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Accepted Manuscript

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Systematic Review and Meta-analysis of Clinical and Observational Studies

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Safety of Adding Oats to a Gluten-free Diet for Patients with Celiac Disease: Systematic Review and Meta-analysis of Clinical and Observational Studies

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and contribution to study design. Data interpretation. Contributed to manuscript writing and scientific discussion.

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ABSTRACT

Background & Aims: Patients with celiac disease should maintain a gluten-free diet (GFD), excluding wheat, rye, and barley. Oats might increase the nutritional value of a GFD, but their including is controversial. We performed a systematic review and meta-analysis to evaluate the safety of oats as part of a GFD in patients with celiac disease.

Methods: We searched the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE databases for clinical trials and observational studies of the effects of including oats in GFD of patients with celiac disease. The studies reported patients' symptoms, results from serology tests, and findings from histologic analyses. We used the GRADE approach to assess the quality of evidence.

Results: We identified 433 studies; 28 were eligible for analysis. Of these, 6 were randomized and 2 were not-randomized controlled trials comprising a total of 661 patients—the remaining studies were observational. All randomized controlled trials used pure/uncontaminated oats. Oat consumption for 12 months did not affect symptoms (standardized mean difference: reduction in symptom scores in patients who did and did not consumed oats, -0.22; 95% CI: -0.56 to 0.13; $P=.22$), histologic scores (relative risk for histologic findings in patients who consumed oats, 0.24; 95% CI, 0.01 to 4.8; $P=.35$), intraepithelial lymphocyte counts (standardized mean difference: 0.21; 95% CI, reduction of 1.44 to increase in 1.86), or results from serologic tests. Subgroup analyses of adults vs children did not reveal differences. The overall quality of evidence was low.

Conclusions: In a systematic review and meta-analysis, we found no evidence that addition of oats to a GFD affects symptoms, histology, immunity, or serologic features of patients with celiac disease. However, there were few studies for many endpoints, as well as limited geographic distribution and low quality of evidence. Rigorous double-blind, placebo-controlled, randomized controlled trials, using commonly available oats sourced from different regions, are needed.

KEY WORDS: nutrition, gluten sensitivity, symptoms, histology

INTRODUCTION

Celiac disease (CD) is an autoimmune disorder, triggered by gluten and related prolamins in genetically susceptible individuals¹. CD primarily affects the proximal small intestine, where it progressively leads to villous atrophy. The cornerstone of treatment for CD is a gluten-free diet (GFD), which excludes wheat, barley and rye². This diet enables CD patients to control their symptoms and avoid intestinal and extraintestinal complications, including osteoporosis with associated increased risk of bone fractures, and development of certain types of cancer³. Celiac patients react adversely if they consume gluten, which is the storage group of proteins in certain cereal grains. The protein fractions considered to be the constituents of most concern in celiac patients include the alcohol-soluble fractions (prolamins) of wheat (gliadins), rye (secalins) and barley (hordeins)⁴. The prolamine fraction in oats (avenins) is structurally different from other prolamin fractions, and represents only a small proportion of total oats protein⁵.

Van de Kamer et al.⁶ were the first to suggest that oats may be harmful for CD patients. Some later studies, however, pointed to a lack of oat toxicity⁷. While oats are included in the list of gluten-free ingredients specified in some countries' regulations, such as Canada⁸, the safety for CD patients remains controversial. Although GFD containing oats has been reported to improve CD symptoms in some studies⁹, others have detected intraepithelial lymphocytosis¹⁰ and the development of avenin-reactive mucosal T-cells in a small proportion of patients¹¹. The general consensus is that pure oats are safe for most patients with CD, however contamination with other cereal sources needs to be avoided⁴.

Although adherence to GFD is the only available treatment for CD, it does not always ensure adequate nutrition. Oats may increase nutritional value^{3,9}, improve palatability, texture, and fiber content of the GFD^{11,12}. Indeed, oats contain a higher percentage of protein of superior amino acid balance, vitamins and minerals as compared with other cereals^{13,14}. On the other

hand, up to 70% of those with CD experience either voluntary or inadvertently ingest gluten¹⁵ indicating the diet is difficult¹⁶. Thus, oats could also improve GFD compliance and quality of life, although contamination with prolamins from toxic cereal grains is a concern^{3,5,9}. Traditional commercial oats are often contaminated with other gluten-containing grains, however oats grown and processed without contamination, or even cleaned of contaminating grains, so called pure oats, are available^{6,17}.

Previous systematic reviews^{7,18-21} attempted to address these outstanding controversies; however, none of them were able to perform a quantitative analysis. Therefore, we performed a systematic review of the literature and a meta-analysis on the symptomatic, serological and histological response to dietary oats in patients with CD and DH.

METHODS

We included studies evaluating the effect of oats in patients with CD or DH on a GFD. For CD diagnosis, we used any accepted criteria (duodenal biopsy and/or compatible serology and HLA DQ2/8 positivity, where reported). For DH, we considered any criteria reported, such as IgA deposits in skin biopsies. Any intervention involving any amount and type of oats (pure, non-pure, kilned, unkilned) along with GFD was considered and the control group had to receive GFD alone or placebo (negative control) or gluten challenge (positive control). Any other type of comparison and non-controlled studies (before and after comparison) were included in the review but not considered for quantitative synthesis. We considered the following outcomes: improvement in gastrointestinal symptoms (significant decrease in gastrointestinal symptom rating scale (GSRs) score, visual analogue scale (VAS) or other questionnaire), improvement or stable CD autoimmunity (no increase in the levels of CD specific serology), improvement or stable duodenal histology (defined by Marsh

classification, villous/crypt ratio, and/or IEL counts), and symptomatic, serological and mucosal response to oats during long-term follow-up (>1 year).

Types of studies

For the systematic review, we included observational studies (cohort or case-control studies) or clinical trials (randomized controlled trials, RCTs) up to January 2017. Case reports or case series were excluded. Only results from RCTs were pooled in meta-analysis. We considered cross-over trials only if the results were available before cross-over, so that the study could be evaluated as a parallel group. We considered publications regardless of language and publication status. We included published abstracts only if we could obtain further details from the investigators. We excluded duplicate studies, or those in which the diagnosis of CD was not confirmed by either serology or biopsy. The search strategy is outlined in supplementary Table 1.

Selection of studies

To ensure that we captured all eligible studies, two authors (MIP and NCC) screened the titles and abstracts and selected the studies. Obvious duplicate studies were removed at this stage. The same reviewers performed the full text screening independently, using the full text of articles and translation of foreign language articles, where required. Data were entered into an Excel sheet and results were compared. We calculated the agreement at each step (1: title and abstract screening, 2: full text screening and 3: data extraction) by using Kappa statistics (GraphPad software). Raw agreement was reported in percentage and Kappa as fair agreement ($k=0.4-0.59$), good agreement ($0.6-0.74$) or excellent agreement (≥ 0.75). In cases of disagreement, a third author (PM) with experience in the topic was consulted for the final decision. All these steps were properly documented in a table of excluded studies. The two

reviewers (MIP and NCC) independently extracted the data and a form was developed to collect information regarding study design, population, intervention, control intervention and outcomes. The form included information on authors, setting (primary, secondary or tertiary care), funding source (industry sponsored, grant sponsored, investigator funded), CD activity (information on specific serology and/or biopsy), source (pure/uncontaminated/contaminated) and quantities of oats consumed, number of patients, and adverse events. Patient demographics, treatment, outcomes and adverse events were recorded as a mean and standard deviation (SD) for continuous data, or proportions with the outcome of interest for dichotomous data. Randomization, concealment, blinding of participants and outcome assessors, incomplete outcome data, and evidence of selective reporting were collected in order to assess risk of bias. The first author entered the information in RevMan software (RevMan 5.3, Cochrane collaboration) for further analysis and the second author checked for consistency of data.

Assessment of Risk of bias for included studies

We used the GRADE system²² to assess the quality of the body of evidence according to study design, consistency, directness, imprecision and reporting bias.

Measures of treatment effect

Total number of participants who did or did not develop the outcome in each arm at each time point, and the amount of oats consumed, were collected and reported as the number over the total sample population (n/N). Comparison of dichotomous data was reported as a relative risk (RR), with an associated 95% confidence interval (CI). For quantitative analysis, we performed a meta-analysis using RevMan V5.3. Data were pooled using a random effects model. Statistically significant heterogeneity was assessed through the I^2 statistic test and the

Chi-squared test. A value of 0% indicates no observed heterogeneity and larger values denote heterogeneity. Significant heterogeneity was considered present when either the I^2 value was >30%, or the P value for the Chi-squared test was <0.10²². In order to address the most important possible sources of heterogeneity, we performed subgroup analysis considering the effect of oats consumption on CD activity according to age (children vs adults).

RESULTS

The literature search identified 433 citations, and two additional ones were identified by a recursive bibliography search. Three hundred and ninety-five citations remained after removing duplicates. From these, 342 were excluded at the title and abstract screening stage, and 53 were eligible for full-text screening (Figure 1). A very good inter-reviewer agreement was found at the title and abstract screening stage ($k= 0.85$) and in the full text screening step ($k= 0.96$). After full text review, 25 papers were excluded. The reasons for exclusion are detailed in supplementary Table 2. Twenty-eight studies met the inclusion and exclusion criteria for qualitative synthesis and data was extracted from them. The studies included in the systematic review are summarized in Table 1 and supplementary Table 2. Excluded studies are shown in supplementary Table 3. A graphical representation of the summary of risk of bias and the risk of bias for individual studies is shown in Figure 2.

Characteristics of included studies

Of the 28 studies, twelve were clinical trials; six were RCTs (three in children²³⁻²⁵; three in adults^{11,26,27}), two non-RCTs,^{28,29} and four post-hoc analyses from RCTs^{27,30-32}. There were also 10 before and after comparison studies^{5,33-41} and six observational studies. Of the observational studies, two involved long-term follow-up of patients exposed or non-exposed to oats that had participated in previous RCTs^{42,43} and four had a cross-sectional design^{12,44-46}.

Further details on geographical distribution and sample size are described in Table 1 and supplementary Table 2.

No study compared the effect of regular versus pure/uncontaminated oats on the outcomes assessed. Five of the 28 studies failed to report whether oats were from a contaminated or uncontaminated source^{29,42,43,45,46}. However, only one of them⁴⁶ showed increased IELs in a proportion of patients after oats consumption. The effect of oats over 1 year was assessed by 14 studies^{11,12,23,25-27,30-46,34,40,44}. Six studies^{25,11,26,30,41,45} evaluated the impact of oats on symptoms, 12 on serological and histological responses.

The effect of oats on gastrointestinal symptoms

Twelve papers evaluated the effect of GFD plus oats on gastrointestinal symptoms. Three RCTs^{11,24,26} involving 168 patients, reported symptomatic responses to GFD plus oats, compared with GFD alone. Two studies^{11,24} used GSRS scores, and the other²⁶ a VAS. In a double-blind placebo-controlled trial, Gatti et al.²⁴ found a significant decrease in gastrointestinal symptoms in both groups after 6 months, however, the results were published while the study was still blinded. Therefore, we excluded this study from the meta-analysis. The meta-analysis was based on only two studies in adult patients with CD that reported no symptomatic differences after 12 months of GFD with or without oats^{12,21} (SMD: -0.22; 95% CI -0.56 to 0.13; p=0.22) (Figure 3a).

Two RCTs compared GFD with oats with other positive control (i.e gluten free diet or another type of oat). The first study²⁵ assessed the symptomatic response to a challenge with gluten-free oats versus a “gluten challenge” that allowed the consumption of wheat, rye and barley in children with CD on a strict GFD. In the oat-challenged group, 4 out of 10 patients had symptoms that resolved while continuing the consumption of oats and none of whom showed signs of CD activity. In the gluten-challenged group, 4 out of 10 patients developed

abdominal symptoms coincident with small bowel histological deterioration. All of the patients included became asymptomatic during an oat-containing GFD²⁵. In the second study, Kempanien et al.²⁷ randomized patients to GFD plus kilned or GFD plus unkilned oats, and found no difference in symptoms between the groups (RR: 1.88; 95% CI: 0.57-6.19; p=0.30). Of the remaining 7 studies, six were small, and before and after comparison trials, five in adults^{5,35,38-40} and one in children³⁷, and one had a cross-sectional design⁴⁵. None of them demonstrated CD activity after oat consumption. Further study characteristics are summarized in Table 1 and supplementary Table 2.

Overall the quality of evidence for the effect of oats on gastrointestinal symptoms was very low. There were two RCTs, involving 131 patients, that were at high risk of performance and detection bias and one study was at high risk of attrition bias. We detected serious risk of indirectness, as the effect estimates were in both directions and had large CIs. Therefore, we have very little confidence in the effect estimate, and the true effect is likely to be substantially different from the estimate of effect. Summary of findings are shown in Table 2.

The effect of oats on duodenal histology

Villous atrophy:

Seventeen studies evaluated the histological response to oats in patients with CD. Of these, five were RCTs, two of which were conducted in children^{23,25} and three in adult patients^{11,26,27}. Three out of five RCTs compared GFD with and without oats^{11,26,27}, one compared a challenge with oats versus a gluten challenge in patients on a GFD²⁵, and one investigated GFD with kilned and unkilned oats²⁷. Two of the studies reported histological lesion graded according to Marsh classification^{23,27}, two as villous/crypt (V/C) ratios^{11,25} and one as histopathological grade index²⁶. Two out of five studies^{11,26} reported histological response as a continuous measurement in adult patients with CD treated with GFD plus 50g

of oats/day versus GFD without oats, for 12 months. One of these studies¹¹ reported no difference in villous structure between the groups (mean for intervention versus control 2.5 and 2.4 respectively; $P=NS$), although a SD was not provided. The authors were contacted, however the information was not provided, therefore this study was not included in the meta-analysis. Data were therefore available from one paper²¹, which reported no change in histological index in patients with CD treated with GFD with/without oats after 12 months (MD: -0.0; 95% CI -0.01 to 0.01; p : 0.92; Figure 3b).

Three out of the five RCTs^{11,23,27} reported on the proportion of patients with either histological improvement or no deterioration as a dichotomous outcome. Hogberg et al.²³ compared the histological response during GFD with/without pure oats for 12 months in 116 children with CD. A similar proportion of patients in both groups had histological remission (Marsh) (RR 0.24; 95% CI 0.01-4.81; $p=0.35$). Kemppanen et al.²⁷ compared the histological response to GFD plus kilned vs unkilned oats after 12 months, and found no differences in the proportion of patients with histological remission, according to Marsh criteria, after treatment (RR 0.63; 95% CI 0.12-3.24; $p=0.58$). Holm et al.²⁵ compared the effect of a challenge with gluten-free oats versus a gluten challenge on histological remission. The response was significantly different, as all patients challenged with oats, but none of the patients challenged with gluten, maintained histological remission after the study period (RR 0.04; 95%CI 0-0.66; $p=0.02$).

Of the 12 remaining studies, seven were before and after comparison trials, six in adults^{33-36,38,39} and one in children³⁷. One was a non-RCT²⁸, two were cross sectional studies^{45,46}, and two were post hoc analyses of RCTs^{31,32}. None of them showed CD activation after oats. The characteristics of these studies are summarized in Table 1 and supplementary Table 2.

The quality of evidence for the effect of oats on histology was low, and was downgraded due to the fact that the only study included was not blinded, and had high dropout rates, and was

therefore at high risk of attrition bias (Table 2). There was also some imprecision detected, as the study was small and had large CIs.

Intraepithelial lymphocyte counts:

Thirteen studies evaluated changes in IELs in response to oat consumption. Of them, three RCTs (two in adults^{11,26}; one in children²³) assessed changes in IELs after moderate consumption of oats for 1 year. A meta-analysis was performed on these studies. There were no differences in IEL counts in patients with CD on a GFD consuming, compared with those not consuming, oats (overall SMD 0.1; 95% CI -0.15 to 0.35; Figure 3c). One RCT²⁵ assessed histological response to oat challenge compared with challenge with wheat, rye and barley (“gluten challenge”) in children with CD. After 2 years, IEL density decreased in the oat-challenged group, but increased in the gluten-challenged group.

In the 10 remaining studies, there were three post-hoc analyses from RCTs³⁰⁻³²; four before and after comparisons (three in adults^{33,35,40}; one in children³⁷), one non-RCT study²⁸, one cross sectional⁴⁵ and one cohort study⁴⁶ evaluating the effect of GFD plus oats in CD patients. The amount of oats and the length of the study period differed between studies. Their characteristics are summarized in Table 1 and supplementary Table 2.

The quality of evidence on the effect of oats on IEL counts was rated as low due to high risk of attrition bias in one study, and imprecision and indirectness in both studies. Therefore, we are moderately confident in the effect estimate and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

The effect of oats on CD serology

Four RCTs assessed the effect of oats on tTGA (three in children²³⁻²⁵; one in adults¹¹). Two studies, one performed in adults in remission¹¹ and the other in newly diagnosed children²³,

compared GFD with pure oats and GFD without oats, for 12 months. There was no significant difference in tTGA between the groups (RR 1.71; 95% CI 0.62-4.71; $p=0.89$).

One double-blind placebo-controlled study comparing GFD with and without oats reported that tTGA was measured, but no actual values were shown²⁴.

Four RCTs assessed the effect of oats on EmA (two in children^{23,25}; two in adults^{11,42}). Two^{11,23} out of the four studies compared the effect of a GFD with and without oats. There was no significant difference in EmA between the groups (RR 1.45; 95% CI 0.77-2.74; $p=0.25$; Figure 3d).

One RCT²⁰ compared the effect of challenge with oats with a gluten challenge. The results were in favor of oats, as tTGA and EmA were normal in all patients after oat challenge and elevated in all patients after gluten challenge (RR 0.04; 95% CI: 0-0.57 $p=0.02$), (RR 0.11; 95% CI 0.02-0.51; $p=0.005$).

Three RCTs assessed the effect of oats on AGA IgA (two in children^{23,25}; one in adults³⁰). Two studies^{23,30} compared the effect of a GFD with and without oats for 12 months. Hogberg et al.²³ evaluated the effect of GFD with a median of 25g of pure oats compared with a GFD without oats in 116 children. After 3 months of diet, AGA were below the cut-off for the majority of children in both groups. Janatuinen et al.³⁰ evaluated the effect of GFD with and without oats in 52 adult patients with CD in remission and in 40 newly diagnosed CD patients at 12 months. AGA IgA and IgG did not change significantly at any point during the study in the oats group compared with the control group. Holm et al. performed a study in 36 children with either previously diagnosed, or newly detected, CD who were challenged with oats or with gluten. Two patients had borderline-positive values after 2 years of oat-containing GFD.

Two studies evaluated the effect of GFD with and without oats on anti-avenin antibodies. Emanuel et al.⁴⁷ assessed 32 children with biopsy-proven CD and 10 non-celiac controls.

Both groups were treated with two types of oats: ancient grains or imported oats. Patients with CD showed a different immune reaction to avenin proteins compared with controls. Guttormsen et al.⁴⁴ investigated 136 adult CD patients on a GFD, 82 of whom had been consuming oats for 6 months or more. All patients had increased levels of IgA against wheat, oats and tTG compared with healthy controls, but no significant differences were found in IgA against oats between oat- and non-oat consuming patients.

There were no studies evaluating the effect of GFD with oats on deaminated gliadin peptides (DGP) antibodies. Further study details are shown in Table 1 and Supplementary Table 2. The quality of evidence for the effect of oats on serological response was low, and was downgraded due to the fact that the outcome assessors were not blinded in one study, but also had high dropout rates, and therefore was at high risk of attrition bias. There was also some imprecision detected, as the study was small and had large CIs. Summary of findings for each individual outcome are shown in Table 2.

The effect of oats on dermatitis herpetiformis (DH)

Three non-RCT studies in adult patients assessed the effect of oats on DH, all with different study design. Reunala et al.²⁸ enrolled 22 CD patients with DH in remission on a GFD. Eleven patients were treated with GFD plus 50g of pure oats, and 11 without oats, for 6 months. There was no difference in terms of the recurrence of skin lesions in DH patients on GFD with and without oats after the study period. Kaukinen et al.⁴⁵ found 13 patients with DH in a cross-sectional study; nine were on a GFD with oats (mean 60g/day; purity of oats not confirmed) and four on GFD without oats. There was no difference in the recurrence of skin lesions in DH patients on GFD with and without oats. Finally, Hardman et al.³¹ performed a before and after comparison trial in which 10 patients with DH were treated with GFD plus pure oats (mean 62g/day) for 12 weeks. None of the patients reported pruritus,

rash, or recurrence of DH during this period. Further details are shown in Table 1 and supplementary Table 2.

Long-term effect of oats

No study compared the effect of regular versus pure/uncontaminated oats on any of the outcomes assessed. Five of the 28 studies did not report whether oats were from a contaminated or uncontaminated source^{29,42,43,45,46} however, only one of them⁴⁶ showed increased IELs in a proportion of patients after oats consumption. The long-term effect of oats over 1 year was assessed by 14 studies^{11,12, 23,25-27,30-46,34,40,44}. Six studies^{11,25,26,30,41,45} evaluated the effect of oats on gastrointestinal symptoms and 12 on serological and histological responses. There was no change on any of the previous outcomes after long term consumption of oats.

DISCUSSION

There is still uncertainty regarding the effect of oats in CD despite previous reviews^{7,8,49-52}. In our updated review of the literature, we found no deterioration in gastrointestinal symptoms in CD patients consuming oats for 12 months. Although the evidence on oats and lack of symptom induction in adult patients comes from RCTs, the quality was rated as very low. Of six small, before and after comparison studies, two reported more frequent gastrointestinal symptoms after oats intake^{5,40}. These had limitations due to small sample size, lack of control group and unclear assessment of diet compliance. Furthermore, there was no clear association between the presence of symptoms and CD activity making it unclear whether symptoms were related to mild CD activation or to the increased fiber contained in oats⁴⁶.

Studies investigating changes in histological parameters have mostly shown no change or, slight improvement in Marsh scores, V/C ratios, and IEL counts. Once more, the quality of evidence from RCTs was low, due to attrition bias detected in one of the studies and also imprecision in the results.

There were no RCTs evaluating the effect of oats in DH patients. However, the results of the 3 non-RCTs suggest that skin manifestations were not worsened after consumption of oats.

All serologic markers associated with celiac autoimmunity are gluten-dependent, and a rise in their values suggests exposure to gluten⁴⁸. Our review found no difference in the levels of tTG, AGA or EmA antibodies in CD patients on GFD with or without oats. However, the values were increased after gluten challenge²⁵. The results were confirmed by non-controlled studies in both adults and children. Although the RCTs overall suggest that pure oats do not trigger immune activation, this should be taken with caution, as the overall quality of evidence was low. A position statement by the Canadian Celiac Association⁴ suggested that screening for tTG or EmA may not identify the rare patient who reacts to oats, as these tests may not be sufficiently sensitive for detecting 'mild' dietary transgressions, especially with

short-term challenge. Therefore, a positive tTG or EmA result helps to confirm celiac disease activity, but a negative test may not exclude it⁴.

Only one RCT involving 60 patients⁴³ evaluated the effect of kilning process. Kilning is an industrial heating process performed to preserve the main properties of oats and to lengthen its shelf life⁴⁹. Both kilned and unkilned oats were tolerated by CD patients⁴⁹, however, the results will need to be confirmed in future studies.

There are numerous aspects to consider when comparing studies evaluating the safety of oats, such as the compliance with GFD, amount and frequency of oats consumption, as well as the cultivars used in the production of pure oats¹⁸. This information was often omitted. Similar to previous reviews¹⁸, we found that the available studies differed in study design, number of subjects, time period, and clinical and biological parameters used. Furthermore, there was disparity and lack of information regarding the quantity, source and the cultivar(s) of oats¹⁸. Accuracy of assays measuring oat immunotoxicity was out of the scope of this review but is an important area for future research since there is no accepted standard for detection of immunoreactive proteins.

The purity of oats will depend on the country of origin and local regulations. While the majority of gluten-free products containing oats have been confirmed safe in countries like Finland, and Norway⁴⁴, regular oats in North America are likely to be contaminated with wheat and barley⁵⁰⁻⁵⁴. For this reason, oats used in gluten-free foods should be produced/processed under protocols that ensure purity during all phases of production. Ensuring safety will depend on reliable testing measures that consistently guarantee less than 20ppm of gluten¹⁷. Recently, oats that have been optically or mechanically cleaned to eliminate other grains have been used to produce gluten-free cereal products for the mass market. These are available and have, in some cases, been determined to be gluten-free (<20 ppm of gluten). None of these oat products have as yet been subjected to clinical studies. All

RCTs published to date investigating the safety of pure oats consumption in CD were conducted in Europe, which emphasizes the urgent need for studies in North America and other regions of the world where CD is prevalent. Results from studies in Europe using locally sourced oats cannot be extrapolated to North America.

The methodology of our systematic review and meta-analysis, including the search and selection of studies, data extraction and final analysis of results, was rigorous. We attempted to increase the scope of our review and reducing the risk of biases in all steps of this process. We acknowledge that the data are not robust enough to make definitive, evidence-based recommendations on the safety of oats for CD patients at this point. In this sense, we endorse the recommendations by the North American Society for the Study of Celiac Disease NASSCD⁵⁵ to support the use of pure oats in CD, but to monitor levels of tTGA before and after their introduction into the diet. Persistent or recurrent symptoms should prompt an assessment that may include an intestinal biopsy¹⁷.

In conclusion, the results of our systematic review evaluating oat safety in adults and children with CD are reassuring, and suggest that non-contaminated oats are tolerated by the great majority of patients. However, our confidence is limited by the low quality and limited geographic distribution of the data. Current evidence suggest that non-contaminated oats can be used in patients with CD but there is still a need for more rigorous data from well-designed RCTs evaluating the effect of pure oats in the short and long-term, in both children and adult patients with CD. Ideally, relevant information regarding the source of oats including cultivars and amount of oats consumed and compliance to GFD should be provided.

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Table 1: Characteristics of included studies

Table 2: Summary of findings for the following outcomes: gastrointestinal symptoms, histological response and CD specific serology.

Figure 1: Flowchart of study selection (PRISMA)

Figure 2a: Risk of bias for individual studies according to Cochrane tool for assessment of risk of bias.

Figure 2b: Risk of bias graph: Summary of risk of bias presented as percentages across all included studies.

Figure 3a: Forest plot of comparison of RCTs: symptomatic response (gastrointestinal symptoms) in CD patients on GFD with oats vs GFD without oats, continuous outcome.

Figure 3b: Forest plot of comparison of RCTs: histological response: GFD with oats vs GFD without oats, continuous outcome.

Figure 3c: Forest plot of comparison of RCTs: 1) intraepithelial lymphocyte (IEL) counts on GFD with oats vs GFD without oats- continuous outcome; 2) IEL counts on GFD with and without oats (dichotomous outcomes).

Figure 3d: Forest plot of comparison of CD specific serology: tTG after challenge with oats vs challenge with gluten.

Author (ref)	Country of origin/study design	Population	Intervention	Outcomes assessed
Baker 1976 ⁵	UK Single center Single cohort Before and after comparison	12 biopsy-proven CD patients; 1 child and 11 adults for \geq 6 months on GFD	GFD + 60 g of non-contaminated oats/d for 28 d. British Drug Houses Avenin, prepared from oat flakes ⁵	Improvement in GI symptoms Mean reduction in xylose excretion
Cooper 2012 ³⁴	Ireland/UK Single center. Single cohort/ Before and after comparison	46 biopsy-proven CD adult patients. 37 for \geq 10 yrs on GFD, and 9 newly diagnosed	GFD+ 50 g x day of pure oats for a period of 1 year. Oats sourced from Peter Kölln and confirmed to be free from other grains	Improvement in GI symptoms Immune activation (tTGA) Improvement in CD activity (Marsh, IELs) IHC staining anti-Ki-67, CD ³ , CD8 and SM α -actin deposits
Gatti 2013 ²⁴	Italy Multicenter DBPC-RCT	307 biopsy-proven CD children \geq 2 yrs on GFD.	2 arms: GFD+ purified oats; GFD+ placebo; 6 months	Improvement in GI symptoms (GSRs) Immune activation (tTGA) Intestinal permeability (LAMA)
Guttormsen 2008 ⁴⁴	Norway. Single center. Cross-sectional	136 biopsy-proven CD (adult; 82 consuming oats) \geq 2 years of GFD and 139 controls from community	GFD+ 24 g/d ecologically grown GF oats vs GFD vs controls Oats consumed for at least 3 months.	IgA anti-gliadin IgA anti-avenin tTGA
Hardman C.1987 ³³	UK Single center Single cohort/ Before and after comparison	10 adults biopsy proven CD and DH, on GFD for a mean of 10 yrs.	GFD + mean 62.5 g/d pure oats confirmed GF; for 3 months Oats sourced from Peter Kölln and confirmed to be free from other grains	Changes in dermal IgA deposits Changes in AGA, ARA, EmA Changes in CD activity (V/C), enterocyte height and IELs
Hoffenberg 2000 ³⁷	US Single center Single cohort/ Before and after comparison	10 children biopsy-proven newly diagnosed CD following a GFD	GFD + mean 21 g/d of pure oatmeal confirmed GF; 6 months of treatment Oatmeal by ConAgra (Omaha, Neb) Gliadin contamination measured by RIDASCREEN ELISA (R-Biopharm GmbH, Darmstadt, Germany)	Improvement in GI symptoms (diary-Likert scale) Changes in tTGA and histology (Marsh) Changes in α -tocopherol to total lipids ratio, iron, zinc, hemoglobin and erythrocyte folate
Hogberg 2004 ²³	Sweden Single center RCT	116 children biopsy-proven CD newly diagnosed	GFD+ median 20 g (20-50 g) of non-contaminated oats (pure Semper AB, Sweden) for 1 yr	Changes in AGA, tTGA Changes in mucosal morphology (Marsh)
Holm K	Finland. Single	31 children biopsy-	GFD+ challenge with 45 g x	Improvement in GI

2006 ²⁵	center. RCT	proven CD; 23 in remission and 9 newly diagnosed	day of pure oats (ELISA confirmed) vs challenge with 20 g of gluten 24 months	symptoms Changes in mucosal morphology (Marsh, IELs) Changes in tTGA, EmA, AGA
Janatuinen 1995 ²⁶	Finland Two centers RCT	52 adults biopsy proven CD in remission FU 6 months and 40 newly diagnosed CD FU x 12 months	GFD+ 50-70 g oats vs GFD no oats for 12 months Products (Raisio Factories) supplemented with oats	Improvement in GI symptoms (100 mm VAS) Changes in histology Nutrients: Hb, iron, calcium, folate, albumin
Janatuinen 2000 ³⁰	Finland Post hoc analysis from Janatuinen 1995 ⁴⁰	52 adults biopsy proven CD in remission FU 6 months and 40 newly diagnosed CD FU period of 12 months	GFD+ 50-70 g oats vs GFD no oats x 12 months. Products (Raisio Factories) supplemented with oats	Changes in AGA IgA, AGA IgG and Anti-reticulin antibodies
Janatuinen 2002 ⁴³	Finland Two centers	63 adult biopsy proven CD; 35 on GFD+oats and 28 on GFD. Follow up on cohort from Janatuinen 1995 ⁴⁰	GFD+ mean 34 g/ d of oats vs GFD x 5 years The purity of the oats monitored only during the 6–12 month-intervention	Changes in nutritional status Changes in histopathology Changes in EmA, ARA, AGA antibodies.
Kaukinen 2013 ⁴⁵	Finland. Single center. Cross-sectional.	106 long-term treated adult CD; independently if they consumed oats or not	GFD + oats vs GFD no oats. Mean oat consumption 20 g (range 1-100g) Purity of the oats not confirmed Mean oat consumption 5 years.	Improvement in GI symptoms (GSRS) Improvement in DH Changes in histopathology (Marsh) and densities of IELs CD3+, $\alpha\beta$ + and $\gamma\delta$ + Changes in tTGA; EmA
Kemppainen 2007 ⁴²	Finland. Post hoc analysis from Janatuinen 2002 ⁴²	42 adult CD (22 consuming oats and 20 not consuming oats)	Refer to Janatuinen 2002 ⁴²	Changes in densities of CD3 and IELs
Kemppainen 2008-a ⁴⁹	Finland. Post hoc analysis of ⁴⁶	32 biopsy-proven CD adult patients in remission	100 g/ d of Killed vs unkillned oats for a period of 12 months.	Changes in nutritional status Changes in EmA Improvement in GI symptoms (VAS) Changes in histopathology (Marsh)
Koskinen O 2009 ³¹	Finland. Single center. Post hoc analysis of ³⁹	23 children biopsy-proven CD; in remission and newly diagnosed.	GFD+ challenge with 45 g x day of pure oats (ELISA confirmed) vs challenge with 20 g of gluten. Period of 24 months.	Changes in histopathology (V/C) IgA deposits in duodenum Changes in tTGA,
Lundin 2003 ³⁸	Norway Single center CT open label,	19 biopsy proven adult CD on a GFD for a mean of 7 yrs	GFD + oats. 50 g pure /d x 3 months Oats harvested from fields	Improvement in GI symptoms (Likert scale) Changes in histopathology

	Before and after comparison		where no wheat, rye, barley, or oats had been grown during the last 10 years 120 samples tested GF	(Marsh) Changes in tTGA, EmA, AGA IgA and AGA IgG Changes in D-Xylose Changes in IFN- γ
Peraaho 2004 ⁹	Finland Single center RCT	39 biopsy-proven CD on GFD without oats.	GFD+50 g of oats-containing GF products vs GFD no oats for 1 year.	Improvement in GI symptoms (GSRS) Changes in histopathology (V/C and IELs) Changes in quality of life (PGWB) Changes in tTGA, EmA
Reunala 1998 ²⁸	Finland Single center Non RCT	23 biopsy-proven adult CD with DH in remission with a GFD	GFD+ 50 g/ d of oats vs GFD no oats x 6 months. The oat cereal (Melia Ltd, Raisio, Finland) confirmed GF (ELISA; Ridascreen Gluten Kit, Biopharm)	Symptoms DH, rash Changes in histopathology (V/C and IELs) Changes in IgA fluorescence of the skin. Changes in EmA, AGA
Sey 2011. ³⁹	Canada Single center. Before and after comparison	15 biopsy-proven adult CD on GFD for at least 1 year. Negative TTG	GFD+350 g/ week of pure uncontaminated oats for a period of 12 weeks. Oats were donated by Cream Hill Estates.	Improvement in GI symptoms (VAS) Changes in histopathology (Marsh) Changes in tTGA
Sjoberg 2014 ³²	Sweden Multicenter Post hoc analysis of ³⁷	28 biopsy-proven children CD	GFD+ 25-50 g of non-contaminated oats vs GFD no oats for 12 months	Changes in histopathology (Marsh) Changes in tTGA, EmA Changes in inflammatory markers; IL-17A, IFN- γ , CXCL8/IL-8, IL-10, TGF- β 1, TNF- α and CX3CL1 mRNAs
Srinivasan 1996 ³⁵	Ireland Single center Before and after comparison	Ten biopsy-proven adult CD patients in clinical and histological remission	GFD+ oats. Pure- 50g of oats porridge daily for 12 weeks. The oats cereal (Peter Kolln, Germany) tested for gluten contamination using HPLC, ELISA and PCR.	Improvement in GI symptoms Changes in histopathology (enterocyte height, IELs) Changes in tTGA, EmA, AGA IgA
Srinivasan 2006 ³⁶	Ireland Single center Post-hoc of ⁵³	Post-hoc of Srinivasan ⁵³	Post-hoc of Srinivasan ⁵³	Immunohistochemistry and IF antibodies to HLA-DR, ICAM-1 (CD54), Ki-67, CD25 and mast cell tryptase
Srinivasan 1999 ²⁹	Ireland Single center Non RCT Post-hoc of ⁵³	26 adult patients (11 non-celiac disease controls, 9 active CD, 6 CD in remission). 10 of CD were from previous study ⁵³ after oat challenge)	GFD+oats vs GFD no oats	Immunohistochemistry and IF antibodies to human lactase (M-LAC) activity Changes in tTGA, EmA, AGA IgA

Storsrud 2003-a ⁴⁰	Sweden Single center Before and after comparison.	20 adult biopsy-proven CD patients on GFD for more than 1 yr	GFD+ mean 90 g of rolled oats (Kungsornen, Sweden) which was free from wheat, rye and barley (ELISA). Study period of 24 months.	Changes in histopathology (Villous architecture, IELs) Changes in BMI and nutritional status Changes in EmA
Storsrud 2003-b ⁴¹	Sweden. Single center. Post hoc analysis of ⁵⁶	Post hoc analysis of ⁵⁶	Post hoc analysis of ⁵⁶	Changes in GI symptoms (questionnaire unclear) Intakes of energy and nutrients in the diet (Food Composition Tables, Energy and Nutrients; Sweden)
Tapsas 2014-b ¹⁰	Sweden Multicenter Cross-sectional study	316 children and adolescents biopsy-proven CD on GFD.	GFD exposed to oats (89.2% of population) vs GFD not exposed to oats (10.8% of population)	Assessment of GFD compliance Prevalence of oats consumption in CD population
Tuire 2012 ⁴⁶	Finland Single center Cross-sectional study	177 adult CD patients adhering to long-term strict GFD	GFD with and without oats.	Identify factors (including oats consumption) contributing to increased IELs with normal villous architecture.

*Studies in alphabetical order.

Abbreviations: CD: Celiac disease; GFD: Gluten-free diet; AGA: Serum gliadin antibodies; tTGA: serum IgA-class tissue transglutaminase antibodies; EmA: serum IgA-class anti-endomysium antibodies; IHC: Immunohistochemistry, V/C: villous crypt ratio; GSRS: gastrointestinal symptoms rating scale; PGWB: psychological general well-being.

Patient or population: celiac disease

Intervention: GFD with oats

Comparison: GFD without oats

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with GFD without oats	Risk with GFD with oats				
Overall symptoms improvement-Continuous outcome	-	-	-	131 (2 RCTs)	⊕○○○ VERY LOW ^{a,d,e,f}	Outcome was assessed by GSRS scores and VAS.
Symptoms improvement-Kilned vs unkilned oats	200 per 1,000	376 per 1,000 (114 to 1,000)	RR 1.88 (0.57 to 6.19)	31 (1 RCT)	⊕○○○ VERY LOW ^{a,b,c}	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; SMD: Standardised mean difference

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Study was not blinded for participants, personnel or outcome assessors. High risk of performance and detection bias

b. Small study, few patients and large CI

c. No explanation was provided

d. One study was at high risk of attrition bias

e. Both studies differ in population, and outcome measurement, however results were similar after subgroup analysis

f. Effect estimate in both directions and large CI

Histological response

Patient or population: celiac disease – adult and children

Intervention: GFD with oats

Comparison: 1-GFD without oats 2- gluten challenge

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with GFD without oats	Risk with GFD with oats				
Histological response- Continuous	The mean histological response- Continuous was 0	The mean histological response- Continuous in the intervention group was 0 (0.01 lower to 0.01 higher)	-	92 (1 RCT)	⊕⊕○○ LOW ^{a,b}	Subgroup analyses in children and adult similar results
Histological response- dichotomous	40 per 1,000	10 per 1,000 (0 to 192)	RR 0.24 (0.01 to 4.81)	92 (1 RCT)	⊕⊕○○ LOW ^{b,c}	Subgroup analyses in children and adult similar results
Histological response- kilned vs unkilned oats	200 per 1,000	126 per 1,000 (24 to 648)	RR 0.63 (0.12 to 3.24)	31 (1 RCT)	⊕⊕○○ LOW ^{a,b}	
Histological response- challenge with oats vs challenge with gluten	1,000 per 1,000	40 per 1,000 (0 to 660)	RR 0.04 (0.00 to 0.66)	21 (1 RCT)	⊕⊕○○ LOW ^{a,b}	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. The study was not blinded for participants and personnel; high risk of performance bias

b. Large CI

c. The study was identified at high risk of attrition bias

CD specific serology

Patient or population: celiac disease children and adults

Intervention: GFD with oats

Comparison: GFD 1- without oats 2- gluten challenge

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with GFD without oats	Risk with GFD with oats				
Anti tissue transglutaminase antibodies	76 per 1,000	130 per 1,000 (47 to 357)	RR 1.71 (0.62 to 4.71)	131 (2 RCTs)	⊕○○○ VERY LOW ^{a,b,c}	
Anti tissue transglutaminase antibodies- Oats challenge vs gluten challenge	1,000 per 1,000	40 per 1,000 (0 to 570)	RR 0.04 (0.00 to 0.57)	23 (1 RCT)	⊕⊕⊕○ MODERATE ^{c,e}	
EmA	182 per 1,000	264 per 1,000 (140 to 498)	RR 1.45 (0.77 to 2.74)	131 (2 RCTs)	⊕○○○ VERY LOW ^{a,b,c}	
EmA- Oats challenge vs gluten challenge	1,000 per 1,000	110 per 1,000 (20 to 510)	RR 0.11 (0.02 to 0.51)	23 (1 RCT)	⊕⊕⊕○ MODERATE ^c	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

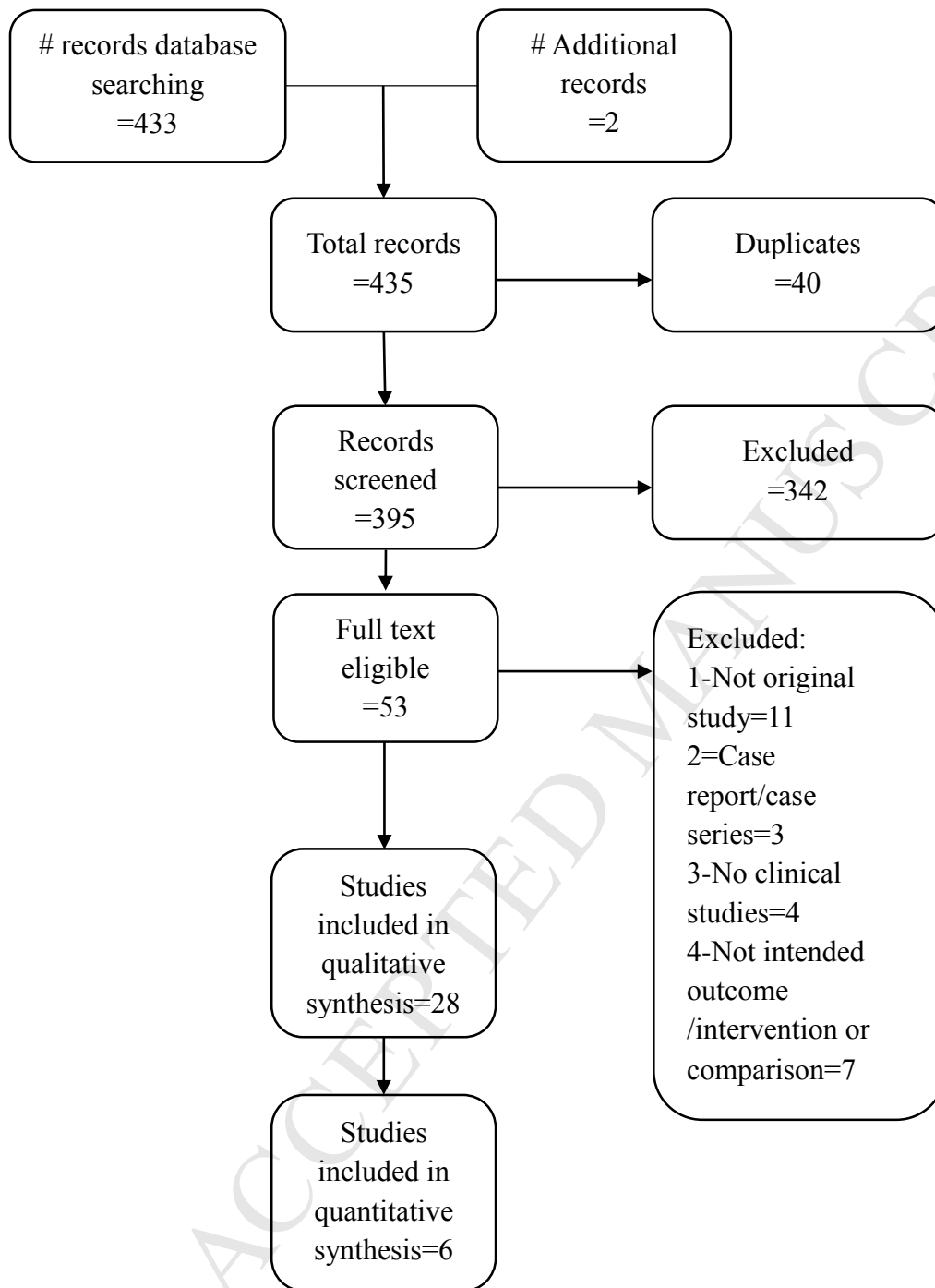
a. Outcome assessors not blinded in one study

b. High rate of drop outs in both studies

c. One small study with large CI

d. No explanation was provided

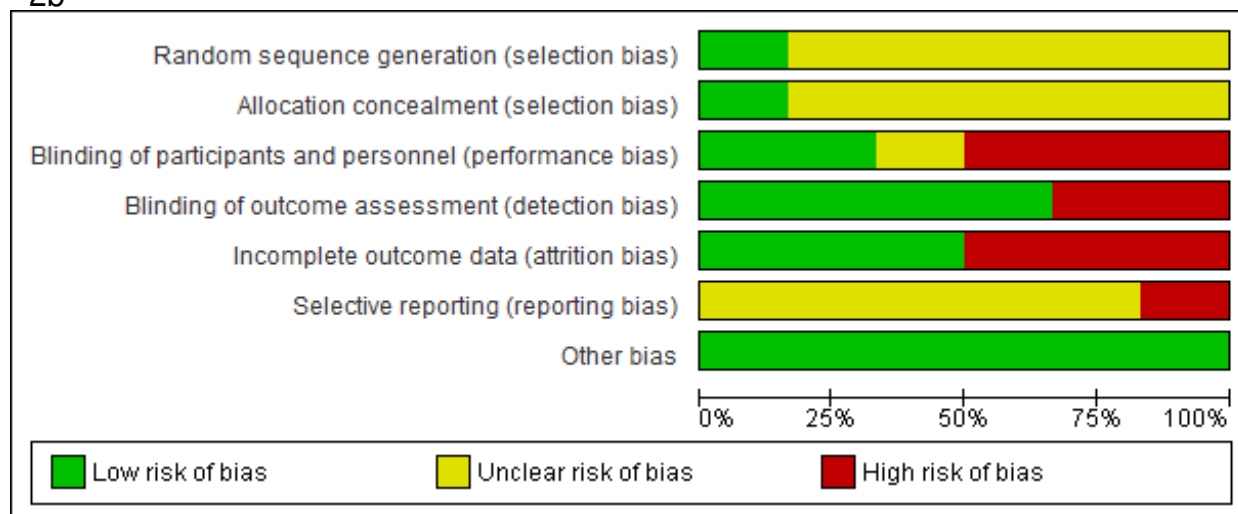
e. Participants and personnel not blinded, but outcome assessor blinded

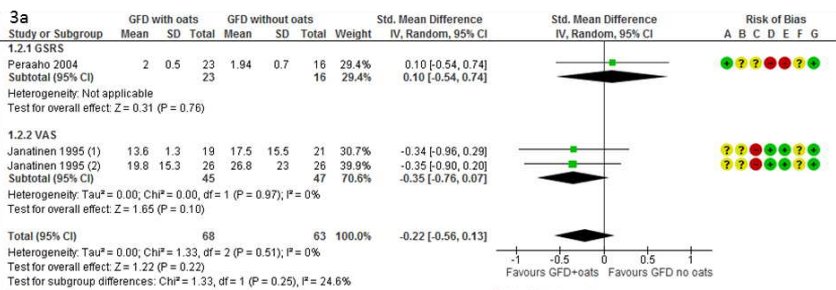


2a

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Gatti 2013	?	?	+	+	-	-	+
Hogberg 2004	?	+	+	+	-	?	+
Holm 2006	?	?	-	+	+	?	+
Janatinen 1995	?	?	-	+	+	?	+
Kemppainen 2008	?	?	-	-	+	?	+
Peraaho 2004	+	?	?	-	-	?	+

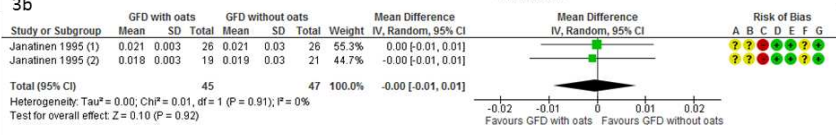
2b





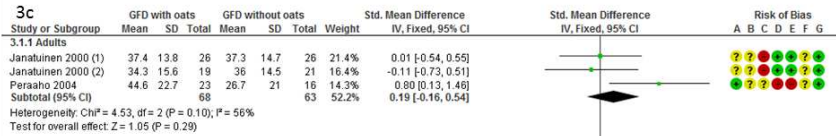
Footnotes:
(1) Report on Newly diagnosed CD patients
(2) Report on CD patients in remission

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias



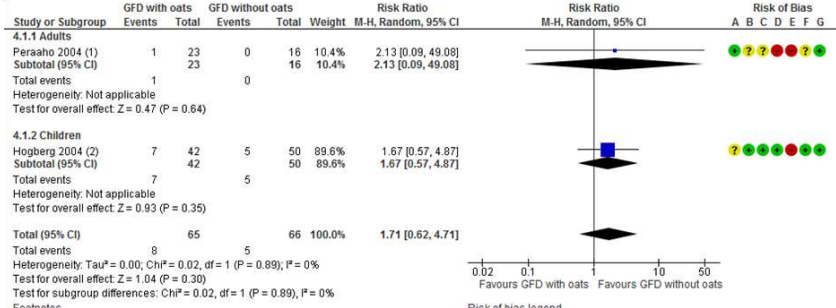
Footnotes:
(1) Report on newly diagnosed CD patients
(2) Report on CD patients in remission

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias



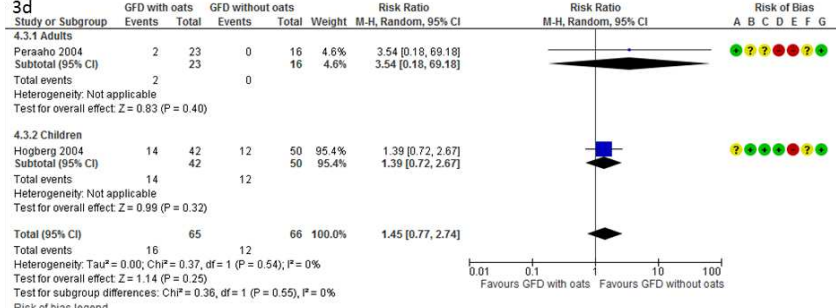
Footnotes:
(1) Report on CD patients in remission
(2) Report on newly diagnosed CD patients

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias



Footnotes:
(1) Adults in remission
(2) Children new diagnosis

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Supplementary Information**Supplementary Table 1: Search strategy**

SEARCH OVID-MEDLINE (MESH Terms)

1. Celiac Disease
2. celiac.mp
3. Celiac Disease/ or Glutens/ or coeliac.mp
4. gluten.mp. or Glutens
5. enteropathy.mp
6. 4 and 5
7. gluten-sensitive.mp
8. sprue nontropical.mp
9. oats.mp. or Avena sativa
10. pure-oats.mp
11. 9 or 10
12. 1 or 2 or 3 or 4 or 6 or 7 or 8
13. 11 and 12

Supplementary Table 2: Summary of all studies evaluating the effect of oats in celiac disease:

Study , Yr	Country	Yr	Ref	Study design	Age category	N	Amount of oats (g)	Source of oats	Length of treatment (months)	Outcomes					
										GI	Serology	Histology	IELs	DH	
RCTs															
Gatti	Italy	2013	24	1	Children	306	unclear	GF	6						
Hogberg	Sweden	2004	23	1	Children	116	moderate	pure	12						
Holm K	Finland	2006	25	1	Children	32	moderate	GF	24						
Janatuinen	Finland	1995	26	1	Adults	92	moderate	GF	12						
Kemppainen	Finland	2008	27	1	Adults	32	large	GF	12						
Peraaho	Finland	2004	11	1	Adults	39	moderate	GF	12						
Non-RCTs															
Reunala	Finland	1998	28	2	Adults	23	moderate	GF	6						
Srinivasan	Ireland	1999	29	2	Adults	21	unclear	unclear	3						
Baker	UK	1976	7	3	11 adults 1 children	12	moderate	pure	1						
Cooper	Ireland, UK	2012	34	3	Adults	54	moderate	pure	12						
Hardman C.	UK	1987	33	3	Adults	10	moderate	pure	3						
Hoffenberg	US	2000	37	3	Children	10	moderate	GF	6						
Lundin	Norway	2003	38	3	Adults	19	moderate	pure GF	3						
Sey	Canada	2011	39	3	Adults	15	moderate	pure	3						
Srinivasan	Ireland	1996	35	3	Adults	10	moderate	Pure	3						
Srinivasan	Ireland	2006	36	3	Adults	10	moderate	Pure	3						
Storsrud	Sweden	2003	40	3	Adults	20	large	GF	24						
Storsrud1	Sweden	2003	41	3	Adults	20	large	GF	24						
Guttormsen	Norway	2008	44	4	Adults	170	moderate	pure	unclear						
Kaukinen	Finland	2013	45	4	Adults	110	small	unclear	60						
Tapsas 2	Sweden	2014	10	4	Children	316	unclear	GF and no GF	NA						
Tuire	Finland	2012	46	4	Adults	177	unclear	unclear	NA						
Janatuinen	Finland	2000	30	5	Adults	92	moderate	GF	12						
Koskinen	Finland	2009	31	5	Children	23	moderate	GF	24						
Sjoberg	Sweden	2014	32	5	Children	28	moderate	pure	12						
Janatuinen	Finland	2002	43	6	Adults	63	moderate	unclear	60						
Kemppainen	Finland	2007	42	7	Adults	44	moderate	unclear	60						

*Study design; 1=Randomized controlled trial; 2= Non randomized controlled trial, 3=Before and after comparison; 4=Cross-sectional; 5= Post hoc from RCT; 6=Cohort; 7=Post-hoc cohort; GF gluten-free; GI= gastrointestinal symptoms

Green: no change in outcome after oats consumption, yellow: change of outcome in low proportion of patients; red: significant worsening after oat consumption.

Supplementary Table 3: Excluded studies

Author, yr	Reason for exclusion
1. Anonymous	Not original study-commentary
2. Arentz-Hansen H, 2004 (12)	Not clinical trial - study in vitro
3. Branski D, (14)	Not original study
4. Butzner JD (15)	Not original study
5. Campbell JA (13)	Not original study
6. Chaptal J (17)	Case series
7. Dissanayake (18)	Case report
8. Hardy M (19)	Not clinical trial - study in vivo
9. Emmanuel (20)	Not intended outcome
10. Hollen 2003 (21)	Not clinical study
11. Hollen 2006 (22)	Post- hoc analysis
12. Lovik 2009 (23)	Post –hoc analysis
13. Lovik	Abstract from Lovik 2009
14. Kemppainen 2010 (24)	Post-hoc analysis
15. Kumar 1995(25)	Not original study-commentary
16. Peraaho 2004 (26)	Not intended outcome
17. Sharkey 2012 (27)	Not intended intervention
18. Souza C (28)	Not original study
19. Tapsas D (29)	Not intended outcome
20. Tjellstrom (30)	Not intended outcome
21. Troncone R (31)	Not clinical trial
22. Van de Kamer 1953	Not intended comparison

Supplementary references:

- 13- Arentz-Hansen H, Fleckenstein B, Molberg O, et al. The Molecular Basis for Oat Intolerance in Patients with Celiac Disease. *PLoS Med.* 2004 Oct; 1(1): e1.
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- 15- Butzner JD. Pure oats and the gluten-free diet: are they safe? *JPEN J Parenter Enteral Nutr.* 2011 Jul;35(4):447-8.
- 16- Campbell JA. Foods for patients with celiac disease. *Can Med Assoc J.* 1982 Nov 15;127(10):963-5.
- 17- Chaptal J, Jean R, Dossa D, et al. Celiac disease caused by intolerance to gliadin from wheat, oats & milk products. *Pediatric.* 1957;12(7):737-47.
- 18- Dissanayake AS, Truelove SC, Whitehead R. Lack of harmful effect of oats on small-intestinal mucosa in coeliac disease. *Br Med J.* 1974 Oct 26;4(5938):189-91.
- 19- Hardy MY, Tye-Din JA, Stewart JA, et al. Ingestion of oats and barley in patients with celiac disease mobilizes cross-reactive T cells activated by avenin peptides and immuno-dominant hordein peptides. *J Autoimmun.* 2015 Jan; 56:56-65.
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- 21- Hollén E, Högberg L, Stenhammar L et al. Antibodies to oat prolamines (avenins) in children with coeliac disease. *Scand J Gastroenterol.* 2003 Jul;38(7):742-6.
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- 23- Lovik A, Gjoen AU, Morkrid L, Guttormsen V et al. Oats in a strictly gluten-free diet is associated with decreased gluten intake and increased serum bilirubin. *e-SPEN* 2009;4(6): 315-20.
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- 25- Khumar PJ, Farthing MGJ. Oats and celiac disease. *NEJM* 1995; 1075-6.
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- 30- Tjellström B, Stenhammar L, Sundqvist T, et al. The effects of oats on the function of gut microflora in children with coeliac disease. *Aliment Pharmacol Ther*. 2014 May;39(10):1156-60.
- 31- Troncone R, Auricchio S, De Vincenzi M, et al. An analysis of cereals that react with serum antibodies in patients with coeliac disease. *J Pediatr Gastroenterol Nutr*. 1987 May-Jun;6(3):346-50.