

Thesis

**Effects of lifestyle factors on Inflammatory Bowel
Disease and possible implications for clinical treatment –
a Scoping Review**

submitted by

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In partial fulfillment of the requirements for the degree of

Doktor(in) der gesamten Heilkunde

(Dr.(in) med. univ.)

at the

Medical University of Graz

executed at the

Lehrstuhl für Immunologie

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Graz, June 1st, 2023

Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than the cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, June 1st, 2023

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Acknowledgement

I want to thank all those who supported and motivated me during my master thesis.

In particular, I want to thank Assoz. Prof.ⁱⁿ Priv.-Doz.ⁱⁿ Mag.^a Dr.ⁱⁿ Sandra Holasek at the Institute of Immunology, Medical University of Graz for her helpful suggestions, constructive criticism and for supervising me throughout the project.

This work is dedicated to my great family for always encouraging me during my study of medicine, for their unwavering love and for making my life a never-ending adventure.

Zusammenfassung

Einleitung: Schwere Nebenwirkungen einer lebenslangen Immunsystem-modulierenden Behandlung können das therapeutische Ergebnis und die Lebensqualität von Patient*innen mit Chronisch Entzündlichen Darmerkrankungen (CED) negativ beeinflussen. Wissenschaftliche Ergebnisse zeigen, dass die tiefere Betrachtung von Lebensstilfaktoren nicht nur bei Entstehung und Verlauf von CED eine Rolle spielt, sondern auch bei der medizinischen Therapie von CED eine wesentliche Bedeutung zukommt.

Ziel: Zusammenführung des aktuellen Wissensstandes über die Relevanz von Lebensstilfaktoren in der medizinischen Behandlung von CED, die den Anforderungen und Grundsätzen einer bio-psycho-sozialen Therapie entspricht.

Methode: Basierend auf den Vorgaben eines 'Preferred Reporting Items for Systemic Reviews and Meta-Analyses extension for Scoping Reviews' (PRISMA-ScR) wurde ein Scoping Review über den Einfluss von Lebensstilfaktoren auf CED mit initialer Detektion wissenschaftlich hochrangiger Publikationen durchgeführt und tabellarisch zusammengefasst. Zudem erfolgte eine Endauswertung über die therapeutische Bedeutung der Kategorien ‚Ernährung‘, ‚Psychische Gesundheit‘ und ‚Körperliche Bewegung‘.

Ergebnisse: Im PRISMA Flow Diagramm wurde, nach Vordefinition von Ausschlusskriterien (Impact-Faktor, Sprache, Aktualität), der Verlauf der Literatursuche graphisch dargestellt: ausgehend vom Ergebnis der PubMed-Recherche (n = 1052), über den Selektionsprozess für das Volltext-Screening (n = 129), bis hin zu den ausgewählten, relevanten Publikationen (n = 40). Nach Zusammenfassung der wichtigsten Kernaussagen der selektierten Übersichtsarbeiten wurden die Ergebnisse des Scoping Reviews nochmals in Tabellenform gegenübergestellt. Neben einer Aufstellung von schützenden und schädlichen Lebensstilfaktoren, erfolgte die Auflistung von Vor- und Nachteilen der gängigsten ernährungsmedizinischen Interventionen. Die zur Behandlung von psychischen Belastungen von CED-Patient*innen am häufigsten empfohlenen psychologischen Interventionen wurden ebenso zusammengefasst, wie die positiven und negativen Auswirkungen von physischer Aktivität auf das Wohlbefinden von CED Patient*innen.

Diskussion: Die Einbeziehung von verschiedenen Lebensstilfaktoren in die medizinische Behandlung von CED, die dem Prinzip einer bio-psycho-sozialen Therapie entspricht, gewinnt zunehmend an Bedeutung. Die vorliegende strukturierte Darstellung evidenzbasierter, ernährungsmedizinischer und psychologischer Interventionen sowie körperlicher Aktivität bietet im Sinne einer individuellen, personalisierten medizinischen Behandlung von CED-Patient*innen eine mögliche Entscheidungshilfe.

Abstract

Introduction: Severe side effects of a lifelong immune modulating therapy can negatively affect outcome and quality of life for patients with Inflammatory Bowel Disease (IBD). Scientific results show that a deeper consideration of lifestyle factors does not only play a role in the development and progression of IBD, but also represents an important part in medical IBD therapy.

Aim: To bring together the current state of scientific knowledge about the relevance of lifestyle factors in medical treatment of IBD that meets the requirements and principles of a bio-psycho-social therapy.

Method: Based on the guidelines of a 'Preferred Reporting Items for Systemic Reviews and Meta-Analyses extension for Scoping Reviews' (PRISMA-ScR), a scoping review about the impact of lifestyle factors on IBD was conducted with initial detection of high-ranking scientific publications and was subsequently summarized in tabular form. Besides, a final evaluation on the therapeutic significance of the categories 'Nutrition', 'Mental Health' and 'Physical Activity' was performed.

Results: The course of the literature selection was presented graphically in PRISMA flow diagram, after predefinition of exclusion criteria (impact factor, language, actuality): starting with results of the PubMed search (n = 1052), and via the selection process for full-text screening (n = 129), to the final choice of relevant publications (n = 40). The most important key statements of selected review papers were summarized, and main results of the scoping review were provided in tabular form. Beside the comparison of protective and harmful lifestyle factors, the advantages and disadvantages of the most common nutritional interventions were listed. In addition, the most frequently recommended psychological interventions for the treatment of IBD patients with psychological disorders were summarized. Finally, positive, and negative effects of physical activity on the well-being of IBD patients were compared with each other.

Discussion: The inclusion of different lifestyle factors in the medical treatment of IBD, which corresponds with the principle of a bio-psycho-social therapy, is becoming increasingly important. The structured presentation of evidence-based, nutritional, and psychological interventions as well as physical activity offers a possible decision-supporting tool in the sense of an individual, personalized medical treatment of IBD patients.

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List of Abbreviations

AZA = Azathioprine

CBT = Cognitive behavioural therapy

CD = Crohn's Disease

CDED = Crohn's Disease Exclusion Diet

CED = Chronisch Entzündliche Darmerkrankungen

CD-TREAT = Crohn's Disease Treatment with Eating Diet

CRP = C-reactive Protein,

EEN = Exclusive Enteral Nutrition

FODMAP = Fermentable Oligo-, Di-, Monosaccharides And Polyols

GBD = Global Burden of Disease

IBD = Inflammatory Bowel Disease

IBD-AID = Inflammatory Bowel Disease Anti-Inflammatory Diet

IBS = Inflammatory Bowel Syndrome

IF = Impact Factor

IMID = Immune Mediated Inflammatory Disease

IOIBD = International Organization for Study of Inflammatory Bowel Diseases

MP = Mercaptopurine

NSAIDs = Nonsteroidal Anti-Inflammatory Drug

PEN = Partial Enteral Nutrition

PRISMA-ScR = Preferred Reporting Items for Systemic Reviews and Meta-Analyses
for Scoping Reviews

PST = Problem-Solving Therapy

RCTs = Randomized Controlled Trials

SCD = Specific Carbohydrate Diet

SCFA = Short-Chain Fatty Acids

SFT = Solution-Focused Therapy

TNF = Tumor Necrosis Factor

UC = Ulcerative Colitis

YLDs = Years Lived with Disability

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1 Introduction

1.1 Rationale

Inflammatory Bowel Disease (IBD) is a chronic immune disease of the gastrointestinal tract with acute recurring flares. A dysfunctional mucosal barrier combined with locally activated immune cells are leading to inflammation and consequently to necrotic tissue. Acute flares of IBDs should be treated immediately with the goal to reduce tissue damage and to induce remission [1]. A growing number of IBDs have been observed not only in western countries in Europe and North America but also in developing countries in Asia, Africa and South America as well, making it an important topic for health care providers, physicians, medical research teams and clinical trials worldwide [2].

The fast-growing numbers of IBDs are questioning the long hold theory of genetical predisposition together with a too hygienic environment ('hygiene hypothesis') as the main determinants for the onset of this autoimmune disease [3]. During the last decade, an enormous amount of IBD papers has been published, concerning possible environmental and lifestyle factors which could act as possible triggers for the development and progression of IBD. A better understanding of its pathophysiology and possible underlying mechanisms are essential in order to develop more effective therapeutic approaches in the treatment of IBD.

Immunosuppressive treatments with severe side-effects embedded in a lifelong therapy do not only have negative effects on the quality of life for IBD patients but also represent an economic challenge for national and international healthcare systems. The need to provide an adequate therapy for a growing number of patients around the world, highlights the importance of finding valuable supportive treatments, which should be easily available and affordable in order to limit adverse side-effects, improve patient's lives and reduce treatment-costs [4].

1.2 Background

The term IBD generally includes Crohn's Disease (CD), Ulcerative Colitis (UC) and indeterminate Colitis. The diagnosis of an 'indeterminate colitis' is made when symptoms of both CD and UC are present or no clear distinction between the two diseases can be made, and therefore a clear classification as CD or UC is not possible [5,6].

CD is a chronic disease with acute recurring flares which mainly occur between the age of 15 to 35. While the whole gastrointestinal tract from mouth to anus may be discontinuously affected, the most preferred location is the terminal Ileum, at the junction between the small and the large intestine. Typical symptoms comprise diarrhea, abdominal pain, anal fissures, and weight loss. Depending on the affected intestinal section, a malabsorption syndrome may lead not only to weight loss but also to anemia, gallstones, and growth disorders. CD has the tendency to form abscesses, stenoses and fistulas to other organs, which makes it so important to treat flares immediately and keep the patient in remission. Diagnostic procedures include

endoscopic and histologic examinations, where characteristic inflammatory patterns can be seen with ulcerations and inflammatory cells in all layers of the intestinal wall. Because of the occurrence of discontinuous infestations within and outside the gastrointestinal system, therapy of CD should treat flares and induce remission but may not cure the disease [5].

UC is a chronic immune disease of the intestine, where inflammation often starts in the rectum and spreads continuously to the adjacent area of the colon (image CU). Leading symptoms are often a slimy, bloody diarrhea, fever and abdominal pain. Imaging procedures like ultrasound and X-ray are used to show changes in intestinal architecture and motility. In histological samples inflammatory cells and ulcerations are not transmural as in specimen of CD but restricted to the intestinal mucosa of the bowel. Unsuccessful treatments may lead to complications like severe blood loss, toxic megacolon or colon perforation may occur. The complete surgical removal of the affected rectum and colon (proctocolectomy) is a final but possible option to eventually cure UC [5,6].

Both CD and UC may not only affect the gastrointestinal tract, but also show symptoms caused by extraintestinal manifestations like arthritis, osteoporosis, uveitis, primary sclerosing cholangitis (PSC), inflammations of the skin (Erythema nodosum, Pyoderma gangrenosum), and painful aphthous ulcers in the oral mucosa, etc [5,6].

The medicinal therapy of IBD is designed to treat the symptoms and should bring the patient into remission as early as possible. According to current guidelines [7,8], treatment of acute flares includes therapies with 5-aminosalicylic acid (5-ASA) and antibiotics. They should help to reduce inflammation and stabilize the patient. To keep patients in remission, the long-term treatment with immunosuppressants like Azathioprine (AZA) or Mercaptopurine (6-MP) has been recommended. As the immunosuppressive treatment needs some time to be effective, the use of glucocorticoids has been recommended to bridge the time, either locally (e.g., Budesonid) or systemically (e.g., Prednison). The invention of biologicals and their implementation in the treatment of IBDs have been a big step in the therapy of this chronic autoimmune disease. Biologicals like Tumor Necrosis Factor α antagonists (TNF α), Infliximab, show rapid immunosuppressive effects by decreasing the endogenous production of cytokines and limiting migration of immune defense cells [5]. If patients respond well to this treatment, severe side effects should be less frequent than with traditional immunosuppressants. A disadvantage of this costly therapy is that the treatment with biologicals may lead to the production of antibodies with consequent loss of effectivity. Though the therapy with immune-modulating medications may cause severe adverse side effects and complications, late and insufficient treatment has serious consequences for patients with IBD, showing an elevated risk for cancer [1,7,8].

Beside medications, modern techniques of minimal invasive surgeries have opened a new possibility of effective therapies to provide substantial benefit for patients, without the risk of severe medicinal side effects. Surgical interventions may therefore not be considered as 'ultima ratio' anymore [7]. But because of operation risks and possible risks of interference with the physiological integrity of the bowel, advantages and disadvantages have to be carefully compared beforehand.

Beneficial improvements have also been achieved concerning better follow-up examinations of patients in remission. Fecal calprotectin, an inflammation marker in the stool helps to control the course of inflammation without invasive blood analysis. In addition, high-resolution sonographic units allow a non-invasive overview of actual intestinal inflammation, helping to reduce colonoscopies. According to current guidelines [7], therapeutic approaches don't have to be only step-up but can also be top-down if they seem more adequate to meet individual needs, based on the recommendations for personalized medicine. In addition to improve the therapeutic outcome and to manage functional symptoms in patients with IBD, the consideration and implementation of lifestyle modifications in the clinical treatment of IBD has been recommended [9].

Lifestyle changes have shown to modify the microbiome of the gut. The intestinal microbiome is an ecological community consisting of trillions of bacteria that form a diverse and complex ecosystem in the gastrointestinal tract [10]. The microbiota affects the barrier function of the gut and supports the intestinal homeostasis. It also provides nutrients, regulates the epithelial development, participates in the signaling network and shows effects on the immune system [11].

The microbiome is able to ferment non-digestible dietary remnants by producing SCFA (short-chain fatty acids) which are able to cross the gut barrier to enter into the bloodstream. This way they reach different organs where they are involved in metabolic processes for producing energy, like the gluconeogenesis in hepatocytes. SCFAs are also found in the brain-gut-axis, needed for the release of 5-hydroxytryptamine, better known as serotonin. In addition, SCFAs are also known to help regulating inflammatory and immune responses of the body [12].

1.3 Geographical differences

During the last century, IBD was considered to be a chronic immune disease of high-income countries, affecting 2 million people in North America and 3.2 million in Europe [2]. Genetic susceptibility together with an elevated hygiene standard and a germ-reduced environment in the western culture, were the accepted theory for the rising number of incidences in the western world. But as descendants of migrants from developing countries have shown a higher risk to develop IBD in their new environment than their ancestors, it has been questioned whether the genetic predispositions might be as important as anticipated in the development of IBDs. This has also been supported by observations of a distinct increase of IBDs in newly industrialized countries in eastern Europe, South America, Asia, and Africa for the last decades, suggesting that environmental exposure combined with a western lifestyle may play an important role in the genesis of IBD [2].

1.4 Diagnosis and therapy

The implementation of new microbiological methods in the research field of IBD has made it possible to analyze the diversity of the intestinal microbiome, showing an altered and less diverse microbiome in patients with IBD at an early stage in life. Results suggest that microbial dysbiosis combined with genetic variations and environmental factors may be considered to play a major part in the development of

IBD [10]. Though it has become clear that the pathogenesis of IBD may be multifactorial, the exact cause which triggers this immune disease is still unknown. An early diagnosis of the chronic disease followed by the adequate treatment is crucial to limit the progression of the inflammation and to avoid long-term disability, especially for patients, who are affected at a young age. About 20 % of the patients with CD are diagnosed under the age of 20 years [5], at a time, when the immune system is not fully developed [3]. A life-long treatment with possible severe side-effects is required to prevent acute flares and keep patients in remission. But the therapy does not only affect their quality of life but is also very expensive, making it an economical challenge for the public health system and its local facilities [4].

To provide an early and effective treatment of IBD, the need for adequate medical infrastructure and diagnostic equipment as well as well-trained professionals and expensive medications put an increasing pressure onto the national healthcare systems [4]. This emphasizes the importance of a better understanding of the influence of environmental factors leading to this chronic disease. Despite of therapeutic improvements and new medications, adverse side effects of the treatment, diminishing effects of a long-term treatment as well as persisting physical and psychological symptoms have negative effects on the quality of life of patients with IBD. Especially the fact that IBD often affects patients at an early age, complementary medicine may reduce adverse side effects as well as sustain compliance and adherence to a lifelong therapy. This might not only lower the increase of IBDs worldwide with significant economic effects but may also have a valuable impact on the quality of life for patients with IBD [4].

1.5 Lifestyle interventions

Living with IBD is known to considerably compromise the physical, psychological, familial, and social aspects of life, ranking it as the fourth-leading cause of years lived with disability (YLDs) among digestive diseases [4]. Because of the rising number of IBD cases worldwide with an essential lifelong therapy, IBDs are not only a heavy burden for patients but also have considerable economic effects on public healthcare systems. During the last years, there has been a fast-growing interest in the effects of different lifestyle interventions on the outcome of the IBD-treatments. Especially diets, physical activity and psychological interventions have become topics of research studies and clinical trials, aiming to better understand the underlying mechanisms of this chronic disease in order to prevent the global increase of IBD [2].

In pediatrics, a different therapeutic approach has been chosen for the treatment of children with IBD. Because of severe side effects of the recommended clinical treatment for adult patients, with an increased vulnerability for infections, current guidelines recommend the Exclusive Enteral Nutrition (EEN) as first-line therapy for the treatment of pediatric CD [7]. Clinical studies showed that the therapeutic outcome with EEN was comparable with the treatment of cortico-steroids and was showing better results concerning the healing of the intestinal mucosa in colonoscopies of IBD patients [10]. This successfully proved what was long suspected that nutrition as part of a lifestyle intervention may have an impact on the treatment of IBD.

With the understanding that environmental factors show effects on the development of IBD, the main goal has been to define the most common lifestyle factors which

contribute to the genesis of or protecting from this chronic disease. Different environmental and lifestyle parameters have been studied to understand the underlying mechanism of IBD, starting with prenatal exposure followed by breastfeeding, the exposure to a certain climate, various hygienic conditions, certain infections, treatment with diverse medications, active or passive smoking, changing living situations, etc [3]. Given the wide variety of influencing factors, the development of a bio-psycho-social approach in the treatment of this chronic disease might help to improve the therapeutic outcome, patient's well-being, and treatment costs.

Diets have been the most explored lifestyle factors in research papers and clinical trials. Especially the influence of specific diets and the exclusion of certain food groups has been studied in the treatment of IBD patients. The reasons for the focus on nutritional therapies may be because of the success of EEN in the treatment of pediatric CD and because of well-known effects of an unhealthy western diet with a high amount of sugar and fat [12].

The enteric nervous system is the third largest accumulation of nerve cells beside the central nervous system and the peripheral nervous system. According to surveys among patients affected by IBD, one of the leading causes triggering symptoms or worsening their physical condition was 'perceived stress' [13]. That did not automatically mean that there had been real 'stressful' events in their lives, but IBD patients claimed to feel emotionally vulnerable towards their surroundings. It has been known for quite some time that there is a connection between the gastro-intestinal nervous system and the brain, forming the so-called 'brain-gut-axis'. Its communication works in both ways, meaning that gastro-intestinal symptoms may be affected by psychological conditions and vice-versa. Disorders in one area are more likely to cause disturbances in the other area. It has therefore been suggested that therapeutic interventions concerning the psychological health might have positive effects on the gastro-intestinal system and consequently on the patient's well-being [14]. Within the last years, a growing number of publications examined the therapeutic outcome of psychological interventions in the treatment of patients with IBD, according to a bio-psycho-social approach [15].

Physical activity has been one of the lifestyle-interventions that has become more relevant in the treatment of IBD during the last years. To improve not only the therapeutic outcome but also the quality of life of patients, physical exercises have been implemented in the treatment of chronic diseases for some time now [16]. Adequate and regular physical activity shows positive effects on the healing process by inducing the body to produce anti-inflammatory agents, by strengthening muscles and the connective tissue and by supporting the bone grafting and remodeling. Activity may also help to reduce the negative effects of malnutrition caused by IBD or, in other cases, will support to maintain a balanced body weight. In addition, physical exercise improves the psychological well-being by releasing endorphins [16].

1.6 Objective

In this thesis a scoping review of the current literature was conducted to analyze the impact of different lifestyle interventions on IBD and to show possible implications in the clinical treatment of this disease in accordance with a bio-psycho-social approach.

Systemic reviews and meta-analysis were studied, based on the ‘Preferred Reporting Items for Systemic Reviews and Meta-Analyses extension for Scoping Reviews’ (PRISMA-ScR) [17], to provide an overview of the current knowledge of lifestyle interventions and their effects on the therapeutic outcome of IBD. Besides, a closer look on the impact of dietary interventions, psychological therapies and physical activity should be provided and listed in a structured summary.

2 Materials and Methods

This thesis is designed to provide an overview of the current literature concerning the impact of lifestyle interventions on IBD. Based on the ‘Preferred Reporting Items for Systemic Reviews and Meta-Analyses extension for Scoping Reviews’ (PRISMA-ScR) a checklist served as guidance for implementing a relevant scoping review [17] to our chosen topic. The list was established by 26 experts and included 20 items (plus 2 optional items), which should ensure structure and reproducibility of the scoping review. The goal of the scoping review is defined to conduct an overview of the current research on a specific topic rather than getting specific results to a certain question. A scoping review should help to understand the development of the past and to identify priorities and gaps of research studies in the present. And finally, based on the findings and results, a scoping review should help to make decisions and facilitate recommendations for future research activities and clinical studies [17].

2.1 Literature research

Before a strategic search was started, several eligible criteria had been defined to ensure a valuable overview of current knowledge concerning the impact of lifestyle factors on IBD. It was decided to include only systematic reviews and meta-analyses in our search, which were published in English. Because of the fast-growing number of overview articles within the last decade, it was our goal to focus on the most substantial findings of recent years. Publications released in the chosen time frame between the years 2016 till 2022 were included in our search. As the worldwide increase of IBD has become more prominent during this time, numerous papers were published in high-ranking journals. To emphasize the clinical aspect of our topic, articles with focus on human studies were included in the screening process. And finally, the high-quality of selected papers concerning our research topic should be guaranteed by only selecting publications with impact factors of at least 3.5 and higher.

After defining eligible criteria, the search was performed on PubMed and repeated several months later (05/2021, 12/2021, 05/2022) to ensure a comprehensive search for relevant literature, and to include the latest findings in this thesis. It has been our intention to set the limits of the research strategies wide enough to get all relevant publications of the last years and tight enough to stay focused on our research objective. The results of the final search, which was done on May 1st, 2022, were exported to ‘Microsoft/Office/Excel’, where duplicates could be easily identified and removed from our list of search results.

2.2 Search strategy

Based on the objective of our scoping review to provide an overview of current literature concerning the impact of lifestyle interventions on IBD in general, as well as the effects of diets, psychological interventions, and physical activities, in particular, the following keywords were defined:

- ‘inflammatory bowel disease’
- ‘IBD’
- ‘lifestyle’
- ‘diet’
- ‘psychological’
- ‘physical activity’
- ‘exercise’

The Boolean Operators ‘AND’ plus ‘OR’ were implemented in our search strategy, interconnecting our keywords in order to narrow our search strategies. The searching procedure was repeated after several months to ensure the latest publications concerning the chosen topic were included in this thesis. The latest search was done on May 1st, 2022. The exact search strategies are listed in the table below:

Table 1 Search strategies in PubMed

Database	Search Strategies
PubMed	((inflammatory bowel disease) OR (IBD)) AND (lifestyle) AND ("2016/01/01"[Date - Publication] : "2022/05/01"[Date - Publication])
PubMed	((inflammatory bowel disease) OR (IBD)) AND (diet) AND ("2016/01/01"[Date - Publication] : "2022/05/01"[Date - Publication])
PubMed	((inflammatory bowel disease) OR (IBD)) AND (psychological) AND ("2016/01/01"[Date - Publication] : "2022/05/01"[Date - Publication])
PubMed	((inflammatory bowel disease) OR (IBD)) AND (physical activity) AND ("2016/01/01"[Date - Publication] : "2022/05/01"[Date - Publication]) OR ((inflammatory bowel disease) OR (IBD)) AND (exercise) AND ("2016/01/01"[Date - Publication] : "2022/05/01"[Date - Publication])

2.3 Selection of sources of evidence

After removing duplicates and before starting with the screening process of the titles it was made sure that all publications, identified by our keyword search, matched the defined criteria for inclusion. Articles with publishing dates before 2016, papers in other languages than English, and science journals with impact factors below 3.5 were excluded. Publications with focus on animal studies and preclinical studies were also excluded from the scoping review to emphasize the human and clinical aspect of our topic. Only systematic review papers and meta-analyses in English, published in high-ranking journals before the year of 2016 were included to provide a valuable overview of scientific research results and clinical studies concerning the impact of lifestyle factors on IBD.

Remaining publications underwent our selection process, with the goal to get all substantial research findings about the chosen topic. After the screening of the titles, the contents of the abstracts were subsequently examined and evaluated. According to predefined, eligible criteria with focus on clinical studies and human interventions, the most promising publications were selected for a full-text screening followed to identify which of the papers should be included in our scoping review, to provide a valuable overview of current, relevant results in the field of IBD research.

As mentioned earlier, our goal was to summarize the latest findings concerning the impact of different lifestyle factors and potential implications for the clinical treatment of IBD. The focus was on clinical studies, which examined the effects of various treatments. Review papers and meta-analyses were preferred, when they compared and discussed results of Randomized Controlled Trials (RCTs), as they represent the highest available standard of clinical studies. Besides, review papers were also chosen, when they included observational studies which had been carried out to investigate different outcomes of lifestyle interventions in the treatment of IBD.

As the effects of lifestyle factors on the development and the course of IBD represent a relatively new field of research, the amount of RCTs and observational studies have been limited. To provide a comprehensive overview of the current trend and level of knowledge in this field, it was decided to include review article, published in high-ranking journals, which also included cross-sectional clinical studies in their analyses.

2.4 Synthesis of results

First of all, it was important to find out whether lifestyle factors showed essential impacts on the development and/or on the course of IBD. By comparing substantial results and important outcomes of current literature, the next step was to identify which kind of lifestyle factors were agreed to show significant influence on the clinical treatment of IBD. Three modifiable lifestyle factors, which have shown to be beneficial in clinical trials – diets, psychological health, and physical activity - were chosen for the next literature search. Finally, the results about their impact on the outcome of IBD were summarized. It has been our ambition to provide an overview about modifiable lifestyle factors which, on the one hand, could delay or even prevent the development of IBD, and, on the other hand, could be implemented in clinical treatments of IBD to improve not only the course of the disease but also the quality of life for patients with IBD.

To provide a decision-supporting tool in the sense of an individual, personalized medical treatment of IBD patients, a structured comparison of protective and harmful lifestyle factors was provided as well as a summary of the most common diets, implemented in IBD therapy. Besides, recommended psychological interventions for the treatment of frequent symptoms of IBD patients were summarized, and finally, positive, and negative effects of physical activities on the outcome of IBD treatments were listed in tabular form.

3 Results

3.1 PRISMA flow diagram

The PRISMA flow diagram below in Fig. 1, shows the result of our literature search. Beside the number of duplicates, it shows how many papers were removed because of predefined criteria for exclusion (impact factor, language, date of publication) by title screening. The remaining articles were found suitable for abstract screening. Finally, publications that appeared to contain substantial information about the chosen topic, were included in the full-text screening process. Our goal was to find relevant review papers and meta-analysis which covered not only the impact of lifestyle factors on development and/or course of IBD, but also possible implications of different lifestyle interventions like diets, psychological health, and physical activity in the clinical treatment of IBD.

When entering the pre-defined search strategies in PubMed, mentioned above in table 1, 1052 review papers and meta-analyses in total were indicated to meet the entered criteria. The sum comprised 144 publications concerning lifestyle factors, 594 articles about diets, 152 papers on psychological health and 162 articles dealing with physical activity and exercise.

Before starting with the screening process, 158 duplicates were removed from our list of results, leaving 894 publications. The application of the predefined criteria of inclusion reduced the number of papers further by 478 titles, leaving 421 articles for abstract screening. After removing 292 papers, which did not seem to cover the chosen topic of our thesis, 129 articles remained for a full-text analyses. Finally, 40 review papers and meta-analyses were selected to be included in our scoping review about the impact of lifestyle factors on IBD with possible implications for clinical treatment.

The final decision, which of the articles should be included in our scoping review, was the most difficult one. One of our goals was to determine, whether lifestyle and environmental factors showed an impact on development and course of IBD. The next aim was to determine, whether the implementation of lifestyle factors in the clinical treatment of IBD influenced the therapy outcome and the quality of life for patients with IBD. Above all, to meet the expectations of a scoping review, different approaches and perspectives should be represented in our analysis to provide a valuable overview of the current literature.

As lifestyle and environmental factors have shown to modify the microbiome, it was important to include the role of the microbiome and its impact on the outcome of IBD in this work. Because of improved technologies and new methods, the huge number

of knowledge about the importance of the microbiome, analyzed in numerous microbiological publications would fill at least one other master thesis. According to our predefined goals, it was decided, to include only papers, which covered the topic concerning medically and clinically relevant findings.

IBD articles about diets outnumbered the sum of IBD papers about lifestyle, psychological health and physical activity combined. Nutraceuticals represent a new field of growing interest within dietary interventions with an increasing number of publications during the last years. To manage the big amount of information and to provide a valuable overview of clinically relevant diets, it was decided to exclude nutraceutical from this scoping review.

Finally, because of recurring findings of different publications without new, essential insights and no significant clinical outcomes, it was decided to favour papers with higher impact factors. This should emphasize the attention and recognition, which lifestyle and environmental factors have gained by the research community during recent years.

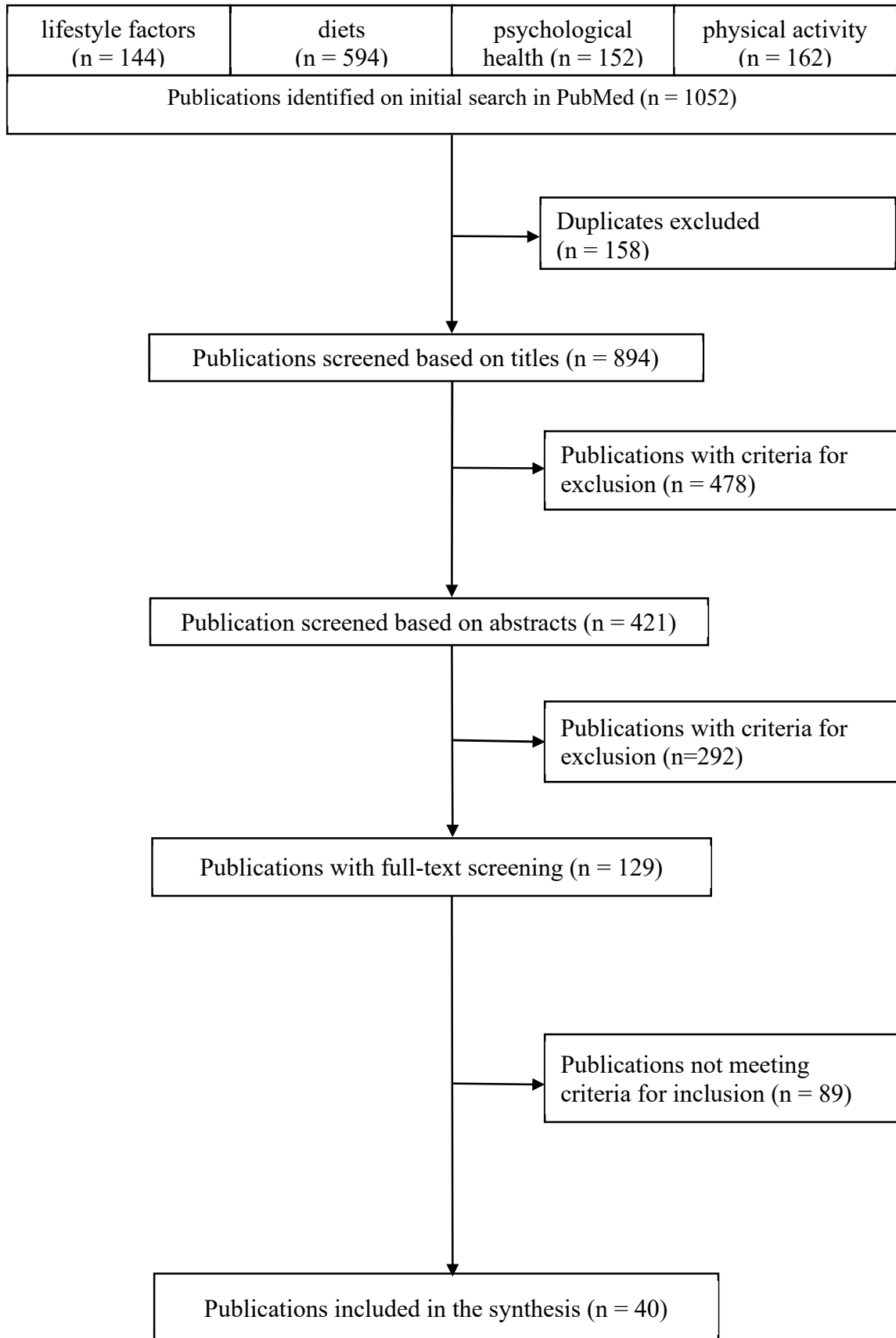


Figure 1 PRISMA-ScR flow diagram [17]

3.2 Characteristics of sources of evidence

According to our search strategies, the obtained results were divided into four different categories in order to meet our goal to provide:

- (1) a basic overview concerning the impact of different lifestyle factors on development and outcome of IBD;
- (2) a closer look into several dietary strategies used to improve the patient's symptoms and its effects on inflammation parameters;
- (3) the influence of IBD on psychological health of patients as well as the impact of stress and mental problems on the outcome of IBD;
- (4) the effects of physical activity on the course of IBD and its importance in the treatment of this disease;

According to the four different categories, we summarized the selected publications with a short description of the covered topic (table 2, 3, 4 and 5). When indicated, the numbers of included meta-analyses, cohort studies, case-control studies, randomized controlled trials and cross-sectional studies were added to the characteristics of the chosen review papers. In some articles, these numbers were not specified separately, so we referred to the original publication, where the list of included references could be found.

3.2.1 Lifestyle factors and IBD

The growing number of patients with IBD in westernized societies has drawn the attention of the research community to environmental and lifestyle factors during the last years. 11 review articles were found to be adequate for providing a substantial overview about the impact of lifestyle and environmental factors on development and course of IBD, as summarized below in table 2 and followed by a short description of the chosen publications.

Table 2: Selected review papers on lifestyle factors and IBD

Nr	Paper	Year	IF	Topic and reviewed studies
1	Dutta AK et al. World J Gastroenterol [18]	2016	5.4	Impact of environmental factors on IBD: - 6 meta-analyses (2007 to 2012) - 1 RCT (2006) - 15 cohort studies (2012 to 2014) - 15 case control studies (2005 to 2014)
2	Kaplan GG et al. Gastroenterology [2]	2017	33.9	Development of IBD since 1859: Epidemiologic studies in 63 countries
3	Van der Sloot KWJ et al. Inflamm Bowel Dis [3]	2017	7.3	Protective factors and risk factors for the development of IBD in children and adults: - 13 meta-analyses (2000 to 2012) - 14 cohort studies (2006 to 2015) - 4 case control studies (2005 to 2010) - 2 cross-sectional studies (2008)
4	Shouval DS et al. JAMA Pediatr [10]	2017	26.8	Impact of environmental factors in the pathogenesis of paediatric IBD.
5	Ho SM et al. Inflamm Bowel Dis [19]	2019	7.3	Causative role of environmental triggers in the pathogenesis IBD.
6	Barnig C et al. Front Immunol [20]	2019	8.8	Impact of lifestyle factors on the resolution of inflammation in IBD and asthma.
7	Ananthakrishnan AN et al. Clin Gastroenterol Hepatol [21]	2020	13.6	Changing epidemiology of IBD and steps for sustainable IBD care.
8	Rozich JJ et al. Am J Gastroenterol [13]	2020	12.0	Effects of modifiable lifestyle factors on IBD, including the impact of obesity.
9	Global Burden of Disease (GBD) IBD collaborators Lancet Gastroenterol Hepatol [4]	2020	45	Global, regional, and national burden of IBD in 195 countries (1990 to 2017).
10	Caparrós E et al. Gut Microbes [22]	2021	9.4	Role of the intestinal microbiome in the pathogenesis of IBD.
11	Ananthakrishnan AN et al. International Organization for Study of Inflammatory	2022	45.0	19 consensus statements concerning lifestyle, behavior, and environmental modifications in the management of IBD.

	Bowel Diseases consensus (IOIBD) [23]			
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GBD = Global Burden of Disease, IOIBD = International Organization for Study of Inflammatory Bowel Diseases consensus

In Dutta AK et al [18] several environmental factors were linked not only with the onset of IBD but also with disease exacerbation in patients with ongoing IBD. It was concluded that lifestyle factors may increase the risk for developing IBD or may be protective against the onset of IBD. They might also influence the course of the disease in a positive or negative way. Based on the different pathogenesis of CD and UC, it was emphasized that a distinction between CD and UC should be made when analyzing the effects of different lifestyle factors on the onset and the course of IBD.

The global development of IBD during the last century was analyzed by Kaplan GG et al [2], showing data from 63 different countries. The increase of IBD was related to the westernization and industrialization of societies, especially because of diets and environmental factors. A better understanding of underlying mechanisms of protective and risk factors together with the knowledge of geographical differences might be essential for the development of a long-term plan to reduce the global increase of IBD in the future.

In the publication of IBD Collaborators in the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) [4] data about prevalence, mortality, and overall burden of IBD were collected in 195 countries and territories around the world between the years 1990 to 2017. The included overview on the changing epidemiology of IBD during the last decades should not only bring insight into the burden and trends of this disease but could also help to understand the underlying cause of IBD.

The authors of Ananthakrishnan AN et al [21] observed a changing pattern in the global epidemiology around the beginning of the 21st century. While the number of cases of IBD has stabilized in Western countries due to more effective but costly medical treatments, the incidence of IBD has risen in newly industrialized countries. Observational studies identified environmental exposure together with Westernization of societies as driving forces of this development. Primary prevention by changing environmental exposures for patients might be important to provide globally sustainable medical care for a growing number of IBD patients in the future.

In the clinical review of Van der Sloot KW et al [3] the influence of environmental factors was analyzed for UC and CD, separately. The authors emphasized the significance of different times of exposure of environmental factors. It was indicated that an evolving immune system during childhood is affected differently than a fully developed one during adulthood. Protective and risk factors were summarized for both children and adults. In addition, environmental factors which showed to be independent of the lifetime exposure were also analyzed.

In the work of Shouval DS et al. [10], it was pointed out that the upward trend of IBD in children worldwide could not only be explained by genetic susceptibility. It

was emphasized that environmental factors should not be underestimated in the genesis of IBD. In addition, the microbiome was identified to represent an important link between IBD and environmental factors, which in turn may lead to microbial dysbiosis. The paper of Rozich JJ et al. [13] covered the impact of modifiable lifestyle factors on the course and outcome in patients with established IBD. In addition, obesity and its effects on IBD were analyzed in order to provide a better understanding of its influence on the natural history of this autoimmune disease. It was shown that obesity was associated with an increased risk of relapse or persistent disease activity and a lower rate of clinical remission.

In Ho SM et al. [19] the significance of environmental factors and its role in susceptibility, progression, and relapse of IBD was highlighted. According to their findings, the underlying cause for the onset of IBD could not be traced to one trigger only but rather to a cumulative or acute impact of all exposures during an individual's lifetime. Onset and outcome of IBD were determined by a phase of vulnerability, like an early period of life or an impaired immune system. The way that different lifetime exposures interact with one individual's genome were defined as the so-called 'exposome'.

Barnig C et al [20] pointed out that the ability to resolve an inflammatory process was poor or inappropriate in patients with chronic diseases like IBD. Therapies with immuno-suppressant medications have come with an increased risk of infections without altering the natural history of the disease. A better understanding of how lifestyle factors could influence the resolution phase of the inflammatory response would be essential to find new ways of affordable and personalized therapies for IBD patients.

The review paper of Caparrós E et al. [22] focused on the intestinal microbiome and its role in the pathophysiology of IBD. Beside genetic background, immune inflammatory and fibrotic processes, they highlighted the impact of lifestyle factors, like diets, smoking and physical exercise, on the modification of the intestinal microbiome in order to achieve stable remission in patients with CD. Finally, perspectives into future disease management of IBD with a personalized approach were provided.

Finally, in the publication of Ananthakrishnan AN et al [23], on behalf of the International Organization for Study of IBD (IOIBD), a group of international experts voted on the significance of different lifestyle factors as well as on behavioural and environmental modifications. The defined goal was to publish a list of proposed consensus statements for modifications in the management of patients with IBD. From an initial list of 22 lifestyle, behavioural, and environmental factors, a set of 11 content areas were selected by task force members in a first round of voting. After individual working groups finished literature reviews, 60 consensus statements were proposed. In a second round of voting by all members, content areas were condensed into 20 proposed statements. Finally, 19 consensus statements were accepted in a third round of voting by all members.

3.2.2 Diets and IBD

Diets and their impacts on development and course of IBD have caught the attention of the research community leading to the successful implementation of dietary interventions in the treatment of IBD in children [12]. 10 worthwhile review papers were selected out of a large number of highly interesting scientific publications to provide an overview on the relevance of diets, implemented in the clinical therapy of IBD. It would go beyond the scope of this thesis to list all different kinds of available diets, so it was decided to describe the most common dietary interventions implemented in the treatment of IBD.

Table 3: Selected review papers on diets and IBD

Nr.	Paper	Year	IF	Topic of Review
12	Lewis JD et al. Gastroenterol [12]	2017	33.9	Role of diets not only as a trigger but also as therapy for IBD.
13	Pigneur B et al. Ther Adv Gastroenter [24]	2019	4.8	Impact of different nutritional interventions on IBD.
14	Gu P et al. Inflamm Bowel Dis [25]	2020	7.3	Effect of diets on pathogenesis, exacerbation, and treatment of IBD.
15	Levine A et al. Clin Gastroenterol Hepatol [26]	2020	13.6	Dietary recommendations for IBD: - 1 meta-analyse (2017) - 6 RCTs (1987-2019) - 10 cohort studies (2004-2017) - 13 case control studies (1989-2018) - 8 cross-sectional studies (2010-2018)
16	Sasson AN et al. Clin Gastroenterol Hepatol [27]	2021	13.6	Diet as a modifiable risk factor, implemented in the therapy of IBD: - 22 RCTs (1984-2019)
17	Starz E et al. nutrients [28]	2021	6.7	Diets with altering effects on the gut microbiota in patients with IBD.
18	Trakman GL et al. J Gastroen Hepatol [29]	2021	4.4	Dietary effects on the microbial composition and function.
19	Walter M et al. Nat Rev Gastro Hepat [30]	2022	73.1	Importance of diets in the modification of the gut microbiome. - 14 studies in humans (meta-analysis, RCTs, cross-over, cross-sectional studies).
20	Jian Y et al. nutrients [31]	2021	6.7	Dietary interventions in the treatment of IBD and IMID:

				- 20 studies on IBD, - 14 studies on IMID.
21	Simões CD et al. Eur J Nutr [32]	2021	5.6	Therapeutic effects of low-FODMAP diets on IBD and gut microbiota: - 7 RCTs - 2 cross-sectional studies - 2 interventional studies

IMID: Immune Mediated Inflammatory Disease;

In the paper of Lewis JD et Abreu MT [12], findings of clinical and basic science studies concerning the role of different diets as trigger or therapy for IBD were presented. The authors showed an overview of several diets, foods, and food groups and discussed the potential of various dietary strategies with the purpose to alter the risk of disease development and intestinal inflammation.

The link between diets and IBD as well as the impact of diets on the composition of the intestinal microbiota was pointed out in the publication of Pigneur B et Ruellemele FM [24]. The most common dietary interventions were summarized, including benefits and drawbacks of the different dietary approaches. Based on the obtained results, recommendation for both clinicians and IBD patients were summarized.

Gu P et Feagins LA [25] highlighted the imbalance between patient's request for dietary information and limited dietary resources for physicians. The authors summarized the findings from the most studied diets, implemented in the treatment of IBD, and included advantages and disadvantages of the different dietary approaches. Especially the need for more studies concerning the effectiveness of dietary interventions in adult patients with IBD was emphasized.

In the publication of Levine A et al [26] dietary guidelines from the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) were provided, based on the best available evidence. Instead of recommending certain dietary strategies for the treatment of IBD, it was decided to limit recommendations to food groups, dietary components, and food additives. A group of 12 experts, forming the Nutrition Cluster of IOIBD, voted on proposed recommendations. Consensus was defined when expert agreement reached at least 75%.

As diets represent a modifiable environmental risk factor in the development and course of IBD, dietary interventions were identified to be important tools in the treatment of IBD by the authors Sasson AN et al [27]. Diets have been known to affect the immune system, to alter the intestinal permeability and to modify the microbiome of the gut. Details of clinical studies about the most common dietary interventions in the management of IBD were summarized and compared with each other in this publication.

The impact of diets on gastrointestinal symptoms of IBD patients as well as on composition and diversity of the intestinal microbiome were investigated in the paper of Starz E et al [28]. Effects of different reduction and elimination diets, which were

frequently used in the treatment of IBD, and possible consequences for the gut microbiota composition were analyzed by the authors.

The relationship between diets, intestinal microbiome, and IBD were reviewed in the paper of Trakman GL et al [29]. The implementation of new microbial technologies in the analysis of the microbiome have supported the understanding of dietary effects on the composition and diversity of the gut microbiota.

The current knowledge about the impact of diets on the modification of the gut microbiome was presented in the work of Walter M et al [30]. The importance of changing diet and modified environmental factors in the development and rise of autoimmune diseases were investigated in this review paper.

Evidence-based recommendations for the implementation of diets in the treatment of IBD have been limited. In the work of Jiang Y et al [31], adjunctive dietary interventions in the therapy of IBD were analyzed and compared with results from common diets in other immune-mediated inflammatory diseases to gain additional information for health care providers.

Dietary approaches as adjunctive therapies for IBD often imply an exclusion of certain food and/or food groups. Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) have been one of the best-known restrictive diets in the management of IBD. Possible consequences of nutritional deficiencies and intestinal dysbiosis of FODMAPs were investigated in the review paper of Simões CD et al. [32].

3.2.3 Psychological health and IBD

The observed correlation between psychological intervention and the outcome of IBD has led to an increasing number of publications within the last years. The interaction of the ‘brain-gut-axes’ with possible effects on the microbiome as well as the impact of psychological health on development and course of IBD has been investigated by a number of high-ranking publications.

The ability of adjusting to IBD and its correlation with outcome of IBD treatments were investigated in the paper of Jordan C et al [14]. Their declared goal was to find certain psychological factors, which would be modifiable through psychological interventions, in order to improve therapeutic results and health-related quality of life of IBD patients.

Abdominal pain has been identified as a common but often under-treated symptom in IBD patients with negative impacts on their quality of life. The review paper of Norton C et al [34] summarized different psychological approaches with the purpose to improve the pain management of patients with IBD.

To meet the requirements of a bio-psycho-social approach, it has become more relevant to highlight the influence of psychological health on the outcome of IBD. In the paper of Gracie DJ et al [15], a systematic review and meta-analysis on the effects of psychological therapy on disease activity and well-being of IBD patients was provided.

The need for a better understanding of the interaction between neurobiology, psychological symptoms, and social ramification was emphasized in the publication of Regueiro M et al [35], with the aim to provide an adequate and comprehensive treatment for patients with IBD.

An update of best clinical practice was summarized in the expert review paper of Keefer L et al [14], published by the American Gastroenterological Association (AGA). Recommendations and practice advice about the implementation of psychogastroenterology in the treatment of IBD patients were presented in their article.

Table 4: Selected review papers on psychological health and IBD

No.	Paper	Year	IF	Topic of Review
22	Jordan C et al. Clin Psych Rev [33]	2016	11.4	Identification of psychological factors related to adjustments in IBD patients: - 24 cross-sectional studies (1982-2015), - 1 longitudinal correlation (2005).
23	Norton C et al. Pharmacol Ther [34]	2017	9.5	Psychologic interventions for pain management in patients with IBD. - 13 interventional studies, - 2 cross-sectional studies
24	Gracie DJ et al. Lancet Gastroenterol Hepatol [15]	2017	45.0	Impact of psychological therapy on the course of IBD, and quality of life: - 14 RCTs (1998-2016)
25	Regueiro M et al. Gastroenterology [35]	2017	33.9	Comprehensive treatment of pain and psychosocial conditions in IBD patients.
26	Keefer et al. Gastroenterology [14]	2018	33.9	Implementation of psychogastroenterology in the treatment of digestive disorders like IBD: best practice update.
27	Borren NZ et al. Nat Rev Gastro Hepat [36]	2019	73.1	Pathogenesis and therapy of fatigue in patients with IBD: - 17 clinical studies (2003-2017).

28	Olischlaeger Y et al. Cells [37]	2019	7.7	The role of stress in the pathophysiology of IBD: - 8 RCTs (2005-2015), - 8 clinical studies (2001-2016), - 1 meta-analysis (2017).
29	Gracie DJ et al. Lancet Gastroenterol Hepatol [38]	2019	45.0	Effect of the brain-gut axis on IBD outcome and management: - 2 RCTs (2017), - 1 meta-analysis (2017).
30	Thomann AK et al. Aliment Pharmacol Ther [39]	2020	9.5	Influence of microbiota-brain-gut interactions on psychiatric symptoms in IBD patients: - 10 clinical studies (2009-2019), - 3 RCTs (2015-2018).
31	Labanski A et al. Psychoneuroendocrinology [40]	2020	4.7	Correlation between stress and the brain-gut-axis in patients with IBD.

Fatigue has been named as one of the most disturbing clinical symptoms by IBD patients. New insights about pathophysiology and treatment of fatigue were provided in the publication of Borren NZ et al [36]. The findings about incorporation of psychological interventions in the management of fatigue in patients with IBD were summarized in this review.

Stress, as a common lifestyle factor, with known effects on the development and course of IBD were analyzed in the paper of Olischlaeger Y et al [37]. Possible implications of stress management in the treatment of IBD were evaluated by the authors. Another publication about the impact of stress on IBD was published by Labanski A et al [40]. The influence of stress on the brain-gut-axis and their correlation on the outcome of IBD management was investigated in their paper.

The bi-directional communication between the enteral nervous system and the central nervous system was described as the ‘brain-gut-axis’. Its relevance to the development and the course of IBD as well as to the well-being of IBD patients with possible implications for treatment were analyzed in the review of Gracie DJ et al. [38].

Finally, in the paper of Thomann AK et al [39], the correlation between brain and gut was expanded by the inclusion of the intestinal microbiota. The so-called ‘microbiota-brain-gut’ interaction and their impact on the pathogenesis of psychiatric symptoms in IBD patients were reviewed by the authors.

3.2.4 Physical activities and IBD

Even though the relevance of physical activity and exercise training in the management of chronic diseases like IBD have been known for quite some time, clinical studies about the impact of physical activity on the outcome of IBD treatments are still limited. Nonetheless, the effects of physical exercise were investigated in remarkable scientific publications, which are listed in table 5 below.

Table 5: Selected review papers on physical activity and IBD

No.	Paper	Year	IF	Topic of Review
32	Wang Q et al. Dig Liver Dis [41]	2016	5.2	Correlation between physical exercise and the risk of IBD: - 5 case control studies (1987-2013), - 2 cohort studies (2013).
33	Artom M et al. J Crohns Colitis [42]	2016	9.1	Identification of modifiable factors for the treatment of fatigue in patients with IBD.
37	Monda V et al. Oxida Med Cell Longev [11]	2017	6.5	Positive effects of exercise on the intestinal microbiome.
35	Sharif K et al. Autoimmun Rev [16]	2018	9.8	Impact of physical activity on autoimmune diseases.
36	Elia J et al. Inflamm Bow Dis [43]	2018	5.3	Role of physical rehabilitation programs on patients with IBD.
34	Farrell D et al. Cochrane Database Syst Rev [44]	2020	12.0	Interventions for the management of fatigue: - 16 RCTs.
38	McGing JJ et al. Aliment Pharmacol Ther [45]	2020	8.2	Potential therapies in the treatment of fatigue in IBD patients: - 2 RCTs (2016-2019), - 9 interventional studies (1998-2020).
39	Skrzypczak D et al. nutrients [46]	2021	5.7	Pathogenesis and management of osteosarcopenia in patients with IBD.
40	Koutouratsas T et al. World J Gastroenterol [47]	2021	5.7	Influence of physical exercise on gut dysbiosis in IBD patients: - 12 clinical studies.

In the meta-analysis of Wang Q et al [41], the relationship between physical activity and the risk of developing IBD was investigated. The identification of modifiable, physical factors as possible targets in the treatment of IBD was the objective of the paper from Artom M et al [42], in order to improve fatigue-related symptoms in IBD patients. An overview of the impact of physical activity on the outcome of autoimmune diseases in general was provided in the review of Sharif K et al [16]. Therapeutic effects and the benefit of exercise training on wellbeing and quality of life for patients were evaluated.

A Cochrane Database of Systemic Reviews, published by Farrell D et al [44] summarized research findings of non-pharmacological interventions for the treatment of fatigue in patients with IBD. Including the comparison of therapeutic results between physical activity groups and groups with no physical activity.

The importance of a better understanding of the pathogenesis of fatigue in patients with IBD was highlighted by the authors of McGing JJ et al [45]. Based on the scientific findings of their analysis, exercise training was included as potential strategy in the management of fatigue in IBD patients.

The influence of physical exercise on the composition and diversity of the intestinal microbiota was analyzed in the publication of Monda V et al [11], with possible implications for the treatment of patients with IBD. Another review about the importance of exercise on the modification of the intestinal microbiome was highlighted by Koutouratsas T et al [47]. The role of physical activity in the prevention and restoration of dysbiosis in the gut was summarized in their work.

In the paper of Elia J et al [43], the existing knowledge about effects of physical rehabilitation programs and structured exercise on the treatment of primary and secondary symptoms of IBD were analyzed. Osteoporosis and sarcopenia have been identified to frequently affect patients with chronic diseases like IBD. The impact of physical activity on the management of osteosarcopenia in IBD patients were evaluated by the group of Skrzypczak D et al [46].

3.3 Results of individual sources of evidence

A summary of relevant outcomes from the selected review-paper are shown in tables no. 6, 7, 8, and 9 below. Beside authors, journal, publishing year and key findings, we decided to add the impact factor (IF) of the journal. This should not lead to a ranking of the different results but rather show the shifting of attention that the influence of lifestyle and environmental factors on IBD received in the research community during the last years. The listing was done according to the year of publication, starting with the earliest papers. This way the history of the rise in knowledge should be more comprehensible.

3.3.1 Lifestyle and IBD

A listing of key findings from the selected publications about the effects of lifestyle factors on IBD is found in table 6 below. It should give a simple overview about the provided results concerning the impact of lifestyle factors and environmental factors

on development, course, and clinical outcome of IBD. The short summary of statements may not always draw a complete picture of the selected paper, but it should emphasize the main finding of the review, which is printed in bold letters.

Table 6: Important findings about lifestyle factors and IBD

Effects of lifestyle factors on IBD			
Ref. #	Paper	IF	Key findings
18	Dutta AK et al. World J Gastroenterol 2016	5.4	<ul style="list-style-type: none"> • Environmental factors have an important impact on development and course of IBD. • Smoking shows negative effects on the course of CD but not on UC. • Perceived stress is associated with an increased disease exacerbation in patients with IBD. • Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) may increase the risk of flares in patients with IBD. • Higher intake of meat and alcohol was associated with a higher risk of relapse in patients with UC. • Physical activity is associated with decreased disease activity in patients with IBD.
2	Kaplan GG et al. Gastroenterology 2017	33.9	<ul style="list-style-type: none"> • Industrialized societies show an increase of patients with IBD. • A less hygienic environment is inversely associated with the risk of IBD • Smoking increases the risk of CD, whereas quitting of smoking enhances the risk of UC. • The western diet with an increased intake of sugar and fat as well as fewer dietary fibers is associated with a higher risk of IBD.

			<ul style="list-style-type: none"> • An enhanced use of antibiotics represents a risk factor for IBD. • Breastfeeding and a high level of vitamin D might be protective against the development of IBD. • The consumption of tea and coffee show protective effects against IBD.
3	Van der Sloot KWJ et al. Inflamm Bowel Dis 2017	7.3	<ul style="list-style-type: none"> • During childhood, environmental exposures play an important role in the development of the immune system. • During adulthood, lifestyle is a more apparent factor to modify an already existing immunologic system. • Regardless of the current stage in life, environmental factors like geographical variations, acute bacterial gastroenteritis, and vitamin D affect the immune system. • Protective factors during childhood are breastfeeding, a less hygienic environment and an infection with <i>Helicobacter pylori</i>. • Risk factors during childhood include the use of antibiotics, an urban environment, and a high hygiene level. • Risk factors during adulthood are smoking, depression and medications like antibiotics, NSAIDs and oral contraceptive pills.
10	Shouval DS et al. JAMA Pediatr 2017	26.8	<ul style="list-style-type: none"> • Environmental factors are playing a critical role in the development of IBD in children. • The microbiome represents the link between environment and the potential risk of IBD. • Microbial dysbiosis is observed in patients with IBD.

			<ul style="list-style-type: none"> • Protective factors against IBD are early life events like breastfeeding, higher intake of fibers from fruits and vegetables, vitamin D and regular physical activity. • Risk factors for the development of IBD like smoking, antibiotics, nonsteroidal anti-inflammatory drugs, oral contraceptive pills, specific diets, pollution, psychosocial stressors, and sleep disturbances may lead to alterations of the microbiome.
19	Ho SM et al. Inflamm Bowel Dis 2019	7.3	<ul style="list-style-type: none"> • It is important to understand the causative role of the environment in development, course, and relapse of IBD. • High priority environmental triggers of IBD include: => smoking (risk for CD, protective in UC), => diet, => dysbiosis of the gut microbiome, => psychosocial stressors, => medication (NSAIDs, antibiotics, oral contraceptives), => pollution;
20	Barnig C et al. Front Immunol 2019	8.8	<ul style="list-style-type: none"> • Lifestyle factors together with physical condition and psychological health show an impact on the response of the immune system. • A better understanding of how IBD is influenced by environmental factors may lead to new forms of personalized therapies. • Protective factors against IBD include: => dietary interventions; => physical activity, => stress management.

21	Ananthakrishnan AN et al. Clin Gastroenterol H 2020	13.6	<ul style="list-style-type: none"> • The modulation of environmental exposures has the potential to prevent the development of IBD. • Protective factors for IBD are: <ul style="list-style-type: none"> => breastfeeding during infancy, => non-smoking, => diets high in fruits, vegetables, fibres and fish or oil. => avoiding Vit D deficiency, => reducing the use of NSAIDS, => minimizing the use of antibiotics => less food that contains emulsifiers and food additives, => moderate physical activity, => regular sleep, => low stress and healthy weight,
13	Rozich JJ et al. Am J Gastroenterol 2020	12.0	<ul style="list-style-type: none"> • Lifestyle factors show impacts on the outcome of IBD treatments. • Recreational activity decreases the risk of flares, obesity increases the risk of flares. • Perceived stress may trigger symptomatic exacerbations. • Sleep disturbances increase the risk of relapses. • Cigarette smoking is associated with negative outcomes in patients with Crohn’s Disease (CD) but not in patients with Ulcerative Colitis (UC).
4	Global burden of disease (GBD) 2017 IBD Collaborators Lancet Gastroenterol 2020	45.0	<ul style="list-style-type: none"> • The global burden of IBD increased considerably during the last 30 years. • Rising number of IBD worldwide plus an ageing population will show substantial consequences for health care and economic systems. • About 3.9 million females and 3 million males live with IBD worldwide, with a lower death rate among women.

			<ul style="list-style-type: none"> • Importance of understanding environmental determinants of IBD for successful clinical interventions. • Growing interest to find simple and cost-effective interventions at the primary-care level. • Potential risk factors for IBD are: => Smoking, => Discontinued breastfeeding, => Enteric infections, => Air pollution, => Diets high in meat and low in dietary fibres, => Urbanization.
22	Caparrós E et al. Gut Microbes 2021	9.4	<ul style="list-style-type: none"> • Not only genetics, but also epigenetic factors like the environment are relevant in the development and course of IBD. • Lifestyle factors like diets, smoking and exercise have substantial influence on the shaping of the microbiome. • Changing diets, quitting smoking, and boosting exercise may shift the microbiome to eubiosis, which in turn may lead to stable remission in CD. • The dysbiosis of the gut microbiota challenges the intestinal barrier function, resulting in a pathological immune response of the host.
23	Ananthakrishnan AN et al. (IOIBD) Lancet Gastroenterol 2022	45.0	<ul style="list-style-type: none"> • Lifestyle and environmental factors play an important role in the natural history of IBD. • Cigarette smoking should never be started to reduce the risk of IBD. • Regular physical activity and maintaining a normal body-mass index should be recommended to patients with IBD. • Adopting an evidence-based diet and monitoring for nutrition

			<p>deficiencies is recommended, when using elimination diets.</p> <ul style="list-style-type: none"> • Screening for psychosocial stressors and symptoms of depression and anxiety when treating patients with IBD. • Patients with IBD don't have to avoid alcohol consumption, but excessive intake of alcohol does harm the health. • Long-term or frequent use of NSAIDs should be avoided when having IBD. • When prescribing contraceptives for women with IBD, risk factors for venous thromboembolism should be evaluated. • Breastfeeding and a reasonable use of antibiotics during childhood to reduce the risk of developing IBD. • Shared decision making between clinicians and their patients will improve the clinical outcome and reduce health-care costs.
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Abbreviations: IF = Impact Factor, NSAIDs = Nonsteroidal Anti-Inflammatory Drug, CD = Crohn's Disease, UC = Ulcerative Colitis, GBD = Global Burden of Disease Study, IOIBD = International Organization for Study of Inflammatory Bowel Diseases,

Worldwide development and global burden of IBD

IBD is an autoimmune disease known to cause symptoms persisting throughout life, leading to considerable disability and morbidity for patients [4]. While the number of patients with IBD has increased in industrialized countries in Europe and North America since the mid-19th century, the cases of IBD started to rise in developing countries in Asia and Africa hundred years later, making IBD a global burden around the world for patients, medical professionals, and health care providers [2]. Reported 6.9 million people living with IBD worldwide, plus an increasingly ageing population are going to pose an enormous challenge for national and international health care systems with considerable health and economic effects. To show the global development of IBDs, the years lived with disability (YLD) almost doubled during the last 30 years from 0.56 million in 1990 to 1.02 million in 2017. Understanding the triggering factors of this substantial rise of IBDs around the world together with the underlying reasons for geographical differences are important to find effective and affordable strategies for the prevention and treatment of IBD [4].

A higher prevalence of IBDs in high-income countries suggest that common environmental exposures or lifestyles may act as important risk factors for the development of this autoimmune disease. An observed increase of IBD in newly industrialized countries with formerly known low prevalence rates also support the assumption of a connection between behavioral as well as environmental factors and the progressive number of IBD [4].

Despite an improved availability of medical treatment, early effective therapies and a decline of surgeries, health care costs of IBDs have continued to increase, mainly because of costly therapies. A growing implementation of a western lifestyle in societies worldwide has been identified to cause the changing epidemiology of IBD. In order to provide globally sustainable care in the future, it will become more and more important to prevent the further increase of IBD and to take several steps to change environmental exposures not only in the general population but especially in patients with genetic susceptibility. First-degree relatives of patients with IBD were found to be at-risk individuals for the development of IBDs [21].

Even though over 200 known risk loci for CD and UC, only a small amount of predicted heritability can be explained by genes or loci [2]. To slow down the increase of IBD, it will be therefore important to focus on protective factors to prevent the outbreak of IBD at an early stage of life. Several factors have been defined to be protective, like breastfeeding in infancy for at least 6 months, a reasonable prescription of antibiotics especially during the first years of life, and a sufficient level of vitamin D. Besides, a rural environment as well as having pets and living in larger families showed positive and protective effects (hygiene hypothesis) [2]. Additionally, the avoidance of smoking and the reduction of certain medications like nonsteroidal anti-inflammatory drugs and antibiotics have also been identified to be protective against the onset of IBD. Besides, a healthy diet with a daily consumption of fresh fruits, vegetables, fiber and fish or oil as well as the elimination of food additives and emulsifiers showed positive effects on the course of IBD. And finally, a balanced way of life with regular sleep, low perceived stress combined with moderate physical activity and a healthy weight are not only advised to improve the quality of life but may also protect against IBD [2,21].

Impact of the exposome on IBD

The exposome, a combination of the terms ‘exposure’ and ‘genome’, represents a combination of all relevant environmental exposures during a lifetime and how it interacts with the genome in order to risk or protect against the onset, recurrence and progression of IBD. While environmental factors do play a more important role in the development of IBD during childhood, lifestyles are affecting an already shaped immunologic system during adulthood. Independent of the current stage in life, there are several aspects like geographical variations, acute bacterial gastroenteritis, and a sufficient level of vitamin D, which show substantial impacts on the immune system [3].

In contrast to genetic predispositions, the exposome represents a modifiable factor, not only for the development but also for the course of this autoimmune disease. Therefore, the combination of relevant environmental factors into the ‘exposome risk score’ could be a valuable tool not only in the prevention of IBD in genetic

susceptible individuals but also lead to a more personalized level of medicine in the treatment of patients with IBD [19].

Beside exposome and genetic susceptibility, microbial dysbiosis plays an important role in the development of IBD. The microbiome represents the link between environment and the potential risk of IBD. Environmental exposures may not only change the microbiome but interfere with the immune response and lead to intestinal inflammation. Risk factors like smoking, antibiotics, NSAIDs, oral contraceptives, pollution, and psychosocial stressors may modify the intestinal microbiome and lead to dysbiosis. Protective factors like breastfeeding, diets high in soluble fibers and regular physical activity may positively affect the microbial composition by contributing to enriched diversity of the microbiome in the gut [10,19].

A better understanding of underlying mechanism in the onset and maintenance of IBD is essential in order to develop effective treatments for patients with IBD. Environmental factors like breast feeding, smoking, diets, antibiotics, obesity, etc. have shown to affect the composition of the microbiome. In addition, epigenetic modifications can alter intestinal permeability and even change immune function. Perceived stress, long-term use of NSAIDs and sleep disturbances were associated with severe flares and increased disease activity for IBD patients. Smoking showed negative effects on the course of CD but was associated with lower colectomy rates in UC patients. An elevated risk factors for relapse in patients with UC included a higher intake of red meat and alcohol. Physical activity, on the other hand showed protective effects both on the course of CD and UC [13,18].

Lifestyle and environmental modifications

Different exogenous factors with the potential to prevent or resolve inflammation processes have been compared in chronic diseases like IBD and asthma. As pharmacological interventions are known to come with severe side effects and lead to impaired immune function, new resolution-based strategies are needed to direct inflammatory processes in a controlled way. The gut microflora shows to play an important role in the stimulation of a balanced immune response. In addition, evidence indicates that lifestyle factors as well as physical and psychological conditions have impacts on the extent of the response of the immune system. Thus, beside pharmacological treatment, the implementation of dietary interventions, physical activities, and stress management techniques may be proposed as new resolution-based strategies to control the inflammatory process in chronic diseases like IBD [20].

Changed microbial composition together with a reduction in species diversity has been observed in IBD patients, leading to barrier dysfunction in the gut and modulated immune response. Lifestyle and exogenous factors like diets, smoking and exercise have substantial influence on the microbiome, especially in genetically susceptible individuals. It has been therefore suggested that changes in diets, quitting smoking and physical activity may have the potential to shift the intestinal microbiome from dysbiosis to eubiosis. This may help to bring IBD patients to a more stable phase of clinical remission [22].

In patients with established IBD, several lifestyle factors were associated with different outcomes, showing the importance of more interventional studies in this field of applied research. While obesity is associated with an increased risk of relapse and higher health care utilization, recreational activity decreases the risk of flares and fatigue. Sleep disturbances as well as perceived stress have shown to negatively affect the course of the disease by triggering symptomatic exacerbations and leading to relapses. Concerning cigarette smoking, inconsistent results were found in patients with different types of IBD. While some studies suggest a positive impact of smoking on the outcome in patients with UC, it shows clear negative effects on the progression and outcome in patients with CD. The impact of alcohol and cannabis on IBDs is also less clear and needs further investigation [13].

The International Organization for Study of IBD (IOIBD) published a list of recommendations concerning lifestyle and environmental modification for the management of patients with IBD [23]. It was agreed that smoking should never be started to reduce the risk of IBD, neither from patients with CD, nor from patients with UC. When adapting diets with evidence in the treatment of IBD, monitoring of inflammation, symptoms and nutritional deficiencies is also recommended. Mental health assessment and care should be provided to IBD patients, as poor psychological health like depressions and anxiety are worsening the course of the disease. Integrating regular physical activity into the daily routine as well as maintaining a normal body weight shows beneficial effects on IBD therapy outcomes. Besides, certain medications like long-term use of NSAIDs and oestrogen-containing contraceptives should be avoided by IBD patients because they show negative effects on the gastro-intestinal mucosa and increase the risk of blood clots, respectively. A small intake of alcohol does not negatively affect the course of IBD. Finally, breastfeeding during the first months of life and the reasonable use of antibiotics is recommended for children, especially for offspring of IBD patients. Above all, a shared decision making between physicians and patients is recommended to improve the clinical outcome and may even reduce health-care costs [23].

Evidence supports the understanding that the microbial dysbiosis plays an important role in the development and course of IBD. Epigenetic, environmental and lifestyle factors have shown to shape the composition and to modulate the diversity of the intestinal microbiome. They should be therefore considered to be of utmost relevance for the management of this chronic disease [22].

3.3.2 Diet and IBD

To provide an overview of dietary interventions, common diets were listed together with some of their most significant impacts on therapeutic outcomes in table 7 below. Pros (+) and cons (-) mark positive and negative effects of the described diet on the course of IBD. Besides, table 7 below includes authors, journal, year of publication, impact factors and key messages of the selected papers. The year of publication defined the chronology of the listing.

Table 7: Selected review papers with key findings about diets and IBD

Effects of diets on IBD			
Ref #	Paper	IF	Key findings
12	Lewis JD et al. Gastroenterol 2017	33.9	<ul style="list-style-type: none"> • Diets high in animal fat and sugar and low in fruits and vegetables show elevated risks for IBD. • Diets have an influence on the gut microbiome and metabolites of the microbiota, as well as on the intestinal permeability and the function of the immune system. • Dietary fibers should be recommended to IBD patients in remission with no intestinal strictures. • Exclusive Enteral Nutrition (EEN): + reduction of mucosal inflammation in children, - lower rates of clinical response in adults, - no normalized fecal calprotectin, • Partial Enteral Nutrition (PEN): + reduction of relapse by 50% in CD-patients, - no normalized fecal calprotectin, • Specific Carbohydrate Diet (SCD): + clinical improvement and mucosal healing, + prolonged phase of remission, - small uncontrolled studies, • Diet low in FODMAPs: + improved GI symptoms; - no improved inflammation; - reduction of favorable species in the gut microbiota,
24	Pigneur B et al. Ther Adv Gastroenter 2019	4.8	<ul style="list-style-type: none"> • Dietary interventions like EEN show an impact on the intestinal microbiota composition. • Most patients believe that food plays a role in the relapse of IBD. • A healthy lifestyle together with a diet rich in dietary fiber and low in processed food should be recommended to patients with IBD. • EEN: + rate of remission comparable to oral

			<p>steroids, + higher potential of mucosal healing than steroids, + positive effects on dysbiosis in CD patients, - no additional food allowed beside formular, - difficulties in compliance in adult CD patients,</p> <ul style="list-style-type: none"> • Crohn’s Disease Exclusion Diet (CDED): + comparable rate of clinical remission like EEN, + normalization of CRP, + higher rate of tolerance than EEN, - no data about mucosal healing available, • Crohn’s Disease–Treatment with Eating (CD-TREAT) + better tolerance than EEN, + decrease of fecal calprotectin, - few data available, • Specific Carbohydrate Diet (SCD): + most studied exclusion diet for IBD treatment, + significant improvement of inflammatory markers, + induction and maintenance of remission, + potential to induce mucosal healing, + possible weight loss for obese or overweight patients, - difficulty of adherence, • Paleolithic Diet: + positive case reports, - no data about the use in treatments of IBD, • Gluten-free Diet: + better digestive well-being of IBS-patients, - no controlled trials available, • Diet low in FODMAPs: + reducing gastrointestinal symptoms, - risk of aggravating dysbiosis on the long run, • Semi-Vegetarian Diet: + extended period of clinical remission compared with omnivorous diets, - few data available,
25	Gu P et al. Inflamm Bowel Dis 2020	7.3	<ul style="list-style-type: none"> • Results of clinical studies show that diets play a role both in the pathogenesis and in the exacerbation of IBD.

			<ul style="list-style-type: none"> • Diets have an impact on the intestinal microbiome as well as on the barrier function of the gut. • Need of nutritional information concerning the treatment of IBD from both patients and health care providers. • EEN: <ul style="list-style-type: none"> + reduction of pro-inflammatory cytokines, + alteration of the microbiome followed by a decrease in inflammation, + maintaining remission in patients on biologics, + best studied dietary intervention, - problems with tolerability and adherence, • CD-TREAT, CDED and PEN: <ul style="list-style-type: none"> + similar effectiveness as EEN, + better compliance than EEN, - few data available, • Specific Carbohydrate Diet (SCD): <ul style="list-style-type: none"> + significant improvement of clinical symptoms, + positive effects on mucosal healing, + higher rate of adherence than other diets, - limited data to confirm efficacy, • Diet low in FODMAPs: <ul style="list-style-type: none"> + improvement of clinical symptoms, - no impact on inflammation parameters, - risk of nutritional deficiencies on the long-term, • Semi-Vegetarian Diet: <ul style="list-style-type: none"> + improved symptoms and remission rates, - available data are sparse and conflicting, - no reduced risk of flares in patients with CD,
26	Levine A et al. Clin Gastroenterol Hepatol 2020	13.6	<ul style="list-style-type: none"> • Current knowledge supports the importance of diets as well as the microbiome in pathogenesis and inflammation of IBD. • Dietary interventions may induce remission in patients with CD. • Dietary components have been correlated with exacerbations in UC patients. • Available information about food and food groups, being protective or detrimental in the treatment of IBD, have been insufficient for physicians, dietitians, and patients.

			<ul style="list-style-type: none"> • Foods prudent to increase when having CD: Fruits and Vegetables (EL low) • Foods prudent to increase when having UC: Marine fish containing omega-3 fatty acids (EL low) • Foods prudent to decrease when having CD: Saturated fat (EL low) • Trans fat (EL very low) • Foods prudent to decrease when having UC: Red meat and processed meat (EL low) • Palm oil and coconut oil (EL low) • Foods prudent to avoid when having CD or UC: Unpasteurized dairy products (low-level) • It may be advisable to decrease food additives like maltodextrins and artificial sweeteners, emulsifiers, carrageenan, and titanium dioxide for patients with CD or UC. • No consent was found for consumption of pasteurized dairy products for patients with CD and UC. • Insufficient evidence was found regarding exclusion of refined sugars and carbohydrates, wheat/gluten, poultry, and alcoholic beverages.
27	Sasson AN et al. Clin Gastro-enterol Hepatol 2021	13.6	<ul style="list-style-type: none"> • Diets may promote dysregulation of the immune system leading to intestinal inflammation. • Diets can modify the diversity of the microbiome and affect the function of the gut microbiota. • Dietary components can disrupt colonic mucin layers and alter the integrity of the epithelial barrier. • Total Parenteral Nutrition: + significant reduction of disease activity, - no significant benefit compared to partial enteral nutrition,

		<ul style="list-style-type: none"> • EEN: <ul style="list-style-type: none"> + effective in achieving mucosal remission, + improved endoscopic and histologic results, + improving the response rate of biologicals - less efficient in adults with IBD, - difficulties due to complete avoidance of table foods, • PEN: <ul style="list-style-type: none"> + successful in maintaining remission, - less successful in inducing remission, • Crohn’s Disease–Treatment with Eating (CD-TREAT): <ul style="list-style-type: none"> + individualized anti-inflammatory diet, + successful induction of remission (60%), + positive effects on the microbiome, + improved tolerability than EEN, - few available studies and small sample size, • Crohn’s Disease Exclusion Diet (CDED): <ul style="list-style-type: none"> + CD plus PEN clinical effects like EEN, + CD plus PEN better outcomes than PEN + CD plus PEN better sustaining remission, - few data available, • Autoimmune Protocol Diet: <ul style="list-style-type: none"> + significant reduction of disease activity (Mayo score), - no significant change in inflammatory markers like CRP and fecal calprotectin, • Inflammatory Bowel Disease Anti-Inflammatory Diet (IBD-AID): <ul style="list-style-type: none"> + improvement of GI-symptoms, + reduction of medication, - no measurement of fecal calprotectin, - no comparator group as reference, • Specific Carbohydrate Diet (SCD): <ul style="list-style-type: none"> + induction of clinical remission, + improvement of intestinal mucosa, - limited availability of objective inflammatory markers, - potential risk of micronutrient deficiency, • Semi-Vegetarian Diet: <ul style="list-style-type: none"> + prolonged maintenance of remission, + improved rate of compliance, - small sample size, - no control group as reference,
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28	Starz E et al. Nutrients 2021	6.7	<ul style="list-style-type: none"> • CD patients show a dysbiosis of the gut microbiome with a reduced diversity of intestinal microbes. • Elimination diets, like the gluten-free diet, the lactose-free diet and the SDC, have shown to minimize gastrointestinal symptoms but involve the risk of nutritional deficiencies in the long-term. • The low-FODMAP diet and other elimination diets, can have adverse effects on the gut microbial composition by further decreasing favorable bacterial species. • CEDED positively affects the course of IBD and the intestinal microbiome by decreasing pro-inflammatory bacteria and increasing anti-inflammatory bacteria. • EEN shows that positive effects on the composition of the microbiome reverse after a while.
29	Trakman GL et al. J Gastroen Hepatol 2021	4,4	<ul style="list-style-type: none"> • Diets are one of the potent factors to shape the microbiome in a way that effects the development and activity of IBD. • Technological advances in microbiology and computational biology have facilitated the characterization of the microbiome, caused by dietary interventions. • Interindividual variations of microbiota composition support the approach of a personalized, disease-specific diet. • Protective factors: <ul style="list-style-type: none"> + fibers show anti-inflammatory effects in CD. + tea increases microbial diversity in UC. • Risk factors: <ul style="list-style-type: none"> - ultra-processed foods: increase of intestinal permeability and inflammation in CD. - soft drink & sucrose: reduction of beneficial bacteria in UC. • EEN: <ul style="list-style-type: none"> + removal of antigenic food proteins, - reduction of anti-inflammatory bacteria (!), - increase of pro-inflammatory bacteria (!),

			<ul style="list-style-type: none"> • CD-TREAT: + composition and diversity of the microbiome like EEN, + induction of remission, • CDED: => protective factors of the microbiome like soluble fibers and resistant starch (potatoes, apples, bananas) lead to production of anti-inflammatory butyrate, => reduction of adverse factors of the microbiome like additives, red meat, milk fat and saturated fat minimize the decrease of microbial diversity, • Mediterranean diet: + intake of protective factors of the microbiome like soluble fibers, fruits, vegetables, yoghurt, olive oil: => anti-inflammatory butyrate production, => increase of microbial diversity, => increase of beneficial bacteria, - adverse factors for the microbiome like additives, red meat, and animal fat: => increase of intestinal inflammation, => reduced permeability of the gut, • Sulfide reducing diet: recommended for UC => plant-based diet shows protection against relapse, => reduction of animal proteins to prevent inflammation and disruption of mucosal integrity of the gut.
30	Walter M et al. Nat Rev Gastro Hepat 2022	73.1	<ul style="list-style-type: none"> • Autoimmune diseases like IBD show underlying patterns of dysbiosis of the gut microbiome and dysfunction of the intestinal barrier. • Diets have shown to affect the gut microbiota directly by changing its composition or its metabolic output. • Dietary interventions, implemented to shape the gut microbiome, need the verification of being effective for the individual patient. • Combination of dietary interventions together with other microbiome-modulating approaches may lead to more stable results.

			<ul style="list-style-type: none"> • EEN or PEN: <ul style="list-style-type: none"> + increased rate of remission, + improved score of disease, + decrease of inflammation markers, => improved tolerability of PEN than EEN, • CDED: <ul style="list-style-type: none"> + increased rate of remission, + decreased inflammation markers, + improved score of disease, + more patients with normal intestinal permeability, • Specific Carbohydrate Diet (SCD): <ul style="list-style-type: none"> + increased rate of remission, + decreased inflammation markers, + normalization of albumin, + improved score of disease, • Diet low in FODMAPs: <ul style="list-style-type: none"> + improved score of disease, - no impact on inflammation parameters, • Autoimmune Protocol Diet: <ul style="list-style-type: none"> + increased rate of remission, + improved score of disease, - no significant decrease of inflammatory markers,
31	Jiang Y et al. Nutrients 2021	6.7	<ul style="list-style-type: none"> • IBD is associated with microbial dysbiosis, which can be shaped by dietary factors like in related Immune-Mediated Inflammatory Diseases (IMIDs). • Treatments with individual approaches of personalized dietary recommendations will be needed, as genetic variabilities affect the absorption and metabolism of nutrients. • Mediterranean diet: <ul style="list-style-type: none"> + reduction of C-reactive protein (CPR), + normalization of the microbiota, + weight-loss, + lower risk of developing CD, + better rate of adherence than to other diets, => beneficial for CD but not for UC; • Vegetarian and Vegan Diet: <ul style="list-style-type: none"> + fewer rates of relapse for patients with

			<p>UC, + prolonged remission periods, - high drop-out rates, - limitations based on confounding effects,</p> <ul style="list-style-type: none"> • Gluten-free Diet: + improvement of at least one clinical symptom, - no association with disease activity, hospitalization, or surgery rate, • Specific Carbohydrate Diet (SCD): + improvement of inflammation markers, + maintaining remission, + improving clinical symptoms, - few studies on adult patients with IBD. • Calories Restriction/Fasting: + decrease of clinical symptoms in UC patients, + no adverse effects, - no significant improvement for CD patients.
32	Simões CD et al. Europ J Nutr 2021	5.6	<ul style="list-style-type: none"> • When implementing dietary restrictions in the treatment of IBD, malnutrition and adverse effects on the gut microbiome must be avoided. • Low-FODMAP diet has shown positive effects on the outcome of IBD, increasing remission periods and improving the quality of life. • Dietary interventions should be individualized and monitored to achieve the best possible outcome for patients with IBD. • Low-FODMAP diet: + improved therapeutic outcome, - possible adverse effects on the gut microbiota, - drastic restriction of food over a certain period, - risk of nutritional deficiencies and malnutrition, - lack of soluble fibres with risk of constipation.

CRP = C-reactive Protein, IBS = Inflammatory Bowel Syndrome

Impact of diets on the gut microbiome

While the role of diets in the development of IBD is not quite clear, results of clinical studies show, that diets may have an impact on both the pathogenesis as well as on the exacerbation of IBD [25]. Diets seem to modify the gut microbiome, its composition, its diversity, and the metabolites of the microbiota [12,24,25,27,29,30,31,32]. This may lead to microbial dysbiosis, which shows impacts on the gut barrier function and the immune system. By altering the intestinal permeability, diets might therefore contribute to dysregulation of the immune system and promote intestinal inflammation [17,27,29,30]. The impact of dietary factors in shaping the microbial composition has been studied in related Immune-Mediated Inflammatory Diseases (IMIDs) like Psoriasis and Rheumatoid Arthritis (RA), which might help to bring light into the effect of diets in the treatment of patients with IBD [31].

Patients with IBD display underlying patterns of dysbiosis of the gut microbiome with a reduced diversity of intestinal microbes and dysfunction of the intestinal barrier. Diets implemented in the treatment of IBD should be evaluated according to their effect on the intestinal microbiota. CDED has shown to positively affect the gut microbiome, by decreasing pro-inflammatory bacteria and increasing anti-inflammatory bacteria. In contrast to the low-FODMAP diet, which can have adverse effects on the gut microbial composition by further decreasing favorable bacterial species [28].

Role of diets in the treatment of IBD

A majority of patients with IBD believe, that food plays a role in the relapse of this chronic disease. Diets are the lifestyle factors, which are most frequently linked with deteriorating symptoms of IBD by patients. Physicians are therefore often confronted with questions about the appropriate diet, which diets are anti-inflammatory or what kind of food should be avoided. There is an imbalance in demand and supply regarding dietary approaches suitable for the treatment of IBD. Beside the lack of dietary recommendations, available information about different food and food groups, being protective or detrimental in the treatment of IBD, are insufficient for physicians, dietitians, and patients [12,26].

In pediatrics, the implementation of EEN as dietary intervention in the treatment of children with CD achieved clinical outcomes, comparable to the treatment with cortico-steroids, but with less negative side effects for the patients [12,24,25,27,29,30]. Thus, the EEN diet is now recommended to be the first-line therapy when treating children with CD [8]. Unfortunately, these results have not been seen in adult patients with CD, where the treatment with EEN was less effective [12].

While certain foods and food groups may be associated with exacerbation of disease activity, elimination diets, like the gluten-free diet, the lactose-free diet and the SDC, have shown to minimize gastrointestinal symptoms and improved the well-being of patients with IBD. The low-FODMAP diet has shown positive effects on the outcome of IBD, increasing remission periods and improving the quality of life. When implementing dietary restrictions in the treatment of IBD, malnutrition and adverse effects on the gut microbiome have to be avoided. Thus, it is important to keep in mind, that the exclusion of certain food groups may involve the risk of

malnutrition in the long-term, which should be avoided by regular monitoring for nutritional deficiencies during treatment [12,24,25,27,28,29,30,31,32].

Common dietary interventions in IBD therapy

Based on the results of our scoping review, a short characterization of the most studied nutritional interventions, implemented in the treatment of IBD are summarized below [25,30,31]:

Exclusive Enteral Nutrition (EEN) is a liquid formula diet (elemental, semi-elemental or polymeric) with no solid food allowed for 1 to 3 months. This diet is designed to support the healing of the gastro-intestinal tract by decreasing the exposure to food antigens.

Partial Enteral Nutrition (PEN) is a modification of EEN. The liquid formula covers half of the calorie requirements, the rest is covered by the intake of solid food. This variation of EEN was made to improve the tolerability and compliance of EEN in adult patients.

Crohn's Disease Exclusion Diet (CDED) is a combination of enteral nutrition and whole-food restrictive diet. The diet is low in fat and animal protein, but rich in compound carbohydrates and dietary fibers. Food additives are excluded. After the first period, a certain amount of whole-grain bread, nuts, fruits, legumes, and vegetables is allowed. A combination of CDED plus PEN has shown better effects on the microbiome than PEN alone.

Crohn's Disease Treatment with Eating Diet (CD-TREAT) is an anti-inflammatory, tailored diet to induce remission. In this approach, a diet of individualized whole foods is allowed with exclusion of food groups like complex carbohydrates and increased proportion of proteins, vitamins, minerals.

Specific Carbohydrate Diet (SCD) is an exclusion diet, eliminating complex carbohydrates like poly- and disaccharides with the risk of bacterial overgrowth because of undigested product. Solid proteins, and fats are allowed, together with monosaccharides, which are absorbed in the proximal small intestine.

Diets low in FODMAP (Fermentable Oligo-, Di-, Monosaccharides And Polyols) is based on a reduced intake of short-chain carbohydrates, which are indigestible and slowly absorbed. This should help to reduce gastro-intestinal symptoms by eliminating the virtue of osmotic effects and fermentation.

Paleolithic Diet excludes foods that were not available during the period of human evolution. It is assumed, that the gastrointestinal system is poorly adjusted to the modern diet which leads to the development of several diseases of civilization.

Gluten-free Diet was originally designed for patients with celiac disease or non-celiac gluten intolerance. Gluten is a protein, which is included in many grains, like wheat, rye, and barley.

Semi-Vegetarian Diet is a plant-based diet, which mainly consists of brown rice, soup, yogurt, miso, vegetables, fruits, and legumes with fish (once a week) and meat (once every 2 weeks). Instead of a restrictive approach, the semi-vegetarian diet wants to encourage the consumption of dietary fibers in order to increase the presence of beneficial bacteria in the gut.

The Autoimmune Protocol Diet is a further development of the Paleolithic diet. While fresh nutrient-dense foods, lean protein, and high fiber should be included in the daily diet, the exclusion of refined sugar and gluten is recommended.

Inflammatory Bowel Disease Anti-Inflammatory Diet (IBD-AID) follows the hypothesis that certain carbohydrates enhance pathogenic bacteria in the gut. Therefore, the elimination of carbohydrates like substrate refined sugar, gluten-based grains, and particular starches is recommended for patients with IBD.

Mediterranean Diet includes high amounts of fruits, vegetables, whole grains, nuts, monounsaturated fats like olive oil, and is low in red meat. This diet became popular, when it was discovered that lower rates of cardiovascular disease mortality occurred in Mediterranean regions compared to other western countries.

Future perspectives on diets and IBD therapy

Technological advances in microbiology and computational biology have facilitated the characterization of the microbiome, and its alterations caused by dietary interventions [29].

Diets have been known to be one of the potent factors to shape the microbiome directly by changing its composition or its metabolic output. But dietary interventions, implemented in IBD treatments to modify the gut microbiome, need the verification of being effective for the individual patient. As genetic variabilities affect the absorption and metabolism of nutrients, individual approaches with personalized dietary recommendations will be needed. Therefore, dietary interventions should be individualized and monitored to achieve the best possible outcome for patients with IBD. The interindividual variations of microbiota composition, based on the complex interactions between genetical and environmental factors, would support an approach of a personalized, disease-specific diet [29,30].

3.3.3 Psychological health and IBD

An overview of important outcomes concerning the influence of psychological health on IBD and possible psychological interventions in the treatment of IBD patients are provided below in table 8, with a summary of essential key findings on this topic. The listing of the selected articles was done according to the year of publication in ascending order.

Table 8: Summary of key findings about psychological health and IBD

Effects of psychological health on IBD			
Ref #	Paper	IF	Key findings
33	Jordan C et al Clin Psych Rev 2016	11.4	<ul style="list-style-type: none"> • Psychological factors play a significant role in the adjustment to IBD beside disease activity, lower socioeconomic status, and female gender. • Feelings of stigmatization and social isolation are accompanied by psychological distress and reduced quality of life. • Depression has been identified as a risk factor for increased disease activity. • Disease activity and psychological functioning appear to be interrelated and bidirectional which might create a vicious cycle. • Psychological interventions that focus on coping strategies, perceived stress, and cognition of IBD may lead to improved outcomes for patients. • Acceptance and tolerance of IBD may help to deal with the symptoms more effectively and improve the quality of life. • Few studies, almost only cross-sectional and no longitudinal data, have been available.
34	Norton C et al Aliment Pharmacol Ther 2017	9.5	<ul style="list-style-type: none"> • Chronic abdominal pain has a negative impact on the quality of life and imposes a heavy burden on patients with IBD. • Analgesics contain the risk of exacerbation and may mask a relapse with the risk of abuse and addiction. • Pain may be modulated by psychological factors like depression, anxiety, stress, etc. • Psychological interventions like relaxation, disease anxiety related Cognitive Behavioral Therapy (CBT) and stress management reduce pain in patients with quiescent IBD.

			<ul style="list-style-type: none"> • Negative coping strategies and dysfunctional cognitions have led to greater pain severity and functional disability. • The relation between pain and psychological factors lead to the recommendation of a biopsychosocial approach when treating IBD.
15	Gracie DJ et al Lancet Gastroenterol Hepatol 2017	45.0	<ul style="list-style-type: none"> • Cognitive behavioral therapy (CBT) seems to have the best benefit for patients with IBD improving depression and anxiety. • Psychological therapies did not show effects on disease activity indices or other wellbeing scores in patients with quiescent disease. • Most studies included IBD patients in remission, while the most psychological burden has been noted in patients with active disease or ongoing gastrointestinal symptoms. • Fatigue, which has been identified to affect up to 40 % of the patients with IBD, has shown to be associated with depression and reduced quality of life, independent of disease activity. • IBD patients with fatigue seemed to benefit the most from solution-focused therapy (SFT) and problem-solving therapy (PST), which showed improved scores of fatigues and quality of life. • Further studies are needed to examine the effects of psychological interventions, not only in the general group of IBD patients, but in patients with coexistent psychological distress.

35	Regueiro M et al Gastroenterology 2017	33.9	<ul style="list-style-type: none"> • Chronic abdominal pain, anxiety and depression are the most common psychological conditions in patients with IBD. • While acute pain is correlating with IBD activity, chronic pain involves the dysregulation of the brain-gut-axis, which may patients predispose to anxiety and depression. • Rates of anxiety and depression are elevated among patients with IBD and are often reported before its diagnosis. • Depression is associated with inflammation, pain, IBD relapse and poorer response to treatment. • Cognitive depressive symptoms may even occur in quiescent IBDs, leading to a higher risk of suicide among patients with IBD compared to matched controls. • Anxiety is associated with a reduced adherence to medication, an elevated risk for surgery and perceived stress. • Stress can not only amplify the pain signal, but it can change motility and permeability in the gastrointestinal system and therefore interact with the microbiome of the gut. • The vagal tone plays an important role in the endocrine-immune-autonomic nervous system and has anti-inflammatory properties. As observed in patients with CD, a lower vagal tone is associated with a higher level of tumor necrosis factor-α. • Narcotic analgesics have not been proven to be an effective treatment for IBD as they show several side effects like constipation, narcotic bowel syndrome, and an increased risk of infection and even death. • An approach that focuses on behavioral skills, social support and stress reduction would provide comprehensive biopsychosocial care for patients with IBD.
14	Keefer L et al Gastroenterology 2018	33.9	<ul style="list-style-type: none"> • The substantial burden of IBD is co-determined by disease severity and

			<p>the ability of the patient to cope with symptoms in order to live a normal daily life.</p> <ul style="list-style-type: none"> • Psychosocial factors like chronic pain, depression and poor social support amplify the burden of this chronic disease by contributing to flares, surgery, and disability. • Stress has shown adverse effects on gastrointestinal functions by neural-, immune- and microbiome-altering interactions. • It is important to educate patients early in the treatment about the brain-gut axis and to emphasize its bi-directional effects. • Brain-gut psychotherapies focus on the alleviation of GI symptoms and the improvement of coping, resilience, and self-regulation. • Patients with comorbid chronic depression or anxiety are not good candidates for brain-gut psychotherapy. • While behavioral and psychosocial factors may exacerbate symptoms, they are generally not the cause of IBD.
36	Borren NZ et al Nat Rev Gastro Hepat 2019	73.1	<ul style="list-style-type: none"> • Fatigue is a disabling and underreported symptom, affecting over 80 % of patients with active IBD and 50 % of patients in remission. • Fatigue is defined as difficulty to initiate and maintain activities in addition to struggling with concentration and emotional stability. • Fatigue, which limits the working capacity, is more common in women than in men. • Fatigue is ranked fourth on the list of patients concerns before pain and bowel problems. • Based on its multifactorial pathophysiology, the treatment of persistent fatigue proposes a multidisciplinary management like psychological interventions, physical exercise, and microbiota-directed therapy.

			<ul style="list-style-type: none"> • Psychological interventions like ‘Cognitive behavioural therapy’ (CBT) and ‘Solution-focused therapy’ (SFT) have shown the most promising results.
37	Oligschlaeger Yet al Cells 2019	7.7	<ul style="list-style-type: none"> • The bidirectional interactions between the brain and the gastrointestinal system are affected by the gut’s microbiota forming the gut/microbiota/brain axis. • Stress alters the permeability of the intestinal mucosa and the secretion of cytokines. • Stress negatively affects the gut/microbiota/brain axis by leading to increased risk of relapse and disease severity of IBD. • IBD patients show higher rates of psychological stress with direct impacts on the quality of their lives. • Perceived stress correlates with symptoms of disease activity, but not with inflammation. • Stress management techniques could help to reduce negative effects of stress and improve the patient’s coping skills.
38	Gracie DJ Lancet Gastroenterol Hepatol 2019	45.0	<ul style="list-style-type: none"> • Psychological disorders like depression and anxiety may generate a stress response with increased permeability of the gut and elevated levels of glucocorticosteroids. • The stress response may allow the intestinal microbiome to interact with the nervous system, forming the so-called microbiota-brain-gut axis. • During stress response, the parasympathetic reflex diminishes, limiting the vagus nerve, which would play an anti-inflammatory role by inhibiting proinflammatory cytokines. • Painful stimuli from the gut to the brain include visceral hypersensitivity, emotional distress s and psychological disorders by involving afferent sensory nerve fibers and the limbic system. • Risk factors for psychological disorders include disease activity, aggressive disease phenotype and female sex.

			<ul style="list-style-type: none"> Integrating a biopsychosocial approach in the treatment of IBD might not only reduce health care use and improve the quality of life for patients with IBD, but also change the course of the disease.
39	Thomann AK et al Aliment Pharmacol Ther 2020	9.5	<ul style="list-style-type: none"> Patients with IBD are far more at risk to develop psychological disorders like depression or anxiety compared to the general population. Both IBD and psychological disorders are associated with alterations of the gut microbiome, showing a decreased diversity of microbial bacteria. Psychiatric comorbidities might influence the course of IBD, either directly by exacerbating inflammation or indirectly by non-adherence to medical therapy. Targeting the microbiome of the gut may be a new approach in the treatment of psychological co-morbidities in patients with IBD. Perceived stress has been reported to be one of the most relevant factors concerning health-related quality of life. Because of the importance of mental well-being on the quality of life, “psychological remission” should be implemented as endpoint in future clinical studies.
40	Labanski A et al Psychoneuro- endocrinology 2020	4.7	<ul style="list-style-type: none"> Acute stress shows effects on GI motor functions, inflammatory process, and permeability of the gut. Acute stress could facilitate disease relapse and symptom exacerbation which might be due to an imbalance between pro- and anti-inflammatory responses. Stress-induced elevated levels of cortisol have shown to increase visceral pain sensitivity in healthy individuals, especially in women. Chronic stress as well as symptoms of anxiety and depression correlate with the severity of GI symptoms, resulting in reduced quality of life.

			<ul style="list-style-type: none"> • Chronic stress, major life events and negative affectivity are associated with increased risk of relapse and disease exacerbation in patients with quiescent IBD. • The implementation of relaxation therapy in the treatment of IBD may have positive effects on pain and psychological outcomes but randomized controlled studies (RCTs) are rare. • Vagus nerve stimulation may lower pain sensitivity and enhance gastro-duodenal motility, involving the microbiota-gut-brain axis. • While stress induces alterations of the microbiome, manipulations of the gut microbiota lead to altered stress responses, confirming the multi-directional character of the microbiota-brain-gut axis. • Resilience to stress together with adaptive coping mechanisms could improve clinical GI symptoms and quality of life for patients with IB in the future.
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Impact of psychological health on adjustment to IBD

Mental factors have been identified to play a significant role in the adjustment to IBD, beside disease activity, a lower socioeconomic status, and the female gender. It is important to understand, that psychological factors also interact with each other. Especially disease activity and psychological functioning appear interrelated and bidirectional, creating a vicious cycle for the patient [33]. But cognitive depressive symptoms were also observed to occur in patients with quiescent IBD, leading to a higher risk of suicide among these patients [35]. On the one hand, the feeling of stigmatization and social isolation may lead to psychological distress and poor quality of life. But on the other hand, the acceptance of IBD because of improved adjustments to this chronic autoimmune disease may help to deal more effectively with the symptoms and improve the personal well-being. Thus, psychological interventions that focus on coping strategies, perceived stress, and cognition of IBD may lead to improved therapeutic outcomes for patients with IBD [33].

Studies show that psychosocial factors like chronic pain, depression and poor social support amplify the burden of IBD by contributing to flares, surgery, and disability [14,33,34,35,38,39]. Besides, the feeling of stigmatization and social isolation may create additional psychological distress [33]. Psychological health therefore maintains a significant influence in the adjustment to this chronic disease, especially for female patients [33,38]. Psychological interventions that focus on

coping strategies, perceived stress, and cognition of IBD may lead to improved adjustments and outcomes for patients with IBD [15,34]. Acceptance and tolerance of IBD because of the ability to manage the disease may help to deal with the symptoms more effectively and improve the quality of life [14,33,38].

It is important to educate patients early in the treatment about the bi-directional interactions between the brain and the gastrointestinal system, which are affected by the gut's microbiota, forming the gut/microbiota/brain axis [14,37]. Stress negatively affects the gut/microbiota/brain axis by leading to increased risk of relapse and severe disease activity [37]. Brain-gut psychotherapies focus on the improvement of coping, resilience, and self-regulation in order to alleviate GI symptoms, decrease deteriorating effects of perceived stress, and consequently, to lead to improved psychological health. But it was noted that patients with comorbid chronic depression or anxiety are not good candidates for brain-gut psychotherapy [14].

Management of pain in IBD patients

Abdominal pain, one of the most common symptoms of IBD, imposes a heavy burden on patients' lives. But pain does not only reflect physical conditions. Pain can also be modulated by psychological factors like depression, anxiety, and stress [34]. While acute pain is correlating with IBD activity, chronic pain involves the dysregulation of the brain-gut-axis, which may predispose IBD patients to anxiety and depression [35]. The association of chronic pain with psychological factors support a biopsychosocial approach in the treatment of IBD [34].

Narcotic analgesics have not been proven to be an effective treatment for pain in patients with IBD as they show serious side effects like constipation, narcotic bowel syndrome, and an increased risk of infection or even death [35]. While analgesics contain the risk of masking a relapse with the possibility of abuse and addiction, psychological interventions like relaxation, disease anxiety related Cognitive Behavioral Therapy (CBT) and stress management reduce pain in patients with quiescent IBD. In contrast to negative coping strategies and dysfunctional cognitions, which have led to greater pain severity and functional disability [34].

Treatment of fatigue in patients with IBD

Chronic abdominal pain, anxiety and depression have been identified to be the most frequent psychological conditions among patients with IBD [35]. But fatigue is another very common symptom, which has been identified to affect up 50 % of patients in remission and over 80 % of patients with active IBD [15,36]. Fatigue has been more commonly diagnosed in women than in men. Fatigue is a disabling and underreported symptom, which is defined as difficulty to initiate and maintain activities in addition to struggling with concentration and emotional stability. It therefore limits the working capacity and reduces the quality of life for patients with IBD, who have ranked fatigue fourth on the list of concerns, before pain and bowel problems. Fatigue has been associated with depression and reduced quality of life, independent of disease activity. Based on its multifactorial pathophysiology the treatment of persistent fatigue proposes a multidisciplinary management like psychological interventions, physical exercise, and microbiota-directed therapy [36].

Impact of stress on therapy outcome

Painful stimuli from the gut to the brain, involving afferent sensory nerve fibers to the limbic system, form a link between visceral hypersensitivity of the gut, emotional distress and psychological disorders. Psychological disorders, like depression and anxiety, may generate a stress response with increased permeability of the gut and elevated levels of glucocorticosteroids [38]. Stress-induced elevated levels of cortisol in turn have shown to increase visceral pain sensitivity in healthy individuals, especially in women [40]. But stress does not only amplify the pain signal, it is also associated with adverse effects on gastrointestinal functions by neural-, immune- and microbiome-altering interactions, confirming the microbiome-brain-gut-axis [35,40]. While stress induces alterations of the microbiome, manipulations of the gut microbiota lead to altered stress responses, confirming their bi-directional character [37].

Perceived stress has been reported to be one of the most relevant factors concerning health-related quality of life for patients with IBD [14,35,37,38,39,40]. Chronic stress, major life events and negative affectivity are associated with increased risk of relapse and disease exacerbation in patients with quiescent IBD [40]. Stress changes the motility of the gut as well as the intestinal mucosal permeability and alters the level of secreted cytokines [38]. Additionally, during stress response, the parasympathetic reflex diminishes, limiting the vagus nerve, which would play an anti-inflammatory role by inhibiting proinflammatory cytokines [35,38]. Perceived stress correlates with symptoms of disease activity and thus, higher rates of psychological stress directly affect the patients' wellbeing [37,40]. Stress management techniques could help to reduce negative effects of stress and improve the patient's coping skills [37,40]. Integrating a biopsychosocial approach in the treatment of IBD might not only reduce health care use and improve the quality of life for patients with IBD, but also change the course of the disease [40].

Psychological interventions and IBD

IBD patients with fatigue seemed to benefit the most from 'Cognitive behavioural therapy' (CBT), solution-focused therapy (SFT) and problem-solving therapy (PST), which showed improved scores of fatigues [36]. Cognitive behavioral therapy (CBT) has decreased depression scores the most and improved symptoms of anxiety for a certain period of time [15]. The implementation of relaxation therapy and stress management techniques in the treatment of IBD may have positive effects on pain and psychological outcomes but randomized controlled studies (RCTs) are rare [37,40]. Based on its multifactorial pathophysiology the treatment of persistent fatigue proposes a multidisciplinary management like psychological interventions, physical exercise, and microbiota-directed therapy [36].

It was shown that the evaluation of patient's psychological health is important to find the suitable psychological therapy in order to improve therapeutic outcomes in patients with IBD [39]. But it was also emphasized to point out to patients, that while behavioral and psychosocial factors may exacerbate symptoms, they are generally not the cause of IBD [14].

Future perspectives on psychological health and IBD

Further studies are needed to examine the effects of psychological interventions, not only in the general group of IBD patients, but in patients with coexistent psychological distress [15]. An approach that focuses on behavioral skills, social support and stress reduction would provide comprehensive biopsychosocial care [35]. Therefore, the implementation of ‘psychological remission’ as clinical endpoint in future clinical studies should be recommended to confirm the importance of mental well-being on the outcome of IBD treatments [39].

Both IBD and psychological disorders are associated with alterations of the gut microbiome, showing a decreased diversity of microbial bacteria with known effects on the development and course of IBD. Consequently, a new approach in the treatment of psychological co-morbidities in patients with IBD could define the gut microbiome as possible target for future psychological interventions [39].

A low vagal tone was observed in CD patients to be associated with a higher level of tumor necrosis factor- α . By considering the anti-inflammatory properties of the vagus nerve and the interaction of the endocrine-immune-autonomic nervous system interactions, a possible therapeutic intervention might implement a vagus nerve stimulation with the goal to lower pain sensitivity and to enhance gastro-duodenal motility in patients with IBD [35,40].

3.3.4 Physical activity and IBD

The key findings about the impact of physical activity on development and course of IBD are shown in table 9 below. It summarizes the effects of exercise implemented in the treatment of this chronic disease. The list of review papers starts with older publications and ends with more recent papers to provide an overview of the evolving knowledge in this field of research during the last years.

Table 9: Essential key findings about physical activity and IBD

Effects of physical activity on IBD			
Ref #	Paper	IF	Key findings
41	Wang Q et al Dig Liver Dis 2016	5.2	<ul style="list-style-type: none">• Based on a more sedentary lifestyle worldwide compared to the past, physical exercise has shown protective effects against diseases of western civilization.• High physical activity was associated with lower risks of developing CD but no significant protection against the development of UC.

42	Artom M et al J Crohns Colitis 2016	9,1	<ul style="list-style-type: none"> • Physical exercise is, beside smoking cessation, a possible modifiable factor to improve fatigue in patients with IBD. • Behavioral factors may be associated with fatigue in patients with IBD. • According to a biopsychosocial approach, fatigue management might include increased physical exercise, dietary modifications, quitting smoking, etc.
11	Monda V et al Oxida Med Cell Longev 2017	6.5	<ul style="list-style-type: none"> • Physical exercise can modify the microbiome of the gut by enriching the diversity of the microbiome and increasing the number of beneficial microbial bacteria. • Low-intensity exercise shows protective effects against IBD by increasing the gut motility and reducing the time between pathogens and mucus layer of the GI system. • Endurance sports induce variations in the GI system by reducing the splanchnic blood flow, which may result in an elevation of toxins in the blood system. • Prolonged exercise training affects the gut-barrier function by increasing the intestinal permeability and leading to bacterial translocation from the gut. • Physical exercise as a modifiable, environmental factor, shows positive effects in maintaining the balance of the microbiome or in rebalancing the dysbiosis of the gut.
16	Sharif K et al Autoimmun Rev 2018	9.8	<ul style="list-style-type: none"> • Physical activity has shown to improve fatigue, pain, and stress, when implemented in the treatment of other autoimmune diseases. • Increased physical activity is inversely associated with the risk of developing IBD, more pronounced in CD than in UC. • Physical activity promotes the release of anti-inflammatory agents and decreases intestinal barrier dysfunctions. • Engagement in physical activity leads to better outcomes in extraintestinal

			<p>manifestations of IBD, peripheral arthritis.</p> <ul style="list-style-type: none"> • Low-impact physical exercise shows positive effects in the treatment of IBD patients with osteopenia and osteoporosis by increasing bone mineral density and bone marrow density. • The integration of physical activity in the daily routine may also improve mental health in patients with IBD leading to better compliance and improved quality of life. • High energy consuming physical activities are not advisable for IBD patients with high intestinal resections.
43	Elia J et al Inflamm Bowel Dis 2018	5.3	<ul style="list-style-type: none"> • Physical therapy and structured exercise may lead to an increased release of anti-inflammatory cytokines, to a reduction of visceral fat and to an improved therapeutic outcome. • Prehabilitation programs, including aerobic exercise, could improve postoperative recovery periods, which are delayed in women and older individuals (>75years). • Postoperative rehabilitation improves the recovery of physical function, decreases fatigue, and help to restore physical capacity. • Strong intensity training can have negative effects on the GI system, increasing its permeability and leading to diarrhea and nausea.
44	Farrell D et al. Cochrane Database Syst Rev 2020	12.0	<ul style="list-style-type: none"> • More adverse gastrointestinal events, like diarrhea and bloating, were reported from patients with IBD when no physical activity was done. • Physical activity may improve fatigue in patients with IBD, but results are uncertain. • Fatigue should be measured as primary outcome when evaluating interventions designed to effectively treat patients with IBD.

45	McGing JJ et al Aliment Pharmacol Ther 2020	8,2	<ul style="list-style-type: none"> • Beside psychological interventions, exercise training may ameliorate the burden of fatigue in patients with IBD. • Aetiological factors of fatigue may include a reduced respiratory fitness, a decreased muscle strength as well as alteration in immune profile and faecal microbiome. • Available data support positive effects of exercise training interventions on functional and psychological outcomes in patients with IBD by reducing self-reported stress and improving quality of life. • While physical exercise increased the abundance of beneficial bacteria in the gut microbiota in lean to normal weight individuals, no effect was identified in the gut microbiota of obese IBD patients.
46	Skrzypczak D et al Nutrients 2021	5.7	<ul style="list-style-type: none"> • Modifiable risk factors for the development of osteosarcopenia include low levels of physical activity beside inflammation and nutritional deficiencies. • Osteosarcopenia, a reduction of muscle mass (sarcopenia) and bone tissue (osteoporosis), is often caused by chronic diseases like IBD. • Resistance trainings increase muscle mass and muscle strength as well as reduced inflammation markers like CRP-levels. • Patients with mild to moderate disease activity may take part in endurance training units on a regular basis without the risk of disease symptoms. • Positive side effects of physical activity on a regular basis include improved social well-being and better quality of life.
47	Koutouratsas T et al World J Gastroenterol 2021	5.7	<ul style="list-style-type: none"> • Physical exercise has been identified to modify the gut microbiome by increasing the gut motility and the diversity of bacteria as well as supporting the growth of beneficial species.

			<ul style="list-style-type: none"> • Sedentary occupations and low physical activity show higher risks for the development of IBD. • While excessive exercise training could have negative effects on patient's health, physical activity of mild-to-moderate intensity harbours multiple benefits for patients with IBD.
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Impact of physical exercise on IBD

The western culture with a sedentary lifestyle and an unhealthy diet may partly be responsible for the increase of multiple diseases of western civilization and for the rise of IBD [47]. The implementation of physical exercise on a regular basis has shown protective effects not only against cardiovascular diseases but also against different autoimmune disorders [41]. High physical activity was associated with a lower risk of developing IBD. The positive impact of physical exercise was more pronounced in patients with CD, than in patients with UC. Besides, the engagement in physical activities has also led to better outcomes in peripheral arthritis, an extraintestinal manifestations of IBD [41,16].

Physical therapy and structured exercise are known to lead to an increased release of anti-inflammatory cytokines, to a reduction of visceral fat tissue, and to a decrease of intestinal barrier dysfunction. Thus, it has been assumed that physical activity supports the physiological immune response, modifies the microbiome, and finally, improves the therapeutic outcome of IBD patients [16,43].

Physical exercise, as a modifiable lifestyle factor, shows positive effects in maintaining the balance of the microbiome or in rebalancing the dysbiosis of the gut. Studies have shown that regular training units, executed on a daily basis, could alter the intestinal microbiota by enriching the diversity of the microbiome and increasing the number of beneficial microbial bacteria [11,47].

Furthermore, physical exercise has shown positive impacts on extra-intestinal manifestations of IBD, including pelvic dysfunction, sarcopenia, and osteopenia, which are often underdiagnosed and undertreated, but have substantial influence on the quality of patients' lives [43]. A sedentary lifestyle with a low-level of physical activity has been known to elevate the risk of developing osteo-sarcopenia in IBD patients [46]. In contrast to low-impact physical exercise, which has shown positive effects on the outcome of IBD patients with osteoporosis by increasing bone mineral and bone marrow density. In addition, resistance training has led to increased muscle mass and muscle strength as well as to reduced inflammation markers like CRP [46].

Different types of physical training

Depending on duration, intensity and regularity, physical activities do have different impacts on physiological processes in the gastro-intestinal system [47]. Low-intensity exercises show protective effects by increasing the gut motility and

reducing the time between pathogens and mucus layer of the GI system. In addition, available data support positive effects of exercise training interventions on functional and psychological outcomes in patients with IBD by reducing self-reported stress and improving patients' well-being and quality of life. Thus, the integration of physical activity in the daily routine may not only improve mental health in patients with IBD, but also lead to better compliance and outcomes [45,47].

Postoperative recovery periods are known to be delayed in women and in older patients. Prehabilitation programs with exercise training units have shown to improve postoperative recovery periods. In addition, postoperative rehabilitations have shortened the recovery of physical function, decreased fatigue, and helped to restore the physical capacity [43].

But while patients with mild to moderate disease activity may take part in endurance training units without the risk of deterioration, it may be risky for patients in severe medical conditions. Strong intensity training can have negative effects on the GI system, by increasing its permeability and leading to diarrhea and nausea [43]. Endurance exercises induce variations in the GI system by reducing the splanchnic blood flow, which may result in an elevated level of toxins in the blood system. Furthermore, prolonged exercise units may affect the gut-barrier function not only by increasing the intestinal permeability but also by leading to bacterial translocation from the gut into the blood [11]. Besides, high energy consuming physical exercises may lead to negative outcomes on IBD patients with substantial intestinal resections [16].

Regular physical activity is an important and healthy way to maintain a normal weight or to reduce obesity. But, while moderate physical exercise increased the abundance of beneficial bacteria in the gut microbiota in lean individuals, no effect was identified in the gut microbiota of obese IBD patients [45].

Physical activity and fatigue in IBD patients

Fatigue is one of the most common symptoms of patients with IBD. As fatigue is substantially worsening the quality of life for patients with IBD, it should be measured as primary outcome when evaluating interventions designed to effectively treat patients with IBD [44]. The different reasons leading to fatigue are often multifactorial and correlate with disease activity, psychological comorbidities, sleep difficulties, biochemical causes, and behavioral factors [42]. The implementation of physical exercise in the treatment of other autoimmune diseases, improved not only fatigue, but reduced also pain and relieved stress [16]. Physical activity, as one of the modifiable environmental factors, may improve fatigue in IBD patients. But results of scientific studies are still uncertain. What is certain, on the other hand, that more adverse gastrointestinal events, like diarrhea and bloating, were reported from IBD patients, when no physical activity was part of the daily routine [44].

When treating fatigue in patients with IBD, the initial treatment should target potentially reversible factors like active disease, anaemia, and micronutrient deficiency. In the absence of an improved outcome, fatigue management should then include psychologic interventions, increased physical exercise, dietary modifications, and quitting smoking, according to a biopsychosocial approach [42,45].

3.4 Synthesis of results

3.4.1 Lifestyle factors and IBD

An overview of lifestyle and environmental factors, which have been known to influence the development and the course of IBD, are provided in table 10 below. After summarizing the outcomes of our literature search, a group of protective factors against disease development, and/or disease exacerbation are listed on the left side of the table. On the right side of the table are defined risk factors summarized, which have shown negative effects on IBD. The highlighting of the condensed data was chosen according to the agreement about their protective or negative impact on IBD (see chapter discussion for further information).

Table 10: Summary of protective factors and risk factors on IBD

IBD Lifestyle and Environmental factors	
Protective factors	Risk factors
Diets high in fruits, vegetables, fibres [2,4,10,19,20,21,22,23]	Smoking [2,3,4,10,13,18,19,21,22,23]
Moderate physical activity [2,10,13,18,20,21,22,23]	Antibiotics during pregnancy and childhood [2,3,4,10,19,21,23]
Breastfeeding [2,3,4,10,21,23]	Frequent or long-term use of NSAIDs [3,10,18,19,21,23]
Growing up in a less hygienic environment [2,3,4,10,18]	Perceived Stress [10,13,18,19,23]
Vitamin D [2,3,10,21]	Oral contraceptives [3,10,19,23]
Normal body weight [13,21,23]	Sleep disturbances [10,13,21]
Stress management [20,21]	Depression and anxiety [3,23]

High intake of meat (UC) [4,18]
High intake of fat and sugar [2]
Food additives [21]

3.4.2 Diets and IBD

A summary of the most studied dietary interventions implemented in the treatment of IBD are provided below in table 11. The most frequently observed positive effects on the left side of the table are compared with the most frequently observed negative effects. The highlighting of the summarized comparison of the studied diets was chosen according to the frequency of their positive or negative impact on the outcome of IBD (see chapter discussion for further information).

Table 11: Comparison of Pros and Cons of dietary interventions

IBD Dietary interventions	
Exclusive Enteral Nutrition (EEN)	
+	-
<ul style="list-style-type: none"> + induction of remission comparable with steroids [24,30] + better results of mucosal healing than steroids [24,27] + positive effects on dysbiosis in patients with CD [24,25] + maintaining remission in patients on biologics [25,27] + improved endoscopic and histologic results [27,30] + reduces pro-inflammatory cytokines [25] + reduction of mucosal inflammation in children [12] 	<ul style="list-style-type: none"> - lower rates of clinical response than steroids in adults [2,27] - problems with tolerability and adherence [24,25] - no normalized fecal calprotectin [12] - no additional food allowed beside formular [24] - positive effects on the microbiome reverse after a while [28] - reduction of anti-inflammatory bacteria [29] - increase of pro-inflammatory bacteria [29]

<ul style="list-style-type: none"> + best studied dietary intervention [25] + removal of antigenic food proteins [29] + decreased inflammation markers [30] 	<ul style="list-style-type: none"> – difficulties due to complete avoidance of table foods [27]
Specific Carbohydrate Diet (SCD)	
+	–
<ul style="list-style-type: none"> + clinical improvement and mucosal healing [12,25,27,30,31] + induction and maintenance of remission [12,24,27,30,31] + significant improvement of inflammatory markers [24,31] + most studied exclusion diet for IBD treatment [24] + potential to induce mucosal healing [24] + possible weight-loss for obese or overweight patients [24] + significant improvement of clinical symptoms [25] + higher rate of adherence than other dietary strategies [25] + decreased inflammation markers [30] + normalization of albumin [30] 	<ul style="list-style-type: none"> – small uncontrolled studies [12,25] – limited data to confirm efficacy in treatment of IBD in adults [25,31] – difficult adherence like other exclusion diets [24] – limit availability of objective inflammatory markers [27] – potential risk of micronutrient deficiency [27]
Diet low in FODMAPs	
+	–
<ul style="list-style-type: none"> + improved GI symptoms [12,25] + improved disease scores [30,31] + beneficial for reducing gastrointestinal symptoms [24] + improvement of clinical symptoms [30] 	<ul style="list-style-type: none"> – no improved inflammation parameters [12,25,30] – reduction of favorable species in the microbiome [12,28,32] – risk of aggravating dysbiosis on a prolonged diet [24,32] – risk of nutritional deficiencies on the long-term [25,32] – drastic restriction of food over certain period [32] – risk of constipation because of a lack of soluble fibres, [32] –

Partial Enteral Nutrition (PEN)	
+	–
<ul style="list-style-type: none"> + similar effects as EEN [25,30] + better compliance than EEN [25,30] + reduction of relapse by 50% in CD [12] + increased rate of remission [30] + successful in maintaining remission [27] + decreased inflammation markers [30] 	<ul style="list-style-type: none"> – no normalized fecal calprotectin [12] – few data available [25] – less successful in inducing remission [27]
Crohn’s Disease Exclusion Diet (CDED)	
+	–
<ul style="list-style-type: none"> + higher tolerance of patients than with EEN [24,25,30] + comparable rate of clinical remission like EEN [24,30] + normalization of inflammation markers [24,30] + improved therapeutic results [30] + positive effects on the microbiome [28] + normalized intestinal permeability [30] 	<ul style="list-style-type: none"> – no data about mucosal healing [24] – few data available [25]
Crohn’s Disease–Treatment with Eating (CD-TREAT)	
+	–
<ul style="list-style-type: none"> + better tolerance than EEN [24,25,27] + positive effects on composition and diversity of the microbiome [25,27,29] + successful induction of remission (60%) [27,29] + decrease of fecal calprotectin [24] + individualized anti-inflammatory diet [27] 	<ul style="list-style-type: none"> – few available studies and small sample sizes [24,25,27]

Semi-Vegetarian Diet	
+	-
<ul style="list-style-type: none"> + longer clinical remission than omnivorous diets in UC [24,27] + improved symptoms and remission rates [25] + improved rates of compliance [27] 	<ul style="list-style-type: none"> - data are sparse and conflicting [24,25] - no reduced risk of flares in patients with CD [25] - small sample size [27] - no control group as reference [27]
Mediterranean Diet	
+	-
<ul style="list-style-type: none"> - reduction of C-reactive protein (CPR) [31] - normalization of the microbiota [31] - weight-loss [31] - lower risk of developing CD [31] - better adherence than with other diets, [31] - anti-inflammatory butyrate production [29] - increase of microbial diversity [29] - increase of beneficial bacteria [29] 	<ul style="list-style-type: none"> - no decreased risk for development of UC [31] - increase of intestinal inflammation [29] - reduced permeability of the gut [29]
CDED plus PEN	
+	-
<ul style="list-style-type: none"> + clinical effects like EEN [27] + better outcomes than PEN alone, [27] + sustaining remission better than PEN, [27] + minimize decrease of microbial diversity [29] + production of anti-inflammatory butyrate [29] 	<ul style="list-style-type: none"> - few data available [25]

Autoimmune Protocol Diet	
+	–
<ul style="list-style-type: none"> + significant reduction of disease activity (Mayo score) [27,30] + increased rate of remission [30] 	<ul style="list-style-type: none"> – no significant decrease of inflammation markers [27,30]
Inflammatory Bowel Disease Anti-Inflammatory Diet (IBD-AID)	
+	–
<ul style="list-style-type: none"> + improvement of GI-symptoms [27] + reduction of medical therapy [27] 	<ul style="list-style-type: none"> – no measurement of fecal calprotectin [27] – no control group as reference [27]
Vegetarian and Vegan Diet	
+	–
<ul style="list-style-type: none"> + fewer rates of relapse for patients with UC [31] + prolonged remission period [31] 	<ul style="list-style-type: none"> – high drop-out rates [31] – limitations based on confounding effects [31]
Gluten-free Diet	
+	–
<ul style="list-style-type: none"> + better digestive well-being of IBS-patients [24] + improvement of clinical symptoms [31] 	<ul style="list-style-type: none"> – no controlled diets available [24] – risk of nutritional deficiencies [28] – no association with disease activity, hospitalization, or surgery rate [31]
<p>Protective factors: [29] CD: fibers (anti-inflammatory) UC: tea (increased microbial diversity)</p>	<p>Risk factors: [29] <u>CD:</u> ultra-processed foods (increased intestinal permeability and inflammation) <u>UC:</u> soft drink & sucrose (dysbiosis)</p>
<p>Foods recommended to increase: CD: Fruits and Vegetables [26] UC: Marine fish (omega-3 fatty acids) [26] plant-based diet [29]</p>	<p>Foods recommended to decrease: CD: Saturated fat, Trans fat, food additives [26] UC: Red meat, processed meat, Palm oil, coconut oil, food additives [26,29]</p>

3.4.3 Psychological health and IBD

An assembly of the most frequent psychological symptoms, observed in IBD patients and suggested psychological treatments are listed in table 13. The highlighting of the indicated psychological interventions was chosen according to the degree of consensus between the selected publications to restore mental health and improve psychological burden of IBD patients (see chapter discussion for further information).

Table 12: Recommended psychological interventions of IBD patients

IBD Psychological Health	
Psychological burden	Psychological interventions
Perceived stress	⇒ Stress management [14,33,34,35,37,38,39,40]
Fatigue	⇒ Cognitive Behavioral Therapy (CBT) [14,33,35,36] ⇒ Solution-focused therapy (SFT) [15,36] ⇒ Problem-Solving Therapy (PST) [15] ⇒ Stress management [37]
Pain	⇒ Cognitive Behavioral Therapy (CBT) [14,33,34,35] ⇒ Hypnosis [35] ⇒ Mindfulness techniques [35] ⇒ Relaxation [34] ⇒ Stress management [37]
Depression	⇒ Cognitive Behavioral Therapy (CBT) [15] ⇒ Mindfulness techniques [35]
Anxiety	⇒ Cognitive Behavioral Therapy (CBT) [15] ⇒ Hypnosis [35] ⇒ Mindfulness techniques [35]
Sleep disturbances	⇒ Cognitive Behavioral Therapy (CBT) [35]

3.4.4 Physical activity and IBD

A comparison of different forms on physical activity and exercise training, integrated in the treatment of IBD is listed below in table 13. In addition, the most frequent positive and negative effects on physical and psychological health, observed in patients with IBD are summarized. The highlighting of the condensed data was chosen according to the agreement about their protective or negative impact on IBD (see chapter discussion for further information).

Table 13: Pros and Cons of physical activity for IBD patients

IBD Physical activity exercise	
+	–
<ul style="list-style-type: none"> + Low-intensity training [11] + Low-impact exercise [16] + Regular activity [16] + Preoperative training programs [43] + Postoperative rehabilitation programs [43] + Resistance training [46] 	<ul style="list-style-type: none"> – endurance sport [11] – High-energy consuming activity [16] – prolonged physical activity [37] – strong-intensity training [43]
+	–
<ul style="list-style-type: none"> + Enriching the diversity of the microbiome [11,45,47] + Increasing beneficial microbial bacteria. [11,45,47] + Improvement of fatigue and reducing its burden [16,42,45] + Release of anti-inflammatory cytokines [16,43,46] + Lower risk of developing CD [16,41] + Better outcomes for extraintestinal manifestations (e.g. peripheral arthritis, osteosarcopenia) [16,46] + Increasing the gut motility [11] + Reducing the dwelling time of pathogens in the gut. [11] + Decrease of intestinal barrier dysfunction [16] + Improving mental health and leading to better compliance. [16] + Reduction of visceral fat [43] 	<ul style="list-style-type: none"> – Leading to increased levels of toxins by reducing the splanchnic blood flow [11] – Increasing intestinal permeability, causing bacterial translocations [11] – Not advisable for patients with short bowel syndrome. [16] – No protection against UC [41] – Inducing diarrhea and nausea [43] – No observed positive effects on intestinal microbiota in obese patients. [45]

<ul style="list-style-type: none"> + Reducing postoperative recovery periods [43] + Decreasing fatigue and restore physical capacity. [43] + Less adverse gastrointestinal events [44] + Positive effects on functional and psychological outcomes, [45] + Reducing self-reported stress and improving quality of life, [45] + Improvement of social well-being, [46] 	
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4 Discussion

4.1 Summary of Evidence

During the last decades, the number of patients with IBD has risen not only in western countries in Europe and North America, but also in developing countries in Asia and Africa, making IBD a global problem for patients and health care providers worldwide [2,4]. IBD is an autoimmune disease with recurring flares, which is requiring a lifelong, expensive therapy with possible adverse side effects. IBD has a significant impact on the quality of life for patients and represents a challenge for national and international health care systems [4].

Negative side effects for patients and increasing costs for health care providers highlight the need for a better understanding of possible trigger factors responsible for the worldwide rise of this autoimmune disease. Because of constantly evolving and improving molecular biology technology, researchers have been able to bring light into underlying processes which hadn't been understood before. This has led to a rising number of publications about the impact of environmental and lifestyle factors on development and outcome of IBD. A scoping review about the most important lifestyle factors and their impact on the development and course of IBD shall provide new insights and support the ambition of a personalized therapy, according to a modern, bio-psycho-social oriented, medicine.

4.1.1 Impact of lifestyle factors on IBD

The use of new technologies during the last decade has shown the important influence of the intestinal microbiome on physiological and pathophysiological processes, not only on the gut but also on the immune system [10]. Microbial dysbiosis challenges the gut barrier function and results in a pathological immune response of the host. As microbial dysbiosis has been observed in patients with IBD, the intestinal microbiome might represent the link between environmental exposure and the risk to develop IBD. Its microflora evolves within the first years of life and plays an important part not only in human's metabolism, but also in the development of the immune defense system. A decreased diversity in the bacterial colonization, fungal microbiota and viral composition of the gastrointestinal tract has been noted

in patients with IBD. It stays unclear whether the reduced variability of the microbiota is the cause or the consequence or even both, underlying the persisting inflammation observed in IBD. But it is known that environmental and lifestyle factors like smoking, diets, antibiotics, exercise, psychosocial stressors, etc. can lead to significant changes in the composition and function of the intestinal microbiome. It seems therefore reasonable to implement lifestyle changes in the management of IBD. Studies showed that changing diets, quitting smoking, and boosting exercise may bring the microbiome from dysbiosis closer to eubiosis, which may lead to stable remission in patients with CD [2,3,10,18,19,21,22].

Lifestyle factors like diets, physical activity, sleep, stress, and cigarette smoking have shown impacts on the response of the immune system [2,3,4,10,13, 18,19,20,21,22,23]. These modifiable factors may not only change the risk of developing IBD but may also have an impact on the outcome of IBD treatments. While an active lifestyle has been correlated with a positive and protective influence, perceived stress and obesity increased the risk of IBD and lead to negative outcomes of IBD therapies [13,21,23].

Cigarette smoking has shown negative effects on CD by leading to unfavorable outcomes, disease progression and corticosteroid-dependency [2,3,4,10,13, 18,19,21,22,23]. In contrast to the impact of smoking on UC, where no significant adverse effects like flares, corticosteroid-dependency and disease extension were observed [13,16,19]. While smoking increases the risk of CD, quitting of smoking enhances the risk of UC [2]. But according to recommendations of the International Organization for Study of Inflammatory Bowel Disease (IOIBD) cigarette smoking should never be started to reduce the risk of IBD [23].

The prescription of medications for patients with IBD should be done with precaution as different drugs were accompanied with deteriorating effects on the course of IBD. The long-term or frequent use of NSAIDs, for example, should be avoided from patients with IBD, as they may increase the risk of flares [3,10,18,19,21,23]. An enhanced use of antibiotics, especially during pregnancy and in early childhood, may represent a risk factor for the development of IBD [2,3,4,10,19,21,23]. Geographical differences in the prescription of antibiotics may be partly responsible for the protective impact of antibiotics on immigrants from Asia and the Middle East while it has been generally defined as a risk factor for individuals from Western countries [2]. Physicians should evaluate the risk factors for venous thromboembolism, before prescribing contraceptives for female patients with IBD [23].

Physical activity has been associated with decreased risk of flares in patients with mild to moderate forms of IBD [2,10,13,18,20,21,22,23]. Advanced physical exercise at a regular basis showed a lower risk of relapse among IBD-patients in remission. In addition, a good physical condition helped to improve the outcome of major abdominal surgeries [13]. The implementation of endurance and resistance exercises in the daily routine is recommended to maintain a normal weight in patients with IBD [23]. Obesity, on the contrary, has been correlated with a higher risk of persistent disease activity or repeating flares [13,21]. Besides, patients with obesity showed less successful outcomes on pharmaceutical treatments or had higher rates of post-operative complications [13]. According to the IOIBD regular physical activity and maintaining a normal body-mass index should be recommended to patients with IBD [23].

When treating patients with IBD, they should be screened for psychosocial stressors and symptoms of depression and anxiety [23]. Perceived stress has shown negative effects on the outcome of IBD treatments and was associated with an increased disease exacerbation [10,13,18,19,23]. Stress shows adverse impacts on the immune, nervous, and endocrine system by affecting the gastrointestinal function and the permeability of the gut, consequently leading to flares and elevated clinical disease activity indices [13,19]. But while stress management therapies like mindfulness-based therapies, cognitive behavioral therapy and gut-directed hypnotherapy did improve the quality of life for a certain time [20], these therapies did not significantly improve results on disease activity and recurring flares in RCTs [13].

Like stress, the lack of sleep is known to have a bidirectional relationship with IBD [10,13,21]. Active disease showed to be a risk factor for sleep disturbances and consequently for fatigue and circadian misalignment in patients with CD, which could again lead to a higher risk of flares and a more aggressive clinical course with structuring and fistulizing behavior. However, no clinical trials have evaluated whether improved sleep hygiene may positively influence the course of the disease and decrease the risk of inflammation in patients with IBD. Because of its impact on the quality of life, a systemic evaluation of sleep and the education on sleep hygiene are recommended when treating patients with IBD [13].

The consumption of alcohol has not been clearly identified as a risk factor for the development of IBD. Studies observing the use of alcohol concerning the clinical outcome showed either worsening disease activity or no significant impact on patients in remission [13]. These findings suggest that a moderate consumption of alcohol may be secure for patients with IBD, but that excessive intake of alcohol does harm the health [23].

According to the ‘hygiene hypothesis’ is a less hygienic environment inversely associated with the risk of IBD [2,3,4,10,18]. It was discovered that pets during childhood, large family sizes, living on a farm and drinking unpasteurized milk were associated with protective effects against the development of IBD. But geographical differences seem to play an essential role in the determination of being protective or not. A sufficient amount of vitamin D was found to be a protective factor for Caucasians, and the deficiency of vitamin D was found to be correlated with an increased risk for CD. The consumption of tea and coffee, on the other hand, was identified to show protective effects among Asians by reducing the risk of IBD [2]. Genetic distinctions may play an important role in the development of IBD. But while over 200 risk loci for IBD have been discovered so far in genetic screens, they are only able to explain a moderate amount of predicted heritability of this chronic disease [2]. The rapid rise of IBD cases in developing countries as well as the increasing risks for immigrants in western countries to develop IBD, show, that genetic susceptibility may not be the only underlying reason to trigger this autoimmune disease. It supports the assumption, that beside genetics, epigenetic factors like environmental and lifestyle factors may be relevant in the development and course of IBD [2,3,4,10,13,18,19,20,21,22,23].

Besides, the time of exposure to this risk factors may play a significant role in the development and outcome of IBD. During childhood, when the immune system is

still evolving, exposures to different risk factors are assumed to influence the development of the immune system, while exposures during adulthood are expected to modify an already established immunologic pathway.

Therefore, environmental factors do play a critical role in the development of IBD during childhood. Protective factors, like breastfeeding, animal contact, infection with *Helicobacter pylori* and living in a rural environment, may decrease the incidence of IBD. Consequently, a higher level of hygiene might lead to a less efficient immune system which could increase the risk of IBD [2,3,4,10]. When the formation of the immune system is still not completed, the use of antibiotics should be reasonable, as it is an important risk factor by changing the microbiome and enabling pathogenic bacteria to disturb the mucosal immune system [2,3,10,19,21,23].

During adulthood, the influence of lifestyle factors become more apparent, because of a more mature immune system and the freedom of choice, making tobacco smoking and the lack of physical activity substantial risk factors for IBD [2,3,4,10,13,18,19,20,21,22,23]. In addition, the enhanced use of medications like NSAIDs, oral contraceptives and hormone replacement therapies as well as depressive feelings and psychosocial stressors show negative effects and represent common risk factors, facilitating the development of IBD [3,10,13,18,19,21,23].

Independent from the phase of life, several lifelong exposures have been identified to play a role in the development of IBD. Living in southern latitudes, sufficient vitamin D and tap water consumption are environmental factors which may decrease the risk of IBD. In comparison, acute gastroenteritis, air pollution, and toxicants may increase the possibility of IBD in genetic susceptible individuals [2]. But only few studies have examined those lifestyle and environmental factors and further evaluation is needed to be done.

In contrast to genetic predisposition, the exposome is a modifiable factor in the development and course of IBD. The exposome represents the correlation of environmental exposures throughout a lifetime with the risk of IBD. In susceptible individuals, the modification of environmental and lifestyle factors could delay or even prevent IBD. Assessment and combination of protective and risk factors of an individual patient into an exposome risk score, might represent a helpful tool, when implemented in the therapy of IBD. It could lead to a more personalized treatment of IBD, according to modern medicine with a bio-psycho-social approach [3,10,19].

4.1.2 Impact of diets on IBD

The western lifestyle is known to be a diet high in animal fat and sugar and low in fruits and vegetables with negative consequences, e.g., for the body weight, the cardiovascular system and for the development of IBD. Large longitudinal studies have provided data about the influence of dietary patterns on the development of IBD. According to the consistency of the obtained findings, it was concluded that diets with more fruits and vegetables, as a source for soluble fibers, decreased the risk of IBD for participants. In contrast to the group of people who consumed more animal fat and sugar, who faced an increased risk of IBD [12].

First of all, dietary interventions were successfully implemented in the treatment of acute flares in children with IBD, in order to prevent known side effects associated with glucocorticoid therapy [12]. Current S3 guidelines still recommend the Exclusive Enteral Nutrition (EEN) as first line therapy for the clinical treatment of CD in children [8]. EEN showed better results of mucosal healing in the GI system, less side effects and similar decrease of inflammatory markers than glucocorticoides. Even though the implementation of EEN in the treatment of adult CD patients hasn't been as successful as in children with CD, the influence of diets and nutritional interventions has been recognized as one of the most important lifestyle factors in the development and progression of IBD [12,24,25,27,29,30].

Even though EEN has shown remarkable results in the treatment of children with IBD, this therapy did not show the same rate of success in adult patients with IBD. A disadvantage of this nutritional intervention is the complete exclusion of table food, which have been extremely difficult for patients with IBD, leading to difficulties in adherence with this dietary approach. Other dietary interventions have been tested with the goal to achieve similar therapeutic outcomes as EEN but better rates of compliance. Finally, a combination of Partial Enteral Nutrition (PEN) together with Crohn's Disease Exclusion Diet (CDED) have been tested but there are still too few data available for evidence-based recommendations.

The Specific Carbohydrate Diet (SCD), another elimination diet, has also been studied in the treatment of patients with CD. This dietary intervention with an exclusion of complex carbohydrates has shown to reduce gastrointestinal symptoms, to induce mucosal healing, to decrease intestinal inflammation and prolong the phase of remission in CD patients [12,24,25,27,28,30,31]. Despite of improved therapeutic outcomes, it has been pointed out that the exclusion of certain food and food groups may involve the risk of nutritional deficiencies [27,28]. It has been therefore recommended that patients with elimination diets should be regularly monitored for malnutrition [32]. When implementing these kinds of diets in the treatment of IBD, the difficulty of adherence and compliance to the chosen elimination diet was found to be a significant challenge for IBD patients [24]. Nonetheless, a majority of patients with IBD believe that diets do play a role in the development and the course of this chronic disease [24], but questionnaires among patients and physicians have revealed a lack of information concerning dietary approaches and their effects on the outcome of IBD [25].

New analytical methods have revealed the important role of the microbiome in the genesis and activity of IBD by affecting not only the intestinal permeability but also the immune system [10,19,22,27]. Patients with IBD show a microbial dysbiosis of the gut with an altered bacterial composition and a reduced diversity of microbes, which is known to promote intestinal inflammation [28]. Technological advances in microbiology and computational biology have not only facilitated the characterization of the microbiome but have also shed light on the impact of nutritional interventions. Diets have been identified to be a potent factor in shaping the microbiome in a way that effects both development and activity of IBD [29].

As genetic variabilities affect the absorption and metabolism of nutrients, diets implemented in the treatment of IBD need the verification of being effective for the individual patients [31]. Based on interindividual variations of the microbiota

composition as well as complex interactions between genes and environmental factors, an individual approach of a personalized, disease-specific diet may be recommendable for effective IBD therapy in the future [31].

As diets are not the only lifestyle factors that have shown effects on the microbiota composition and its alteration, a combination of dietary interventions together with other microbiome-modulating factors are recommended to lead to more stable and successful results in the treatment of IBD patients [23].

4.1.3 Impact of psychological health on IBD

Disease activity of IBD patients and their psychological health appear to be interrelated and bidirectional, which holds the possibility to create a vicious cycle for them [33,38]. IBD patients are far more at risk to develop psychological disorders like depression or anxiety compared to general population [39]. Psychiatric comorbidities, which are often reported before the diagnosis of IBD, might influence the course of the disease either directly by exacerbating inflammation or indirectly by non-adherence to medical therapy [35,39]. Depression is associated with inflammation, pain, relapse, and poorer response to treatment of IBD [33,35,]. Anxiety has been associated with a reduced adherence to medication and has shown an elevated risk for surgery, perceived stress, and lower quality of life [35]. Disease exacerbations in turn may worsen symptoms of depression and anxiety [14,33].

Perceived stress has been reported to be one of the most relevant lifestyle factors concerning increased risk of relapse and disease exacerbation by IBD patients with quiescent disease [33,35,37,39]. Stress does not only change the motility of the gut, but also affects the intestinal permeability, alters the level of secreted cytokines, and induces alterations of the microbiome [14,34,35,37,38,40]. Besides, the parasympathetic reflex diminishes during a stress response, which consequently limits the anti-inflammatory role of the vagus nerve [35,38]. Especially women have been sensitive to increased visceral pain caused by elevated stress-induced cortisol levels [38]. As perceived stress has shown to be correlated with disease activity, higher rates of psychological stress have directly affected the course of IBD [14,35,37,38,40]. Integrating stress management as a biopsychosocial approach in the treatment of this chronic disease may improve therapeutic outcomes and reduce health care costs [14,33,34,35,37,38,39,40].

The negative impacts of stress have been partly attributed to a diminished parasympathetic reflex and a limited vagus nerve [14,35,38]. The vagus nerve plays an important role in the endocrine-immune-autonomic nervous system and is known to have anti-inflammatory properties. While a lower vagal tone is associated with a higher level of tumor necrosis factor- α , the stimulation of the vagus nerve may lower pain sensitivity and enhance gastro-duodenal motility by involving the microbiota-brain-gut axis [35,38,40]. While stress has been known to alter the microbiome, manipulations of the gut's microbiota have led to alterations of the stress response, confirming the multi-directional character of the microbiota-brain-gut-axis [39,40]. Chronic abdominal pain has been identified as one of the most common symptoms affecting and disturbing a patient's life, even with quiescent IBD activity [14,34,35,38]. Pain itself may be modulated by psychological factors like depression, anxiety, and stress [34]. While acute pain is correlating with disease activity, chronic

pain involves the brain-gut-axis with the potential to predispose IBD patients to anxiety and depression [35]. Drug-treated pain with narcotic analgesics may not only mask a relapse and bear the risk of addiction, but may also show serious side effects like constipation, narcotic bowel syndrome and increased risk of infection [34,35]. The connection between pain and psychological factors might therefore recommend a biopsychosocial approach in the treatment of IBD patients for improving the therapeutic outcome [38].

Fatigue is another disabling but underreported symptom of IBD, which is affecting over 80 % of patients with active disease and still over 50 % of IBD patients in remission [15,36]. It has been ranked fourth on the list of concerns by patients before pain and bowel problems because it strongly affects their mental performance and their physical working capacity [36]. A gender-specific gap has been identified as women seem to be affected by fatigue more often than men. The underlying reasons for the discrepancy are still unknown [36]. What is known is, that the etiology of fatigue is supposed to be multifactorial [15]. The recommended treatment of persistent fatigue should therefore follow a multidisciplinary approach with psychological interventions, physical exercise, and microbiota-directed therapy [36,44].

The substantial burden of IBD is not only determined by disease severity, but also by the ability of the patient to cope with symptoms in order to live a normal daily life. To provide comprehensive care for patients with IBD, a therapeutic approach should therefore focus on behavioral skills, social support, and stress reduction. Psychological interventions that emphasize coping strategies, perceived stress, and cognition of IBD are suggested to improve adjustments and outcomes. The ability to manage the disease might help to deal with disturbing symptoms more effectively and improve the quality of life for IBD patients [14,33,34,35,38,39,40].

Cognitive Behavioral Therapy (CBT) has been identified as one of the most promising psychological treatments of IBD, improving depression scores and quality of life for a studied period of time. Disease anxiety related CBT as well as stress management and relaxation techniques have shown to reduce pain in IBD patients with quiescent disease [14,15,33,34,35,36]. In contrast to negative coping strategies and dysfunctional cognition, which have led to increased pain severity and functional disability [34]. As IBD patients show higher rates of psychological stress, leading to increased risk of relapse and disease activity, stress management as well as relaxation techniques could help to reduce negative effects of stress and improve resilience to stress together with adaptive coping skills [14,33,34,35,37,38,39,40].

Solution-Focused Therapy (SFT) and Problem-Solving Therapy (PTF) have shown the most promising result in the treatment of fatigue [15,36]. But based on its multifactorial pathophysiology, the treatment of persistent fatigue proposes a multidisciplinary management not only with psychological interventions but also with physical exercise, and microbiota-directed therapy [36,44].

When treating patients with IBD, it is important to identify possible risk factors for psychological disorders, which include disease activity, aggressive disease phenotype, lower socioeconomic status, and female sex [14,33,38]. The importance of mental well-being and its impact on the course of IBD, 'psychological remission' should be implemented as possible endpoint in future clinical studies [39]. In

addition, IBD patients should be educated early about the multi-directional communication system of the microbiota-gut-brain-axis in order to improve therapeutic outcomes [14,39,40].

4.1.4 Impact of physical activity on IBD

The more sedentary lifestyle of western culture has led to several diseases of civilization like obesity, hypertension, cardiovascular diseases, etc. Physical activity, in contrast, has proven protective effects on a range of these illnesses [41]. Physical exercise has shown positive impacts on the therapeutic outcome of IBD and might even help to reduce the risk of developing this chronic disease [43]. Integrating regular training units in the daily routine has also been associated with a balanced body weight, a reduction of visceral fat, and an elevated level of anti-inflammatory cytokines [16,41]. Besides, engagement in physical activity has positive effects on extraintestinal manifestations of IBD, like peripheral arthritis, osteopenia, and sarcopenia [16,43].

Physical fitness has been identified to be an important modifiable lifestyle factor to ameliorate the burden of fatigue in IBD patients [42,45]. Even though the influence of exercise on IBD related fatigue is not quite clear, more adverse gastrointestinal symptoms were reported from patients, who did not engage in physical activity [44]. Besides, clinical studies have shown that the implementation of physical activity in the treatment of other autoimmune diseases have significantly improved fatigue, pain, and stress [16].

As surgical treatments might be required in severe cases of IBD, implemented prehabilitation programs in have shown to reduce postoperative recovery periods, which have been prolonged especially in women and elderly patients. In addition, it has been discovered that postoperative rehabilitation programs decreased fatigue, ameliorated physical recovery, and restored physical capacity [43]. Physical activity has shown to increase the motility of the gut and therefore to decrease the passage time of pathogens in the intestinal system [11]. Exercise has been identified to modify the intestinal microbiome by enriching the microbial diversity, by increasing the number of beneficial bacteria in the gut, and by decreasing the intestinal barrier dysfunction [47]. But while these positive effects were observed in lean to normal weight IBD patients, no effect was identified in the intestinal microbiome of obese patients [45].

High-energy consuming physical activities and endurance sports have been associated with negative effects on the gastro-intestinal system by reducing the splanchnic blood flow, increasing toxin levels and bacterial translocations [11,37,43]. In addition, strong intensity training units should not be carried out by patients with short bowel syndrome [16]. But low-intensity exercise has led to better outcomes in the treatment of IBD patients with mild to moderate disease activity [11,16,46]. Finally, the integration of physical activity in the treatment of IBD has also ameliorated mental health and has led to better compliance of patients, who have noticed positive effects like the reduction of self-reported stress and the improvement of health-related quality of life [45].

4.2 Limitations

Despite the growth of knowledge about the effects of lifestyle and environmental factors on IBD, further interventional studies and RCTs are highly needed. When providing information about diets, psychological health, and physical activity, influencing factors like patient's age, disease activity, pre-existing conditions, etc. should be taken into consideration in clinical study-designs.

Most studies about the impact of psychological interventions included IBD patients in remission, while the most psychological burden has been noted in patients with active disease or ongoing gastrointestinal symptoms. In addition, it cannot be excluded, that the successful use of drugs in the treatment of IBD has positive effects on the psychological wellbeing of patients with IBD as well.

Even though the influence of physical activities on development and course of chronic diseases have been known for quite some time, clinical studies about the impact of exercise on IBD have still been scarce. Our review about the impact of physical activity on the outcome of IBD but should emphasize the importance of this essential lifestyle factor in the treatment of IBD.

4.3 Conclusions

The growing number of IBD cases worldwide highlights the importance of a better knowledge of underlying mechanisms, in order to find efficient and affordable therapies, which should slow down this global trend. It has been discovered that beside genetic susceptibility, lifestyle, and environmental factors show impacts on development and course of IBD. Summarizing and simplifying the results of this scoping review, lifestyle and environmental factors can be divided into being protective or being a risk factor for the development or the exacerbation of this chronic autoimmune disease. Protective factors include early life events like breastfeeding, growing up in a less hygienic environment, increased intake of fibres from fruits and vegetables, sufficient level of vitamin D, regular sleep, stress management and moderate physical activity. Risk factors, including smoking, antibiotics during childhood, regular intake of NSAIDs, psychological disorders, oral contraceptive pills, diets with high amount of fat and sugar, etc., may cause dysbiosis of the microbiome and facilitate the development of IBD.

A healthy, non-smoking lifestyle with a diet rich in vegetables, fruits, dietary fibres, and low in animal fat and processed food should be recommended to patients with IBD. The combination of dietary interventions together with other microbiome-modulating factors like regular physical activity and mental-health supporting measurements may lead to better outcomes in the treatment of IBD patients. Especially children, adolescents and women seem to benefit the most from a holistic approach in IBD therapy. But all in all, the education of IBD patients about the impact of behavioural and lifestyle factors together with a process of shared decision-making between physicians and patients about important lifestyle changes, may improve not only the clinical outcome of the treatment but also help to reduce health-care costs.

The International Organization for Study of Inflammatory Bowel Diseases (IOIBD) published consensus recommendations for the management of patients with IBD [23], based on votings among their members, and simplified in Fig. 2.

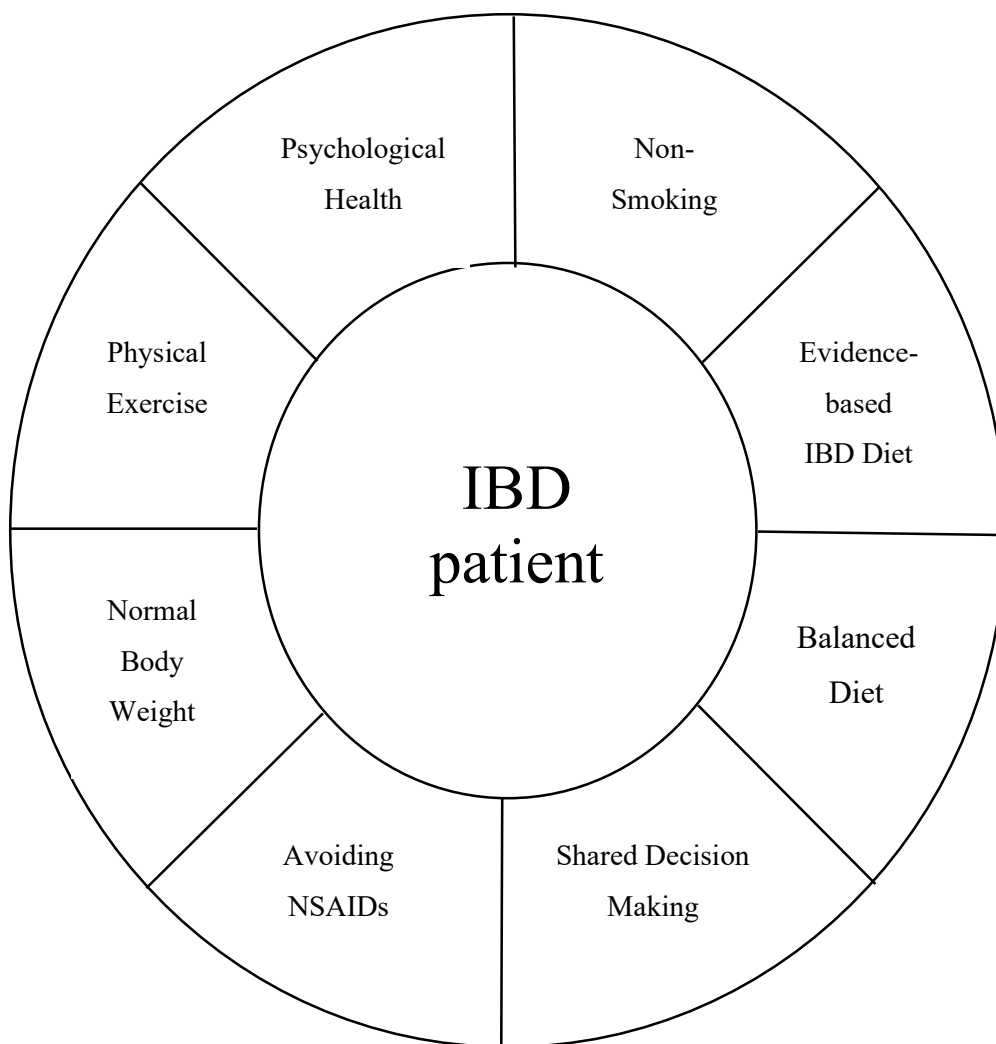


Figure 2: Recommendations for patients with IBD [23]

Keypoints:

- Fast rise and epidemiologic changes of IBD cases worldwide point to an involvement of lifestyle and environmental factors in onset and outcome of IBD.
- The implementation of microbiome modulating lifestyle factors in the treatment of IBD might affect therapeutic success and show positive effects on the quality of life of IBD patients.
- The education of physicians and patients about supporting lifestyle modulations in IBD treatment could improve therapy outcome and complies with a bio-psychosocial approach of modern personalized medicine.

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