linked immunosorbent assay (ELISA). Faecal calprotectin concentrations for this assay ranged from 0 to 2500 μ g/q.

Assessment of participant characteristics

All participants completed a general questionnaire on demographics, level of education, smoking, medication use and previous IBD-related surgeries. Disease phenotype according to the Montreal classification was derived from their medical records.

Evaluation of lifestyle intervention

After 6 months, participants completed a questionnaire consisting of questions about meeting expectations, number and timing of consults, and feasibility of dietary and physical activity advice to gain insight into their experiences with the intervention.

Sample size calculation and statistical analysis

Sample size calculation revealed that a sample of 24 participants was needed to detect a change in IBD-DI of 10 points with a standard deviation of 17 points, a 5% significance level and a power of 80%. Accounting for a 20% drop-out, a total of 30 participants needed to be enrolled.

Normally distributed data are presented as mean ± standard deviation (SD), skewed data as median with interquartile range (IQR) and categorical data as counts and percentages. Linear mixed models were used to analyse changes in diet quality, physical activity and disease-related outcomes within subjects over time (fixed main factor) to account for repeated measures. Baseline values were used as reference. If effect of time was significant, pairwise comparisons between baseline and each subsequent time point were performed with Bonferroni correction to adjust for multiple comparisons. Further linear mixed models were performed to assess whether changes in diet quality and physical activity (fixed main covariates) were associated with changes in the disease-related outcomes (dependent variables). Again, baseline values were used as reference with time as repeated measure. A random intercept was used with an identity covariance structure. Linear mixed model data are reported as the fixed effect estimates with 95% confidence intervals or standard error. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 24.

Results

Participant characteristics

In total, 29 participants were included. Within two weeks after the start, one participant required extra medication for active disease and was therefore excluded from the study. It was unlikely that her flare-up was due to the lifestyle intervention, as we learned afterwards that she withheld information about increasing complaints before the start of the study. During the study, three female participants withdrew after respectively two, three and eight weeks because of time constraints. One other female participant dropped out after eight weeks because she was diagnosed with breast cancer. In total, 24 participants (83%) completed the study. For the analysis, all participants with at least two measurements were included, resulting in 26 participants for the analysis. Baseline characteristics of these participants are shown in *Table 1*. Most participants were female (58%), had UC (54%) and were highly

educated (61%). Their median age was 36 years [IQR 30-52], mean BMI was 26.4 ± 3.8 kg/m² and median disease duration was 11 years [IQR 5-14].

Table 1. Baseline characteristics of study population

	n = 26
Female, <i>n (%)</i>	15 (58)
Age (years), median [IQR]	36 [30-52]
BMI (kg/m²), <i>mean ± SD</i>	26.4 ± 3.8
Level of education#, n (%)	
Low	2 (8)
Intermediate	8 (31)
High	16 (61)
Current smoker, n (%)	2 (8)
Crohn's disease, n (%)	12 (46)
A1 - Diagnosis <16 years	1 (8)
A2 - Diagnosis 17-40 years	9 (75)
A3 - Diagnosis >40 years	2 (17)
L1 - Ileum	4 (33)
L2 - Colon	2 (17)
L3 - Ileocolon	6 (50)
L4 - Upper GI tract	1 (8)
B1 - Non-stricturing, non-penetrating	9 (75)
B2 - Stricturing, non-penetrating	2 (17)
B3 - Stricturing, penetrating	1 (8)
Perianal	1 (8)

Table 1. Continued

	n = 26
Ulcerative colitis, n (%)	14 (54)
E1 - Proctitis	0 (0)
E2 - Left-sided colitis	7 (50)
E3 - Pancolitis	7 (50)
Disease duration (years), median [IQR]	11 [5-14]
Medication use, <i>n</i> (%)	
5-ASA	10 (38)
Corticosteroids	1 (4)
Immunomodulators	11 (42)
Biologicals	14 (54)
None	0 (0)
Prior IBD-related surgery, n (%)	3 (12)

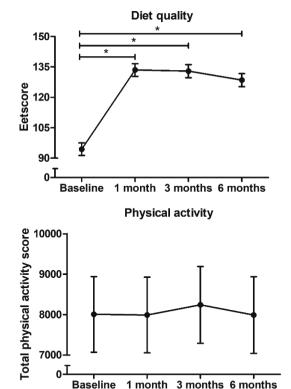
^{*}Education level: no education, primary or lower vocational education and lower general secondary education (low); secondary vocational education and higher general secondary education (intermediate); higher vocational education and university (high).

Assessment of diet quality and level of physical activity

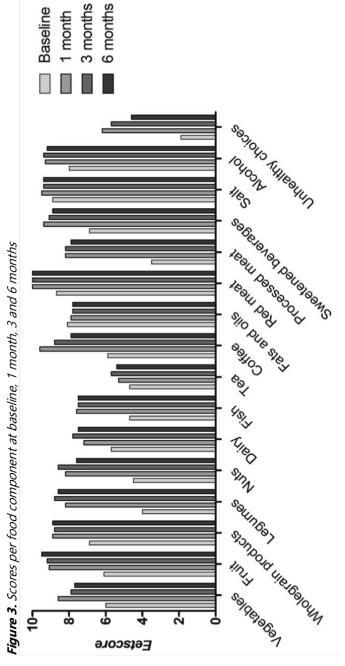
At baseline, mean diet quality was 94.4 ± 3.1 and mean total physical activity score was 8006 ± 936 (*Figure 2 / Appendix 1 – Supplementary Table 1*). During the intervention, diet quality improved in all participants. Mean diet quality significantly improved with 39 points to 133.5 ± 3.1 after 1 month (p<0.001) and was still 128.5 ± 3.2 after 6 months (p<0.001). When looking at the different components of diet quality, a significant increase was seen in the intake of vegetables, fruit, wholegrain products, legumes, nuts, dairy, and fish (p<0.01 for all), while a significant decrease was seen in the intake of red meat, processed meat, sweetened beverages, alcohol, and unhealthy choices (p<0.01 for all) (*Figure 3*). The intake of fat and oils (p=0.76)

and salt (80.0=q)did not significantly change. We also observed no significant changes in total physical activity score or in the amounts of low, moderate and high intensity physical activity. However, mean BMI significantly decreased from 26.4 \pm 3.8 kg/m² at baseline to $25.0 \pm 3.9 \text{ kg/m}^2$ after 6 months (p<0.001).

Figure 2. Diet quality and physical activity at baseline, 1 month, 3 and 6 months



Data are presented as estimated marginal mean \pm standard error as derived from linear mixed model analysis with time as main fixed factor. Diet quality scores can range from 0 to 160. * p<0.001



Data are presented as estimated marginal mean as derived from linear mixed model analysis with time as main fixed factor. Except for fat and oils and salt intake, all food components improved with a significance level of p < 0.01. Higher scores indicate better adherence to dietary guidelines.

Assessment of clinical effects of lifestyle intervention

The estimated marginal means and standard errors of all disease-related outcomes at each time point are shown in *Figure 4 (Appendix 1 – Supplementary Table 1)*. Impact of disease on daily life (IBD-DI, p=0.009) and fatigue (IBD-F, p=0.001) significantly reduced over time, while no change was found for clinical disease activity and HRQoL. In pairwise comparisons between baseline and subsequent time points, mean IBD-DI significantly increased between baseline and 3 months (p=0.037) and baseline and 6 months (p=0.011), although not between baseline and 1 month (p=0.38). Pairwise comparisons for IBD-F showed a significant decrease in mean IBD-F between baseline and 3 months (p=0.002) and baseline and 6 months (p=0.008), although not between baseline and 1 month (p=0.07).

When looking at associations between lifestyle change and change in disease-related outcomes, linear mixed models showed that improvement in diet quality over time was significantly associated with impact of disease on daily life (β = 0.09, 95%CI 0.03; 0.15, p=0.003) and fatigue (β = -0.13, 95%CI -0.20; -0.07, p<0.001) (*Table 2*). These associations remained when corrected for physical activity. Physical activity alone was not associated with any of the disease-related outcomes. Overall, the association between diet quality and disease-related outcomes was small with each 10-point increase in diet quality being associated with a 0.9-point reduction in impact of disease on daily life and a 1.3-point decrease in fatigue.

Fatique Impact of disease on daily life 25 20 BD-DI ¥-08 15∙ n. T₀ Baseline 1 month 3 months 6 months Baseline 1 month 3 months 6 months **HRQoL** Faecal calprotectin 205 100-Faecal calprotectin 200 80-BDQ 60-195 40-190 20-185 32I 0 Baseline 1 month 3 months 6 months Baseline 3 months 6 months Clinical disease activity - CD Clinical disease activity - UC 2.0-3 1.5 P-SCCAI 1.0 0.5 1 0.0 Baseline 1 month 3 months 6 months Baseline 1 month 3 months 6 months

Figure 4. Disease-related outcomes at baseline, 1 month, 3 and 6 months

Data are presented as estimated marginal mean \pm standard error as derived from linear mixed model analysis with time as main fixed factor. *p < 0.05, **p < 0.01

Impact of disease on daily life scores can range from -80 to +22: higher scores represent less disabilities and thus less impact of disease on daily life. Fatigue scores can range from 0 to 120. HRQoL scores can range from 32 to 224.

Faecal calprotectin (n = 24): statistical tests were performed on the log2 scale. Hereafter, data were back transformed for presentation in this figure. Median faecal calprotectin: baseline 15 ug/g [IQR 5 - 42], 3 months 18 ug/g [IQR 8-31], 6 months 12 ug/g [IQR 4-54].

Table 2. Linear mixed model analysis of associations between lifestyle change and outcomes over time

	Diet quality		Physical activity ^{\$}	tys	Diet quality + physical activity ^{\$}	itys
	β (95%CI)	p-value	β (95%CI)	p-value	β (95%CI)	p-value
Impact of disease on daily life (IBD-DI)	0.09 (0.03; 0.15)	0.003	0.02 (-0.03; 0.06)	0.49	Diet quality: 0.09 (0.04; 0.15) PA: 0.03 (-0.02; 0.07)	0.001 0.21
Clinical disease activity						
CD (P-HBI)	0.004 (-0.02; 0.03)	0.75	-0.01 (-0.03; 0.005)	0.16	Diet quality: -0.005 (-0.03; 0.02) PA: -0.01 (-0.03; 0.005)	0.74 0.16
UC (P-SCCAI)	-0.009 (-0.02; 0.005)	0.20	-0.008 (-0.02; 0.001)	0.10	Diet quality: -0.008 (-0.02; 0.005) PA: -0.007 (-0.02; 0.002)	0.21
Fatigue (IBD-F)	-0.13 (-0.20; -0.07)	<0.001	-0.03 (-0.09; 0.03)	0.35	Diet quality: -0.14 (-0.20; -0.07) PA: -0.03 (-0.09; 0.02)	<0.001 0.21
Health-related quality of life (IBDQ)	0.12 (-0.01; 0.24)	0.07	0.05 (-0.04; 0.14)	0.29	Diet quality: 0.13 (-0.001; 0.25) PA: 0.06 (-0.03; 0.15)	0.05
Faecal calprotectin#	-0.002 (-0.02; 0.02)	0.85	-0.003 (-0.01; 0.01)	0.62	Diet quality: -0.002 (-0.02; 0.02) PA: -0.003 (-0.01; 0.01)	0.81

Data are tested by using linear mixed models with an identity covariance structure and indicating time as repeated measure. Impact of disease on daily life, disease activity, fatigue, HRQoL and faecal calprotectin are dependent variables and diet quality and physical activity are added as fixed main covariates to the model. Bold values are significant.

* n=24; \$ per 100 points change in total physical activity score

Assessment of biochemical effects of lifestyle intervention

At baseline, median faecal calprotectin was 15 ug/g [IQR 5-42], which reflects that all participants were in remission. No significant change was found over time (p=0.69, *Figure 4 / Appendix 1 – Supplementary Table 1*) and no associations were found with diet quality and physical activity (p=0.85 and p=0.62, *Table 2*).

Evaluation of lifestyle intervention

The lifestyle intervention was rated with a 8.4 out of 10 and 79% of participants would recommend the lifestyle intervention to other patients with IBD. Consults with the dietician were rated with a 4.5 ± 0.5 and consults with the physiotherapist were rated with a 4.4 ± 0.7 on a 5-point Likert scale. Time interval between consults was rated a 4.1 ± 0.8 on a 5-point Likert scale. Participants found the physical activity advice more feasible and easy to apply in daily life than the dietary advice (8.1 out of 10 vs 7.4 out of 10). After 6 months, the extent to which participants felt able to continue the recommendations without guidance of a dietician and physiotherapist was rated with a 7.9 out of 10.

Discussion

In this single-arm intervention study in IBD patients in remission or with mildly active disease, we found that a lifestyle intervention that combined dietary and physical activity advice significantly improved diet quality while level of physical activity remained the same. Over time, a significant decrease was found in impact of disease on daily life and fatigue, while no significant change was observed in clinical disease activity, health-related quality of life and faecal calprotectin. Improvement in diet quality was associated with a reduction in impact of disease on daily life and fatigue. No association was found with clinical disease activity, health-related quality of life and faecal calprotectin, nor was physical activity associated with any of the outcomes. The majority of participants would recommend this lifestyle intervention to other patients with IBD.

To our knowledge, this is the first study in IBD patients to examine the effects of a combined lifestyle intervention focussing on diet and physical activity. Therefore, it is difficult to compare the current study to previous lifestyle studies, since they all differ in treatment approach, patient inclusion, outcomes and follow-up. Nevertheless, one research group performed two other combined lifestyle intervention studies in IBD patients. Those consisted of a 10-week training program, including stress management, moderate exercise, moderate Mediterranean diet and behavioural techniques [17, 31]. In their first study, no effect was found on HROoL or disease status in 15 UC patients 3 months after completion of the intervention [31]. Their second study only included UC patients with a reduced HROoL (IBDO <170) and showed a significant improvement in HROoL in 47 UC patients at week 12, while disease status did not change [17]. Whether the intervention actually changed the lifestyle of these patients is unknown, since changes in diet and level of physical activity were not reported. In both studies, only patients in remission or with mildly active disease were included. As known from other studies, disease status at baseline clearly determines the room for improvement [32-34]. Also in our study, the participants were in remission or had only mildly active disease which most likely explains the lack of an effect on clinical disease activity and faecal calprotectin since these were already low at baseline.

As shown in previous studies, exclusion of certain food components may reduce proinflammatory processes and thereby benefit IBD patients [10, 11]. In our study,

participants improved their diet quality and reduced the inflammatory potential of their diet by increasing their intake of products high in anti-inflammatory components, such as vegetables, fruit, wholegrain products, legumes, fish and nuts, while decreasing their intake of products high in pro-inflammatory components, such as red and processed meat, sweetened beverages and alcohol. Adherence to such an anti-inflammatory dietary pattern has the potential to prevent intestinal inflammatory processes via the gut microbiome [35]. Moreover, it is associated with less inflammation and a lower disease activity [36], which is associated with a lower impact of disease [26]. Therefore, reduction of the inflammatory potential of diet might have decreased the impact of disease on daily life and fatigue in our study population, since the improvement in diet quality was followed by improvement of those disease-related outcomes. Moreover, our intervention diet is not a restrictive exclusion diet but in line with the general dietary guidelines on healthy eating [18]. Therefore, the diet is more acceptable for patients, has a lower risk of nutritional deficiencies and undernutrition, and also has broader health effects [37].

In contrast to the effect of our lifestyle intervention on diet quality, we found no improvement in level of physical activity. This may be explained by the limited room for improvement since a large percentage of participants already exercised regularly compared to another cohort of IBD patients [38]. Another explanation for the lack of improvement in level of physical activity may be the COVID-19 pandemic [39]. Participants reported that their possibilities to be physically active were restricted due to COVID-19 measures. Gyms and sports clubs were closed, so physical activity was generally limited to walking, cycling, running and at home resistance exercises. Level of physical activity might have improved if we had included supervised exercise training as was done in other physical activity interventions instead of only providing participants with recommendations and examples [33, 34]. However, this is more difficult to implement in daily life and more expensive.

The evaluation revealed that participants were satisfied with the lifestyle intervention and would recommend it to other patients with IBD. Although we did not find changes in level of physical activity, participants found the physical activity advice more feasible and more easy to apply than the dietary advice. This can be explained by our study population already exercising regularly. Furthermore, difficulty to comply with the dietary advice may in part be explained by the social aspects of

eating and drinking. Participants reported to experience difficulties with dietary adherence when going out for dinner or when having something to celebrate, since in those situations the consumed foods and drinks are generally not (fully) in line with dietary guidelines.

During the lifestyle intervention, mean BMI of our participants significantly decreased which is likely the result of their healthier lifestyle. In addition to the benefits of a reduced inflammatory potential of diet, improvement in BMI may further decrease low grade inflammation and is associated with broader health benefits [40].

As mentioned previously, to our knowledge, this is the first study in IBD patients to examine a combined lifestyle intervention focussing on diet and physical activity. Other strengths of this study are the follow-up of 6 months, the personalized approach and the inclusion of a representative group of IBD patients including comparable numbers of CD and UC, males and females, and patients of all ages. This study also has limitations that should be considered. We did not include a control group because there is no ideal placebo treatment. Several types of control groups were considered, but all had their drawbacks leading to bias. As a result, we could not correct for natural changes over time and we could not determine whether diet quality solely improved because of our intervention or also as a result of dietary awareness. However, dietary awareness would also be a positive result of our intervention. Furthermore, participants may have given socially desirable answers to the diet and physical activity questionnaires. However, the fact that we found a change in diet quality but not in level of physical activity suggests that the degree of social desirability is limited. Nevertheless, memory bias and estimation error may still have occurred during completion of the diet and physical activity guestionnaires [41]. Another limitation is that we only included patients in remission or with mildly active disease, as high disease activity would require more intense pharmacological treatment or even surgery which would distort the results of lifestyle changes. In that case, we would not be able to distinguish between medication and lifestyle effects anymore. Also, we excluded patients with a stoma or pouch in situ as these patients might have specific dietary needs that may interfere with our dietary recommendations. As a result of this participant selection, our results cannot be extrapolated to the whole IBD population. It remains unknown whether patients with high disease activity would benefit from our lifestyle intervention. Finally, this study

started just before the COVID-19 pandemic and finished during the pandemic. COVID-19 measures not only restricted the possibilities to be physically active, but also limited social activities which might have led to an underestimation of social limitations because of IBD complaints. Moreover, we can speculate about the impact of psychosocial aspects, such as anxiety and depression, on our outcomes as a result of the pandemic.

Conclusions

We found that a combined lifestyle intervention significantly improved diet quality. This improvement in diet quality was associated with a reduction in impact of disease on daily life and fatigue in patients with IBD in remission or with mildly active disease. The level of physical activity remained the same, and no associations with disease-related outcomes were found. This combined lifestyle intervention was mainly based on general dietary and physical activity guidelines meant for healthy adults. The study results suggest that these general guidelines, when actively supervised while applying, might also benefit IBD patients. To further support these findings, future studies should be performed outside pandemic times to ensure representative daily life, in patients with a low diet quality and level of physical activity, and in larger study populations.

Acknowledgements

The authors would like to thank all participants for taking part in this study. We also would like to thank the secretaries and laboratory personnel for their organisational and practical support. A special thanks to Marloes Snijders for her help with participant recruitment and data collection, and to Mirjam Holverda and Irene Wittendorp-Essink for their dietetics and physiotherapy consultations.

Funding

This work was supported by a grant from the Province of Gelderland as part of the EAT2MOVE project (proposal PS2014-49) and by a grant from the Nutrition and Healthcare Alliance.

References

- 1. 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):2769-78.
- 2. Charlebois A, Rosenfeld G, Bressler B. The Impact of Dietary Interventions on the Symptoms of Inflammatory Bowel Disease: A Systematic Review. Crit Rev Food Sci Nutr. 2016;56(8):1370-8.
- 3. Engels M, Cross RK, Long MD. Exercise in patients with inflammatory bowel diseases: current perspectives. Clin Exp Gastroenterol. 2018;11:1-11.
- 4. Duff W, Haskey N, Potter G, et al. Non-pharmacological therapies for inflammatory bowel disease: Recommendations for self-care and physician guidance. World J Gastroenterol. 2018;24(28):3055-70.
- 5. Torres J, Ellul P, Langhorst J, et al. European Crohn's and Colitis Organisation Topical Review on Complementary Medicine and Psychotherapy in Inflammatory Bowel Disease. J Crohns Colitis. 2019;13(6):673-85e.
- 6. 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 Gastroenterol. 2019;19(1):115.
- 7. Pigneur B, Ruemmele FM. Nutritional interventions for the treatment of IBD: current evidence and controversies. Therap Adv Gastroenterol. 2019;12:1756284819890534.
- 8. IsHak WW, Pan D, Steiner AJ, et al. Patient-Reported Outcomes of Quality of Life, Functioning, and GI/Psychiatric Symptom Severity in Patients with Inflammatory Bowel Disease (IBD). Inflamm Bowel Dis. 2017;23(5):798-803.
- 9. Lo CH, Khalili H, Song M, et al. Healthy Lifestyle Is Associated With Reduced Mortality in Patients With Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol. 2021;19(1):87-95.e4.
- 10. Jowett SL, Seal CJ, Pearce MS, et al. Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study. Gut. 2004;53(10):1479-84.
- 11. Lewis JD, Abreu MT. Diet as a Trigger or Therapy for Inflammatory Bowel Diseases. Gastroenterology. 2017;152(2):398-414.e6.
- 12. Monda V, Villano I, Messina A, et al. Exercise Modifies the Gut Microbiota with Positive Health Effects. Oxid Med Cell Longev. 2017;2017:3831972.
- 13. Bilski J, Mazur-Bialy A, Brzozowski B, et al. Can exercise affect the course of inflammatory bowel disease? Experimental and clinical evidence. Pharmacol Rep. 2016;68(4):827-36.
- 14. Jones PD, Kappelman MD, Martin CF, et al. Exercise decreases risk of future active disease in patients with inflammatory bowel disease in remission. Inflamm Bowel Dis. 2015;21(5):1063-71.

- 15. Johns DJ, Hartmann-Boyce J, Jebb SA, Aveyard P. Diet or exercise interventions vs combined behavioral weight management programs: a systematic review and meta-analysis of direct comparisons. J Acad Nutr Diet. 2014;114(10):1557-68.
- 16. Elsenbruch S, Langhorst J, Popkirowa K, et al. Effects of mind-body therapy on quality of life and neuroendocrine and cellular immune functions in patients with ulcerative colitis. Psychother Psychosom. 2005;74(5):277-87.
- 17. Langhorst J, Schöls M, Cinar Z, et al. Comprehensive Lifestyle-Modification in Patients with Ulcerative Colitis-A Randomized Controlled Trial. J Clin Med. 2020;9(10).
- 18. Kromhout D, Spaaij CJ, de Goede J, Weggemans RM. The 2015 Dutch food-based dietary quidelines. Eur J Clin Nutr. 2016;70(8):869-78.
- 19. Wong C, Harris PJ, Ferguson LR. Potential Benefits of Dietary Fibre Intervention in Inflammatory Bowel Disease. Int J Mol Sci. 2016;17(6).
- 20. Campmans-Kuijpers MJE, Dijkstra G. Food and Food Groups in Inflammatory Bowel Disease (IBD): The Design of the Groningen Anti-Inflammatory Diet (GrAID). Nutrients. 2021:13(4).
- 21. Weggemans RM, Backx FJG, Borghouts L, et al. The 2017 Dutch Physical Activity Guidelines. Int J Behav Nutr Phys Act. 2018:15(1):58.
- 22. Michie S, Richardson M, Johnston M, et al. The Behavior Change Technique Taxonomy (v1) of 93 Hierarchically Clustered Techniques: Building an International Consensus for the Reporting of Behavior Change Interventions. Annals of Behavioral Medicine. 2013;46(1):81-95.
- 23. van Lee L, Feskens EJ, Meijboom S, et al. Evaluation of a screener to assess diet quality in the Netherlands. Br J Nutr. 2016:115(3):517-26.
- 24. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003;56(12):1163-9.
- 25. Leong RW, Huang T, Ko Y, et al. Prospective validation study of the International Classification of Functioning, Disability and Health score in Crohn's disease and ulcerative colitis. J Crohns Colitis. 2014;8(10):1237-45.
- 26. Lo B, Prosberg MV, Gluud LL, et al. Systematic review and meta-analysis: assessment of factors affecting disability in inflammatory bowel disease and the reliability of the inflammatory bowel disease disability index. Aliment Pharmacol Ther. 2018;47(1):6-15.
- 27. Bennebroek Evertsz F, Hoeks CC, Nieuwkerk PT, et al. Development of the patient Harvey Bradshaw index and a comparison with a clinician-based Harvey Bradshaw index assessment of Crohn's disease activity. J Clin Gastroenterol. 2013;47(10):850-6.
- 28. Bennebroek Evertsz F, Nieuwkerk PT, Stokkers PC, et al. The patient simple clinical colitis activity index (P-SCCAI) can detect ulcerative colitis (UC) disease activity in remission: a comparison of the P-SCCAI with clinician-based SCCAI and biological markers. J Crohns Colitis. 2013;7(11):890-900.

- 29. Russel MG, Pastoor CJ, Brandon S, et al. Validation of the Dutch translation of the Inflammatory Bowel Disease Questionnaire (IBDQ): a health-related quality of life questionnaire in inflammatory bowel disease. Digestion. 1997;58(3):282-8.
- 30. Czuber-Dochan W, Norton C, Bassett P, et al. Development and psychometric testing of inflammatory bowel disease fatigue (IBD-F) patient self-assessment scale. J Crohns Colitis. 2014;8(11):1398-406.
- 31. Langhorst J, Mueller T, Luedtke R, et al. Effects of a comprehensive lifestyle modification program on quality-of-life in patients with ulcerative colitis: a twelve-month follow-up. Scand J Gastroenterol. 2007;42(6):734-45.
- 32. Chicco F, Magrì S, Cingolani A, et al. Multidimensional Impact of Mediterranean Diet on IBD Patients. Inflamm Bowel Dis. 2021;27(1):1-9.
- 33. Klare P, Nigg J, Nold J, et al. The impact of a ten-week physical exercise program on health-related quality of life in patients with inflammatory bowel disease: a prospective randomized controlled trial. Digestion. 2015;91(3):239-47.
- 34. Ng V, Millard W, Lebrun C, Howard J. Low-intensity exercise improves quality of life in patients with Crohn's disease. Clin J Sport Med. 2007;17(5):384-8.
- 35. Bolte LA, Vich Vila A, Imhann F, et al. Long-term dietary patterns are associated with pro-inflammatory and anti-inflammatory features of the gut microbiome. Gut. 2021;70(7):1287-98.
- 36. 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. Inflamm Bowel Dis. 2021;27(2):190-202.
- 37. Voortman T, Kiefte-de Jong JC, Ikram MA, et al. Adherence to the 2015 Dutch dietary guidelines and risk of non-communicable diseases and mortality in the Rotterdam Study. Eur J Epidemiol. 2017;32(11):993-1005.
- 38. Lamers CR, de Roos NM, Koppelman LJM, et al. Patient experiences with the role of physical activity in inflammatory bowel disease: results from a survey and interviews. BMC Gastroenterology. 2021;21(1):172.
- 39. Ammar A, Brach M, Trabelsi K, et al. Effects of COVID-19 Home Confinement on Eating Behaviour and Physical Activity: Results of the ECLB-COVID19 International Online Survey. Nutrients. 2020;12(6).
- 40. Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373(9669):1083-96.
- 41. Lewis JD, Albenberg L, Lee D, et al. The Importance and Challenges of Dietary Intervention Trials for Inflammatory Bowel Disease. Inflamm Bowel Dis. 2017;23(2):181-91.

Supplementary Table 1. Estimated marginal means of outcomes at the various time points

	Baseline	1 month	3 months	6 months	p-value
Diet quality (<i>Fetscore</i> -FFQ)	94.4 ± 3.1	133.5 ± 3.1	132.9 ± 3.2	128.5 ± 3.2	<0.001
Physical activity (SQUASH)	8006 ± 936	7990 ± 936	8241 ± 949	7990 ± 949	0.98
Impact of disease on daily life (IBD-DI)	0.7 ± 1.6	3.7 ± 1.6	5.2 ± 1.7	5.9 ± 1.7	0.009
Clinical disease activity					
CD (P-HBI)	1.9 ± 0.6	1.6 ± 0.6	1.6 ± 0.7	2.8 ± 0.7	0.55
UC (P-SCCAI)	1.2 ± 0.4	0.7 ± 0.4	0.9 ± 0.4	0.7 ± 0.4	0.51
Fatigue (IBD-F)	20.1 ± 2.6	15.6 ± 2.6	13.2 ± 2.6	14.1 ± 2.6	0.001
Health-related quality of life (IBDQ)	192 ± 3.3	197 ± 3.3	197 ± 3.4	196 ± 3.4	0.37
Faecal calprotectin#	39.8 ± 21.5	-	53.0 ± 21.5	46.1 ± 21.5	0.69

Data are presented as estimated marginal mean ± standard error as derived from linear mixed model analysis with time as main fixed factor. Bold values are significant.

Impact of disease on daily life scores can range from -80 to +22: higher scores represent less disabilities and thus less impact of disease on daily life. Fatigue scores can range from 0 to 120. Health-related quality of life scores can range from 32 to 224.

Appendix 1

 $^{^{\#}}$ n = 24, statistical tests were performed on the log2 scale. Hereafter, data were back transformed for presentation in this table. Median faecal calprotectin: baseline 15 ug/g [IQR 5-42], 3 months 18 ug/g [IQR 8-31], 6 months 12 ug/g [IQR 4-54].



Chapter 6

Web-based dietary assessment and advice helps inflammatory bowel disease patients to improve their diet quality

Lamers CR*, van Erp LW*, Slotegraaf AI, Groenen MJM, de Roos NM, Wahab PJ*, Witteman BJM*
* Shared first author * Shared last author

Accepted for publication in British Journal of Nutrition

Abstract

Time to evaluate diet quality and give dietary advice is limited in clinical IBD practice. The *Eetscore* is a web-based tool that assesses diet quality according to the Dutch dietary guidelines and provides personalised dietary advice. We aimed to assess diet quality of IBD patients using the *Eetscore* and to study changes in diet quality, healthrelated quality of life (HROoL) and clinical disease activity over time. A prospective cohort study was performed in 195 adult IBD patients. Participants were invited to fill out questionnaires (Eetscore-FFQ, short IBDQ and p-HBI/p-SCCAI) at baseline and after 1 and 4 months. The Eetscore calculates diet quality based on 16 food components (10 points per component, total score 0-160; the higher the better) and provides dietary advice per component based on the assessment. At baseline, mean diet quality was 98±19. Diet quality was positively associated with age, female gender and level of education. Component scores were highest for red meat, wholegrain products, and sweetened beverages, and lowest for legumes, nuts, and processed meat. Over time, diet quality increased to 107±21 at 4 months (p<0.001). Each 10point improvement in diet quality was associated with an increase in HRQoL (β=0.4 (95%CI 0.02; 0.7), p=0.04). Clinical disease activity did not change. In conclusion, diet quality of IBD patients significantly improved following personalised dietary advice of the *Eetscore*. Improvement of diet quality was associated with a slight improvement in HROoL. The *Eetscore* is a practical and useful tool to monitor and support a healthy diet in IBD patients.

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD) with a complex aetiology including genetic, microbial, immune and environmental factors [1]. Increasing evidence suggests that a person's diet is an important environmental factor contributing to the development of IBD and its disease course [2]. Dietary components may influence the pathogenesis of IBD through their effects on the microbiome, mucosal barrier and immune response [2]. Although many IBD patients believe diet affects the course of their disease and is at least as important as medication in their IBD treatment, evidence supporting beneficial effects of specific dietary patterns in adult IBD patients is limited [3, 4].

Recently, the International Organization for the Study of Inflammatory Bowel Diseases attempted to establish a consensus document stating which foods may be either beneficial, harmful or safe to consume [5]. Due to lack of evidence, recommendations were limited but in line with the general guidelines for a healthy diet, such as to consume more fruit, vegetables and omega-3 fatty acids, and to consume less saturated, trans, and dairy fat and red and processed meat [5]. Therefore, general dietary quidelines may also be recommended to patients with IBD. In the Netherlands, the composition of a healthy diet is described by the Health Council in the Dutch dietary guidelines [6, 7]. These guidelines advise to adopt a more plant-based and less animal-based dietary pattern by eating sufficient fruit, vegetables, and wholegrain products, moderating the intake of meat, varying between fish, legumes, nuts and eggs and taking sufficient dairy products and fluids. In clinical practice, IBD patients are interested in the beneficial effects of diet on the course of their disease. However, time is limited to assess a patients' food intake and to support a healthy diet. It would be helpful if patients could assess their own diet quality and receive personal advice outside the consultation room.

A web-based tool that may be used to assess diet quality and to support a healthy diet is the *Eetscore* ("Eatscore") [8]. This is a validated tool to assess adherence to the Dutch dietary guidelines, i.e., diet quality [9]. Based on the assessment, the *Eetscore* provides personalised dietary advice to eat healthier and more in line with the Dutch dietary guidelines. It can also be used to monitor diet quality over time. So far, the *Eetscore* has only been used in healthy populations and cardiovascular disease patients, but not in IBD patients [10, 11].

We used the *Eetscore* tool to assess diet quality of IBD patients, to evaluate if diet quality improves after personalised dietary advice and to study factors associated with diet quality in IBD patients. In addition, we aimed to evaluate whether changes in diet quality resulted in changes in HRQoL and clinical disease activity. We also evaluated the experiences of IBD patients with the *Eetscore* tool.

Materials and Methods

Study population and design

A prospective cohort study was performed in adult IBD patients. Participants were recruited between October 2020 and February 2021 from the outpatient clinics of Hospital Gelderse Vallei in Ede and Rijnstate Hospital in Arnhem, the Netherlands. Both are secondary care referral centres, with IBD-dedicated gastroenterologists and nurses, and are collaborative partners of the Nutrition & Healthcare Alliance, an expert centre in nutrition and healthcare. Inclusion criteria were diagnosis of Crohn's disease (CD), ulcerative colitis (UC) or IBD-unclassified (IBD-U), 18 years of age or older, ability to read and understand the Dutch language, and access to an e-mail address and a device to complete the online questionnaires. Exclusion criteria were current dietary counselling by a dietician or lifestyle coach, allergy for nuts, peanuts, fish or cow's milk protein (to protect them from potential harmful recommendations to consume these products), adherence to a vegan lifestyle (to avoid invalid dietary assessment as the *Eetscore* does not assess plant-based alternatives) and participation in another intervention study. This study was approved by the Medical Ethical Committee of Wageningen University (METC nr. 20/16) and conducted in accordance with the Declaration of Helsinki and registered at trialregister.nl (NL8784). All participants provided written informed consent.

Data collection

After the informed consent form was signed, participants were invited via e-mail to complete questionnaires assessing diet quality, HRQoL and clinical disease activity. Participants that completed the baseline assessment were invited to complete the questionnaires again after 1 and 4 months. These timepoints were chosen to assess short-term changes in diet quality as well as to evaluate effects at longer term. At baseline, participants were also asked about their level of education, smoking behaviour, dietary restrictions, and height and weight. At 4 months, participants were also invited to complete an evaluation about the *Eetscore*. Non-responders were reminded 5, 10 and 15 days after each invitation.

Relevant participant and disease characteristics were retrieved from medical records, including age, gender, diagnosis, disease duration, disease phenotype according to the Montreal classification, extra-intestinal manifestations, IBD medication used and

IBD-related surgeries. The highest treatment step was documented, classified as 5-aminosalicylic acids, steroids, immunomodulators and biologics.

Eetscore

The *Eetscore* is a validated web-based tool that consists of: 1) a short Food Frequency Questionnaire assessing food intake (*Eetscore*-FFQ), 2) a diet quality score calculated by using the Dutch Healthy Diet 2015 (DHD15)-index, and 3) personalised dietary advice based on the assessment [8-10].

The *Eetscore*-FFQ assesses intake of the following 16 components: vegetables, fruit, wholegrain products, legumes, nuts, dairy, fish, tea, fats and oils, coffee, red meat, processed meat, sweetened beverages and fruit juices, alcohol, salt and unhealthy choices. Participants reported their intake frequency of each component during the past month ('never' to 'every day') together with portion size (standard and natural portions (e.g., piece of fruit) or commonly used household measures (e.g., spoons or cups). It takes approximately 10-15 minutes to complete the *Eetscore*-FFQ.

The DHD15-index is calculated based on a person's food intake as assessed by the *Eetscore*-FFQ. The criteria to calculate the DHD15-index have been described in detail elsewhere and are summarized in *Table 1* [9]. Components are categorised into five types: adequacy, ratio, optimum, qualitative and moderation component. Scores range from 0 to 10 points with cut-offs for each component based on the dietary guidelines (*Table 1*). In the total score all 16 components are combined, resulting in a score range of 0 to 160. Higher scores indicate better adherence to Dutch dietary guidelines.

The *Eetscore* tool provides personalised dietary advice every time the *Eetscore*-FFQ is completed and aims to improve a person's adherence to the Dutch dietary guidelines. The dietary advice is automatically personalised based on the calculated diet quality score and is provided per component. It consists of general healthy diet information and practical advice to improve the intake of each component. Participants are presented their total diet quality score (*Appendix 1 - Supplementary Figure 1*) and diet quality score per component together with dietary advice (*Appendix 1 - Supplementary Figure 2*). In addition, the tool presents an overview of results to monitor changes in diet quality over time.

Table 1. Cut-off and threshold values for calculation of the 16 components

	Component	Component type *	Dutch dietary guidelines 2015	Minimum score (= 0 points)	Maximum score (= 10 points)
<u></u>	Vegetables	∢	Eat at least 200g of vegetables daily	0 g/day	≥ 200 g/day
5.	Fruit	∢	Eat at least 200g of fruit daily	0 g/day	≥ 200 g/day
ĸ;	Wholegrain products	∢	Eat at least 90g of wholegrain products daily	0 g/day	≥ 90 g/day
	-	œ	Replace refined cereal products by wholegrain products	No consumption of wholegrain products or ratio of whole grains to refined grains ≤0.7	No consumption of refined products <u>or</u> ratio of whole grains to refined grains ≥11
4.	Legumes	∢	Eat legumes daily	0 g/day	≥ 10 g/day
.5	Nuts	∢	Eat at least 15g of unsalted nuts daily	0 g/day	≥ 15 g/day
9	Dairy	0	Eat a few portions of dairy products daily, including milk or yogurt	0 g/day <u>or</u> ≥ 750 g/day	300-450 g/day
7.	Fish	∢	Eat one serving of fish weekly, preferably oily fish	0 g/day	≥ 15 g/day
ω ં	Теа	∢	Drink three cups of black or green tea daily	0 g/day	≥ 450 mL/day
ത്	Fats and oils	ď	Replace butter, hard margarines and cooking fats by soft margarines, liquid cooking fats and vegetable oils	No consumption of soft margarines, liquid cooking fats and vegetable oils or ratio of liquid cooking fats to solid cooking fats ≤0.6	No consumption of butter, hard margarines and cooking fats <u>or</u> ratio of liquid cooking fats to solid cooking fats ≥ 13
10.	Coffee	Ø	Replace unfiltered coffee by filtered coffee	Any consumption of unfiltered coffee	Consumption of only filtered coffee OR No coffee consumption

Tab	Table 1. Continued				
	Component	Component type *	Dutch dietary guidelines 2015	Minimum score (= 0 points)	Maximum score (= 10 points)
<u>–</u>	Red meat	Σ	Limit consumption of red meat	≥ 100 g/day	≤ 45 g/day
15.	Processed meat	Σ	Limit consumption of processed meat	≥ 50 g/day	0 g/day
13.	Sweetened beverages and fruit juices	Σ	Limit consumption of sweetened beverages and fruit juices	≥ 250 g/day	0 g/day
4.	Alcohol	Σ	If alcohol is consumed at all, intake should be limited to one Dutch unit	Women: ≥ 20 g ethanol/day Men: ≥ 30 g ethanol/day	Women: ≤ 10 g ethanol/day Men: ≤ 10 g ethanol/day
15.	Salt	Σ	Limit consumption of table salt to 6g daily	≥ 3.8 g Na/day	≤ 1.9 g Na/day
16.	Unhealthy choices⁺	Σ	Limit consumption of unhealthy day and week choices	> 7 choices/week	≤ 3 choices/week

* A, adequacy component (minimum consumption); R, ratio component (replace products by more healthy alternatives); O, optimum component (optimal consumption range); Q, qualitative component (choose healthier option); M, moderation component (limit consumption). † For example: sweet spreads, cakes, cookies, chips or pretzels, savoury snacks and sauces.

Health-related quality of life

Health-related quality of life (HRQoL) was assessed with the validated short inflammatory bowel disease questionnaire (SIBDQ). It consists of 10 items each with a 7-point Likert scale resulting in a possible score range of 10-70. Higher scores indicate better HRQoL [12].

Clinical disease activity

Clinical disease activity was assessed with the Patient Harvey Bradshaw Index (P-HBI) for participants with CD and the Patient Simple Clinical Colitis Activity Index (P-SCCAI) for participants with UC and IBD-U [13, 14]. Clinical remission was defined as a P-HBI score ≤ 4 and a P-SCCAI score ≤ 2 [15, 16].

Evaluation

Participants' experiences with the *Eetscore* tool were evaluated with a self-composed evaluation consisting of questions about the *Eetscore-*FFQ and the personalised dietary advice.

Statistical analysis

Participants that completed baseline and at least one follow-up assessment were included in the analysis. Normally distributed data are presented as mean \pm standard deviation (SD), skewed data as median with interquartile range (IQR) and categorical data as counts and percentages.

Linear mixed models were performed to assess changes in diet quality within subjects over time (fixed main factor) and to account for missing values. Baseline values were used as reference. If effect of time was significant, pairwise comparisons between the different time points were conducted with Bonferroni correction to adjust for multiple comparisons.

Multivariate linear regression analysis was performed to identify factors associated with diet quality at baseline. First, the following variables were evaluated in univariable analysis: age, gender, BMI, level of education, smoking behaviour, diagnosis, disease duration and clinical disease activity. Factors with a p-value < 0.2 in the univariable analysis, and BMI and clinical disease activity were included in the multivariable analysis. Linear mixed models were performed to identify factors

associated with diet quality over time with an identity covariance structure and indicating time as repeated measure. Diet quality was the dependent variable and the same variables as in the regression analysis were added as fixed main effects to the model

Linear mixed models were performed to assess changes in HRQoL and clinical disease activity within subjects over time (fixed main factor) and to account for missing values. Pairwise comparisons were performed similar to the analysis of diet quality. If HRQoL or clinical disease activity significantly changed over time, further linear mixed model analyses were performed to assess if those changes resulted from changes in diet quality (main fixed covariate) with an identity covariance structure and indicating time as repeated measure. After univariate analysis, the following variables were evaluated as fixed main effects: age, gender, BMI, level of education, biologics as highest step-up in IBD medication and clinical disease activity. Variables with a p-value < 0.2 were included in the multivariable analysis.

Linear mixed model data are reported as fixed effect estimates with 95% confidence intervals. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 25.0.

Results

In this study, 212 participants were invited for baseline questionnaires (*Figure 1*). Participants that completed the baseline questionnaires (n = 204) were invited for follow-up assessments after 1 and 4 months. In total, 195 participants completed at least one follow-up assessment and were included in the analysis.

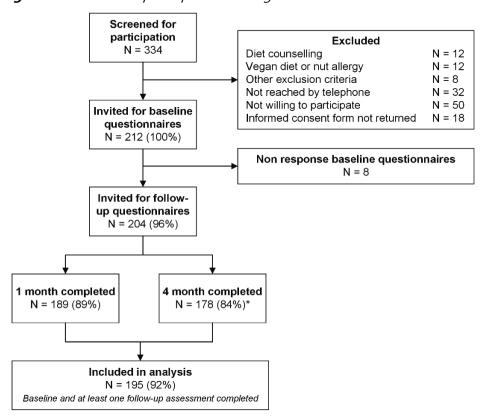


Figure 1. Flowchart of participant screening and inclusion

Of the 195 participants, 60% was female, median age was 47 years [IQR 32 - 57] and BMI 25 kg/m² [IQR 22 - 28] (*Table 2*). The non-responders (n = 17) were slightly different in terms of gender (41% female) and age (37 years [27 - 47]) while BMI was comparable. Median disease duration of participants was 10 years [IQR 4 - 18] and half of the participants had Crohn's disease. At baseline, 77% of participants used IBD medication and 72% was in clinical remission. In their habitual diet, 28% of participants applied certain dietary restrictions. Most common restrictions were

^{*} At 4-month follow-up, 180 participants completed the evaluation about the *Eetscore*.

exclusion or limitation of meat and lactose products. Other frequently mentioned restrictions were exclusion or limitation of gluten, carbohydrates, added sugar and ultra-processed food products.

Table 2. Participant characteristics of the total study population

,	, , ,
	n = 195
Female	117 (60)
Age: years, median (IQR)	47 (32 – 57)
BMI: kg/m², median (IQR)	25 (22 – 28)
Level of education*	
Low	41 (21)
Middle	71 (36)
High	83 (44)
Currently smoking	17 (8.7)
Diagnosis	
Crohn's disease (CD)	97 (50)
Ulcerative colitis (UC)	89 (46)
IBD-unclassified (IBD-U)	9 (4.6)
Disease duration: years, median (IQR)	10 (3.6 – 18)
Age at diagnosis CD	
A1 ≤ 16 years	9 (9.3)
A2 17 – 40 years	62 (64)
A3 > 40 years	26 (27)
Disease localisation CD	
L1 Terminal ileum	25 (26)
L2 Colon	23 (24)
L3 Ileocolon	48 (49)
L4 Upper gastrointestinal	1 (1.0)
Disease behaviour CD	
B1 Non-stricturing, non-penetrating	65 (67)
B2 Stricturing, non-penetrating	25 (26)
B3 Stricturing, penetrating	7 (7.2)
Perianal disease CD	19 (20)

Table 2. Continued

	n = 195
Disease extent UC and IBD-U	
E1 Ulcerative proctitis	11 (11)
E2 Left-sided distal colitis	38 (39)
E3 Extensive pancolitis	49 (50)
Extra-intestinal manifestations	33 (17)
IBD medication currently used [†]	
None	44 (23)
5-aminosalicylic acid	71 (36)
Steroids	31 (16)
Immunomodulators	52 (27)
Biologics	58 (30)
Highest step up in IBD medication	
5-aminosalicylic acid	22 (11)
Steroids	31 (16)
Immunomodulators	58 (30)
Biologics	83 (43)
Prior IBD-related surgery	34 (17)
Clinical disease activity [‡]	
Remission	140 (72)
Active disease	55 (28)
Dietary restrictions [†]	53 (27)
Vegetarian or limited meat intake	20 (10)
Gluten-free or limited gluten intake	5 (2.6)
Lactose-free or limited lactose intake	14 (7.2)
Low in carbohydrates	5 (2.6)
Other	16 (8.2)

Values expressed as number (%), unless stated otherwise. * Level of education: no education, primary or lower vocational education and lower general secondary education (low); secondary vocational education and higher general secondary education (intermediate); higher vocational education and university (high). † Multiple options possible per participant. † Defined by Patient Harvey Bradshaw Index ≤ 4 or Patient Simple Clinical Colitis Activity Index ≤ 2 and expressed as number (%).

Mean diet quality at baseline was 98 \pm 19 points out of 160 points. Component scores were highest for red meat, alcohol, salt, sweetened beverages, and wholegrain products, suggesting that the intake of these food groups was (almost) in line with dietary recommendations (*Figure 2*). Component scores were lowest for legumes, nuts, processed meat, and unhealthy choices. Median intake per food component in grams per day is described in *Supplementary Table 1 (Appendix 2)*. As reflected in diet quality scores, participants' median intake of vegetables, fruit, legumes, nuts, dairy and fish was lower than recommended, while the median intake of processed meat was higher than recommended.

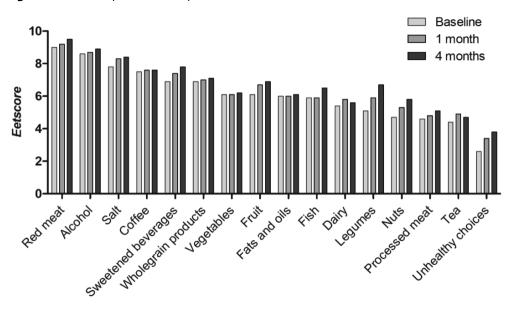


Figure 2. Eetscore per food component at baseline, 1 month and 4 months

After using the *Eetscore*, diet quality increased to 103 ± 21 points after 1 month and 107 ± 21 after 4 months (*Table 3*). This increase was significant between baseline and 1 month (p < 0.001), baseline and 4 months (p < 0.001) and 1 month and 4 months (p = 0.005). Biggest improvements were seen in legumes, unhealthy choices, nuts and sweetened beverages (*Figure 2*).

Diet quality at baseline was positively associated with age, female gender and level of education (*Table 4*). For example, each 10-year increase in age was associated with a 3-point higher diet quality. The same factors were positively associated with diet 142

quality over time. BMI and clinical disease activity were not associated with diet quality.

At baseline, median HRQoL was 54 [IQR 46 – 61] points (*Table 3*). HRQoL of participants significantly increased during the study. This increase was only significant between baseline and 1 month (p < 0.001). At baseline, median P-HBI was 2.5 [1.0 - 4.3] points and median P-SCCAI was 1.0 [0.0 - 3.0] points. Clinical disease activity did not change during the study.

Table 3. Diet quality, health-related quality of life and clinical disease activity at baseline, 1 month and 4 months

	Baseline n = 195	1 month n = 189	4 months n = 178	p-value
Diet quality *	98 ± 19	103 ± 21	107 ± 21	< 0.001
Health-related quality of life #	54 [46 – 61]	56 [48 – 62]	56 [45 – 62]	0.001
Clinical disease activity †				
Crohn's disease	2.5 [1.0 - 4.3]	3.0 [1.0 - 5.0]	3.0 [1.0 - 5.0]	0.878
Ulcerative colitis and IBD-U	1.0 [0.0 - 3.0]	1.0 [0.0 - 2.8]	1.0 [0.0 - 3.0]	0.133

Bold values are significant. * Total mean ± SD Eetscore. * Total median [IQR] short Inflammatory Bowel Disease Questionnaire score. † Total median [IQR] Patient Harvey Bradshaw Index for Crohn's disease and Patient Simple Clinical Colitis Activity Index for ulcerative colitis and IBD-U.

Table 4. Factors associated with diet quality at baseline and with change in diet quality over time

	Diet quality at baseline			Diet quality over time		ime
Variable *	β	95%CI	p-value	β	95%CI	p-value
Age (<i>in years</i>)	0.31	0.12; 0.50	0.001	0.34	0.16; 0.52	< 0.001
Female gender (vs. male)	9.30	4.04; 14.57	0.001	9.33	4.23; 14.43	< 0.001
BMI (<i>kg/m</i> ²)	-0.28	-0.85; 0.29	0.34	-0.41	-0.96; 0.14	0.15
Intermediate level of education (vs. low)	9.05	1.78; 16.31	0.015	9.63	2.60; 16.66	0.008
High level of education (vs. low)	13.70	6.59; 20.82	< 0.001	15.73	8.84; 22.62	< 0.001
Clinically active disease (vs. clinical remission)	-1.21	-7.03; 4.62	0.68	-1.46	-4.52; 1.61	0.35

Bold values are significant. $R^2 = 15\%$ for diet quality at baseline. * Smoking behaviour, diagnosis and disease duration were not associated with diet quality in univariable analysis and therefore not included in the multivariable model.

Linear mixed model analysis showed that each 10-point improvement in diet quality was associated with a 0.5-point increase in HRQoL over time (β = 0.5, 95%CI 0.1; 0.9, p = 0.007). This association remained statistically significant in the multivariate model adjusting for age, gender, BMI, clinical disease activity and previous or current use of biologics with each 10-point increase in diet quality resulting in a 0.4-point increase in HRQoL (β = 0.4, 95%CI 0.02; 0.7, p = 0.04) (*Appendix 2 - Supplementary Table 2*).

After the last assessment at 4 months, 180 participants completed an evaluation about the *Eetscore* tool (*Figure 3*). Of these participants, 23% reported the *Eetscore*-FFQ lacked regularly consumed food components such as eggs, and lactose-free and soy products. Also, 55% did not eat or drink all food components of the *Eetscore*-FFQ given allergies, intolerances or dietary restrictions (28%), personal taste (52%) or gastro-intestinal symptoms (40%). Almost all participants (96%, n = 173) had reviewed their *Eetscore* results of which 92% believed these results gave insight into how healthy their intake was per food component.

Most participants (93%, n = 167) had reviewed the personalised dietary advice of the *Eetscore* (*Figure 3*). After reviewing their dietary advice, 96% of participants knew what to do to eat healthier. Although the primary aim of the advice was to improve diet quality, 47% of participants also believed to know what to do to have less gastro-intestinal symptoms. Putting the dietary advice into practice helped 35% of participants to have less symptoms. To eat healthier, 65% would like to receive additional information such as practical advice with examples (22%), healthy recipes (35%), explanation about why certain food is healthy (23%) or information about portion sizes (19%).

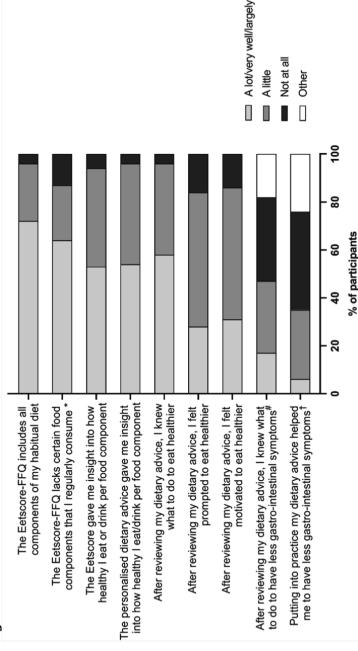


Figure 3. Evaluation of the Eetscore tool

Different answer options: A lot/very well/largely = No, A little = Yes and Not at all = I am not sure. # Most common reason s for choosing 'other' were not having gastro-intestinal symptoms during the study, already knowing what to do to have less symptoms or experiencing the advice as too general. † Most common reasons for choosing 'other' were not having gastro-intestinal symptoms during the study, not implementing the dietary advice yet or not experiencing an association between diet and gastro-intestinal symptoms in general.

Discussion

In this study, we used the web-based *Eetscore* tool to assess diet quality of IBD patients and to provide personalised dietary advice supporting a healthy diet. At baseline, intake of red meat, wholegrain products and sweetened beverages was close to the Dutch dietary guidelines, while intake of dairy, legumes, nuts and processed meat was not. Diet quality significantly improved following personalised dietary advice. IBD patients who were older, female, and higher educated had a better diet quality over time. Improvement of diet quality was associated with a small improvement in HRQoL. Clinical disease activity did not change. The *Eetscore* can provide IBD patients insight into how healthy their habitual diet is and what to do to better adhere to the Dutch dietary quidelines.

To date, the current *Eetscore*-FFQ has only been used once in a general, healthy population cohort of 751 Dutch participants [10]. Compared to this general cohort, diet quality was lower in our IBD cohort (mean 98 ± 19 vs. 111 ± 18) with lower scores on fruit, legumes, processed meat, sweetened beverages and unhealthy choices. This may be explained by differences in characteristics of the study populations. Many of their participants were highly educated (65%), few smoked (6%) and few were overweight or obese (27% and 8%) indicating a health-conscious population. In line with our study, older age, female gender and higher level of education were positively associated with diet quality [10]. Using the web-based *Eetscore*, diet quality of participants improved by 10-points (i.e., 6% out of a maximum of 160 points). This better adherence to the Dutch dietary guidelines has been associated with a lower all-cause mortality and a reduction in the risk of stroke, depression and colorectal cancer [17].

Consistent with our findings, previous studies in IBD patients also reported a consumption of dairy and nuts [18-20] below the recommendations, an overconsumption of processed meat and an adequate consumption of red meat [18]. In contrast to our results, previous studies in IBD patients indicate a sufficient intake of legumes [18, 19]. IBD patients often avoid lactose products and legumes as they believe this prevents abdominal pain, bloating and disease flares, which may explain the low dairy and legume intake [3, 21]. In our study, 7% of participants reported to consume little or no lactose products and while they may have compensated for this with alternatives such as soy milk, this cannot be entered in the *Eetscore*-FFQ. The

reason for a nut consumption below the recommendations is unclear. In our study, participants did not report specific reasons for avoiding nuts and those allergic to nuts were excluded

A recent study showed that long-term dietary patterns enriched with legumes, vegetables, fruits and nuts, more plant-based instead of animal-based products, and avoidance of alcoholic beverages, high-fat processed meats and soft drinks have the potential to prevent intestinal inflammatory processes via the gut microbiome [22]. This potentially favourable dietary pattern for IBD patients is in line with the Dutch dietary guidelines and the *Eetscore* can provide insight in adherence to these guidelines. Moreover, IBD patients consider dietary guidance to be important, while only a minority feels to have received adequate information from their physician [23]. The *Eetscore* can fulfil this need for dietary guidance of IBD patients.

Several studies investigated dietary patterns and their association with HRQoL and clinical disease activity [18, 24, 25]. A Western dietary pattern characterized by the intake of refined grains, red and processed meat, condiments and sauces, and unhealthy choices was associated with flare occurrence [18], while adherence to a Mediterranean dietary pattern characterized by a high consumption of vegetables, fruit, wholegrains and nuts, and a low consumption of red and processed meat and processed foods was associated with a higher HRQoL and lower disease activity [24, 25]. Our observations support that better adherence to the Dutch dietary guidelines, which share characteristics with the Mediterranean diet, is associated with improved HRQoL. In contrast to previous studies, we did not find an association between diet quality and clinical disease activity. This might be explained by the relatively short follow-up time and low number of participants with clinically active disease.

Relatively few participants reported that use of the *Eetscore* tool helped to reduce their gastro-intestinal symptoms. During this study, the majority of participants did not experience gastro-intestinal symptoms. Besides, many participants commented to already know very well which foods work best for them to reduce or prevent gastro-intestinal symptoms after several years of living with IBD. Also, the *Eetscore* tool is not designed to help reduce gastro-intestinal symptoms. For example, IBD patients often avoid certain food components because of abdominal complaints and the *Eetscore* does not provide alternatives (e.g., for dairy products or legumes) [26].

Dietary advice of the *Eetscore* may be optimized for IBD patients by suggesting alternative products to achieve a better diet quality while limiting abdominal complaints.

Main strength of this study is its prospective nature with repeated dietary assessment and advice in a clinical setting using the *Eetscore*. In addition, the *Eetscore* is a guick and easy tool to assess diet quality compared to commonly used extensive FFO's. Besides, we included a large, representative cohort of IBD patients with varying ages and different disease phenotypes. Finally, the response rate was very high (92%) thereby limiting the risk of non-response bias. However, this study was limited by the absence of a control group. Therefore, we cannot conclude whether diet quality improved as a result of the personalised dietary advice of the *Eetscore* or as a result of increased dietary awareness. In line with this, studies on lifestyle factors are prone to socially desirable answers, which may have led to an overestimation of diet quality. However, participation was anonymous and results were not shared with participants' gastroenterologist or IBD nurse. Also, completing the *Eetscore* several times may have induced a learning curve with participants being aware of the correct answers when completing the *Eetscore* for the second or third time. However, a previous study showed no change in diet quality when the *Eetscore*-FFO was completed twice within four months in the absence of dietary advice [10]. Additionally, memory bias and estimation error may have occurred as these are inherent to using food frequency questionnaires [27]. Lastly, the *Eetscore*-FFO covers approximately 85% of dietary intake, is based on regularly consumed food products and does therefore not assess plant-based alternatives of meat and dairy [8, 9].

In conclusion, web-based dietary assessment and advice helps IBD patients to improve their diet quality. The *Eetscore* tool is easy to use, gives practical insight into dietary intake and supports a healthy diet in IBD patients. It may be further optimized by adding healthy alternatives for food products that are commonly avoided by IBD patients.

Acknowledgments

The authors would like to thank all participants for taking part in this study.

Funding

This study was initiated by members of the Nutrition and Healthcare Alliance and financially supported through a grant of the Ministry of Health [nr. 329105] received by the Alliance.

References

- 1. Chang JT. Pathophysiology of Inflammatory Bowel Diseases. N Engl J Med. 2020;383(27):2652-64.
- 2. Wark G, Samocha-Bonet D, Ghaly S, Danta M. The Role of Diet in the Pathogenesis and Management of Inflammatory Bowel Disease: A Review. Nutrients. 2020;13(1).
- 3. de Vries JHM, Dijkhuizen M, Tap P, Witteman BJM. Patient's Dietary Beliefs and Behaviours in Inflammatory Bowel Disease. Dig Dis. 2019;37(2):131-9.
- 4. Sasson AN, Ananthakrishnan AN, Raman M. Diet in Treatment of Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol. 2021;19(3):425-35.e3.
- 5. 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):1381-92.
- 6. Health Council of the Netherlands. Dutch dietary guidelines 2015. 2015:1-95.
- 7. Kromhout D, Spaaij CJ, de Goede J, Weggemans RM. The 2015 Dutch food-based dietary quidelines. Eur J Clin Nutr. 2016;70(8):869-78.
- 8. van Lee L, Feskens EJ, Meijboom S, et al. Evaluation of a screener to assess diet quality in the Netherlands. Br J Nutr. 2016;115(3):517-26.
- 9. Looman M, Feskens EJ, de Rijk M, et al. Development and evaluation of the Dutch Healthy Diet index 2015. Public Health Nutr. 2017;20(13):2289-99.
- 10. de Rijk MG, Slotegraaf AI, Brouwer-Brolsma EM, et al. Development and evaluation of a diet quality screener to assess adherence to the Dutch food-based dietary guidelines. Br J Nutr. 2021:1-11.
- 11. van der Haar S, Hoevenaars FPM, van den Brink WJ, et al. Exploring the Potential of Personalized Dietary Advice for Health Improvement in Motivated Individuals With Premetabolic Syndrome: Pretest-Posttest Study. JMIR Form Res. 2021;5(6):e25043.
- 12. Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. Am J Gastroenterol. 1996;91(8):1571-8.
- 13. Bennebroek Evertsz F, Hoeks CC, Nieuwkerk PT, et al. Development of the patient Harvey Bradshaw index and a comparison with a clinician-based Harvey Bradshaw index assessment of Crohn's disease activity. J Clin Gastroenterol. 2013;47(10):850-6.
- 14. Bennebroek Evertsz F, Nieuwkerk PT, Stokkers PC, et al. The patient simple clinical colitis activity index (P-SCCAI) can detect ulcerative colitis (UC) disease activity in remission: a comparison of the P-SCCAI with clinician-based SCCAI and biological markers. J Crohns Colitis. 2013;7(11):890-900.
- 15. Best WR. Predicting the Crohn's disease activity index from the Harvey-Bradshaw Index. Inflamm Bowel Dis. 2006;12(4):304-10.

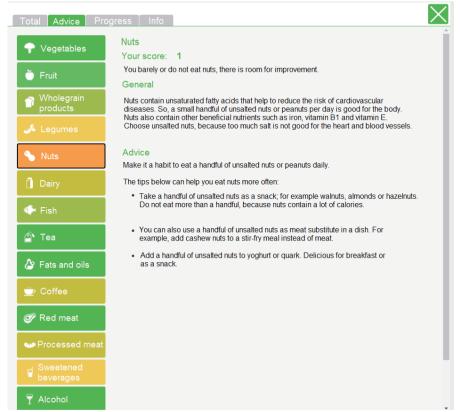
- 16. Turner D, Seow CH, Greenberg GR, et al. A systematic prospective comparison of noninvasive disease activity indices in ulcerative colitis. Clin Gastroenterol Hepatol. 2009;7(10):1081-8.
- 17. Voortman T, Kiefte-de Jong JC, Ikram MA, et al. Adherence to the 2015 Dutch dietary guidelines and risk of non-communicable diseases and mortality in the Rotterdam Study. Eur J Epidemiol. 2017;32(11):993-1005.
- 18. Peters V, Spooren C, Pierik MJ, et al. Dietary Intake Pattern is Associated with Occurrence of Flares in IBD Patients. J Crohns Colitis. 2021;15(8):1305-15.
- 19. Peters V, Tigchelaar-Feenstra EF, Imhann F, et al. Habitual dietary intake of IBD patients differs from population controls: a case-control study. Eur J Nutr. 2021;60(1):345-56.
- 20. Opstelten JL, de Vries JHM, Wools A, et al. Dietary intake of patients with inflammatory bowel disease: A comparison with individuals from a general population and associations with relapse. Clin Nutr. 2019;38(4):1892-8.
- 21. Casanova MJ, Chaparro M, Molina B, et al. Prevalence of Malnutrition and Nutritional Characteristics of Patients With Inflammatory Bowel Disease. J Crohns Colitis. 2017;11(12):1430-9.
- 22. Bolte LA, Vich Vila A, Imhann F, et al. Long-term dietary patterns are associated with pro-inflammatory and anti-inflammatory features of the gut microbiome. Gut. 2021;70(7):1287-98.
- 23. Wong S, Walker JR, Carr R, et al. The information needs and preferences of persons with longstanding inflammatory bowel disease. Can J Gastroenterol. 2012;26(8):525-31.
- 24. Papada E, Amerikanou C, Forbes A, Kaliora AC. Adherence to Mediterranean diet in Crohn's disease. Eur J Nutr. 2020;59(3):1115-21.
- 25. Chicco F, Magrì S, Cingolani A, et al. Multidimensional Impact of Mediterranean Diet on IBD Patients. Inflamm Bowel Dis. 2021;27(1):1-9.
- 26. Day AS, Yao CK, Costello SP, et al. 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.
- 27. Lewis JD, Albenberg L, Lee D, et al. The Importance and Challenges of Dietary Intervention Trials for Inflammatory Bowel Disease. Inflamm Bowel Dis. 2017;23(2):181-91.

Appendix 1 – Supplementary figures

Supplementary Figure 1. Diet quality score of an individual participant as shown in the Fetscore tool



Supplementary Figure 2. Personalised dietary advice of an individual participant as shown in the Eetscore tool



Appendix 2 - Supplementary tables

Supplementary Table 1. Intake of relevant food components in grams per day

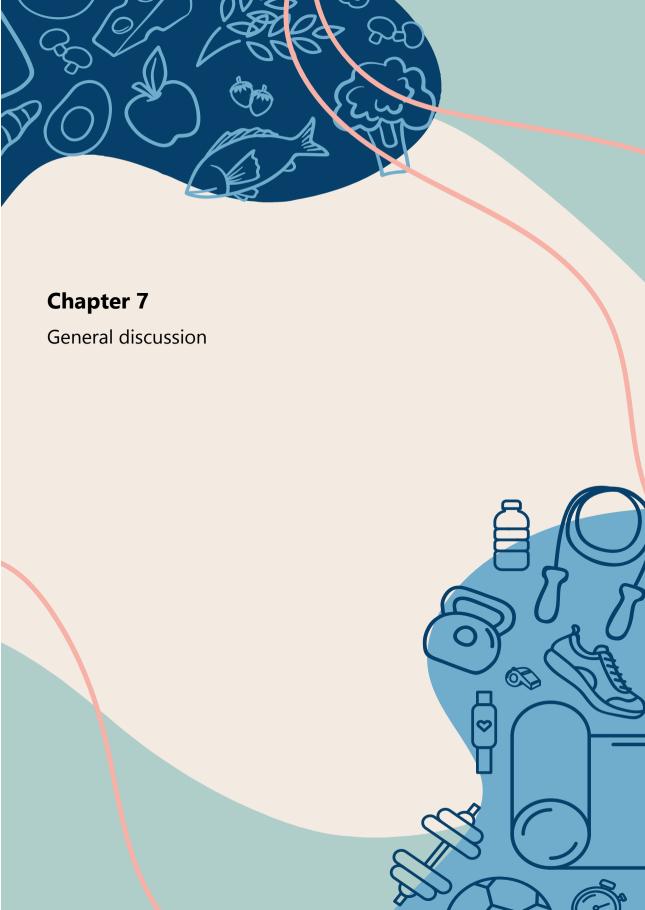
	Intake at baseline n = 195	Recommended intake
Vegetables	126 [72 – 183] g/day	≥ 200 g/day
Fruit	139 [59 – 176] g/day	≥ 200 g/day
Wholegrain products	129 [87 – 189] g/day	≥ 90 g/day
Legumes	4.4 [0.0 – 17] g/day	≥ 10 g/day
Nuts	4.3 [1.4 – 16] g/day	≥ 15 g/day
Dairy*	169 [84 – 316] g/day	300-450 g/day
Fish	9.6 [5.8 – 15] g/day	≥ 15 g/day
Red meat	22 [7.2 – 43] g/day	≤ 45 g/day
Processed meat	25 [9.5 – 49] g/day	0 g/day

Values expressed as median [IQR]. *Including milk, yoghurt and cheese products.

Supplementary Table 2. Factors associated with change in health-related quality of life over time

Variable *	β	95% CI	p-value
Diet quality (total <i>Eetscore</i>)	0.04	0.002; 0.07	0.04
Age (<i>in years</i>)	0.09	0.01; 0.17	0.02
Female gender <i>(vs. male)</i>	- 2.79	- 5.02; - 0.56	0.02
BMI (<i>kg/m</i> ²)	- 0.43	- 0.67; - 0.19	< 0.001
Biologics as highest step-up	- 1.28	- 3.51; 0.95	0.26
Clinically active disease (vs. clinical remission)	- 6.58	- 5.85; - 5.32	< 0.001

Bold values are significant. * Level of education was not associated with health-related quality of life in univariable analysis and therefore not included in the multivariable model.



Besides medication, diet and physical activity can be complementary therapies in the treatment of IBD. However, implementing these lifestyle factors in a patient's daily routine requires sustained changes in habits which may not be easy. Moreover, diets and physical activity programs can deviate greatly from the usual, especially when special foods or supplements are advised, making integration in social life and adherence in the long-term difficult. With sustainable and feasible recommendations based on the Dutch dietary and physical activity guidelines, adherence should be easier. Besides, special guidelines can make patients feel isolated whereas following general guidelines might make them feel less like a patient. Moreover, following these recommendations might also lead to an improved well-being of IBD patients, exert positive effects on the disease course and decrease their risk of other (chronic) diseases.

All currently available evidence regarding beneficial effects of nutrients and physical activity in IBD is in line with the Dutch guidelines for a healthy diet and physical activity, suggesting that disease-specific guidelines might not be necessary. However, these Dutch guidelines have not been investigated in IBD yet. Therefore, the aim of this thesis was to investigate the health effects of the Dutch dietary and physical activity guidelines as part of treatment in IBD patients.

Main findings

We found that the inflammatory potential of the diet and level of physical activity are associated with disease activity in CD patients, while no associations were found in UC patients (**Chapter 2 and 3**). Besides, moderate intensity physical activity does not appear to have harmful effects on IBD and can be safely performed (**Chapter 4**). When applying the Dutch dietary and physical activity guidelines, impact of disease on daily life and fatigue decreased; likely as a result of a substantial improvement in diet quality (**Chapter 5**). Also, when informing patients about the Dutch dietary guidelines via web-based dietary assessment and advice, diet quality improved (**Chapter 6**). A more detailed overview of the main findings of this thesis can be found in the table on the next page.

Overview	Overview of the main findings of this thesis per chapter					
Chapter	Study population	Methods	Main findings			
2	CD/UC patients with varying disease status (n=329)	Survey • FFQ → Dietary Inflammatory Index • sCDAI / P-SCCAI	 Inflammatory potential of diet was associated with clinical disease activity in CD No association in UC 			
3	CD/UC patients with varying disease status (n=338 / n=14)	Survey • SQUASH • sCDAI / P-SCCAI Interviews	 Level of physical activity was inversely associated with clinical disease activity in CD No association in UC Beneficial effects experienced from physical activity Barriers caused by active disease put off to be physically active 			
4	CD/UC patients with varying disease status (n=37) / Controls without IBD (n=19)	Observational study	 Similar cytokine responses to repeated prolonged moderate-intensity walking exercise in CD/UC patients and controls without IBD No change in faecal calprotectin Slight increase in clinical disease activity in CD, no change in UC 			
5	CD/UC patients in remission or with mildly active disease (n=27)	Intervention study • IBD-DI • P-HBI / P-SCCAI • IBDQ • IBD-F • Faecal calprotectin	 Lifestyle intervention improved diet quality, level of physical activity remained the same Improved diet quality was associated with reduced impact of disease on daily life and fatigue No change in clinical disease activity, HRQoL and faecal calprotectin 			

6	CD/UC/IBD-U	Intervention study	Diet quality improved with
	patients with	• Eetscore	web-based dietary
	varying disease	• P-HBI / P-SCCAI	assessment and advice
	status (n=195)	• Short IBDQ	Improved diet quality was
			associated with slight
			improvement in HRQoL
			No change in clinical disease
			activity

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis; FFQ, food frequency questionnaire; sCDAI, short Crohn's Activity Index; P-SCCAI, Patient Simple Clinical Colitis Activity Index; SQUASH, Short Questionnaire to Assess Health-enhancing physical activity; P-HBI, Patient Harvey Bradshaw Index; IBD-DI, IBD disability index; IBDQ, Inflammatory Bowel Disease Questionnaire; IBD-F, Inflammatory Bowel Disease fatique patient self-assessment scale; HRQOL, health-related quality of life.

Dutch dietary and physical activity guidelines in IBD

Nowadays, plenty of information on lifestyle in IBD is available online, especially regarding diet. Since lifestyle information was regarded as the least adequately addressed by health care professionals [1], IBD patients searching the internet for information is a logical consequence. Based on online non-scientific information, several special diets are claimed to cure IBD, and different supplements like vitamins, herbs, and pre- and probiotics, are advocated to further support a healthy life. With all these exciting and special recommendations, IBD patients might feel not to be taken seriously by their health care professionals when they provide them with the Dutch dietary and physical activity quidelines. However, we found that lifestyle advice according to these guidelines can benefit IBD patients by reducing impact of disease on daily life and fatique (Chapter 5). Moreover, the Dutch dietary guidelines are in line with the recently published dietary recommendations of the International Organization of IBD [2]. As shown in a recent systematic review and meta-analysis, adherence of IBD patients to basic healthy eating guidelines is suboptimal [3]. Moreover, the majority of IBD patients do not engage in physical activity at the generally recommended level [4]. An unhealthy lifestyle can sustain a symptom like fatigue that commonly remains despite being in remission with medication, and results in a decreased quality of life and impaired work productivity [5]. Before applying additional interventions, it seems important to pay attention to the general lifestyle basics.

We found the intake of vegetables, fruit, legumes, nuts, dairy and fish to be below the recommendations (**Chapter 6**), which is in line with previous studies in which they found that IBD patients seem to have a poorer dietary intake compared with healthy individuals [3]. Generally, energy and fibre intake are inadequate, and also the intake of micronutrients like fat-soluble vitamins, folate, calcium and potassium is frequently suboptimal or inadequate. This is probably caused by an inadequate intake of major food groups such as dairy, legumes and nuts (**Chapter 6**) [3], which is likely the result of self-imposed food restrictions [6]. The majority of IBD patients has such restrictions as they believe some foods can worsen or induce symptoms or even relapse [6, 7]. Most common restrictions are avoidance of lactose containing products, gluten and added sugar (**Chapter 2 and 6**). However, as these restrictions can result in a poorer dietary intake causing nutritional deficiencies, it may become

It is the job of health care professionals to inform patients about the sense and nonsense of information on the internet and to make them aware of the possible detrimental effects of applying online lifestyle information. Instead of just stating that all information on the internet is bad, health care professionals should discuss lifestyle with their patients and focus on the similarities between information on the internet and the general Dutch guidelines. A good example in this respect is the Mediterranean diet. This diet is considered to be a dietary option for IBD patients, according to research as well as IBD patients themselves [8-10]. The Mediterranean diet is frequently referred to as an anti-inflammatory diet, amongst others because of its ability to improve the diversity of the gut microbiota and thereby to increase the production of short-chain fatty acids (SCFAs) [11]. The anti-inflammatory potential of the Mediterranean diet is confirmed when calculating the Dietary Inflammatory Index (DII) [12]. Intake of foods high in fibre, vitamin A, B3, C, E, magnesium, and poly-unsaturated fatty acids, mainly n-3 fatty acids, characteristics of a Mediterranean diet, results in a more anti-inflammatory DII score [12]. The Dutch dietary quidelines share a lot of characteristics with the Mediterranean diet with a high consumption of vegetables, fruits, legumes, and nuts, a moderate consumption of fish and dairy, and a low consumption of red meat [13, 14]. The main difference seems to be the recommendation regarding alcohol consumption, which is stricter in the Dutch dietary quidelines. Moreover, a recent study showed that a long-term dietary pattern which is rich in vegetables, fruits, legumes and nuts, more plantbased instead of animal-based, and in which intake of alcoholic beverages, high-fat processed meat and soft drinks is avoided, has the potential to prevent intestinal inflammatory processes via the gut microbiota [15]. This potentially favourable dietary pattern for IBD patients is in line with the Mediterranean diet and the Dutch dietary guidelines [14]. Patients should be made aware of all these similarities to stimulate improvement of their diet quality.

Regarding physical activity, there is no evidence that patients with IBD cannot perform regular physical activity. On the contrary, it seems important to break a cycle of physical inactivity to prevent a reduction in muscle mass and physical fitness since patients with IBD already have a reduced muscle mass compared with healthy controls, likely due to chronic inflammation [16-18]. Being physically active will increase muscle mass and physical fitness and thereby reduce fatigue and improve quality of life [19]. Low to moderate intensity physical activity seems to be safe and well tolerated for this purpose [19, 20]. In addition, we showed that repeated and prolonged moderate-intensity physical activity does also not appear to have harmful effects (Chapter 4). The safety of high-intensity physical activity is currently not clear [20], but performing this type of physical activity does not seem to be necessary for health benefits. Low to moderate intensity physical activity is the basis of the Dutch physical activity guidelines [21]. Patients should be advised to be physically active for at least 30 minutes per day. Three to five times per week this should be of moderate intensity, meaning a heart rate between 60-80% of the maximum heart rate, since this is key to improve inflammation [19]. A combination of endurance and resistance exercise is favourable. To increase the probability of maintaining this level of physical activity, patients should engage in enjoyable activities, optionally in a group to increase motivation [19]. The proximity of a toilet was mentioned as a necessity to be physically active (Chapter 3), which can be covered with at home exercises, activities close to home or sport clubs where these facilities are available.

Besides all the possible health benefits of the Dutch guidelines, another very important aspect is to make a sustainable change when changing lifestyle. A lifestyle change should not feel like following a diet and activities should not feel like an obligation. Patients should make their lifestyle their daily routine. To achieve this, diets should not be too restricted and should not include dietary formula or special foods. In a direct comparison between the Specific Carbohydrate Diet and the

Mediterranean diet in CD patients, the latter was preferred because of the greater ease of following [10]. Moreover, suggestions for physical activities should be made that are possible without going to a gym or sports club.

Challenges of diet and physical activity intervention studies

Recommendations are preferably based on scientifically sound evidence from well-performed intervention studies. However, several challenges are faced when designing and executing dietary and physical activity intervention studies. These challenges include amongst others the complex nature of diet and physical activity, (monitoring of) adherence to the intervention, choice of the comparator group, blinding, quality control and reproducibility, and generalizability [22, 23]. In this thesis, some of these challenges were also faced in the interventions described in **Chapter 5 and 6**.

In contrast to drugs, diet and physical activity are no isolated chemical compounds with well-known characteristics and dynamics. They are heterogeneous, multifaceted components that may affect the outcome of interest but also exhibit several off-target properties [23]. Moreover, adherence to the intervention influences its effectiveness. In lifestyle interventions, many factors such as tolerability, ease of preparation or activity, availability of foods or activities, costs, and cultural and social acceptability may influence adherence [22]. In controlled on-site studies, adherence can be monitored relatively easy, but such studies have a high participant burden and are relatively inflexible [24]. Moreover, a less controlled study situation results in a better representation of what is achievable in a real-life setting [25]. For these reasons, we decided to perform a lifestyle study solely based on intensive supervision by a dietician and physiotherapist (**Chapter 5**).

Besides these aspects, the choice of the comparator group is challenging. For our lifestyle intervention, we decided to perform a single-arm study since an ideal control group does not exist (**Chapter 5**). In most trials, intervention diets are compared to 'usual' diets, which are quite variable and might already approximate the study diet, or to diets intentionally including the opposite of the intervention such as a low fibre or high refined carbohydrate diet when investigating a high fibre or low refined carbohydrate diet [26, 27]. In the latter situation, observed differences may be caused by the study diet, control diet or both. The same is seen in physical activity trials. An

intervention group is generally compared to a control group performing their regular physical activities [19, 20]. However, it is likely that participants in the control group implement some aspects of the intervention when an intervention is compared to the usual situation [22]. Participants being aware of the intervention results in a greater risk for bias. However, blinding is almost always impossible when an intervention is built around the entire diet or the level of physical activity. Limiting participant's knowledge about the intervention can reduce this [22]. However, participating in an intervention study regarding lifestyle will lead to awareness. It is likely that this awareness will result in lifestyle changes regardless of knowledge about the intervention and participation in either an intervention or control group. This is an effect that we can also not rule out in our studies. The improvements we found regarding diet quality might be the result of our interventions but might also be a result of dietary awareness (**Chapter 5 and 6**). This awareness does not necessarily have to be a negative aspect as it might help to further improve diet quality which is in the end the aim of the interventions.

Quality control and reproducibility are other challenges. In both our intervention studies, participants only received advice and examples (**Chapter 5 and 6**). Foods were not provided and their physical activity was not supervised. Unless foods are provided to participants, food source and preparation method will differ among participants and influence dietary exposure in terms of actual nutrient composition and amount of consumption [22, 24]. Regarding physical activity, speed of walking, cycling and running may differ and general daily activities such as work and household activities can generally not be changed for research purposes. Moreover, costs that come along in a self-directed study may impose financial constraints on participants leading to differences between participants with a lower and higher economic status.

Most dietary and physical activity interventions have been performed in small and specific study populations which limits the power and generalizability of the results [19, 26]. As in our lifestyle intervention study (**Chapter 5**), generally patients in remission or with mildly active disease are included. A reason for this might be that dietary and physical activity interventions are affected by other therapies like medication. We decided to only include patients in remission or with mildly active disease as they would likely use the same medication throughout the study and

therefore impact of medication on outcome measures would be reduced (**Chapter 5**). As a result of this patient selection, the results cannot be extrapolated to the whole IBD population.

Methodological considerations

Despite efforts to overcome limitations in our studies, some methodological considerations should be taken into account when interpreting the results. We will discuss considerations regarding study designs and populations, assessment of dietary intake and physical activity, and assessment of disease activity.

Study designs and populations

In this thesis, we included patients with different types of IBD, mainly CD and UC, and varying disease status. In general, most patients for the studies in this thesis were recruited via the outpatient gastroenterology clinic of Hospital Gelderse Vallei, Ede, the Netherlands. For Chapter 2 and 3, we also recruited patients via a digital newsletter and the website of the Dutch IBD patient association. This allowed us to include a broad sample of patients representative of the Dutch IBD population and a large enough sample size to conclude about associations. For Chapter 4, most participants were recruited via the Nijmegen Exercise Study database of Radboud University Medical Center, Niimegen, the Netherlands. This is a longitudinal study to examine the impact of a physically active lifestyle on health, quality of life, and development and progression of various (chronic) diseases. All people in this longitudinal study have ever participated in the Nijmegen Four Days Marches. Therefore, this database was the perfect source to recruit IBD patients as well as healthy controls for our Four Days Marches study. However, the IBD patients in this database are likely not a good representation of the whole IBD population. Moreover, as this was an explorative, observational study, the study population was not based on a sample size calculation. Therefore, we cannot conclude about the power of the study. The patients included in **Chapter 5** were solely recruited via the outpatient gastroenterology clinic of Hospital Gelderse Vallei. This allowed us to perform an intervention study with frequent consultations and a limited number of health care professionals involved. The study described in Chapter 6 was in collaboration with Rijnstate Hospital, Arnhem, the Netherlands. About half of the participants was recruited via the outpatient gastroenterology clinic of that hospital which led to a more divers study population. In both intervention studies (Chapter

5 and 6), we did not include a control group which is needed to draw more firm conclusions

In **Chapter 4, 5 and 6**, analyses were performed for the whole study population. No distinctions were made between CD and UC, while differences might be expected and also have been observed in previous studies. Those differences are most likely the result of different disease locations and types of inflammation (transmural vs superficial) [28]. Ideally, analyses were also performed separately for CD and UC, but this was not possible in our studies because of small sample sizes and therefore lack of power in case of separate analyses.

Assessment of dietary intake and physical activity

Consistent and accurate assessment of dietary intake and physical activity is one of the biggest challenges in lifestyle-related research. Various subjective and objective measures are available, each having its own limitations and biases [29]. In this thesis, the aim was to assess diet and physical activity by using validated methods that would provide the best possible reflection of diet and physical activity to be able to fulfil the aims of the studies.

Dietary intake

In **Chapter 2** of this thesis, we used an FFQ to assess dietary intake of the past month since we wanted to test for associations between habitual dietary intake and disease activity. An FFQ is the most efficient option in a large online study since it is perfect for ranking individuals according to their intake rather than estimating their absolute intake. Also in previous studies investigating associations, FFQs were frequently used to assess dietary intake [30, 31]. In **Chapter 5**, we wanted to improve diet quality of participants in a long-term lifestyle intervention. Since improving diet quality in the long-term is about changing a habitual pattern, we also used an FFQ. For this study, we used a short FFQ, the *Eetscore* [32]. This short FFQ was preferred over a regular FFQ as it takes only 10-15 minutes to complete. The *Eetscore* showed good to excellent reproducibility and was considered an acceptable screener for diet quality compared with full-length FFQ [32]. Moreover, the *Eetscore* provides a score for diet quality which makes it easy to determine dietary improvement over time. In previous dietary intervention studies, dietary assessment and adherence to the dietary recommendations were often not reported. When adherence was monitored, this

was mainly done through periodic interviews [26]. Finally in **Chapter 6**, we wanted to assess diet quality and provide web-based personalised dietary advice. For this purpose, so far only the *Eetscore* is available.

Physical activity

In **Chapter 3** of this thesis, we used the SQUASH to assess level of physical activity. No objective measures could be used as it was an online study. Question naires are frequently used when investigating associations of physical activity with various outcomes [4, 20]. In the Four Days Marches study, we used subjective and objective measures of physical activity (Chapter 4). The SQUASH was used to assess the general level of physical activity of our participants to check for baseline differences between groups that might explain any difference in baseline inflammatory markers. Besides this subjective assessment, the participants wore a heart rate monitor on the first walking day to determine exercise intensity. As the aim was to investigate moderate-intensity exercise, we wanted to objectively determine whether this aim was met. In Chapter 5, we wanted to improve level of physical activity of participants in a long-term lifestyle intervention. Again, the SQUASH was used to assess physical activity because of the long-term aspect of the intervention. It was considered impossible and too much of a burden for participants to let them wear a device for a 6-month period. Wearing a device at random days was considered to be of little value, since this might induce the wearer to be more active and monitoring time needs to be sufficient for a reliable assessment [33, 34]. In previous studies on physical activity, adherence to the intervention was not reported or they investigated a supervised intervention [19, 20].

Assessment of disease activity

Disease activity was assessed in all studies in this thesis. Mainly questionnaires were used for this purpose. In **Chapter 4 and 5**, disease activity was also assessed by measuring faecal calprotectin. It would have been better to also objectively assess disease activity in the other studies instead of only subjectively. However, this was impossible because of the nature of those studies (**Chapter 2, 3 and 6**). Therefore, we used questionnaires that have been validated in previous studies in which it was concluded that they are reliable and feasible for disease activity measurement. Despite some significant correlations with biomarkers such as CRP, self-reported disease activity sometimes correlates poorly with endoscopic disease activity,

especially in CD, which should be taken into account when interpreting the results [35-37].

Implications for clinical practice

Diet and physical activity are important in IBD and many patients are interested in lifestyle as part of their IBD treatment [1, 38]. However, limited or absent dietary and physical activity guidance makes IBD patients vulnerable to try out diets and activities derived from non-scientific sources like the internet to manage their symptoms [7]. Several implications can be extracted from this thesis to support IBD patients in clinical practice.

In clinical practice, it seems to be important to lower the inflammatory potential of the diet and to improve the level of physical activity (**Chapter 2 and 3**). For this purpose, advising the Dutch dietary and physical activity guidelines seems to be a good starting point, with positive effects on impact of disease on daily life and fatigue (**Chapter 5**). Currently, adherence to these guidelines is suboptimal and recommendations are not met, which can result in increased inflammation, poorer recovery from illness, fatigue and a decreased quality of life [3, 4]. It is important to improve the basics first, before advising specific adjustments.

There is often no time in clinical practice to assess a patient's food intake and to support a healthy diet, while it is important to discuss the personal beliefs of patients and their possible restrictive dietary behaviours [6]. IBD patients consider dietary guidance to be important, while only a minority feels to have received adequate information from their physician [1, 38]. Fulfilling this need for dietary guidance in a time-efficient manner is possible with web-based dietary assessment and advice (**Chapter 6**). Health care professionals can further support their patients by guiding them in which steps to take first and by providing them with additional advice related to abdominal complaints.

Future research recommendations

Several directions for future research have been indicated in this thesis. In general, more longitudinal studies in larger study populations and with a longer follow-up time are needed. Preferably RCTs with separate analysis of CD and UC patients are performed to further evaluate effects of diet and physical activity on the disease

course. Despite the follow-up time of 6 months in our intervention study (**Chapter 5**), which is already longer than the average follow-up time of lifestyle intervention studies, it is still a relative short period considering IBD is a chronic disease. Moreover, the focus of future studies should be on a long-term sustainable lifestyle change. Although diet and physical activity are often referred to as easy modifiable factors, actually changing patients' habits is one of the hardest things regarding a healthy lifestyle. Therefore, the main goal of a lifestyle intervention should be the maintenance of a healthy, active lifestyle. For this purpose, attention should be paid to behaviour change when designing lifestyle interventions besides providing lifestyle recommendations. Future studies should use psychological techniques to enable patients to actually change their lifestyle in the long term, to make it their new daily routine instead of just a temporary intervention, and to prevent returning to old lifestyle habits [39].

Another aspect that requires attention when designing an intervention study is the composition of the intervention. As in our study, the focus should be on diet and physical activity as a whole instead of single food components or single activity bouts. Moreover, other lifestyle factors such as sleep and stress should be included. To be effective when implemented outside of a trial, we suggest limited control of the study situation as this will give a good representation of what is achievable in a real-life setting. In analogy with the *Eetscore*, activity trackers that provide direct feedback can be used to stimulate physical activity. Furthermore, attention should be paid to a thorough baseline assessment of diet and physical activity since this will affect the effectiveness of the intervention (**Chapter 5**), and it may affect the outcome in the control group if included [19, 23]. Regarding dietary assessment, the accuracy might be increased by including healthy alternatives for food products that are commonly avoided by IBD patients (**Chapter 6**).

Conclusion

Within this thesis, we aimed to investigate the health effects of the Dutch dietary and physical activity guidelines as part of treatment in IBD patients. Before applying these guidelines, habitual diet and physical activity were investigated. We can conclude that the inflammatory potential of the diet and level of physical activity are associated with disease activity in CD patients, while no associations were found in UC patients. Besides, moderate-intensity physical activity does not appear to have harmful effects

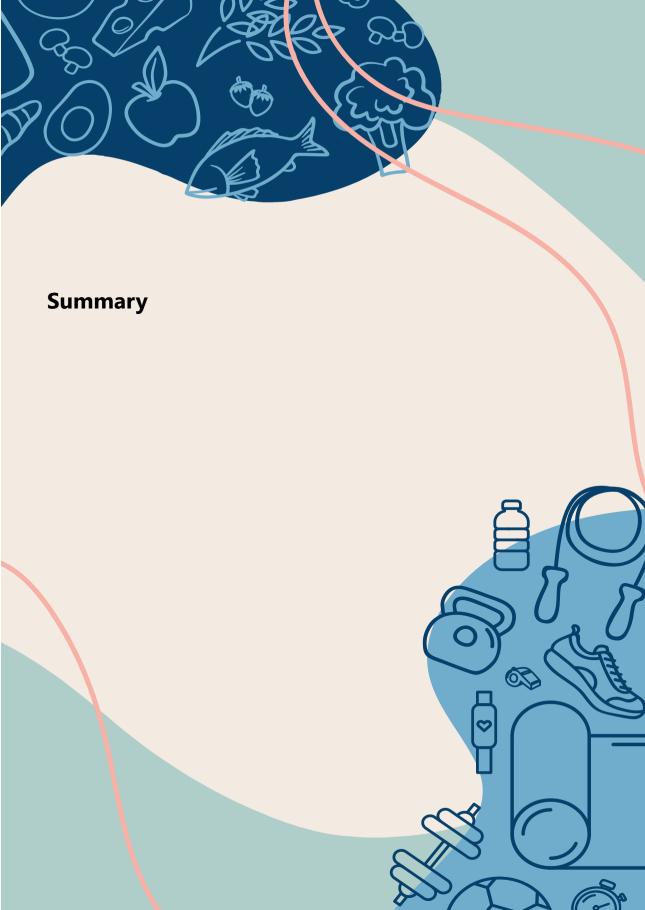
on IBD and can be safely performed. The Dutch dietary guidelines are consistent with a more anti-inflammatory potential of the diet. When applying the Dutch dietary and physical activity guidelines, impact of disease on daily life and fatigue decreased; likely as a result of a substantial improvement in diet quality. Also, when informing patients about the Dutch dietary guidelines via web-based dietary assessment and advice, diet quality improved. Future research should focus on randomized controlled trials in larger study populations combining several subjective and objective disease-related outcomes. This way further insight into application of the Dutch dietary and physical activity guidelines will come available to optimize the lifestyle of IBD patients.

References

- 1. Wong S, Walker JR, Carr R, et al. The information needs and preferences of persons with longstanding inflammatory bowel disease. Can J Gastroenterol. 2012;26(8):525-31.
- 2. 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):1381-92.
- 3. Lambert K, Pappas D, Miglioretto C, et al. Systematic review with meta-analysis: dietary intake in adults with inflammatory bowel disease. Aliment Pharmacol Ther. 2021;54(6):742-54.
- 4. Tew GA, Jones K, Mikocka-Walus A. Physical Activity Habits, Limitations, and Predictors in People with Inflammatory Bowel Disease: A Large Cross-sectional Online Survey. Inflammatory Bowel Diseases. 2016;22(12):2933-42.
- 5. Borren NZ, van der Woude CJ, Ananthakrishnan AN. Fatigue in IBD: epidemiology, pathophysiology and management. Nat Rev Gastroenterol Hepatol. 2019;16(4):247-59.
- 6. Casanova MJ, Chaparro M, Molina B, et al. Prevalence of Malnutrition and Nutritional Characteristics of Patients With Inflammatory Bowel Disease. J Crohns Colitis. 2017;11(12):1430-9.
- 7. Day AS, Yao CK, Costello SP, et al. 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.
- 8. Papada E, Amerikanou C, Forbes A, Kaliora AC. Adherence to Mediterranean diet in Crohn's disease. Eur J Nutr. 2020;59(3):1115-21.
- 9. Chicco F, Magrì S, Cingolani A, et al. Multidimensional Impact of Mediterranean Diet on IBD Patients. Inflamm Bowel Dis. 2021;27(1):1-9.
- 10. 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):837-52.e9.
- 11. De Filippis F, Pellegrini N, Vannini L, et al. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. Gut. 2016;65(11):1812-21.
- 12. Shivappa N, Steck SE, Hurley TG, et al. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr. 2014;17(8):1689-96.
- 13. Trichopoulou A, Martínez-González MA, Tong TYN, et al. Definitions and potential health benefits of the Mediterranean diet: views from experts around the world. BMC Medicine. 2014;12(1):112.
- 14. Kromhout D, Spaaij CJ, de Goede J, Weggemans RM. The 2015 Dutch food-based dietary quidelines. Eur J Clin Nutr. 2016;70(8):869-78.

- 15. Bolte LA, Vich Vila A, Imhann F, et al. Long-term dietary patterns are associated with pro-inflammatory and anti-inflammatory features of the gut microbiome. Gut. 2021;70:1287-98
- 16. Pizzoferrato M, de Sire R, Ingravalle F, et al. Characterization of Sarcopenia in an IBD Population Attending an Italian Gastroenterology Tertiary Center. Nutrients. 2019;11(10).
- 17. Rocha R, Santana GO, Almeida N, Lyra AC. Analysis of fat and muscle mass in patients with inflammatory bowel disease during remission and active phase. Br J Nutr. 2009;101(5):676-9.
- 18. Bryant RV, Trott MJ, Bartholomeusz FD, Andrews JM. Systematic review: body composition in adults with inflammatory bowel disease. Aliment Pharmacol Ther. 2013;38(3):213-25.
- 19. 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 Gastroenterol. 2019;19(1):115.
- 20. Engels M, Cross RK, Long MD. Exercise in patients with inflammatory bowel diseases: current perspectives. Clin Exp Gastroenterol. 2018;11:1-11.
- 21. Weggemans RM, Backx FJG, Borghouts L, et al. The 2017 Dutch Physical Activity Guidelines. Int J Behav Nutr Phys Act. 2018;15(1):58.
- 22. Lewis JD, Albenberg L, Lee D, et al. The Importance and Challenges of Dietary Intervention Trials for Inflammatory Bowel Disease. Inflamm Bowel Dis. 2017;23(2):181-91.
- 23. Mirmiran P, Bahadoran Z, Gaeini Z. Common Limitations and Challenges of Dietary Clinical Trials for Translation into Clinical Practices. Int J Endocrinol Metab. 2021;19(3):e108170.
- 24. Fitzgerald KC, Sand IK, Senders A, et al. Conducting dietary intervention trials in people with multiple sclerosis: Lessons learned and a path forward. Mult Scler Relat Disord. 2020:37:101478.
- 25. Staudacher HM, Irving PM, Lomer MCE, Whelan K. The challenges of control groups, placebos and blinding in clinical trials of dietary interventions. Proc Nutr Soc. 2017;76(3):203-12.
- 26. Limketkai BN, Iheozor-Ejiofor Z, Gjuladin-Hellon T, et al. Dietary interventions for induction and maintenance of remission in inflammatory bowel disease. Cochrane Database Syst Rev. 2019;2(2):Cd012839.
- 27. Charlebois A, Rosenfeld G, Bressler B. The Impact of Dietary Interventions on the Symptoms of Inflammatory Bowel Disease: A Systematic Review. Crit Rev Food Sci Nutr. 2016;56(8):1370-8.
- 28. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet. 2007;369(9573):1641-57.
- 29. McClung HL, Ptomey LT, Shook RP, et al. Dietary Intake and Physical Activity Assessment: Current Tools, Techniques, and Technologies for Use in Adult Populations. Am J Prev Med. 2018;55(4):e93-e104.

- 30. Tian Z, Zhuang X, Zhao M, et al. Index-Based Dietary Patterns and Inflammatory Bowel Disease: A Systematic Review of Observational Studies. Advances in Nutrition. 2021;12(6):2288-300.
- 31. Peters V, Spooren C, Pierik MJ, et al. Dietary Intake Pattern is Associated with Occurrence of Flares in IBD Patients. J Crohns Colitis. 2021;15(8):1305-15.
- de Rijk MG, Slotegraaf AI, Brouwer-Brolsma EM, et al. Development and evaluation of a diet quality screener to assess adherence to the Dutch food-based dietary guidelines. Br J Nutr. 2021:1-28.
- 33. Baumann S, Groß S, Voigt L, et al. Pitfalls in accelerometer-based measurement of physical activity: The presence of reactivity in an adult population. S cand J Med Sci Sports. 2018;28(3):1056-63.
- 34. Aadland E, Ylvisåker E. Reliability of Objectively Measured Sedentary Time and Physical Activity in Adults. PLoS One. 2015;10(7):e0133296.
- 35. Bennebroek Evertsz F, Nieuwkerk PT, Stokkers PC, et al. The patient simple clinical colitis activity index (P-SCCAI) can detect ulcerative colitis (UC) disease activity in remission: a comparison of the P-SCCAI with clinician-based SCCAI and biological markers. J Crohns Colitis. 2013;7(11):890-900.
- 36. Falvey JD, Hoskin T, Meijer B, et al. Disease activity assessment in IBD: clinical indices and biomarkers fail to predict endoscopic remission. Inflamm Bowel Dis. 2015;21(4):824-31.
- 37. Ricanek P, Brackmann S, Perminow G, et al. Evaluation of disease activity in IBD at the time of diagnosis by the use of clinical, biochemical, and fecal markers. Scand J Gastroenterol. 2011;46(9):1081-91.
- 38. Zallot C, Quilliot D, Chevaux JB, et al. Dietary beliefs and behavior among inflammatory bowel disease patients. Inflamm Bowel Dis. 2013;19(1):66-72.
- 39. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci. 2011;6:42.



Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract of which Crohn's disease (CD) and ulcerative colitis (UC) are the main subtypes. Both are characterized by a variable and unpredictable disease course with periods of active disease alternating with periods of remission. The pathogenesis of IBD seems to be a complex interaction between the gut microbiota, immune system, genetics and environmental factors like diet and physical activity. Besides the likely contribution to the development of IBD, diet and physical activity also significantly impact the disease course and clinical outcomes in patients with established IBD. However, evidence-based guidelines in clinical IBD practice are lacking, which hampers the guidance of IBD patients who are interested in diet and physical activity as part of their treatment. All currently available evidence regarding beneficial effects of nutrients and physical activity in IBD is in line with the Dutch quidelines for a healthy diet and physical activity. However, these quidelines as a whole have not been investigated in IBD yet. Therefore, the aim of this thesis was to investigate the health effects of the Dutch dietary and physical activity guidelines as part of treatment in IBD patients.

In **Chapter 2**, we used an online survey to investigate associations between the habitual diet of IBD patients and disease activity. The Dietary Inflammatory Index (DII) was used to determine the inflammatory potential of the diet. A higher DII indicates a more pro-inflammatory diet that is not in line with the Dutch dietary guidelines, while a lower DII indicates the opposite: a more anti-inflammatory diet that is in line with the guidelines. We found that the inflammatory potential of the diet was associated with clinical disease activity in Crohn's disease patients, meaning that patients who consumed a diet more in line with the Dutch dietary guidelines had a lower disease activity and vice versa. No significant association was found in ulcerative colitis patients.

We also used an online survey to investigate associations between level of physical activity of IBD patients and disease activity in **Chapter 3**. We found that the level of physical activity, based on the number of minutes per week and the intensity of activities, was inversely associated with clinical disease activity in Crohn's disease patients, while no significant association was found in ulcerative colitis patients. Interviews performed to further elucidate the association between physical activity and clinical disease activity revealed that IBD patients generally experience beneficial

effects of physical activity, such as improved general fitness, quality of life, and self-image. However, barriers caused by active disease like pain, fatigue and urgency may put them off to be physically active.

In **Chapter 4**, the results of an observational study during the Nijmegen Four Days Marches are described. In that study, we assessed whether moderate-intensity physical activity is safe for IBD patients since this type of physical activity is an important part of the Dutch physical activity guidelines. We found that cytokine responses during this repeated prolonged moderate-intensity walking exercise were not different in IBD patients compared to controls without IBD. Furthermore, faecal calprotectin was not affected by the walking exercise when comparing concentrations of IBD patients who participated in the marches to concentrations of IBD patients who did not. In contrast to these objective findings, there was a slight increase in subjective clinical disease activity in CD patients who participated in the marches, but not in UC patients. Since faecal calprotectin better correlates with endoscopic disease activity than clinical disease activity questionnaires, we overall concluded that it seems safe for IBD patients to perform repeated prolonged moderate-intensity exercise without substantial exacerbation of inflammation.

We then performed a combined lifestyle intervention study based on the Dutch dietary and physical activity guidelines of which the results are described in **Chapter 5**. During this 6-month study, personal dietary and physical activity advice was provided by a dietician and physiotherapist. This resulted in a substantial improvement of diet quality, while the level of physical activity remained the same. Over time, impact of disease on daily life reduced and fatigue decreased, while clinical disease activity, health-related quality of life and faecal calprotectin did not change. Improvement in diet quality was associated with a lower impact of disease on daily life and less fatigue. No associations were found between physical activity and disease-related outcomes.

Lastly, in **Chapter 6** we investigated the use of a web-based tool, the *Eetscore*, to assess diet quality and provide personalized dietary advice to IBD patients based on the Dutch dietary guidelines. In this prospective cohort study, diet quality of IBD patients improved following dietary advice of the *Eetscore* and this improvement was associated with a slight improvement in health-related quality of life. The *Eetscore*

seems to be a practical and useful tool to monitor and support a healthy diet in IBD patients.

From this thesis, we conclude that the inflammatory potential of the diet and level of physical activity are associated with disease activity in CD patients, while no associations were found in UC patients. Besides, moderate-intensity physical activity does not appear to have harmful effects on IBD and can be safely performed. The Dutch dietary guidelines are consistent with a more anti-inflammatory potential of the diet. When applying the Dutch dietary and physical activity guidelines, impact of disease on daily life and fatigue decreased; likely as a result of a substantial improvement in diet quality. Also, when informing patients about the Dutch dietary guidelines via web-based dietary assessment and advice, diet quality improved. Future research on diet and physical activity in IBD should focus on randomized controlled trials in larger study populations combining several subjective and objective disease-related outcomes. This way further insight into application of the Dutch dietary and physical activity guidelines will come available to optimize the lifestyle of IBD patients.



Inflammatoire darmziekten (IBD) ziin chronische ontstekingsziekten van het maaqdarmkanaal waarvan de ziekte van Crohn en colitis ulcerosa de belangriikste subtypes ziin. Beiden worden gekenmerkt door een wisselend en onvoorspelbaar ziektebeloop waarbii perioden van actieve ziekte en remissie elkaar afwisselen. De pathogenese van IBD lijkt een complexe interactie te zijn tussen de darm microbiota, het immuunsysteem, genetica en omgevingsfactoren zoals voeding en bewegen. Voeding en bewegen hebben naast een bijdrage aan het ontstaan van IBD ook een belangrijke invloed op het ziektebeloop en de klinische uitkomsten bij patiënten die reeds IBD hebben. Bovendien zijn IBD patiënten geïnteresseerd in voeding en bewegen als onderdeel van hun behandeling. Wetenschappelijk onderbouwde richtlijnen ontbreken echter wat de begeleiding van IBD-patiënten bemoeilijkt. Al het bewijs dat momenteel beschikbaar is met betrekking tot gunstige effecten van voeding en bewegen bij IBD is in overeenstemming met de Nederlandse richtlijnen voor goede voeding en bewegen. Deze richtlijnen als geheel zijn echter nog niet onderzocht in IBD. Daarom was het doel van dit proefschrift om de gezondheidseffecten van de Nederlandse richtlijnen voor goede voeding en bewegen als onderdeel van de behandeling van IBD-patiënten te onderzoeken.

In **hoofdstuk 2** hebben we een online vragenlijst gebruikt om associaties te onderzoeken tussen het gebruikelijke dieet van IBD-patiënten en ziekteactiviteit. De Dietary Inflammatory Index (DII) werd gebruikt om het inflammatoire potentieel van het dieet te bepalen. Een hogere DII wijst op een meer pro-inflammatoir dieet welke niet in lijn is met de richtlijnen goede voeding, terwijl een lagere DII op het tegenovergestelde wijst: een meer anti-inflammatoir dieet welke wel in lijn is met de richtlijnen. Wij vonden dat het inflammatoire potentieel van het dieet geassocieerd was met klinische ziekteactiviteit in patiënten met de ziekte van Crohn. Dit betekent dat patiënten van wie het voedingspatroon meer in lijn was met de richtlijnen goede voeding een lagere ziekteactiviteit hadden en vice versa. Er werd geen significante associatie gevonden in patiënten met colitis ulcerosa.

Met een online vragenlijst hebben we ook associaties tussen de mate van lichamelijke activiteit van IBD-patiënten en ziekteactiviteit onderzocht, zoals beschreven in **hoofdstuk 3**. We vonden dat de mate van lichamelijke activiteit, gebaseerd op het aantal minuten per week en de intensiteit van de activiteiten, omgekeerd geassocieerd was met klinische ziekteactiviteit in patiënten met de ziekte

van Crohn, terwijl er geen significante associatie werd gevonden in patiënten met colitis ulcerosa. Interviews die gedaan zijn om de associatie tussen lichamelijke activiteit en klinische ziekteactiviteit verder te verduidelijken onthulden dat IBD-patiënten over het algemeen gunstige effecten ervaren van lichamelijke activiteit, zoals een betere algehele fitheid, kwaliteit van leven, en zelfbeeld. Echter, belemmeringen veroorzaakt door actieve ziekte, zoals pijn, vermoeidheid en sterke en frequente aandrang voor ontlasting, kunnen hen ervan weerhouden om lichamelijk actief te zijn.

In **hoofdstuk 4** worden de resultaten beschreven van een observationele studie tijdens de Nijmeegse Vierdaagse. In die studie hebben we gekeken of matig intensieve lichamelijke activiteit veilig is voor IBD-patiënten, omdat dit type lichamelijke activiteit een belangrijk onderdeel is van de Nederlandse beweegrichtlijnen. Wij vonden dat herhaald en langdurig matig intensief wandelen vergelijkbare cytokine responsen gaf in IBD-patiënten in vergelijking met controles zonder IBD. Bovendien werd het fecaal calprotectine niet beïnvloed door het wandelen wanneer de waarden van IBD-patiënten die deelnamen aan de Vierdaagse werden vergeleken met de waarden van IBD-patiënten die dat niet deden. In tegenstelling tot deze objectieve bevindingen was er een lichte toename in de ervaren klinische ziekteactiviteit in patiënten met de ziekte van Crohn die deelnamen aan de Vierdaagse. Deze toename werd niet waargenomen in patiënten met colitis ulcerosa. Aangezien het fecaal calprotectine beter correleert met endoscopische ziekteactiviteit dan vragenlijsten over ziekteactiviteit, concludeerden wij dat het veilig lijkt voor IBD-patiënten om herhaald en langdurig matig intensief te wandelen zonder substantiële verergering van inflammatie.

Hierna hebben we een gecombineerde leefstijlinterventie gebaseerd op de Nederlandse richtlijnen voor voeding en bewegen onderzocht waarvan de resultaten zijn beschreven in **hoofdstuk 5**. Tijdens dit 6 maanden durende onderzoek werden persoonlijke voedings- en beweegadviezen gegeven door een diëtist en een fysiotherapeut. Dit resulteerde in een substantiële verbetering van de dieetkwaliteit, terwijl de mate van lichamelijke activiteit gelijk bleef. Gedurende de studie verminderde de invloed van de ziekte op het dagelijks leven en nam de vermoeidheid af, terwijl de klinische ziekteactiviteit, de gezondheid-gerelateerde kwaliteit van leven en het fecaal calprotectine gelijk bleven. De verbetering in dieetkwaliteit was

geassocieerd met een lagere impact van ziekte op het dagelijks leven en minder vermoeidheid. Er werden geen associaties gevonden tussen lichamelijke activiteit en ziekte-gerelateerde uitkomsten.

Tenslotte onderzochten we in **hoofdstuk 6** het gebruik van een online applicatie, de Eetscore, om de kwaliteit van het dieet te beoordelen en IBD-patiënten gepersonaliseerd voedingsadvies te geven op basis van de richtlijnen goede voeding. In deze prospectieve cohort studie verbeterde de dieetkwaliteit van IBD-patiënten na dieetadvies van de Eetscore en deze verbetering was geassocieerd met een lichte verbetering in gezondheid-gerelateerde kwaliteit van leven. De Eetscore lijkt een praktisch en bruikbaar hulpmiddel te zijn om een gezond dieet bij IBD-patiënten te monitoren en te ondersteunen.

Uit dit proefschrift concluderen wij dat het inflammatoire potentieel van het dieet en de mate van lichamelijke activiteit geassocieerd zijn met ziekteactiviteit in patiënten met de ziekte van Crohn, terwijl er geen associaties werden gevonden in patiënten met colitis ulcerosa. Matig intensieve lichamelijke activiteit lijkt geen schadelijke effecten te hebben op IBD en dit kan veilig worden gedaan. De Nederlandse voedingsrichtlijnen komen overeen met een meer anti-inflammatoir dieet. Door toepassing van de Nederlandse voedings- en beweegrichtlijnen verminderde de invloed van de ziekte op het dagelijks leven en nam de vermoeidheid af wat waarschijnlijk het gevolg is van een substantiële verbetering van de dieetkwaliteit. Ook bij toepassing van de Nederlandse voedingsrichtlijnen via een online applicatie met dieetadvies verbeterde de dieetkwaliteit. Toekomstig onderzoek naar voeding en bewegen bij IBD moet zich richten op gerandomiseerde gecontroleerde trials in grotere studiepopulaties waarbij verschillende subjectieve en objectieve ziektegerelateerde uitkomsten worden gecombineerd. Op die manier zal er meer onderbouwing komen voor de toepassing van de Nederlandse voedings- en beweegrichtlijnen om de leefstijl van IBD-patiënten te optimaliseren.

Dankwoord

About the author

List of publications

Overview of completed training activities

Dankwoord

Wat heb ik een unieke tijd gehad door als arts een PhD te doen bij de Wageningen Universiteit. De afgelopen jaren heb ik ontzettend veel geleerd en met veel verschillende mensen mogen samenwerken met dit proefschrift als resultaat. Ik wil iedereen die op welke wijze dan ook heeft bijgedragen aan mijn proefschrift heel erg bedanken en een aantal mensen in het bijzonder.

Ik wil graag beginnen met alle patiënten die hebben deelgenomen aan één van de onderzoeken: heel veel dank voor de tijd en moeite die jullie ervoor genomen hebben. Zonder jullie was dit proefschrift er niet geweest.

Dan mijn begeleiders. Beste Ben, zonder jou had ik dit proefschrift nooit geschreven. Bedankt voor de kans en het vertrouwen om mij dit promotietraject te laten doen. Ik heb veel bewondering voor jouw arbeidsethos en de manier waarop je werk en privé combineert. Ondanks je overvolle agenda kon je voor mij altijd tijd maken. Dank voor je betrokkenheid, optimisme en enthousiasme.

Beste Nicole, ineens zat je met mij opgescheept, een dokter in plaats van een voedingswetenschapper. Gelukkig klikte het meteen en wat heb ik veel van je mogen leren. Bedankt voor je begeleiding de afgelopen jaren, jouw creativiteit, input en feedback waren onmisbaar. Fijn dat ik altijd bij je terecht kon als een project anders liep dan gepland en dat er naast werk ook ruimte was voor andere onderwerpen, dit alles het liefst onder het genot van goede koffie.

Ik wil de leden van mijn promotiecommissie, prof. dr. Edith Feskens, prof dr. Gerard Dijkstra, prof. dr. Daisy Jonkers en prof. dr. Hans Zwerver, bedanken voor het lezen en beoordelen van mijn proefschrift.

Alle MDL-artsen in Ziekenhuis Gelderse Vallei: bedankt voor het benaderen van patiënten voor deelname aan een van mijn onderzoeken, maar zeker ook voor jullie begeleiding van mijn poli's en mijn ontwikkeling als arts. In het bijzonder Wout, veel dank voor het voorstel om mijn promotietraject te combineren met poli bij de MDL waardoor ik mij de afgelopen jaren niet alleen als onderzoeker, maar zeker ook als

arts verder kon ontwikkelen. Ook dank aan Margreet en Marthe voor alle patiënten die jullie hebben benaderd.

Maria, bedankt voor de mogelijkheid om onderzoek te doen tijdens de Nijmeegse Vierdaagse, wat hebben jullie het goed geregeld op de Wedren. Ook dank aan Coen, Dominique en Yvonne voor al jullie hulp.

Liselot, bijzonder hoe fijn en soepel onze samenwerking verliep, samen staan we sterk in de periferie en met een mooi resultaat!

Thanks to the NAD group. Although I was a bit of an outsider, I felt part of the group and I have learned a lot from all of you! Thanks for the interesting meetings and valuable input during the paperclubs. In het bijzonder Iris, fijn om tegelijk met jou een PhD te hebben gedaan en leuk dat we het nu in dezelfde maand afronden en elkaars paranimfen zijn!

Also thanks to room 1055, Guido, Rachelle, Paulina, Maria, Kamalita and Matjaž. Although it was just for two days per week, I really enjoyed working in the 'loud' room, unfortunately this ended pretty sudden due to COVID. I hope you are all doing great!

Een PhD vanuit twee werkplekken zorgt voor dubbel zoveel fijne kamergenoten. Elbrich, Karin, Laila, Lisanne, Harm, Vera, Kimberly, Anne en Sofie, dank voor alle cappuccino's, lunchpauzes en gedachtewisselingen. Elbrich: de Z is van ZGV en Zevenaar, de stabiele factor in een wisselend en steeds verder uitdunnend gezelschap, dank dat je er mijn hele PhD tijd was!

Bachelor- en masterstudenten Marieke, Charlotte, Ilse, Elaine, Vicky, Anne, Annemiek, Lola, Marloes, Anne en Emma, leuk dat ik jullie mocht begeleiden. In het bijzonder dank aan Vicky en Anne, ik weet niet wat ik zonder jullie had gemoeten tijdens het Vierdaagse onderzoek! Ook speciale dank aan Annemiek voor je enorme bijdrage aan de dieetrichtlijnen voor de Crocodile studie en aan Lola voor alle interviews. En natuurlijk Marloes: de Crocodile studie was een heel stuk minder leuk geweest zonder jou!

Dank aan (iedereen bij) Eat2Move en de Alliantie Voeding in de Zorg voor de financiële ondersteuning van mijn promotietraject en de mogelijkheden om mijn resultaten te delen met het algemene publiek. In het bijzonder Menrike en Anne, dank voor al jullie meedenken en ondersteuning op diverse vlakken. Ook dank aan Henriëtte, Els en Carla voor jullie hulp bij de METC aanvragen, Jasmijn en Gea voor jullie praktische hulp aan deze externe PhD, en Anne, Corine en Hanne voor jullie diëtetische ondersteuning vanuit de WUR. Henrike, Linda, Mirjam en Irene, dank voor jullie enthousiasme en expertise bij de Crocodile studie. Theresia, dank voor je flexibiliteit en het meedenken bij de laboratorium logistiek van mijn onderzoeken.

Natuurlijk ook dank aan mijn dierbare vrienden en familie. Dank voor alle gezellige etentjes, weekendjes weg, vakanties en vele andere activiteiten. Dank voor de goede gesprekken, de bijzondere momenten en onvergetelijke ervaringen. Dank voor jullie support bij mijn promotietraject en het samen invullen van mijn vrije tijd voor de beste ontspanning! Ook dank aan iedereen die mij laat lachen op de dansvloer, wat krijg ik daar toch een boel energie van!

Esje, wat ben ik blij met jou als mijn 'zusje' en paranimf. Bedankt dat ik altijd bij jou terecht kan. Ik koester de band die we hebben. En niet alleen die met jou. Esmee en Loek, dank voor alle gezellige avonden (in Nijmegen), andere uitjes en onze kampeervakantie in Oostenrijk. Ik heb heel veel zin om het dit jaar nog eens dunnetjes over te doen. Wat bof ik met jullie als zus en zwager, jullie zijn toppers!

Pap en mam, dank voor jullie vertrouwen in mij en jullie onvoorwaardelijke steun. Jullie hebben mij een stevige, veilige basis gegeven en de ruimte om mijn eigen keuzes te maken, mij verder te ontwikkelen en vele andere dingen te kunnen doen die mij gelukkig maken. Ik ben dankbaar voor jullie liefde, de band die we hebben en dat hotel pap en mam altijd open is!

About the author

Carliin Rianne Lamers was born on the 6th of May 1992 in Zevenaar, the Netherlands, After completing secondary school in Zevenaar in 2010, she started her study Medicine at Utrecht University. During her study. Carliin went abroad for her clinical internship in Otorhinolaryngology (University Malaya Medical Center, Kuala Lumpur, Malaysia). In the final year of her medical training, she focused on gastroenterology and hepatology. During research internship at the Wilhelmina Children's Hospital, Utrecht, the Netherlands, she investigated



transient elastography and ursodeoxycholic acid in cystic fibrosis-related liver disease. Moreover, she did a clinical internship in gastroenterology at Hospital Gelderse Vallei, Ede, the Netherlands, with a focus on inflammatory bowel disease. After her graduation from medical school in 2016, Carlijn started working as a resident in internal medicine at Hospital Gelderse Vallei. In March 2018, she was appointed as an external PhD candidate at the Division of Human Nutrition and Health of Wageningen University in collaboration with Hospital Gelderse Vallei. Her project focused on diet and physical activity in patients with inflammatory bowel disease. As a PhD student, Carlijn attended several courses and conferences. Furthermore, she was involved in teaching and supervising bachelor and master students from Wageningen University. During the research that led to this thesis, Carlijn worked as a gastroenterology resident at the outpatient clinic of Hospital Gelderse Vallei. Furthermore, she presented and published about interesting cases, was involved in setting up a lifestyle care path for patients with inflammatory bowel disease, and contributed to the brochure on diet and IBD of the Dutch patient association Crohn&Colitis NL. Currently, Carlijn is working as a gastroenterology resident in Isala Hospital, Zwolle, the Netherlands.

List of publications

Publications in peer-reviewed journals

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. IBD. 2022;izac027. Online ahead of print.

Henderson B, Meurs J, **Lamers CR**, Lopes Batista G, Materic D, Bertinetto CG, Bongers CCWG, Holzinger R, Harren FJM, Jansen JJ, Hopman MTE, Cristescu SM. Non-invasive monitoring of inflammation in IBD patients during prolonged exercise. Metabolites. 2022;12:224.

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 Gastroenterol. 2021;21:172.

Lamers CR, de Roos NM, Bongers CCWG, ten Haaf DSM, Hartman YAW, Witteman BJM, Hopman MTE. Repeated prolonged moderate-intensity walking exercise does not appear to have harmful effects on inflammatory markers in patients with inflammatory bowel disease. Scand J Gastroenterol. 2021;56:30-37.

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 Gastroenterol. 2020;20:316.

Lamers CR, Mares WGN, Bac DJ. Black esophagus: a case series and literature review of acute esophageal necrosis. Scand J Gastroenterol. 2018;53:1421-1424.

Lamers CR, Koekkoek WAC, Mares WGN. Abdominal pain: diagnosis based on specific CT findings. Neth J Med. 2018;76:136-137.

Koekkoek WAC, **Lamers CR**, Meiland R, van der Veen MJ, Burgers - Bonthuis DC. Hepatopulmonary syndrome - a rare cause of hypoxaemia. Neth J Crit Care. 2018;26:77-80.

Accepted for publication

Lamers CR, van Erp LW, Slotegraaf AI, Groenen MJM, de Roos NM, Wahab PJ, Witteman BJM. Web-based dietary assessment and advice helps inflammatory bowel disease patients to improve their diet quality. Br J Nutr. 2022.

Van Noort HHJ, **Lamers CR**, Vermeulen H, Huisman - de Waal G, Witteman BJM. Patient education regarding fasting recommendations to shorten fasting times in patients undergoing esophago-gastro-duodenoscopy (EGD): a controlled pilot study. Gastroenterol Nurs. 2022.

Abstracts and presentations

Lamers CR, van Erp LW, Slotegraaf AI, Groenen MJM, de Roos NM, Wahab PJ, Witteman BJM (2021). 'Eetscore' in patients with Inflammatory Bowel Disease: an online tool to assess diet quality and provide personalised dietary advice. European Crohn's and Colitis Organisation (ECCO) Congress, virtual. (poster presentation)

Lamers CR, de Roos NM, Heerink HH, van de Worp - Kalter LA, Witteman BJM (2021). Short term effects of a combined lifestyle intervention in patients with Inflammatory Bowel Disease. European Crohn's and Colitis Organisation (ECCO) Congress, virtual. (poster presentation)

Lamers CR, van Erp LW, Slotegraaf AI, Groenen MJM, de Roos NM, Wahab PJ, Witteman BJM (2021). Eetscore in patients with Inflammatory Bowel Disease: an online tool to assess diet quality and provide personalised dietary advice. Digestive Disease Days (DDD), virtual. (poster presentation)

Lamers CR (2020 / 2021). Voeding bij MDL problematiek. Nursing Maag- Darm-Levercongres, Ede, NL. (oral presentation)

Lamers CR, van der Woerd WL, van der Ent CK, Houwen RHJ (2018). Transient elastography is superior to APRI score in detection of Cystic Fibrosis Related Liver Disease. Annual Meeting of the ESPGHAN, Genève, CH. (poster presentation, Young Investigator Award)

Lamers CR, van der Feen C, van der Doef HPJ, van der Ent CK, Houwen RHJ (2016). Ursodeoxycholic acid treatment is associated with improvement of liver stiffness in Cystic Fibrosis Related Liver Disease. North American Cystic Fibrosis Conference, Orlando, VS. (poster presentation, KNAW van Walree bursary to support attendance)

Overview of completed training activities

Discipline specific courses and activities	Organizer; location	Year
ESPGHAN 51st Annual Meeting	ESPGHAN; Geneva, CH	2018
Multiple GE training evenings	Various organizers; NL	2018- 2021
Digestive Disease Days	NVGE; online	2021
16 th Congress of ECCO	ECCO; online	2021
National Initiative on Crohn's and Colitis day	ICC; Amsterdam, NL	2021

General courses and activities	Organizer; location	Year
Reviewing a Scientific Paper	WGS; Wageningen, NL	2018
Supervising BSc and MSc thesis students	WGS; Wageningen, NL	2018
Competence assessment	WGS; Wageningen, NL	2018
Searching and Organising Literature	WGS; Wageningen, NL	2018
Good Clinical Practice course	TAPAS group; Den Bosch, NL	2018
Communication with the Media and the General Public	WGS; Wageningen, NL	2020
Last Stretch of the PhD Programme & Writing propositions for your PhD	WGS; Wageningen, NL	2021
Posters & Pitching	WGS; Wageningen, NL	2021
Scientific Writing	WGS; Wageningen, NL	2021
Webinar & Workshop: How to present online?	VLAG; Wageningen, NL	2021

Other activities	Organizer; location	Year
Preparation of research proposal	Wageningen, NL	2018
Chair group meetings	Wageningen UR; Wageningen, NL	2018- 2021
PhD tour to Canada	Wageningen UR; CA	2019

MOOC Nutrition and Health: Human microbiome	Wageningen UR; online	2020
MOOC Nutrition, Exercise and Sports	Wageningen UR; online	2020



Colophon

The research described in this thesis was financially supported by Eat2Move and the Nutrition and Healthcare Alliance.

Financial support from Wageningen University, Nederlandse Vereniging voor Gastro-enterologie and Dr. Falk Pharma Benelux B.V. for printing this thesis is gratefully acknowledged.

Cover design by Linne van Kan Printed by ProefschriftMaken

Copyright © Carlijn R. Lamers, 2022

