Accepted author's manuscript. Published in final edited form as: The Journal of Nutrition 2021 (in press). Publisher DOI: 10.1093/jn/nxab245

Systematic review of the role of oat intake on gastrointestinal health

Ezra Valido[1,2]*, Jivko Stoyanov[1]*, Alessandro Bertolo[1], Anneke Hertig-Godeschalk[3], Ramona Maria Zeh[1], Joelle Leonie Flueck[3], Beatrice Minder[4], Stevan Stojic[2], Brandon Metzger[5], Weston Bussler[5], Taulant Muka[4], Hua Kern[5¥], Marija Glisic[1,4¥]

[1]Swiss Paraplegic Research, Nottwil, Switzerland

[2]Department of Health Sciences, University of Lucerne, Lucerne, Switzerland

[3]Institute of Sports Medicine, Swiss Paraplegic Centre, Nottwil, Switzerland

[4]Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland

[5]Standard Process Nutrition Innovation Center, Kannapolis, NC 28018, USA

**denotes equal contributions*
¥ certifies that both authors are considered last authors to all academic and professional effects, and that their names can be legitimately swapped in their respective publication list.

Sources of Support: This research was supported by Standard Process Inc., USA. HK, WB, B. Metzger are scientists at Standard Process Nutrition Innovation Center. The funder, Standard Process, provided support in the form of personal fee for author TM and salaries for HK, WB and B. Metzger, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific roles of these authors are articulated in the 'author contributions' section.

Conflict of Interest: Commercial affiliations of HK, WB, B. Metzger did not alter their adherence to journal policies on sharing data and materials. Other authors have nothing to disclose.

Corresponding Author:

Ezra Valido, MD, MPM, MPH

Swiss Paraplegic Research, Nottwil, Switzerland

Email: ezra.valido@paraplegie.ch

Phone: +41 41 939 66 39

Number of Word Count: 5047/5000

Number of Figures: 2

Number of Tables: 2

Supplementary data:

Supplemental Appendix I: Full search strategy per database for the systematic review for oat and gastrointestinal health; Supplemental Table 1. Characteristics of randomized controlled trials with oat intake conducted in individuals without gastrointestinal diseases; Supplemental Table 2: Characteristics of non-randomized trials on oat intake conducted in individuals without gastrointestinal diseases; Supplemental Table 3: Characteristics of randomized controlled trials with oat intake conducted in individuals with celiac disease and ulcerative colitis; Supplemental Table 4. Characteristics of non-randomized trials conducted in individuals with celiac disease and ulcerative colitis; Supplemental Table 5. Characteristics of observational studies with oat intake conducted in individuals with celiac disease and Crohn's disease; Supplemental Table 6. Characteristics of in vitro studies with oat conducted in individuals with celiac disease; Supplemental Table 7. Characteristics of in vitro studies

with oat conducted in individuals without gastrointestinal diseases; Supplemental Table 8. Quality assessment of randomized controlled trials with oat intake using the Risk of Bias tool for RCT; Supplemental Table 9. Quality assessment of observational studies with oat intake using Newcastle-Ottawa rating scale; Supplemental Table 10. Risk of bias assessment of the non-randomized trials with oat intake based on the National Heart Lung and Blood Institute. Quality Assessment Tool for Before-After (Pre-Post) Studies; Supplemental Table 11. Risk of bias assessment of the non-randomized trials with oat intake based on the National Heart Lung and Blood Institute Quality Assessment Tool; Supplemental Table 12. Quality assessment of in vitro with oat studies using the Toxicological data Reliability Assessment Tool

Running Title: Oat and gastrointestinal health

List of Abbreviations:

GI	Gastro-intestinal
CeD	Celiac disease
UC	Ulcerative colitis
IBS	Irritable Bowel Syndrome
IBD	Inflammatory Bowel Disease
RCT	Randomized Controlled Trial
SCFA	Short Chain Fatty Acid
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
TMAO	trimethylamine oxide
RoB	Risk of Bias
ToxRTool	Toxicological data Reliability Assessment Tool
GFD	Gluten-free diet

CH_4	Methane
GSRS	Gastrointestinal Symptom Reporting Scale
tTG	tissue Transglutamase
IEL	Intraepithelial lymphocytes
IL	Interleukin
NK	Natural killer
TGF	Transforming growth factor
Treg	Regulatory T cell
IFN	Interferon
EmA	Anti-endomysial antibody

ABSTRACT

Background: Oats are a food source with multiple health benefits that could support beneficial bacterial groups and provide important bioactive compounds for the gut.

Objective: This review explores the association between oat intake, gastrointestinal (GI) symptoms and microbial community changes in individuals with celiac disease (CeD), irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) and without GI disease.

Methods: Four databases and Google Scholar were systematically searched from inception until April 29, 2021. Clinical trials, observational studies and *in vitro* studies with human gut derived samples were included.

Results: There were 84 articles (23 RCTs, 21 non-randomized trials, 8 observational and 32 *in vitro* studies) included. Oat intake increased total bacterial count, *Lactobacilli spp.* and *Bifidobacterium spp* in healthy individuals and those with CeD. There was an increased concentration of short chain fatty acids and improved gut permeability with oat intake but with no significant quality of life difference. In some individuals with CeD consumption of certain oat types was associated with worsening of GI symptoms. We found no studies reporting on IBS and only 3 for IBD. The quality of RCTs showed some concerns mostly in domains of randomization (73.9%) while the quality of evidence of non-RCTs, observational and *in vitro* studies was satisfactory.

Conclusion: Oat intake was associated with the increase of beneficial bacterial groups in individuals without GI disease and those with CeD. The majority of studies showed no changes in GI symptoms with oat consumption. *In vitro* studies in CeD provide insight to oat sensitive individuals and their GI mucosa but the clinical studies remain limited, precluding our ability to draw firm conclusions. The prevalence of oat sensitivity in individuals with CeD should be further explored as this could improve clinical management and facilitate inclusion of oat in the diet for this population.

Key Words: Oat; Oat Bran; Gastrointestinal symptoms; Microbiome; Celiac disease

1. INTRODUCTION

Oats (*Avena sativa*) are a valuable food source known for multiple health benefits. They provide substantial amounts of carbohydrates including soluble fibers and other bioactive compounds (1) that have been associated with benefits in lowering the risks for obesity (2), cardiovascular diseases (3), type 2 diabetes (4) and gastrointestinal (GI) diseases (5). The intake of oat dietary fibers can delay gastric emptying and affect absorption of nutrients and the motility in the small bowel (6). Oat intake can affect the gut microbiome by supporting the growth of beneficial bacterial groups (7) thus contributing to improved GI health profile.

Gut dysbiosis has been linked with development or progression of various GI conditions such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), celiac disease (CeD) and GI cancer (8-12). The bacterial population dynamics are dependent on available substrates in the gut. The balance of beneficial and pathogenic bacterial groups depends on food intake, the individual's sex, age and co-morbidities (13). Bacterial fermentation in the colon produces beneficial metabolites such as short chain fatty acids (SCFAs) that are associated with favorable health outcomes in metabolic disorders (14), inflammatory bowel disorders and colon cancer (15). SCFAs are an energy source for gut epithelial cells and promote tightening of cell junctions, improvement of gut mucosal barrier, support optimal colon pH and help control the growth of microorganisms (16). Among the SCFAs, butyrate is the preferred energy source by colonic cells and has anti-inflammatory properties (17, 18). Most bacteria can produce acetate but only specific bacteria produce propionate or butyrate (19). Emerging evidence has suggested that increasing the absolute number or the

proportion of *Lactobacilli* and *Bifidobacteria*, can be used as a success marker for interventions targeting healthy GI microbial populations (20).

Previous systematic reviews and a meta-analysis on oat intake and the intestinal health have been focused on the safety of oats by individuals with bowel disorders (3, 21-23). Their results have outlined that oats are a valuable source of nutrients without gut inflammation but other aspects such as non-inflammatory associated symptoms and the benefits of modulating the gut microbiome have not been studied. Likewise, the effects of the oats on the microbiome not only in individuals with GI disorders but also the general population are lacking in these reviews. Thus, our systematic review aims to summarize and explore the evidence on the effect of oat intake on the GI health and the gut microbiome changes in individuals with (CeD, IBD, IBS) and without GI conditions.

2. METHODS

2.1 Data Sources and Search Strategy

This review was conducted in accordance with the workflow presented by Muka et al. (24) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) (25) guidelines. Four electronic databases were systematically searched: EMBASE (Elsevier, Netherlands), MEDLINE (National Library of Medicine, US), Cochrane central (Cochrane Collaboration, UK) and Web of Science (Thomson Reuters, US) from inception until April 29th 2021 and additionally the first 200 results were downloaded from the Google Scholar search engine. The detailed search strategy is provided in the **Supplemental Appendix I**.

2.2 Study Selection, Eligibility Criteria and Data Extraction

Detailed inclusion and exclusion criteria can be found in the review protocol (PROSPERO ID CRD42020190484). In brief, *in vitro* studies, observational studies, randomized controlled trials (RCT) and non-randomized trials were eligible for inclusion if they: (i) were conducted among individuals of any age without GI conditions or with IBD, IBS or CeD and (ii) investigated associations of oat, oat β-glucan and avenanthramides with any of the following outcomes: (a) digestive symptoms: bloating, abdominal pain, diarrhea, constipation, bowel inflammation, mucosal villus damage, (b) GI conditions: IBD, IBS or CeD focusing on risk of developing a disease and changes in the course of the disease management and/or (c) gut microbiome: changes in gut permeability, bacterial diversity, gut dysbiosis, gut microbiota metabolites and markers [SCFAs and trimethylamine oxide (TMAO)].

Due to the nature of our research question and complexity of the topic studied, to facilitate the interpretation of our findings, we excluded animal studies and studies including participants with GI cancers. In addition, letters to the editor, reviews, commentaries and conference abstracts were excluded. Titles and abstracts were independently evaluated by two reviewers and the full-texts were assessed by two independent reviewers. Disagreement was settled by reaching a consensus or by consulting a third reviewer. Two authors independently extracted the relevant information using a pre-defined data extraction form.

2.3 Methodological Quality Assessment

The quality of RCTs was assessed by two independent reviewers using the Risk of Bias tool for RCT (Rob2.0) (26). Quality of controlled and one arm non-randomized trials was evaluated using the National Heart Lung and Blood Institute Quality Assessment Tool (27, 28). Observational studies were evaluated using the Newcastle-Ottawa Scale (29). Reliability of experimental studies was evaluated using the Toxicological data Reliability Assessment Tool (ToxRTool) (30).

3. RESULTS

3.1 Literature search and study characteristics

There were 5,199 citations identified, with 119 selected for full-text evaluation (**Figure 1**). Of those, 84 articles (23 RCTs, 21 non-randomized trial, 8 observational and 32 *in vitro* studies using human material) comprised 4,022 participants (**Table 1**). Among observational and clinical studies, nine studies (17.3%) were conducted in healthy individuals, eight (15.4%) were conducted in the elderly and individuals with underlying conditions (i.e. hyperlipidemia, glucose intolerance), three (5.8%) were with IBD and 31 (59.6%) were in individuals with CeD. Among the *in vitro* studies, most were done using specimens from healthy individuals (n=24, 75%) and eight studies conducted using specimens from CeD. There were 10 (19.2%) observational/clinical studies and three *in vitro* studies (9.4%) conducted among pediatric populations. Detailed characteristics of the included studies can be found in **Supplemental Tables 1-7**.

<Insert Figure 1>

<Insert Table 1>

3.2 Oat intake and changes in gut microbiome

We identified nine RCTs, four non-randomized trials, one observational and 25 *in vitro* studies that provided information on how oat intake or experimental supplementation may affect either gut microbiome or SCFAs. Among the RCTs, three were conducted in healthy individuals, four in glucose-intolerant or type 2 diabetes and adults with elevated cholesterol, one in a pediatric population with CeD and one with adults with ulcerative colitis (UC). The intervention duration ranged from three weeks to 52 weeks and interventions (e.g. whole grain oat granola, ropy based oat and fermented oat) and controls (gluten-free diet [GFD], condensed milk, placebo) were heterogeneous between the included studies (**Table 2**, **Supplemental Table 1)**. There was a general increase in total bacterial count and the count of *Lactobacilli spp.* and *Bifidobacterium spp*. after the oat-based intervention across different RCTs (31-37).

<Insert Table 1>

In an RCT among healthy individuals, the group receiving 3g of oat fermented in *Lactobacillus plantarum* over a period of three weeks had increased total SCFAs, acetic and propionic and lactic acids at the end of the study, compared to baseline. The placebo group (pure rose hip drink) only had lactic acid increased. Differences between the two groups were not explored (33). In another cross-over RCT with metabolic disorders, after a six-week intervention, when two supplementation periods (whole grain oat granola versus non- whole grain breakfast) were compared, differences in SCFAs were not reported and no differences in SCFAs were found when comparing baseline vs. end of study (33). In a trial that described fecal SCFAs patterns in a pediatric population with newly diagnosed CeD, after being treated for a year with

GFD with or without oats, those treated with GFD-oats had significantly higher acetic acid, n-butyric acid and total SCFAs concentrations after a year of dietary intervention compared to the GFD group but no differences were observed between two groups at 0 and 6 months of intervention. The concentrations of propionic, i-butyric, i-valeric and n-valeric acids did not differ between the study groups at 0, 6 and 12 months respectively. During the year, the fermentation index, the amount of acetic acid minus propionic acid and n-butyric acid divided by the total amount of SCFAs, remained high in both the GFD-oats and the GFD groups with no significant differences (38). In another RCT of adults with UC, the group with a daily intake of 60g of oats for 24 weeks had total SCFAs, propionic acid, i-butyric acid, butyric acid and valeric acid significantly increased when compared to those consuming low fiber wheat products (39). Findings from non-randomized trials and an observational study are consistent with data from RCTs on increased SCFAs(40-43) (**Supplemental Table 2, 5)**.

We found 25 *in vitro* studies looking into oat fermentation and microbial metabolic activity in fecal samples (**Supplemental Table 7**). In general across the studies, the population of anaerobes decreased, Proteobacteria and Bacteroides phyla increased and the populations of the Lactobacillaceae and Bifidobacteriaceae families increased. Furthermore, increased levels of SCFAs and decreased production of proteolytic markers were observed (35, 44-67).

The impact of oat on gut barrier integrity and intestinal permeability has been demonstrated in *in vitro* settings wherein oat bran β-glucan improved gut barrier integrity (65). Pham et al. (65) tested the effect of human gut microbial content with five common dietary fibers (oat β-glucan 28%; oat β-glucan 94%; dried chicory root containing inulin 75%; xylo-oligosaccharide; inulin 90%) and control – maltodextrin.

After fermentation the gut barrier integrity was measured using a Caco-2/HT29-MTX cell lines co-culture model, mucus production HT29-MTX and HT29 cell models. The supernatant from fermentation of all tested fibers led to increased transepithelial electrical resistance suggesting increased junction strength between intestinal cells with oat β-glucan 28% being the most effective in this model (65).

3.3 Oat intake and GI symptoms

We identified five RCTs and four non-randomized trials examining associations between oat intake and GI symptoms among individuals without GI disease (**Supplemental Table 1-2**). In a cross-over RCT comparing the effect of oat and wheat cereal groups to reduce blood lipids in hypercholesterolemic adults, authors reported significantly higher self-reporting of intestinal gas production, looser stools in oat bran and higher frequency of constipation in wheat cereal group (68). In another RCT with moderately hypercholesterolemic adults over a period of 8 weeks, intake of 3g of oat β-glucan and oat-based isocaloric placebo without β-glucan did not exert any significant unfavorable effect on the self-perceived intestinal well-being (69). In a 3-leg crossover RCT among 14 healthy adults, different molecular weights of oat β-glucan did not significantly increase GI symptoms but gender difference in pain experience was observed (70). Conversely, in a RCT of 209 elderly residents in a nursing home, consumption of fermented oat with *Bifidobacterium* significantly increased bowel movements compared to placebo (71) while in a RCT of healthy pediatric individuals, aged six months to three years old, consumption of fermented oat with *L. plantarum* for three weeks was comparable to control (34). In a controlled non-RCT of 30 frail inhabitants of a geriatric ward aged 57-100 years receiving either oat bran (fiber group) or usual diet (control group) for 12 weeks, use of laxatives was reduced significantly at

59% for those taking oat bran with their body weight remaining constant (72). In another single-arm trial, 50 elderly individuals with complaint of constipation were entered into an open trial to assess the benefit on their symptoms by adding oat bran biscuits ('Lejfiber') twice daily to their diet over a period of 12 weeks. Treatment improved their bowel frequency, stool consistency and pain on defecation with no participant complaining of side-effects (73). Another single-arm intervention study of 33 healthy children age 7-12 years old (15 female and 18 male) who reported ≤5 bowel movements per week during screening consumed two servings of instant oatmeal daily for 2 weeks(74). No differences in stool frequency or consistency were observed from beginning and at the end of the trial (76). Kajs et al. (77) investigated whether a high concentration of methanogens influences the host's response to ingestion of non-absorbable, fermentable materials. Participants were placed on a basal diet (primarily rice and hamburger) with minimal amounts of non-absorbable, fermentable substrate and classified them as either high or low methane (CH_4) producers. After stabilization of the breath gas excretion, the participants ingested either sorbitol or oat. Authors found that low producers of CH_4 reported significantly increased bloating and cramping after sorbitol ingestion and increased bloating after oat ingestion compared to high CH_4 producers. The reduced presence of methanogenic organisms has been associated with reduced gut bloating and cramping (75).

Three RCTs, six non-randomized trials and five observational studies looked into changes in GI symptoms with oat intake in individuals with CeD (**Figure 2)**. These studies generally aimed to explore the safety of using oats in addition to GFD (**Supplemental Tables 3-7**). In a one-year RCT, the effect of oats-containing GFD on quality of life and GI symptoms in individuals with CeD were compared to traditional GFD. Quality of life did not differ between the groups but there were more GI symptoms

as assessed by the GI Symptom Rating Scale (GSRS) in the oats-consuming group. The higher the GSRS the more the individual suffers from a GI symptom (76). The oats group had significantly more diarrhea with a trend towards a more severe average constipation symptom score and the severity of symptoms was not dependent on the degree of intestinal inflammation (77). In a large crossover RCT evaluated the long-term validity and safety of pure oats in the treatment of pediatric population with CeD over a period of 15 months, a total of 306 pediatric individuals with CeD on a GFD for less than two years were randomly assigned to eat specifically prepared GFD containing an age-dependent amount of either placebo or purified non-reactive varieties of oats for two consecutive 6-month periods separated by a washout standard GFD for three months. GSRS scores were not different between the two groups in the two treatment periods regarding absolute variations (78). In a RCT with adults with CeD, large daily intake of 100g of kilned (heat sterilized) vs unkilned oats for 52 weeks were compared, kilned vs unkilned oats were comparable in self-reported GI symptoms (79).

<Insert Figure 2>

Results from the non-randomized trials generally show no harm (80-85) of adding oat to GFD though two studies showed potential harms (80-85). Baker et al. (84) investigated the effect of addition of oats and barley to GFD with individuals with CeD using an oral 5g xylose excretion test to assess small bowel function before and after intake. Both oats and barley were found to be potentially harmful to individuals with CeD although barley had more toxic effect (84). On the other hand, 19 adults with CeD on GFD were challenged with 50g of oats per day for 12 weeks and authors found that oats were well tolerated by most patients but reports of initial abdominal discomfort

and bloating were observed (85). Among six observational studies with individuals with CeD, there was no significant increase in GI symptoms in long term intake of oats (86-91).

There was one RCT, one non-randomized trial and an observational study that looked into GI symptoms and IBD. In a RCT among adults with UC who consumed 60g of oat daily for 24 weeks, when compared to those with low fiber wheat products, the oat group had significantly higher diarrhea in the 8^{th} and 16^{th} week but eventually were comparable to the other group at the end of trial (39). In contrast, in a non-randomized trial among adults with UC with 60g of oat bran added to their usual diet for 12 weeks, no increase in GI symptoms was observed (42). In an observational study among individuals with genetic risks for developing Crohn's disease, significantly low consumption of oats, rye and bran played a role in influencing the GI microflora that predisposed the onset of the disease (92).

3.4 Oat supplementation and histopathological/immunological changes

We identified 10 RCTs, 11 non-randomized trials, five observational studies and eight *in vitro* studies exploring histological changes in the small intestines (i.e. intestinal villi structure, number of intraepithelial lymphocytes [IELs]) or immunological effects of oats (i.e. gliadin and reticulin antibodies) (**Supplemental Table 3,4,7**). Among identified studies, the majority of studies were with individuals with CeD (23 in adult and 11 in pediatric population) and those findings are summarized in **Figure 2.**

Among RCTs focusing on individuals with CeD, both in adults and pediatric populations with newly diagnosed CeD or CeD in remission, neither worsening in the small intestine

morphology nor inflammation across diet groups (GFD including oats vs. conventional GFD) were reported (78, 79, 93-97). In adults with CeD, two RCTs reported no worsening of the autoimmune responses (77, 94). The toxicity of oats in a pediatric population with CeD was studied by investigating either anti-avenin antibodies or IgA-class autoantibody deposits targeted against jejunal transglutaminase 2 (TG2)- (a potentially more sensitive disease marker than serum antibodies or conventional histology). The majority of RCTs showed no worsening in these serology markers (78, 95-98). A single RCT compared paired small intestinal biopsies, before and after >11 months on a GFD, collected from pediatric population with CeD who were enrolled either of two diets: standard GFD (GFD-std; n = 13) and non-contaminated oat-containing GFD (GFD-oats; n = 15). Expression levels of mRNAs for 22 different immune effector molecules and tight junction proteins were determined by quantitative reverse transcriptase polymerase chain reaction (RT)-PCR. The number of mRNAs that remained elevated was higher in the GFD-oats group. In particular, mRNAs for the regulatory T cell (Treg) signature molecules interleukin-10 (IL-10) and transforming growth factor-β1 (TGF-β1), the cytotoxicity-activating natural killer (NK) receptors KLRC2/NKG2C and KLRC3/NKG2E, and the tight junction protein claudin-4 remained elevated. Between the two groups, most significant differences were seen for claudin-4 ($P = 0.003$) and KLRC3/NKG2E ($P=0.04$) (99).

In line with findings from RCTs, non-randomized trials and observational studies in general supported no worsening in histopathology nor serological markers (80, 83, 85, 88, 89, 91, 100-105). On the other hand in the study of Hardy et al. (107), 73 individuals with HLA-DQ2.5+ CeD consumed a meal of oats (100g/day over 3 days) to measure the *in vivo* polyclonal avenin-specific T cell responses to peptides contained within comprehensive avenin peptide libraries. Avenin-specific responses were observed in

6/73 (8%) HLA-DQ2.5+ CeD individuals against four closely related peptides. In the same population, an oral barley challenge efficiently induced cross-reactive avenin/hordein-specific T cells in most individuals with CeD, whereas wheat or rye challenge did not. *In vitro*, immunogenic avenin peptides were susceptible to digestive endopeptidases and showed weak HLA-DQ2.5 binding stability (106). Similarly, in a non-randomized trial of 35 in a pediatric population with CeD, oats were tested for immunogenecity and found that avenins derived from local Russian and foreign oat varieties were able to induce immune response(107). Likewise, in an observational study of Tuire et al. (86) oat intake was associated to persistent intraepithelial lymphocytosis among individuals with CeD.

In an *in vitro* model, anti-endomysial antibodies (EMA) production was tested in duodenal mucosa specimens collected from 13 individuals with CeD in remission. EMAs were detected in specimens from all patients after the challenge with gliadin but no EMAs were detected in any of the specimens cultured with avenin and its C fraction (108). Similarly, in another study using duodenal mucosa samples from CeD individuals, increased immunologic activities with expression of IFN-γ and IL2 in all samples with gliadin were reported but no significant stimulation with avenin was observed, suggesting that immunogenic sequences from gliadin are not present or mimicked by avenin (109). Avenin *in sera* were compared in a pediatric population with CeD and reference population in the study of Hollen et al. (110) and they showed that antibodies against avenin (both IgG and IgA type) were developed with levels correlating positively with those against gliadin and these levels were significantly higher than in the reference population. Meanwhile in a study including nine adults with CeD who had a history of oats exposure, authors found oats-avenin-specific and reactive intestinal T-cell lines from three patients who did not tolerate oats and in two

other patients who appeared to tolerate oats. The avenin-reactive T-cell lines recognized avenin peptides in the context of HLA-DQ2. These peptides have proline and glutamine rich sequences resembling wheat gluten epitopes. Deamidation (glutamine→glutamic acid conversion) by tissue transglutaminase was involved in the avenin epitope formation. It has been suggested that the oat intolerance may be a reason for villus atrophy and inflammation in patients with CeD who are eating oats but otherwise are adhering to a strict GFD (111). In the study of Kilmartin et al. (112), prolamins derived from wheat, barley, rye and oats were tested to see if they were able to stimulate T cell lines (measured by (3) H-thymidine incorporation or cytokine [IL-2, IFN-gamma]) proliferated from mucosal lesions of individuals with CeD. They observed that all the prolamins are able to stimulate the T cell lines.

Three *in vitro* studies explored the immunogenicity of different oat varieties. Maglio et al. (113) investigated the immunological and biological effects of *Avena genziana* and *Avena potenza* among CeD individuals. The oat prolamin peptides were not able to induce enterocyte proliferation, increase in IL-15, or increase in CeD25+ cells which suggest that two oat varieties are safe for individuals with CeD (113). Similarly, Comino et al. (114) studied oats from different cultivars from Spanish and Australian sources. They reported a wide range of reactivity of oat cultivars to the anti-33-mer G12 and the reactivity of isolated celiac T cells to oat varieties ranged from none to maximal G12 monoclonal antibodies (114). In another study, Silano et al. (115) studied three oat cultivars (cv. Irina, cv. Potenza e cv. Nave) in activating the gliadin-induced TG2-dependent events in pediatric individuals with CeD. The Nave oat cultivar elicited K562(S) cells agglutination, transepithelial electrical resistance of T84-cell monolayers, intracellular levels of TG2 and phosphorylated form of protein 42–44 in human

leukemic K562(S) and human colon adenocarcinoma T84 cell lines. No reaction was observed from the other 2 cultivars (115).

3.5 Study quality

Among the 23 RCTs, the majority had some concerns (n=17, 73.9%) mostly in domains of randomization and five studies were judged as having high risk of bias. The majority of non-randomized trials were of moderate quality (n=20, 95.2%) with only a single trial being classified as low risk of bias. The eight observational studies seven were judged as moderate quality. Among 32 *in vitro* studies, the majority of studies (n=27, 84.4%) were judged as reliable without restrictions, while only five studies are reliable with restrictions (**Supplemental Tables 8-12**).

4. DISCUSSION

In this systematic review, the effects of oats on GI health in humans were reviewed and the study population included healthy adults, adults with certain conditions (i.e. UC, CeD, elevated cholesterol, obesity) and pediatric population (i.e. healthy and with CeD). Oats are able to influence the GI microbial communities that supports the proliferation of *Lactobacillus* and *Bifidobacterium* in most studies. There were increased levels of SCFAs, increased branch chain fatty acids and decreased of proteolytic enzymes. Clinically, those consuming oats had no significant improvement in quality of life and the majority of studies showed no changes in GI symptoms with oat consumption, whereas, a few studies reported an increase in diarrhea and constipation or showed increasing GSRS scores in individuals exposed to oats. In pediatric and adults with CeD, moderate consumption of oats is generally tolerated and

allows mucosal recovery even in the long-term. Larger amounts of oats are able to add dietary variety and nutritional benefits to CeD patients, however, they may increase the frequency of adverse bowel symptoms. Adding enzymatic activity by fermenting oats or preserving internal enzymes by not kilning may reduce negative symptoms (79). A subset of individuals with CeD may be sensitive to oats wherein there are increased IELs in the intestinal mucosa but a normal histologic villus structure is maintained.

Our findings on increased count of *Lactobacillus spp*. and *Bifidobacterium spp*. with oat consumption could be explained by the nutrient content of the oat and its metabolism. Oat is a rich source of dietary fibers including β-glucans, polysaccharides that are known to modulate gut microbial community (116). They are considered prebiotic, non-digestible food ingredients that are fermented by the intestinal microflora and may selectively regulate the growth of a group or groups of bacteria in the colon that can improve health (117, 118). *Bifidobacterium* and *Lactobacillus* are commonly targeted microorganisms in the gut for their associated health benefits. *Bifidobacterium* has been shown to be protective in diseases such as colorectal cancer, diarrhea, necrotizing entercolitis, inflammatory bowel disease and known to competitively inhibit pathogens to binding sites in the epithelial cells (119, 120). *Lactobacillus*, on the other hand, has protective effects on the intestinal permeability induced by inflammation, chemicals and stress and serves as an important source of lactate that is further metabolized to SCFAs (121). Bacterial fermentation of dietary fibers in the colon generally produces SCFAs such as acetate, propionate and butyrate. *Bifidobacterium* are able to produce acetate (122) and thus contribute to the SCFAs in the gut. Likewise, *Bifidobacterium* allows the co-inhabitation with butyrate producing bacteria and butyrate is significantly enriched with consumption of dietary fibers (123). The most

dominantly represented butyrate producing bacterial genera are *Faecalbacterium, Roseburia, Anaerostipes* and *Eubacterium* (120). Benefits from the consumption of oats could be attributed to their effects on the gut microbial community especially targeting known bacterial groups that promote GI health benefits.

Consumption of oats has encountered barriers among individuals with CeD despite the advantage of providing better nutrient content compared to a regular GFD. Strict consumption of GFD is the main clinical management strategy in preventing development of debilitating symptoms and mucosal inflammation among individuals with CeD. On the other hand, the evidence suggests that the CeD patients' diet generally reproduce, despite minor differences, the eating behavior of the general population, suggesting that these individuals may not follow dietary recommendations strictly (124). In the current review, consumption of oats is generally tolerated among pediatric populations and adults with CeD even up to five years. This corroborates previously published data which shows that oats can be tolerated with no significant changes in clinical symptoms (3, 21-23) but there might be histologic, serologic and immunologic manifestation pointing to an inflammatory reaction at the intestinal mucosa without manifestation of the disease (77, 99). Oat sensitive individuals may experience an increase in diarrhea frequency as consequence of the inflammatory reaction of the gut mucosa to the oat. It may be that oat processing (such as kilning, fermentation, gluten-free cleaning) and cultivar selection may be important factors to determine on whether oat induces a positive or negative health response.

In vitro and clinical studies in this review suggest that individuals with CeD may have villus structure that does not significantly differ in the histomorphology score for normal duodenal mucosa but there is an increase in IELs and upregulated inflammatory

mediators (80, 106, 111). This could explain the increased diarrhea in patients but without the other associated symptoms for a full-blown disease. Inflamed cells of the villous structure in the duodenum especially the apical cells can lead to malabsorption of carbohydrates and solutes leading to water retention and thus the diarrhea. Sensitivity to oats has been seen in few individuals and deemed insignificant (21) though Haboubi et al. (22) argues that the withdrawals from the clinical trials might represent this group and more effort to follow up should have been conducted.

4.1 Strengths and limitations of current review

The review was guided by published guidelines and the best available tools to appraise the quality of the evidence. To our knowledge, this is the first report that includes a comprehensive set of parameters of microbial changes, GI symptoms, histological and immunological markers in the gut. In order to identify as many relevant studies as possible and reduce the risk of publication bias, a sensitive search strategy was used and additional resources were searched including the reference lists of included trials and relevant systematic reviews. However, we were not able to search all existing online databases. No restrictions on language were used but we may have missed articles published in languages other than English. Due to high heterogeneity of interventions and study designs, we were not able to provide a quantitative synthesis. We were able to provide an illustrative summary of the most important findings (**Figure 2**) and provided a summary table (**Table 2**) to simplify the interpretation of the findings. In addition, we acknowledge that our findings were based on not only RCTs but also observational and non-RCT data. Finally, we did not identify any study focusing on IBS and found 3 on IBD therefore we focused the review to individuals with CeD and individuals without GI symptoms.

This review shows that oat consumption has multiple benefits. The grain influences the gut microbiota but studies included in the review are limited in scope of investigating the microbiome. The studies focused and targeted established bacterial genera that might have led to other beneficial bacteria being missed. Some of the studies reported various taxa with the genera being the most commonly used. Improvement in microbial identification with next generation sequencing could lead to improved characterization of beneficial microorganisms, inter-relationships and networks of bacteria. Moreover, metabolites investigated in the studies are limited to SCFAs and have not included metabolites from protein and fat degradation despite being included in the search strategy. Moreover, different oat cultivars showed different effects on GI parameters *in vitro* adding another possible level of complexity with some varieties possibly offering health benefits while others the opposite.

4.2 Conclusions

The clinical studies on the association between oat intake with respect to gastrointestinal health remain to be few and prone to risk of bias. Studies were conducted in a few countries and some trials were characterized by significant participant drop-out. We have included non-randomized controlled trials but most have moderate quality owing to the lack of control groups and reliance to a before-after intervention design. Oat was shown to influence the GI microbial community with no significant differences in GI symptoms to those not taking oats. Oat was generally well tolerated among pediatric population and adults with CeD. The *in vitro* studies provide molecular insights to some controversies especially on oat sensitive individuals and their gut mucosa. However, it remains unknown how prevalent oat sensitive individuals

491 are especially among individuals with CeD and other inflammatory bowel diseases.
492 Further studies are needed to improve clinical management and increase the inclusion
493 of oats in the gluten-free diets.
494
495 **Author Contributions**
496 Study concept and design: MG and HK; Search strategy creation and online database
497 search: BMinder; Acquisition, collection, interpretation of data: EV, JS, AB, AHG, RZ,
498 JLF, SS, BMetzger, WB, TM, MG, HK; Drafting of the manuscript: EV, JS, MG, HK;
499 Critical revision of the manuscript for important intellectual content: EV, JS, AB, AHG,
500 BMinde, RZ, JLF, SS, BMetzger, WB, TM, MG, HK. Study supervision: MG and HK;
501 All authors approved the final version of the manuscript.
502
503

References

1. Raguindin PF, Itodo OA, Stoyanov J, Dejanovic GM, Gamba M, Asllanaj E, Minder B, Bussler W, Metzger B, Muka T, et al. A systematic review of phytochemicals in oat and buckwheat. Food Chem 2021;338.
2. Chang HC, Huang CN, Yeh DM, Wang SJ, Peng CH, Wang CJ. Oat prevents obesity and abdominal fat distribution, and improves liver function in humans. Plant Foods Hum Nutr. 2013;68:18-23.
3. Thies F, Masson LF, Boffetta P, Kris-Etherton P. Oats and bowel disease: A systematic literature review. Br J Nutr. 2014;112 Suppl 2:S31-43.
4. Tapola N, Karvonen H, Niskanen L, Mikola M, Sarkkinen E. Glycemic responses of oat bran products in type 2 diabetic patients. Nutr Metab Cardiovasc Dis. 2005;15:255-61.
5. Korczak R, Kocher M, Swanson KS. Effects of oats on gastrointestinal health as assessed by in vitro, animal, and human studies. Nutr Rev. 2020;78:343-63.
6. Mälkki Y, Virtanen E. Gastrointestinal effects of oat bran and oat gum: A review. Lebensm Wiss Technol. 2001;34:337-47.
7. Rose DJ. Impact of whole grains on the gut microbiota: The next frontier for oats? Br J Nutr. 2014;112:S44-9.
8. Nouvenne A, Ticinesi A, Tana C, Prati B, Catania P, Miraglia C, De' Angelis GL, Di Mario F, Meschi T. Digestive disorders and intestinal microbiota. Acta Biomed. 2018;89:47-51.
9. Altajar S, Moss A. Inflammatory bowel disease environmental risk factors: Diet and gut microbiota. Curr Gastroenterol Rep. 2020;22:57.
10. Hanus M, Parada-Venegas D, Landskron G, Wielandt AM, Hurtado C, Alvarez K, Hermoso MA, Lopez-Kostner F, De la Fuente M. Immune system, microbiota, and microbial metabolites: The unresolved triad in colorectal cancer microenvironment. Front Immunol. 2021;12:612826.
11. Mari A, Abu Baker F, Mahamid M, Sbeit W, Khoury T. The evolving role of gut microbiota in the management of irritable bowel syndrome: An overview of the current knowledge. J Clin Med. 2020;9:685.
12. Valitutti F, Cucchiara S, Fasano A. Celiac disease and the microbiome. Nutrients. 2019;11:2403.
13. Dominianni C, Sinha R, Goedert JJ, Pei Z, Yang L, Hayes RB, Ahn J. Sex, body mass index, and dietary fiber intake influence the human gut microbiome. PLoS One. 2015;10:e0124599.
14. Sanna S, van Zuydam NR, Mahajan A, Kurilshikov A, Vich Vila A, Vosa U, Mujagic Z, Masclee AAM, Jonkers D, Oosting M, et al. Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases. Nat Genet. 2019;51:600-5.
15. Tian Y, Xu Q, Sun L, Ye Y, Ji G. Short-chain fatty acids administration is protective in colitis-associated colorectal cancer development. J Nutr Biochem. 2018;57:103-9.
16. Parada Venegas D, De la Fuente MK, Landskron G, Gonzalez MJ, Quera R, Dijkstra G, Harmsen HJM, Faber KN, Hermoso MA. Short chain fatty acids (scfas)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Front Immunol. 2019;10:277.
17. Liu H, Wang J, He T, Becker S, Zhang G, Li D, Ma X. Butyrate: A double-edged sword for health? Adv Nutr. 2018;9:21-9.
18. Canani RB, Costanzo MD, Leone L, Pedata M, Meli R, Calignano A. Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. World J Gastroenterol. 2011;17:1519-28.
19. Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. Gut Microbes. 2016;7:189-200.
20. Roberfroid M, Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, Wolvers D, Watzl B, Szajewska H, Stahl B, et al. Prebiotic effects: Metabolic and health benefits. Br J Nutr. 2010;104:S1-63.
21. Garsed K, Scott BB. Can oats be taken in a gluten-free diet? A systematic review. Scand J Gastroenterol. 2007;42:171-8.
22. Haboubi NY, Taylor S, Jones S. Coeliac disease and oats: A systematic review. Postgrad Med J. 2006;82:672-8.
23. Pinto-Sánchez MI, Causada-Calo N, Bercik P, Ford AC, Murray JA, Armstrong D, Semrad C, Kupfer SS, Alaedini A, Moayyedi P, et al. Safety of adding oats to a gluten-free diet for patients with celiac disease: Systematic review and meta-analysis of clinical and observational studies. Gastroenterology. 2017;153:395-409.
24. Muka T, Glisic M, Milic J, Verhoog S, Bohlius J, Bramer W, Chowdhury R, Franco OH. A 24-step guide on how to design, conduct, and successfully publish a systematic review and meta-analysis in medical research. Eur J Epidemiol. 2020;35:49-60.

25. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: The prisma statement. PLoS Med. 2009;6:e1000097.
26. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, et al. Rob 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019;366.
27. NIH National Heart Lung and Blood Institute. Qualty assessment of controlled intervention studies. 2014 [cited 2020 27 Feb]; Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
28. NIH National Heart Lung and Blood Institute. Quality assessment tool for before-after (pre-post) studies with no control group. 2014 [cited 2020 27 Feb]; Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
29. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The newcastle-ottawa scale (nos) for assessing the quality of nonrandomised studies in meta-analyses. 2013 [cited 2020 27 Feb]; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
30. Schneider K, Schwarz M, Burkholder I, Kopp-Schneider A, Edler L, Kinsner-Ovaskainen A, Hartung T, Hoffmann S. "Toxrtool", a new tool to assess the reliability of toxicological data. Toxicol Lett. 2009;189:138-44.
31. Mårtensson O, Biörklund M, Lambo AM, Dueñas-Chasco M, Irastorza A, Holst O, Norin E, Welling G, Öste R, Önning G. Fermented, ropy, oat-based products reduce cholesterol levels and stimulate the bifidobacteria flora in humans. Nutr Res. 2005;25:429-42.
32. Connolly ML, Tzounis X, Tuohy KM, Lovegrove JA. Hypocholesterolemic and prebiotic effects of a whole-grain oat-based granola breakfast cereal in a cardio-metabolic "at risk" population. Front Microbiol. 2016;7:1675.
33. Johansson ML, Nobaek S, Berggren A, Nyman M, Björck I, Ahrné S, Jeppsson B, Molin G. Survival of lactobacillus plantarum dsm 9843 (299v), and effect on the short-chain fatty acid content of faeces after ingestion of a rose-hip drink with fermented oats. Int J Food Microbiol. 1998;42:29-38.
34. Berggren A, Söderberg L, Önning G, Hagslätt MLJ, Axelsson I. Intestinal function, microflora and nutrient intake of children after administration of a fermented oat product containing lactobacillus plantarum dsm 9843 (299v). Microb Ecol Health Dis. 2003;15:160-8.
35. Duysburgh C, Van den Abbeele P, Kamil A, Fleige L, De Chavez PJ, Chu Y, Barton W, O'Sullivan O, Cotter PD, Quilter K, et al. In vitro-in vivo validation of stimulatory effect of oat ingredients on lactobacilli. Pathogens. 2021;10:235.
36. Pino JL, Mujica V, Arredondo M. Effect of dietary supplementation with oat beta-glucan for 3 months in subjects with type 2 diabetes: A randomized, double-blind, controlled clinical trial. J Funct Food. 2021;77:104311.
37. Ye M, Sun J, Chen Y, Ren Q, Li Z, Zhao Y, Pan Y, Xue H. Oatmeal induced gut microbiota alteration and its relationship with improved lipid profiles: A secondary analysis of a randomized clinical trial. Nutr Metab (Lond). 2020;17:85.
38. Tjellström B, Stenhammar L, Sundqvist T, Fälth-Magnusson K, Hollén E, Magnusson KE, Norin E, Midtvedt T, Högberg L. The effects of oats on the function of gut microflora in children with coeliac disease. Aliment Pharmacol Therapeut. 2014;39:1156-60.
39. Nyman M, Nguyen TD, Wikman O, Hjortswang H, Hallert C. Oat bran increased fecal butyrate and prevented gastrointestinal symptoms in patients with quiescent ulcerative colitis-randomized controlled trial. Crohn's and Colitis 360. 2020;2:1-13.
40. Nilsson U, Johansson M, Nilsson A, Bjorck I, Nyman M. Dietary supplementation with beta-glucan enriched oat bran increases faecal concentration of carboxylic acids in healthy subjects. Eur J Clin Nutr. 2008;62:978-84.
41. Valeur J, Puaschitz NG, Midtvedt T, Berstad A. Oatmeal porridge: Impact on microflora-associated characteristics in healthy subjects. Br J Nutr. 2016;115:62-7.
42. Hallert C, Björck I, Nyman M, Pousette A, Grännö C, Svensson H. Increasing fecal butyrate in ulcerative colitis patients by diet: Controlled pilot study. Inflamm Bowel Dis. 2003;9:116-21.
43. Li M, Koecher K, Hansen L, Ferruzzi MG. Phenolics from whole grain oat products as modifiers of starch digestion and intestinal glucose transport. J Agr Food Chem. 2017;65:6831-9.
44. Van den Abbeele P, Kamil A, Fleige L, Chung Y, De Chavez P, Marzorati M. Different oat ingredients stimulate specific microbial metabolites in the gut microbiome of three human individuals in vitro. ACS Omega. 2018;3:12446-56.
45. Kristek A, Wiese M, Heuer P, Kosik O, Schär MY, Soycan G, Alsharif S, Kuhnle GGC, Walton G, Spencer JPE. Oat bran, but not its isolated bioactive β-glucans or polyphenols, have a bifidogenic effect in an in vitro fermentation model of the gut microbiota. Br J Nutr. 2019;121:549-59.
46. Connolly ML, Lovegrove JA, Tuohy KM. In vitro evaluation of the microbiota modulation abilities of different sized whole oat grain flakes. Anaerobe. 2010;16:483-8.

47. Connolly ML, Lovegrove JA, Tuohy KM. In vitro fermentation characteristics of whole grain wheat flakes and the effect of toasting on prebiotic potential. J Med Food. 2012;15:33-43.
48. Kim HJ, White PJ. In vitro fermentation of oat flours from typical and high β-glucan oat lines. J Agr Food Chem. 2009;57:7529-36.
49. Tsitko I, Wiik-Miettinen F, Mattila O, Rosa-Sibakov N, Seppanen-Laakso T, Maukonen J, Nordlund E, Saarela M. A small in vitro fermentation model for screening the gut microbiota effects of different fiber preparations. Int J Mol Sci. 2019;20:1925.
50. Hernot DC, Boileau TW, Bauer LL, Swanson KS, Fahey Jr GC. In vitro digestion characteristics of unprocessed and processed whole grains and their components. J Agr Food Chem. 2008;56:10721-6.
51. Wood PJ, Arrigoni E, Miller SS, Amado R. Fermentability of oat and wheat fractions enriched in beta-glucan using human fecal inoculation. Cereal Chem. 2002;79:445-54.
52. Kedia G, Vazquez JA, Charalampopoulos D, Pandiella SS. In vitro fermentation of oat bran obtained by debranning with a mixed culture of human fecal bacteria. Curr Microbiol. 2009;58:338-42.
53. Yang J, Keshavarzian A, Rose DJ. Impact of dietary fiber fermentation from cereal grains on metabolite production by the fecal microbiota from normal weight and obese individuals. J Med Food. 2013;16:862-7.
54. Slade AP, Wyatt GM, Bayliss CE, Waites WM. Comparison of populations of human faecal bacteria before and after in vitro incubation with plant cell wall substrates. J Appl Microbiol. 1987;62:231-40.
55. Akkerman R, Logtenberg MJ, An R, Van Den Berg MA, de Haan BJ, Faas MM, Zoetendal E, de Vos P, Schols HA. Endo-1,3(4)-beta-glucanase-treatment of oat beta-glucan enhances fermentability by infant fecal microbiota, stimulates dectin-1 activation and attenuates inflammatory responses in immature dendritic cells. Nutrients. 2020;12:1660.
56. Wang P, Zhang S, Yerke A, Ohland CL, Gharaibeh RZ, Fouladi F, Fodor AA, Jobin C, Sang S. Avenanthramide metabotype from whole-grain oat intake is influenced by faecalibacterium prausnitzii in healthy adults. J Nutr. 2021;151:1426-35.
57. Queenan KM, Stewart ML, Smith KN, Thomas W, Fulcher RG, Slavin JL. Concentrated oat β-glucan, a fermentable fiber, lowers serum cholesterol in hypercholesterolemic adults in a randomized controlled trial. Nutr J. 2007;6:1-8.
58. Hughes SA, Shewry PR, Gibson GR, McCleary BV, Rastall RA. In vitro fermentation of oat and barley derived β-glucans by human faecal microbiota. FEMS Microbiol Ecol. 2008;64:482-93.
59. Gamage HKAH, Tetu SG, Chong RWW, Ashton J, Packer NH, Paulsen IT. Cereal products derived from wheat, sorghum, rice and oats alter the infant gut microbiota in vitro. Sci Rep. 2017;7:1-12.
60. Brahma S, Weier SA, Rose DJ. Moisture content during extrusion of oats impacts the initial fermentation metabolites and probiotic bacteria during extended fermentation by human fecal microbiota. Food Res Int. 2017;97:209-14.
61. Titgemeyer EC, Bourquin LD, Fahey Jr GC, Garleb KA. Fermentability of various fiber sources by human fecal bacteria in vitro. Am J Clin Nutr. 1991;53:1418-24.
62. Roye C, Bulckaen K, De Bondt Y, Liberloo I, Van De Walle D, Dewettinck K, Courtin CM. Side-by-side comparison of composition and structural properties of wheat, rye, oat, and maize bran and their impact on in vitro fermentability. Cereal Chem. 2020;97:20-33.
63. Nordlund E, Aura AM, Mattila I, Kössö T, Rouau X, Poutanen K. Formation of phenolic microbial metabolites and short-chain fatty acids from rye, wheat, and oat bran and their fractions in the metabolical in vitro colon model. J Agric Food Chem. 2012;60:8134-45.
64. Lebet V, Arrigoni E, Amado R. Measurement of fermentation products and substrate disappearance during incubation of dietary fibre sources with human faecal flora. Lebensm Wiss Technol. 1998;31:473-9.
65. Pham VT, Seifert N, Richard N, Raederstorff D, Steinert R, Prudence K, Hasan Mohajeri M. The effects of fermentation products of prebiotic fibres on gut barrier and immune functions in vitro. PeerJ. 2018:e5288.
66. Dong JL, Yang M, Zhu YY, Shen RL, Zhang KY. Comparative study of thermal processing on the physicochemical properties and prebiotic effects of the oat β-glucan by in vitro human fecal microbiota fermentation. Food Res Int. 2020;138:109818.
67. Glei M, Zetzmann S, Lorkowski S, Dawczynski C, Schlormann W. Chemopreventive effects of raw and roasted oat flakes after in vitro fermentation with human faecal microbiota. Int J Food Sci Nutr. 2021;72:57-69.
68. Keenan JM, Wenz JB, Myers S, Ripsin C, Huang Z. Randomized, controlled, crossover trial of oat bran in hypercholesterolemic subjects. J Fam Pract. 1991;33:600-8.

69. Cicero AFG, Fogacci F, Veronesi M, Strocchi E, Grandi E, Rizzoli E, Poli A, Marangoni F, Borghi C. A randomized placebo-controlled clinical trial to evaluate the medium-term effects of oat fibers on human health: The beta-glucan effects on lipid profile, glycemia and intestinal health (belt) study. Nutrients. 2020;12:686.
70. Hakkola S, Nylund L, Rosa-Sibakov N, Yang B, Nordlund E, Pahikkala T, Kalliomaki M, Aura AM, Linderborg KM. Effect of oat beta-glucan of different molecular weights on fecal bile acids, urine metabolites and pressure in the digestive tract - a human cross over trial. Food Chem. 2021;342:128219.
71. Pitkälä KH, Strandberg TE, Finne-Soveri UH, Ouwehand AC, Poussa T, Salminen S. Fermented cereal with specific bifidobacteria normalizes bowel movements in elderly nursing home residents. A randomized, controlled trial. J Nutr Health Aging. 2007;11:305-11.
72. Sturtzel B, Elmadfa I. Intervention with dietary fiber to treat constipation and reduce laxative use in residents of nursing homes. Ann Nutr Metabol. 2008;52:54-6.
73. Valle-Jones JC. An open study of oat bran meal biscuits ('lejfibre') in the treatment of constipation in the elderly. Curr Med Res Opin. 1985;9:716-20.
74. Paruzynski H, Korczak R, Wang Q, Slavin J. A pilot and feasibility study of oatmeal consumption in children to assess markers of bowel function. J Med Food. 2019;23:554-9.
75. Kajs TM, Fitzgerald JA, Buckner RY, Coyle GA, Stinson BS, Morel JG, Levitt MD. Influence of a methanogenic flora on the breath h2 and symptom response to ingestion of sorbitol or oat fiber. Am J Gastroenterol. 1997;92:89-94.
76. Svelund J, Sjodin I, Doteval G. Gsrs--a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci. 1988;33:129-34.
77. Peraaho M, Kaukinen K, Mustalahti K, Vuolteenaho N, Maki M, Laippala P, Collin P. Effect of an oats-containing gluten-free diet on symptoms and quality of life in coeliac disease. A randomized study. Scand J Gastroenterol. 2004;39:27-31.
78. Lionetti E, Gatti S, Galeazzi T, Caporelli N, Francavilla R, Cucchiara S, Roggero P, Malamisura B, Iacono G, Tomarchio S, et al. Safety of oats in children with celiac disease: A double-blind, randomized, placebo-controlled trial. J Pediatr. 2018;194:116-22
79. Kemppainen TA, Heikkinen MT, Ristikankare MK, Kosma VM, Sontag-Strohm TS, Brinck O, Salovaara HO, Julkunen RJ. Unkilned and large amounts of oats in the coeliac disease diet: A randomized, controlled study. Scand J Gastroenterol. 2008;43:1094-101.
80. Hoffenberg EJ, Haas J, Drescher A, Barnhurst R, Osberg I, Bao F, Eisenbarth G. A trial of oats in children with newly diagnosed celiac disease. J Pediatr. 2000;137:361-6.
81. Størsrud S, Olsson M, Arvidsson Lenner R, Nilsson LÅ, Nilsson O, Kilander A. Adult coeliac patients do tolerate large amounts of oats. Eur J Clin Nutr. 2003;57:163-9.
82. Størsrud S, Hulthén LR, Lenner RA. Beneficial effects of oats in the gluten-free diet of adults with special reference to nutrient status, symptoms and subjective experiences. Br J Nutr. 2003;90:101-7.
83. Sey MSL, Parfitt J, Gregor J. Prospective study of clinical and histological safety of pure and uncontaminated canadian oats in the management of celiac disease. JPEN J Parenter Enteral Nutr. 2011;35:459-64.
84. Baker PG, Read AE. Oats and barley toxicity in coeliac patients. Postgrad Med J. 1976;52:264-8.
85. Lundin KEA, Nilsen EM, Scott HG, Løberg EM, Gjøen A, Bratlie J, Skar V, Mendez E, Loøvik A, Kett K. Oats induced villous atrophy in coeliac disease. Gut. 2003;52:1649-52.
86. Tuire I, Marja-Leena L, Teea S, Katri H, Jukka P, Päivi S, Heini H, Markku M, Pekka C, Katri K. Persistent duodenal intraepithelial lymphocytosis despite a long-term strict gluten-free diet in celiac disease. Am J Gastroenterol. 2012;107:1563-9.
87. Tapsas D, Fälth-Magnusson K, Högberg L, Hammersjö JT, Hollén E. Swedish children with celiac disease comply well with a gluten-free diet, and most include oats without reporting any adverse effects: A long-term follow-up study. Nutr Res. 2014;34:436-41.
88. Janatuinen EK, Kemppainen TA, Julkunen RJK, Kosma VM, Mäki M, Heikkinen M, Uusitupa MIJ. No harm from five year ingestion of oats in coeliac disease. Gut. 2002;50:332-5.
89. Aaltonen K, Laurikka P, Huhtala H, Maki M, Kaukinen K, Kurppa K. The long-term consumption of oats in celiac disease patients is safe: A large cross-sectional study. Nutrients. 2017;9:611.
90. Nylund L, Hakkola S, Lahti L, Salminen S, Kalliomaki M, Yang B, Linderborg KM. Diet, perceived intestinal well-being and compositions of fecal microbiota and short chain fatty acids in oat-using subjects with celiac disease or gluten sensitivity. Nutrients. 2020;12:2570.
91. Kaukinen K, Collin P, Huhtala H, Maki M. Long-term consumption of oats in adult celiac disease patients. Nutrients. 2013;5:4380-9.

92. Van Kruiningen HJ, Joossens M, Vermeire S, Joossens S, Debeugny S, Gower-Rousseau C, Cortot A, Colombel JF, Rutgeerts P, Vlietinck R. Environmental factors in familial crohn's disease in belgium. Inflamm Bowel Dis. 2005;11:360-5.
93. Janatuinen EK, Pikkarainen PH, Kemppainen TA, Kosma VM, Järvinen RMK, Uusitupa MIJ, Julkunen RJK. A comparison of diets with and without oats in adults with celiac disease. New Engl J Med. 1995;333:1033-7.
94. Janatuinen EK, Kemppainen TA, Pikkarainen PH, Holm KH, Kosma VM, Uusitupa MIJ, Mäki M, Julkunen RJK. Lack of cellular and humoral immunological responses to oats in adults with coeliac disease. Gut. 2000;46:327-31.
95. Högberg L, Laurin P, Fâlth-Magnusson K, Grant C, Grodzinsky E, Jansson G, Ascher H, Browaldh L, Hammersjö JÅ, Lindberg E, et al. Oats to children with newly diagnosed coeliac disease: A randomised double blind study. Gut. 2004;53:649-54.
96. Holm K, Maki M, Vuolteenaho N, Mustalahti K, Ashorn M, Ruuska T, Kaukinen K. Oats in the treatment of childhood coeliac disease: A 2-year controlled trial and a long-term clinical follow-up study. Aliment Pharmacol Ther. 2006;23:1463-72.
97. Koskinen O, Villanen M, Korponay-Szabo I, Lindfors K, Mäki M, Kaukinen K. Oats do not induce systemic or mucosal autoantibody response in children with coeliac disease. J Pediatr Gastroenterol Nutr. 2009;48:559-65.
98. Hollen E, Holmgren Peterson K, Sundqvist T, Grodzinsky E, Hogberg L, Laurin P, Stenhammar L, Falth-Magnusson K, Magnusson KE. Coeliac children on a gluten-free diet with or without oats display equal anti-avenin antibody titres. Scand J Gastroenterol. 2006;41:42-7.
99. Sjöberg V, Hollén E, Pietz G, Magnusson KE, Fälth-Magnusson K, Sundström M, Peterson KH, Sandstrom O, Hernell O, Hammarström S, et al. Noncontaminated dietary oats may hamper normalization of the intestinal immune status in childhood celiac disease. Clin Transl Gastroenterol. 2014;5:e58.
100. Dissanayake AS, Truelove SC, Whitehead R. Lack of harmful effect of oats on small intestinal mucosa in coeliac disease. Br Med J. 1974;4:189-91.
101. Srinivasan U, Leonard N, Jones E, Kasarda DD, Weir DG, O'Farrelly C, Feighery C. Absence of oats toxicity in adult coeliac disease. Br Med J. 1996;313:1300-1.
102. Srinivasan U, Jones E, Weir DG, Feighery C. Lactase enzyme, detected immunohistochemically, is lost in active celiac disease, but unaffected by oats challenge. Am J Gastroenterol. 1999;94:2936-41.
103. Cooper SEJ, Kennedy NP, Mohamed BM, Abuzakouk M, Dunne J, Byrne G, McDonald G, Davies A, Edwards C, Kelly J, et al. Immunological indicators of coeliac disease activity are not altered by long-term oats challenge. Clin Exp Immunol. 2013;171:313-8.
104. Srinivasan U, Jones E, Carolan J, Feighery C. Immunohistochemical analysis of coeliac mucosa following ingestion of oats. Clin Exp Immunol. 2006;144:197-203.
105. Kemppainen T, Janatuinen E, Holm K, Kosma VM, Heikkinen M, Maki M, Laurila K, Uusitupa M, Julkunen R. No observed local immunological response at cell level after five years of oats in adult coeliac disease. Scand J Gastroenterol. 2007;42:54-9.
106. Hardy MY, Tye-Din JA, Stewart JA, Schmitz F, Dudek NL, Hanchapola I, Purcell AW, Anderson RP. Ingestion of oats and barley in patients with celiac disease mobilizescross-reactive t cells activated by avenin peptides andimmuno-dominant hordein peptides. J Autoimmun. 2015;56:56-65.
107. Emanuél V, Vokhmianina NV, Gavriliuk IP, Krasil'nikov VN, Alpat'eva NV. Value of serological diagnosis of celiac disease for the determination of intolerance to prolamines of certain varieties of oats in patients with celiac disease. Klin Lab Diagn. 2007:32-4.
108. Picarelli A, Di Tola M, Sabbatella L, Gabrielli F, Di Cello T, Anania MC, Mastracchio A, Silano M, De Vincenzi M. Immunologic evidence of no harmful effect of oats in celiac disease. Am J Clin Nutr. 2001;74:137-40.
109. Kilmartin C, Lynch S, Abuzakouk M, Wieser H, Feighery C. Avenin fails to induce a th1 response in coeliac tissue following in vitro culture. Gut. 2003;52:47-52.
110. Hollen E, Hogberg L, Stenhammar L, Falth-Magnusson K, Magnusson KE. Antibodies to oat prolamines (avenins) in children with coeliac disease. Scand J Gastroenterol. 2003;38:742-6.
111. Arentz-Hansen H, Fleckenstein B, Molberg Ø, Scott H, Koning F, Jung G, Roepstorff P, Lundin KEA, Sollid LM. The molecular basis for oat intolerance in patients with celiac disease. PLoS Med. 2004;1:e1.
112. Kilmartin C, Wieser H, Abuzakouk M, Kelly J, Jackson J, Feighery C. Intestinal t cell responses to cereal proteins in celiac disease. Dig Dis Sci. 2006;51:202-9.

113. Maglio M, Mazzarella G, Barone MV, Gianfrani C, Pogna N, Gazza L, Stefanile R, Camarca A, Colicchio B, Nanayakkara M, et al. Immunogenicity of two oat varieties, in relation to their safety for celiac patients. Scand J Gastroenterol. 2011;46:1194-205.
114. Comino I, Real A, De Lorenzo L, Cornell H, López-Casado MÁ, Barro F, Lorite P, Torres MI, Cebolla Á, Sousa C. Diversity in oat potential immunogenicity: Basis for the selection of oat varieties with no toxicity in coeliac disease. Gut. 2011;60:915-22.
115. Silano M, Penas Pozo E, Uberti F, Manferdelli S, Del Pinto T, Felli C, Budelli A, Vincentini O, Restani P. Diversity of oat varieties in eliciting the early inflammatory events in celiac disease. Eur J Clin Nutr. 2014;53:1177-86.
116. Jayachandran M, Chen J, Chung SSM, Xu B. A critical review on the impacts of beta-glucans on gut microbiota and human health. J Nutr Biochem. 2018;61:101-10.
117. Gibson GR, Probert HM, Loo JV, Rastall RA, Roberfroid MB. Dietary modulation of the human colonic microbiota: Updating the concept of prebiotics. Nutr Res Rev. 2007;17:259-75.
118. Tosh SM, Bordenave N. Emerging science on benefits of whole grain oat and barley and their soluble dietary fibers for heart health, glycemic response, and gut microbiota. Nutr Rev. 2020;78:13-20.
119. O'Callaghan A, van Sinderen D. Bifidobacteria and their role as members of the human gut microbiota. Front Microbiol. 2016;7:925.
120. Riviere A, Selak M, Lantin D, Leroy F, De Vuyst L. Bifidobacteria and butyrate-producing colon bacteria: Importance and strategies for their stimulation in the human gut. Front Microbiol. 2016;7:979.
121. Ahrne S, Hagslatt ML. Effect of lactobacilli on paracellular permeability in the gut. Nutrients. 2011;3:104-17.
122. Fukuda S, Toh H, Hase K, Oshima K, Nakanishi Y, Yoshimura K, Tobe T, Clarke JM, Topping DL, Suzuki T, et al. Bifidobacteria can protect from enteropathogenic infection through production of acetate. Nature. 2011;469:543-7.
123. So D, Whelan K, Rossi M, Morrison M, Holtmann G, Kelly JT, Shanahan ER, Staudacher HM, Campbell KL. Dietary fiber intervention on gut microbiota composition in healthy adults: A systematic review and meta-analysis. Am J Clin Nutr. 2018;107:965-83.
124. Valitutti F, Iorfida D, Anania C, Trovato CM, Montuori M, Cucchiara S, Catassi C. Cereal consumption among subjects with celiac disease: A snapshot for nutritional considerations. Nutrients. 2017;9:396.

Table 1. Summary of the included studies in the systematic review of oat intake and its effect in GI health in individuals with and without GI disease.

Lead Author, Publication Year	Study Design	Population Characteristic	Risk of Bias[1]	Summarized Finding
Oat intake and changes in gut microbiome				
Connolly, 2016(32)	RCT	Adults with glucose intolerance or elevated cholesterol	Some Concern	Table 2; Supplemental Table 1
Johansson, 1998(33)	RCT	Healthy adults	Some Concern	Table 2; Supplemental Table 1
Berggren, 2008(34)	RCT	Healthy pediatric population	Some Concern	Table 2; Supplemental Table 1
Martenson, 2005(31)	RCT	Healthy adults	Some Concern	Table 2; Supplemental Table 1
Duysburgh, 2021(35)	RCT	Adults with elevated cholesterol	Some Concern	Table 2; Supplemental Table 1
Ye, 2020(37)	RCT	Adults with elevated cholesterol	Some Concern	Table 2; Supplemental Table 1
Pino, 2020(36)	RCT	Adults with type 2 diabetes	Some Concern	Table 2; Supplemental Table 1
Tjellstrom, 2014 (38)	RCT	Pediatric population with CeD	Some Concern	Table 2; Supplemental Table 3
Nyman, 2020(39)	RCT	Adults with UC	Some Concern	Table 2; Supplemental Table 3
Nilsson, 2008(40)	Non-randomized trial	Healthy adults	Moderate	Table 2;Supplemental Table 2
Valeur, 2015(41)	Non-randomized trial	Healthy adults	Moderate	Table 2;Supplemental Table 2
Li, 2017(43)	Non-randomized trial	Healthy adults	Moderate	Table 2;Supplemental Table 2
Hallert, 2003(41)	Non-randomized trial	Adults with UC	Moderate	Table 2;Supplemental Table 4
Nylund, 2020(90)	Observational	Adults with CeD and non-CeD with gluten sensitivity	Moderate	Supplemental Table 5
Queenan, 2007(57)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Van den Abbeele, (44)2018	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Kristek, 2019(45)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Hughes, 2008(58)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Gamage, 2017(59)	*in vitro*	Healthy pediatric population	Reliable w/o restrictions	Supplemental Table 7
Connolly, 2010(46)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Brahma, 2017(60)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Titgemeyer, 1991(61)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Roye, 2019(62)	*in vitro*	Healthy adults	Reliable w/ restrictions	Supplemental Table 7
Connolly, 2012(47)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Nordlund, 2012(63)	*in vitro*	Healthy adults	Reliable w/ restrictions	Supplemental Table 7
Lebet, 1998(64)	*in vitro*	Healthy adults	Reliable w/ restrictions	Supplemental Table 7
Kim, 2009(48)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Pham, 2018(65)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Tsitko, 2019(49)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Hernot , 2008(50)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Wood, 2002(51)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Yang, 2013(53)	*in vitro*	Healthy adults and with obesity	Reliable w/o restrictions	Supplemental Table 7
Kedia, 2009(52)	*in vitro*	Healthy adults	Reliable w/ restrictions	Supplemental Table 7
Slade, 1987(54)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Dong, 2020(66)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Glei, 2020(67)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Akkerman, 2020(55)	*in vitro*	Healthy pediatric population	Reliable w/o restrictions	Supplemental Table 7
Wang, 2021(56)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Duysburgh, 2021(35)	*in vitro*	Adults with elevated cholesterol	Reliable w/o restrictions	Supplemental Table 7
Oat intake and GI symptoms				
Cicero, 2020(69)	RCT	Adults with elevated cholesterol	Some Concern	Supplemental Table 1
Keenan, 1991(68)	RCT	Adults with elevated cholesterol	High	Supplemental Table 1
Hakkola, 2020(70)	RCT	Healthy adults	Some Concern	Supplemental Table 1
Pitkala, 2007(71)	RCT	Elderly	Some Concern	Supplemental Table 1

Berggren, 2008(34)	RCT	Healthy pediatric population	Some Concern	Supplemental Table 1
Kemppainen, 2008(79)	RCT	Adults with CeD	Some Concern	Supplemental Table 3
Peraaho, 2004(77)	RCT	Adults with CeD	Some Concern	Supplemental Table 3
Lionetti, 2018(78)	RCT	Pediatric population with CeD	Some Concern	Supplemental Table 3
Nyman, 2020(39)	RCT	Adults with UC	Some Concern	Supplemental Table 3
Sturtzel, 2010(72)	Non-randomized trial	Elderly	Moderate	Supplemental Table 2
Valle-Jones, 1985(73)	Non-randomized trial	Elderly	Moderate	Supplemental Table 2
Paruzynski, 2019(74)	Non-randomized trial	Healthy pediatric population	Low	Supplemental Table 4
Storsud, 2003a(82)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Storsud, 2003b(81)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Lundin, 2003(85)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Baker, 1976(84)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Sey, 2011(83)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Kajs, 1997(75)	Non-randomized trial	Healthy adults	Moderate	Supplemental Table 4
Hallert, 2003(42)	Non-randomized trial	Adults with UC	Moderate	Supplemental Table 4
Hoffenberg, 2000(80)	Non-randomized trial	Pediatric population with CeD	Moderate	Supplemental Table 4
Van Kruiningen, 2005(92)	Observational	Families with Crohn's disease	Moderate	Supplemental Table 5
Tapsas, 2007(87)	Observational	Adults with CeD	Moderate	Supplemental Table 5
Janatuinen, 2002(88)	Observational	Adults with CeD	Moderate	Supplemental Table 5
Kaukinen, 2013(91)	Observational	Adults with CeD	Moderate	Supplemental Table 5
Nylund, 2020(90)	Observational	Adults with CeD and non-CeD with gluten sensitivity	Moderate	Supplemental Table 5
Tuire, 2012(86)	Observational	Adults with CeD	Moderate	Supplemental Table 5
Oat supplementation and histopathological/immunological changes				
Kemppainen, 2008(79)	RCT	Adults with CeD	Some Concern	Supplemental Table 3
Hogberg, 2004(95)	RCT	Pediatric population with CeD	Some Concern	Supplemental Table 3
Peraaho, 2004(77)	RCT	Adults with CeD	Some Concern	Supplemental Table 3
Lionetti, 2018(78)	RCT	Pediatric population with CeD	Some Concern	Supplemental Table 3
Holm, 2006(96)	RCT	Pediatric population with CeD	High	Supplemental Table 3
Janatuinen, 1995(93)	RCT	Adults with CeD	Some Concern	Supplemental Table 3
Sjoberg, 2014(99)	RCT	Pediatric population with CeD	Some Concern	Supplemental Table 3
Hollen, 2006(98)	RCT	Pediatric population with CeD	Some Concern	Supplemental Table 3
Koskinen, 2009(97)	RCT	Pediatric population with CeD	High	Supplemental Table 3
Janatuinen, 2000(94)	RCT	Adults with CeD	Some Concern	Supplemental Table 3
Hoffenberg, 2000(80)	Non-randomized trial	Pediatric population with CeD	Moderate	Supplemental Table 4
Storsud, 2003b(81)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Srinivasan, 1999(102)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Lundin, 2003(85)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Dissanayake, 1974(100)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Sey, 2011(83)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Cooper, 2013(103)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Hardy, 2014(106)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Emanuel, 2007(107)	Non-randomized trial	Pediatric population with CeD	Moderate	Supplemental Table 4
Srinavasan, 2006(104)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Srinavasan, 1996(101)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Janatuinen, 2002(88)	Observational	Adults with CeD	Moderate	Supplemental Table 5
Kempainen, 2007(105)	Observational	Adults with CeD	Moderate	Supplemental Table 5
Tuire, 2012(86)	Observational	Adults with CeD	Moderate	Supplemental Table 5
Kaukinen, 2013(91)	Observational	Adults with CeD	Moderate	Supplemental Table 5
Aaltonen, 2017(89)	Observational	Adults with CeD	Moderate	Supplemental Table 5
Arentz-Hansen, 2004(111)	*in vitro*	Adults with CeD	Reliable w/ restrictions	Supplemental Table 6
Picarelli, 2000(108)	*in vitro*	Adults with CeD	Reliable w/o restrictions	Supplemental Table 6
Silano, 2014(115)	*in vitro*	Pediatric population with CeD	Reliable w/o restrictions	Supplemental Table 6

Hollen, 2003(110)	*in vitro*	Pediatric population with CeD	Reliable w/o restrictions	Supplemental Table 6
Maglio, 2011(113)	*in vitro*	Persons with CeD	Reliable w/o restrictions	Supplemental Table 6
Comino, 2011(114)	*in vitro*	Pediatric population with CeD	Reliable w/o restrictions	Supplemental Table 6
Kilmartin, 2003(109)	*in vitro*	Adults with CeD	Reliable w/o restrictions	Supplemental Table 6
Kilmartin, 2006(112)	*in vitro*	Adults with CeD	Reliable w/o restrictions	Supplemental Table 6

[1] RCT risk assessment categories are Low, Some Concern or High as categories while the non-randomized trials and, observational are rated as Low, Moderate and High and *in vitro* studies as Reliable w/o restrictions, Reliable w/ restrictions or Unreliable. [2] Study by Duysburgh, 2021 was an RCT with experimental component, thus we evaluated it as both, clinical and in vitro study. CeD, celiac disease; GI, gastrointestinal; RCT, randomized controlled trial; UC, ulcerative colitis

Table 2. Summary of clinical trials investigating the association between oat supplementation and changes in microbiome and microbiome GI metabolite status

Lead Author, Publication year	Study design	Study population characteristics			Characteristics of the trial			Microbiome				SCFAs			
		Population	Sample size	Health status	Intervention	Control	Duration (wks)	Between visit differences	Effect	Between group differences	Yes/ no	Between visit differences	Effect	Between group differences	Yes/ no
Duysburg, 2021 (35)	Cross-over RCT	Adults	34	Hypercholesterolemic	40gcooked old fashioned oats/d	40gcream of rice/d	6 (2 periods)	*Lactobacillus*	O	*Lactobacillus*	∧				
								Bifidobacterium	O	*Bifidobacterium*	O				
Pino, 2021 (36)	RCT	Adults	37	Type 2 diabetes mellitus	5g oat β-glucan/d	5g cellulose/d	12	Total bacteria	∨▲	n.a.	---				
								Firmicutes	∨	n.a.	---				
								Bacteroidetes	∨	n.a.	---				
								Verrucomicrobia	∨▲	n.a.	---				
								Lactobacillus	∨	n.a.	---				
								Bifidobacterium spp	∨	n.a.	---				
								Akkermansia muciniphalia	▲	n.a.	---				
								Butyrate producing bacteria	∨▲	n.a.	---				
Ye, 2020[1] (37)	RCT	Adults	28	Hypercholesterolemic	80g oatmeal/d	80g white rice/d	45d	*Subdoligranulum*	∧	n.a.	---				
								Blautia	∧	n.a.	---				
								Erysipelactoclostridium	∧	n.a.	---				
								Odoribacter	∨	n.a.	---				
								Aliihoeflea	∨	n.a.	---				
								Pelagibacterium	∨	n.a.	---				
								Megamonas	▼	n.a.	---				

Martenso, 2005 (27)	RCT	Adult	56	Healthy	84g oat based/d or 84g ropy oat-based/d	84g condensed milk daily/d	8	Ropy oat-based: *Bifidobacterium*	∧	Bifidobacteria	∧
								Ropy oat-based:Total population	∧	n.a	n.a
								Oat based intervention:Bifidobacteria	O	n.a	n.a
								Oat based intervention: Total population	O	n.a	n.a
								Bifidobacteria	▲	Bifidobacteria	O
								Enterobacteriaceae	▼	Enterobacteriaceae	O
								Sulphite-reducing clostridia	O	Sulphite-reducing clostridia	O
Berggren, 2003 (34)	RCT	Pediatric population	69	Healthy	100g oats fermented with *Lactobacillus plantarum*/d	100g oats/d	3 wk	Lactobacilli	↑	Lactobacilli	↑
Li, 2017 (43)	Non-randomized trial	Adult	26	Healthy	Oat	Rice	1	*Anaerotruncus colihominis*	∨	n.a.	---
								Bacteroides cellulosilyticus	∨	n.a.	---
								Bacteroides thetaiotaomicron	∨	n.a.	---
								Bifidobacterium adolescentis	∧	n.a.	---
								Clostridium asparagiforme	∨	n.a.	---
								Clostridium leptum	∨	n.a.	---
								Eubacterium eligens	∨	n.a.	---

								Eubacterium ventriosum	∨	n.a.	---			
								Gordonibacter pamelaeae	∨	n.a.	---			
								Roseburia hominis	∨	n.a.	---			
								Roseburia inulinivorans	∨	n.a.	---			
								Ruminococcus callidus	∨	n.a.	---			
								Ruminococcus torques	∨	n.a.	---			
								Streptococcus thermophilus	∨	n.a.	---			
Connolly, 2016 (28)	Cross-over RCT	Adult	32	Glucose intolerant or mild to moderate hyperchole sterolaemic	45g whole grain oat granola/d	45g non-whole grain/d	6 (2 periods)	*Bifidobacterium*	∧▼	n.a	n.a	Acetic acid	O	Acetic acid	O
								Lactobacillus	∧	n.a	n.a	Propionic acid	O	Propionic acid	O
								Total population	∧▼	n.a	n.a	Lactic acid	O	Lactic acid	O
								Bacteroides and *Prevotella*	O	n.a	n.a				
								Ruminococcus	O	n.a	n.a				
								Clostridium histolyticum/ perfringens	O	n.a	n.a				
								Atopobium	O	n.a	n.a				
Johansso, 1998 (29)	RCT	Adults	48	Healthy	3g oat fermented in *Lactobacillus plantarum*/d	Pure rose hip drink	3	*Bifidobacteria*	∧▲	n.a	n.a	Total SCFA	∧	n.a	n.a
								Lactobacillus	↑	n.a	n.a	Acetic acid	∧	n.a	n.a
								Sulphite-reducing clostridia	∨▼	n.a	n.a	Propionic acid	∧	n.a	n.a

								Anaerobes	O	n.a	n.a	Lactic acid	↑	n.a	n.a
								Aerobes	O	n.a	n.a				
								Gram-negative anaerobes	O	n.a	n.a				
								Enterobacteriaceae	O	n.a	n.a				
Nyman, 2020 (39)	RCT	Adults	130	UC	12g (6g β-glucan) dietary fiber from oat bran/d	5g (<0.5g β-glucan) dietary fiber from wheat/d	24					Total SCFA	∧	Total SCFA	O
												Acetic acid	O	Acetic acid	O
												Propionic acid	∧	Propionic acid	O
												i-Butyric acid	∧	i-Butyric acid	O
												Butyric acid	∧	Butyric acid	∧
												i-Valeric acid	O	i-Valeric acid	O
												Valeric acid	∧	Valeric acid	O
Tjellstrom, 2014[1] (39)	RCT	Pediatric population	69	CeD	25-50g oats/d with GFD	GFD	52					Total SCFA	▼	Total SCFA	↑
												Fermentation index	O	Fermentation index	O
												n.a	---	Acetic acid	↑
												n.a	---	n-Butyric acid	↑
												n.a	---	Propionic acid	O
												n.a	---	i-Butyric acid	O
												n.a	---	i-Valeric acid	O
												n.a	---	n-Valeric acid	O
Valeur, 2015 (41)	Non-randomized trial	Adults	10	Healthy	60g oatmeal/d	None	1					Total SCFA	O	n.a	---

								Acetic acid	O	n.a	---
								Propionic acid	O	n.a	---
								i-Butyric acid	O	n.a	---
								Butyric acid	O	n.a	---
								i-Valeric acid	O	n.a	---
								Valeric acid	O	n.a	---
Nillson, 2008 (40)	Non-randomized trial	Adults	25	Healthy	40g oat bran/d	None	12	Formic Acid	O	n.a	---
								Acetic acid	∧	n.a	---
								Propionic acid	∧	n.a	---
								Butyric acid	O	n.a	---
								i-Butyric acid	∧	n.a	---
								i-Valeric acid	O	n.a	---
								Valeric acid	O	n.a	---
Hallert, 2003 (42)	Non-randomized trial	Adults	22	UC	60g of oat bran added to usual diet/d	Usual diet	12	Total SCFA	O	n.a	---
								Acetic acid	O	n.a	---
								Propionic acid	O	n.a	---
								i-Butyric acid	O	n.a	---
								Butyric acid	∧	n.a	---

		i-Valeric acid	O	n.a	---
		Valeric acid	O	n.a	---

In case of comparison between the two visits (baseline vs post-intervention): **ΛV** indicates changes in intervention group, ▲▼ indicates changes in control group, ↑↓ indicates change in both groups; O indicates no difference reported.[1] Posthoc analysis following a trial. CeD, celiac disease; SCFA, short chain fatty acid; UC, ulcerative colitis