



Microbiota signatures and mucosal healing in the use of enteral nutrition therapy v. corticosteroids for the treatment of children with Crohn's disease: a systematic review and meta-analysis

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(Submitted 11 September 2022 – Final revision received 28 January 2023 – Accepted 6 February 2023 – First published online 15 February 2023)

Abstract

Corticosteroids (CS) and exclusive and partial enteral nutrition (EEN and PEN) are effective therapies in paediatric Crohn's disease (CD). This systematic review of randomised controlled trials (RCT) and cohort studies analyses the impact of EEN/PEN v. CS on intestinal microbiota, mucosal healing as well as other clinically important outcomes, including clinical remission, relapse, adherence, adverse events and health-related quality of life (HRQL) in paediatric CD. Three RCT (n 76) and sixteen cohort studies (n 1104) compared EEN v. CS. With limited available data (one RCT), the effect on intestinal microbiome indicated a trend towards EEN regarding Shannon diversity. Based on two RCT, EEN achieved higher mucosal healing than CS (risk ratio (RR) 2.36, 95 % CI (1.22, 4.57), low certainty). Compared with CS, patients on EEN were less likely to experience adverse events based on two RCT (RR 0.32, 95 % CI (0.13, 0.80), low certainty). For HRQL, there was a trend in favour of CS based on data from two published abstracts of cohort studies. Based on thirteen cohort studies, EEN achieved higher clinical remission than CS (RR 1.18, 95 % CI (1.02, 1.38), very low certainty). Studies also reported no important differences in relapse and adherence. Compared with CS, EEN may improve mucosal healing with fewer adverse events based on RCT data. While limited data indicate the need for further trials, this is the first systematic review to comprehensively summarise the data on intestinal microbiome, mucosal healing and HRQL when comparing enteral nutrition and CS in paediatric CD.

Key words: Systematic review: Child: Inflammatory bowel disease: Enteral nutrition: Corticosteroids: Effectiveness

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory condition of the digestive tract^(1,2). As a type of IBD, Crohn's disease (CD) has no proven cure and can impact proper digestion and absorption, which can result in malnutrition in children^(1–3). Exclusive enteral nutrition (EEN) and corticosteroids (CS) are both proven to be effective therapies for the induction of remission in paediatric CD^(4–6). The use of CS has raised concerns due to possible side effects, including reduced bone density and growth delay⁽⁷⁾. Given the safety concerns, there has been an increasing interest in the use of EEN to induce remission of active CD. EEN may have a profound impact on microbiota diversity and inflammation marker

levels^(8–10). However, conflicting results exist in previous studies^(11–13). Furthermore, the implementation of EEN is challenging as it commonly requires the use of a nasogastric feeding tube for 6–8 weeks along with avoidance of other food intake, which may reduce the compliance of the child and family^(14,15). To improve adherence, more studies have focused on partial enteral nutrition (PEN), which allows children to take some whole food alongside an enteral formula⁽¹⁶⁾. Recent studies in adults and children reported that PEN could be as effective as EEN in inducing clinical and endoscopic remission in children with active CD, and PEN was better tolerated by paediatric patients^(14,16–19).

Abbreviations: CD, Crohn's disease; CS, corticosteroids; EEN, exclusive enteral nutrition; FC, faecal calprotectin; HRQL, health-related quality of life; IBD, inflammatory bowel disease; MD, mean difference; PCDAI, Pediatric Crohn's Disease Activity Index; PEN, partial enteral nutrition; RCT, randomised controlled trial; RoB, risk of bias; RR, risk ratio; SMD, standardised mean difference.

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The mechanism underlying the clinical effectiveness of EEN and PEN in paediatric IBD patients remains unclear. One hypothesis is that EEN and PEN may induce changes in the faecal microbiome and this could promote remission⁽¹⁴⁾. Recent data in humans illustrate that dysbiosis plays an important role in the development of IBD⁽¹⁾, and enteral nutrition may have a profound impact on the microbiota diversity^(8–10). A previous systematic review compared the effectiveness of EEN and PEN *v.* CS, but the authors mostly focused on the clinical remission of CD⁽⁷⁾. In addition to intestinal microbiota, more recently, mucosal healing is an outcome that is gaining acceptance as a recommended measure of disease activity in CD^(6,20). Two systematic reviews assessed mucosal healing between EEN and CS in the paediatric population but did not consider the effect of EEN or PEN on intestinal microbiota^(21,22).

We conducted a systematic review and meta-analysis to determine the impact of both EEN and PEN *v.* CS in children with active luminal CD on intestinal microbiota, mucosal healing, clinical remission, relapse of active disease, post-treatment weight, faecal calprotectin (FC), health-related quality of life (HRQL), adherence to the assigned intervention and adverse events up to 12 months following initial treatment.

Materials and methods

Study selection and patient population (inclusion and exclusion criteria)

Our study protocol was registered on PROSPERO (CRD42021254082). We considered both randomised controlled trials (RCT) and cohort studies in children (≤ 18 years of age) with newly diagnosed or active luminal CD according to the Pediatric Crohn's Disease Activity Index (PCDAI), defined as a score >10 , or alternatively, other clearly defined definitions of newly diagnosed or active CD by investigators. Studies that compared the administration of any type of enteral nutrition (*i.e.* elemental, semi-elemental or polymeric) to CS (*e.g.* methylprednisolone, prednisone or hydrocortisone) were considered for inclusion. Randomised trials and cohort studies were analysed separately. We excluded the following types of studies: trials allowing oral intake other than clear liquids in EEN treatment, trials allowing co-interventions with antibiotics and having outcomes of microbiota analysis and trials not defining CD activity and remission.

Data sources and search strategy

We searched the following five databases from inception until 3 February 2021: Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL) and Clinicaltrials.gov. The references of eligible studies and review articles were searched to identify additional studies. Abstracts or posters without published full-text articles were excluded as the preliminary results often differ from final published reports⁽²³⁾. For our target outcomes, authors were contacted for additional unpublished results, including missing outcome data. Our review had no language restrictions. Google Translate tool was used to translate articles written in non-English languages. If further clarification was required, we considered contacting translators/authors.

Outcome measures

Our primary outcomes included intestinal microbiome signatures (*e.g.* sequencing with 16S ribosomal RNA gene) and mucosal healing rate (endoscopy score)^(4,8–13). Data on α -diversity metrics (*e.g.* relative abundance and Shannon diversity index) and β -diversity metrics (*e.g.* Bray–Curtis index to visualise clustering) were also collected for our outcome of microbiome signatures⁽²⁴⁾. Shannon diversity index, clustering and relative abundance of bacterial genera if available were described as continuous variables. Mucosal healing was defined as complete endoscopic remission using the Simple Endoscopic Score for Crohn Disease (SES-CD) of 0⁽²⁵⁾. When SES-CD scores were not reported, other clear definitions for mucosal healing were also considered (*e.g.* the Crohn's Disease Endoscopic Index of Severity less than 3 points or a drop of $>70\%$ at follow-up endoscopy)^(8,26). Our primary outcomes were assessed at 4–12 weeks after therapy initiation.

Our secondary outcomes included clinical remission (4–12 weeks after induction therapy) and clinical relapse rate (at a 6–12-month time-point). Remission and relapse were measured using the PCDAI score (remission was defined as <15 points, or <7.5 points without the height component of the index) or using other clearly defined author definitions (*e.g.* short PCDAI, abbreviated PCDAI and Lloyd-Still disease activity index)^(27–30). Clinical relapse was defined as the occurrence or worsening of symptoms accompanied by a PCDAI score >10 points in a patient who had previously reached clinical remission⁽³¹⁾. Other secondary outcomes included nutritional status (*i.e.* weight in both kg and Z-score measurements), FC level (*i.e.* a biochemical marker of inflammation to implicate disease activity), adherence (*i.e.* withdrawal rates), adverse events and HRQL (*e.g.* IMPACT I–III questionnaire or other validated health status measurements) at 4–12 weeks after induction therapy^(7,32–37).

Data screening (eligibility assessment) and data extraction

Titles and abstracts were independently screened by two reviewers. If inclusion criteria were met, publications were exported, screened and carried onto independent full-text screening. Discrepancies between reviewers on inclusion and exclusion decisions were resolved among themselves, and a third reviewer was involved if consensus was not reached. A piloted data collection form was used to independently extract data and assess the risk of bias (RoB) in duplicate. Data were extracted for study population characteristics, study design details, information on administration or exposure to EEN/PEN and CS, and eligible outcomes.

Quality assessment

Two reviewers independently appraised the RoB using the Cochrane RoB tool for randomised trials (RoB 2.0)⁽³⁸⁾, while the RoB for non-randomised studies of interventions (ROBINS-I) tool was used to assess cohort studies⁽³⁹⁾. Overall ratings of 'low', 'some concerns' or 'high' were determined for each domain within the RoB 2.0 tool. Ratings of 'low', 'moderate', 'serious' or 'critical' were determined for each domain within the

ROBINS-I tool. We resolved any discrepancies through discussion between the two reviewers and, when necessary, through consultation with a third senior methodologist.

Data synthesis

We analysed aggregated data through quantitative synthesis. A random effects meta-analysis was performed due to potential heterogeneity between studies. The I^2 statistic and inconsistency between studies using forest plots were used to assess heterogeneity⁽⁴⁰⁾.

Data permitting, for cohort studies, we planned to pool adjusted and unadjusted effect sizes separately. For dichotomous outcomes, pooled risk ratios (RR) and 95 % CI were calculated (e.g. mucosal healing, clinical remission, relapse, adherence and adverse events). For continuous outcomes (e.g. microbiota diversity, bacterial abundance, FC level, HRQL score and weight), we pooled mean difference (MD) with a standard deviation or standardised mean differences (SMD) with corresponding 95 % CI. Cohen's D scores, were used to determine the effect of SMD estimates⁽⁴¹⁾.

As an a priori decision, subgroup analyses were planned for the effect of: (1) EEN *v.* CS and PEN *v.* CS separately, (2) mild to moderate CD *v.* severe CD and (3) newly diagnosed CD *v.* all active CD (including previously diagnosed patients) as outcomes may differ based on previous studies^(4,8,14,42,43). Sensitivity analyses removing studies that are high RoB studies for each outcome were also considered. Publication bias was considered using funnel plots if there were >10 included studies for an outcome^(44,45). All analyses were performed using Review Manager (RevMan) Version 5.3 and Stata 16.0.

Assessment of certainty of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool was used to assess the certainty of evidence for the included outcomes⁽⁴⁶⁾. Two review authors independently assessed the certainty of evidence as high, moderate, low or very low using the GRADE approach, which included assessments of RoB, inconsistency, imprecision, indirectness and publication bias.

Results

Characteristics and risk of bias of included studies

Our search (online Supplementary Table 1) retrieved a total of 3272 articles (Fig. 1). After excluding duplicates, we screened 2420 titles and abstracts and reviewed seventy-seven full-text articles for potential eligibility (Fig. 1). Details on important excluded studies are available in online Supplementary Table 2. A total of nineteen studies on patients with CD were included in our systematic review (Table 1). Three studies were RCT (n 76) that assigned participants to receive EN or CS, while the remaining sixteen studies (n 1104) were cohort studies that observed the effect of EN *v.* CS (five of these were prospective while eleven were retrospective) (Table 1). All nineteen studies considered the use of EEN, while CS type and dosage varied (Table 1). None of nineteen studies reported on PEN *v.* CS.

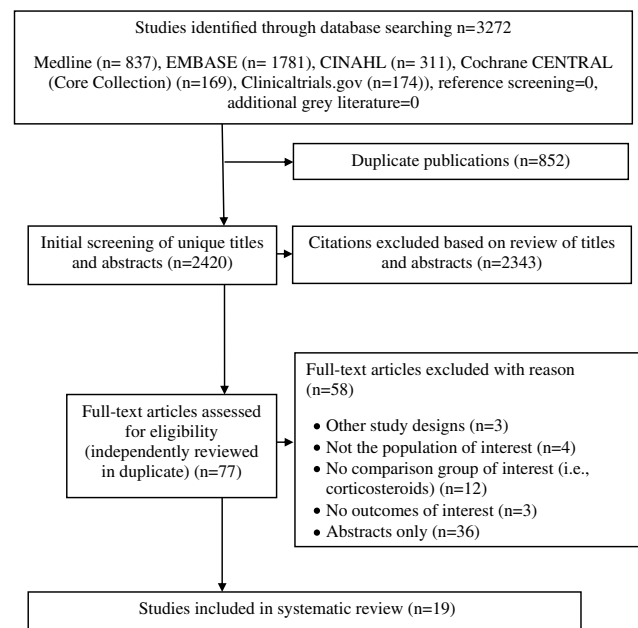


Fig. 1. Flow diagram of the study selection process.

Using the Cochrane RoB 2.0 tool for RCT, three studies had 'some concerns' or 'high RoB' for each outcome when comparing EEN *v.* CS, particularly with respect to bias in the randomisation process and bias in measurement of outcomes (Fig. 2). Similarly, sixteen cohort studies were at serious RoB for each of the outcomes due to a lack of measurement/control of important confounders (Fig. 3).

With regard to subgroup analysis, no studies reported on the use of PEN *v.* CS, or mild to moderate CD *v.* severe CD, so a priori subgroup analyses were not completed. Two RCT enrolled patients with newly diagnosed CD only^(8,42), while one RCT enrolled all active CD⁽⁴⁷⁾. Furthermore, ten cohort studies included patients with newly diagnosed CD only, while the remaining six cohort studies included patients with all active CD (Table 1). Sensitivity analyses based on the RoB were not conducted based on a priori decision in the protocol as no studies had a low RoB.

Effects of interventions

Microbial signatures. One RCT (n 19, 19 CD) and one cohort study (n 30, 20 CD, 10 UC) assessing EEN *v.* CS reported on stool microbial diversity and bacterial abundance^(4,8). In the RCT (n 19), Shannon diversity index, which was assessed in four patients in each group, suggested that microbial α -diversity tended to increase after EEN therapy (from 3.82 to 5.0), whereas the change was minimal on steroid therapy (from 5.39 to 5.75)⁽⁸⁾. The RCT also reported on β -diversity index based on principal components analysis of dominant microbiota composition, indicating a significant clustering before treatment and during CS or EEN treatment. Concerning bacterial abundance at genus and species levels measured at 8 weeks, both EEN (n 4) and CS (n 4) groups caused significant changes in the microbiota composition after treatment (Table 2).

Table 1. Characteristics of included studies

Study, year	Study design	Indication	Follow-up period(s)	Intervention	Control	Outcome and description
Hart <i>et al.</i> , 2020 ⁽⁴⁾	Prospective cohort	Active CD patients	8 weeks	EEN (polymeric formula) administered through a nasogastric tube for 8 weeks	Methylprednisolone (1 mg/kg per d, with a maximum dose of 40 mg/d). Once symptoms improved, patients were transitioned to oral CS and discharged home, followed by a progressive wean by 5 mg/week	• Microbiota changes, including Shannon diversity, β-diversity metrics, and bacteria composition • Clinical remission was defined as a PCDAI score <10
Scarpato <i>et al.</i> , 2020 ⁽³¹⁾	Retrospective cohort	Active CD patients (mild, moderate and severe CD)	8 weeks and 1 year	EEN (polymeric formula) administered orally or through a nasogastric tube for 8 weeks followed by a gradual introduction of foods during the subsequent 4 weeks	Oral methylprednisolone (1 mg/kg per d with a maximum dose of 40 mg/d) for 4 weeks, followed by a gradual tapering off by week 11	• Clinical remission was defined as a PCDAI score <10 with the absence of symptoms • Relapse at 12 months was defined as the occurrence or worsening of symptoms accompanied by a PCDAI score >10, in patients who had already reached clinical remission • Faecal calprotectin was measured using laboratory parameters • Weight after induction therapy (Z-score)
Pigneur <i>et al.</i> , 2019 ⁽⁸⁾	RCT	Newly diagnosed CD patients	8 weeks	EEN (formula not specified) delivered orally or by tube feeding for 8 weeks	Prednisone (1 mg/kg per d with a maximum dose of 60 mg/d) for 4 weeks, followed by tapering	• Microbiota changes, including Shannon diversity, β-diversity metrics, and bacteria composition • Mucosal healing was defined as CDEIS <3 points or a drop of >70 % at follow-up endoscopy compared with the initial diagnostic endoscopy • Clinical remission was defined as an HBI <5 • Clinical remission was defined as a PCDAI score <10
Kang <i>et al.</i> , 2019 ⁽⁵¹⁾	Retrospective cohort	Newly diagnosed CD patients	8 weeks	EEN (polymeric formula) administered orally for 8 weeks	Prednisone (1 mg/kg per d) for 4 weeks and had been weaned over a subsequent 2–4 weeks	• Clinical remission was defined as a PCDAI score <10
Cohen-Dolev <i>et al.</i> , 2018 ⁽⁴⁹⁾	Prospective cohort	Newly diagnosed CD patients (mild and moderate CD only)	8, 12, 78, and 104 weeks	EEN (any formula) provided orally or by a nasogastric tube for 6–8 weeks	Prednisone or methylprednisolone (1–1.5 mg/kg per d) to be tapered by Week 11	• Clinical remission was defined as a PCDAI score <10
Lafferty <i>et al.</i> , 2017 ⁽⁵³⁾	Retrospective cohort	Newly diagnosed CD patients (mild, moderate and severe CD)	8 and 52 weeks	EEN (polymeric or elemental) administered either orally or via a feeding tube for 6–8 weeks	Prednisolone (1 mg/kg per d with a maximum dose of 40 mg/d) for 4 weeks, followed by a weekly 5 mg wean over a subsequent 7 weeks	• Clinical remission was defined as a PCDAI score <10 • Weight after induction therapy (Z-score) • Relapse at 12 months was defined as an increase in disease activity necessitating a repeat course of EEN or CS, an escalation of medical treatment or surgery • Clinical remission was defined as a PCDAI score <7.5
Connors <i>et al.</i> , 2017 ⁽⁵⁰⁾	Retrospective cohort	Newly diagnosed CD patients (mild, moderate and severe CD)	8 weeks and follow-up at 6 years	EEN (formula not specified) administered via nasogastric tube and treated for 8–16 weeks	Prednisone (dose not specified) for 4–12 weeks	• Weight after induction therapy (Z-score)
Hradsky <i>et al.</i> , 2016 ⁽⁵⁷⁾	Retrospective cohort	Newly diagnosed CD patients	Week 6–12 and 40 months	EEN (any polymeric enteral formula) delivered orally or through a nasogastric tube for 6–10 weeks	Prednisolone (1–2 mg/kg per d, up to 40 mg/d and exceptionally 60 mg/d) for approximately 8 weeks with slow tapering	• Weight after induction therapy (Z-score)

Table 1. (Continued)

Study, year	Study design	Indication	Follow-up period(s)	Intervention	Control	Outcome and description
Luo <i>et al.</i> , 2015 ⁽⁵⁸⁾	Retrospective cohort	Newly diagnosed CD patients (mild and moderate CD only)	9.6 weeks	EEN (polymeric formula) administered orally for 8 weeks	Prednisone/hydrocortisone for 8 weeks	• Clinical remission was defined as a PCDAI score <10
Hojdak <i>et al.</i> , 2014 ⁽⁴³⁾	Retrospective cohort	Active CD patients (mild, moderate and severe CD)	12 months	EEN (polymeric formula) administered orally or through a nasogastric tube for 6–8 weeks	'Conventional CS' was used as remission induction therapy	• Clinical remission was defined as a PCDAI score <10 • Relapse at 12 months was defined as a PCDAI > 10 and need for the use of remission induction therapy
Levine <i>et al.</i> , 2014 ⁽⁵⁴⁾	Prospective cohort	Newly diagnosed CD patients (mild and moderate CD only)	8, 12 and 52 weeks	EEN therapy group was given polymeric formula for 6–8 weeks	Prednisone (1–2 mg/kg, with a maximum of 60 mg/d)	• Clinical remission was defined as a PCDAI score <10 or <7.5 • Faecal calprotectin was measured using calprotectin assay kits
Soo <i>et al.</i> , 2013 ⁽⁵⁶⁾	Retrospective cohort	Newly diagnosed CD patients (mild, moderate and severe CD)	6–8 weeks and 12 months	EEN (polymeric or semi-elemental formula) for 6 weeks and then partially over the next 2 weeks	Prednisone (1 mg/kg per d, with a maximum dose of 50 mg/d) for 4 weeks and then weaned over the next 6–8 weeks	• Clinical remission was defined as a PCDAI score <10 • Relapse at 12 months was defined as a PCDAI score >10 on a subsequent visit after achieving remission
Kierkus <i>et al.</i> , 2013 ⁽⁵²⁾	Prospective cohort	Active CD patients (moderate and severe CD only)	8 and 52 weeks	EEN (formula not specified) provided orally or by a nasogastric tube for 6 weeks	'Conventional steroid therapy'	• Clinical remission was defined as a PCDAI score <10 • Weight after induction therapy (kg)
Lambert <i>et al.</i> , 2012 ⁽²⁹⁾	Retrospective cohort	Newly diagnosed CD patients	6 months, 6–12 months and 12–24 months following diagnosis	EEN (polymeric formula) administered for 6–8 weeks, after completion of EEN a normal diet was reintroduced gradually	Prednisone as sole therapy for induction was considered	• Relapse at 12 months was defined as an increase in disease activity necessitating a change in management
Borrelli <i>et al.</i> , 2006 ⁽⁴²⁾	RCT	Newly diagnosed CD patients (moderate and severe CD only)	10 weeks	EEN (polymeric diet), administered orally or through a nasogastric tube for 10 weeks	Methylprednisolone (1.6 mg/kg per d, with a maximum allowed dose of 60 mg/d) for 4 weeks, followed by a 6-week tapering course until a dose between 5 and 10 mg/d was reached	• Mucosal healing was defined as a decrease in both endoscopic and histologic scores by 50 % or more when compared with baseline values • Clinical remission was defined as a PCDAI score <10 and absence of symptoms • Weight after induction therapy (kg)
Canani <i>et al.</i> , 2006 ⁽⁴⁸⁾	Retrospective cohort	Newly diagnosed CD patients	8 weeks and follow-up at 1 year	EEN (polymeric diet) administered orally, whereas the other formulas were administered through a nasogastric tube for 8 weeks	Methylprednisolone (1–2 mg/kg per d, with a maximal dose of 40 mg/d) for 4 weeks with subsequent gradual tapering over another 4 weeks	• Mucosal healing was defined as improvement in endoscopic and histological scores by a reduction ≥ 1 grade on validated endoscopic/histological tools • Clinical remission was defined as a PCDAI score <10 • Relapse at 12 months was defined as a PCDAI score >10
Terrin <i>et al.</i> , 2002 ⁽⁴⁷⁾	RCT	Active CD patients	8 weeks	EEN (polymeric formula) administered through a nasogastric tube for 8 weeks	Methylprednisolone (1.6 mg/kg per d) for 4 weeks and tapering for 4 more weeks	• Clinical remission was defined as a PCDAI score <10

Table 1. (Continued)

Study, year	Study design	Indication	Follow-up period(s)	Intervention	Control	Outcome and description
Azcue <i>et al.</i> , 1997 ⁽³⁶⁾	Prospective cohort	Active CD patients (moderate and severe CD only)	12 weeks	EEN (formula not specified), administered through a nasogastric tube for 5–6 weeks but discontinued after a maximum of 8 weeks	Prednisolone (1 mg/kg per d) for 1 month and then a gradual daily reduction by 5 mg/week over the next 8 weeks	• Weight after induction therapy (kg)
Papadopoulou <i>et al.</i> , 1995 ⁽²⁸⁾	Retrospective cohort	Active CD patients	22 months	EEN (elemental formula) administered orally or through a nasogastric tube for 8 weeks	Prednisolone (2 mg/kg per d up to a maximum dose of 60 mg/d). The dose was reduced gradually according to the clinical response of patients	• Clinical remission was defined as a Lloyd-Still disease activity index score >80

CD, Crohn's disease; EEN, exclusive enteral nutrition; CS, corticosteroids; PCDAI, Pediatric Crohn's Disease Activity Index; RCT, randomised controlled trial; CDEIS, Crohn's disease index of severity; HBI, Harvey–Bradshaw Index.

Another cohort study with twenty CD patients reported microbiota Shannon diversity index, clustering and relative abundance but did not provide specific values for each group⁽⁴⁾. The study noted a significant increase in Shannon diversity over time after treatment ($P=0.006$) in both EEN and CS treatments, but the increase did not differ between the groups. Based on the principal coordinates analysis for bacterial abundance, tighter clustering was observed at the end of treatment when compared with stool microbiota at baseline, independent of treatment type. Patients treated with EEN ($n=16$) showed a marked depletion in the *Fusobacterium*, *Escherichia/Shigella* and *Veillonella* genera, while patients treated with CS ($n=4$) showed reductions in the *Alistipes*, *Veillonella* and *Fusobacterium* genera.

Meta-analysis and forest plots were not generated for the two microbiome signature studies due to limited available data.

Mucosal healing. Two RCT with fifty-six participants provided data on mucosal healing^(8,42). We found an RR of 2.36 (95 % CI (1.22, 4.57); $I^2=0\%$) (Table 3, Fig. 4). In absolute effects, forty more children had mucosal healing per 100 children receiving EEN (95 % CI, from 6 more to 100 more) (Table 3), a moderate effect size based on low certainty of evidence. Subgroup analysis could not be completed as both studies were from the newly diagnosed CD group.

Only one retrospective cohort study with forty-seven participants reported on mucosal healing⁽⁴⁸⁾. From this study, based on very low certainty of evidence, we found a RR of 1.76 (95 % CI (0.80, 3.86)) and a corresponding risk difference indicating that thirty more children will experience mucosal healing per 100 children receiving EEN (95 % CI from 8 fewer to 100 more) (Table 3, Fig. 4).

Clinical remission. Remission was assessed in three RCT^(8,42,47) and thirteen cohort studies^(4,28,31,43,48–56). When considering RCT evidence, seventy-six participants provided data. From the pooled analysis, we calculated a RR of 1.28 (95 % CI (0.99, 1.67); $I^2=0\%$, very low certainty of evidence), which in absolute effects means eighteen more children had remission per 100 children receiving EEN (from 1 fewer to 43 more) (Table 3, Fig. 4).

When considering cohort studies, based on thirteen studies, a total of 958 participants were included in the pooled analysis. We calculated a RR of 1.18 (95 % CI (1.02, 1.38); $I^2=73\%$, very low certainty of evidence), which in absolute effects means twelve more children will experience remission per 100 children receiving EEN (from 1 more to 24 more) (Table 3). However, there was substantial heterogeneity present for this outcome ($I^2=73\%$). The test of interaction for the subgroup analysis based on newly diagnosed CD *v.* all active CD was not significant in cohort studies ($P=0.59$), and heterogeneity remained within the newly diagnosed CD group, suggesting the heterogeneity was not well explained by this subgroup analysis (Fig. 4). Furthermore, there were concerns regarding publication bias ($P=0.005$) (Fig. 5).

Relapse. For relapse at 12 months, we found six cohort studies^(29,31,43,48,53,56) with 395 children that found an overall RR of 0.76 (95 % CI (0.56, 1.03); $I^2=56\%$, very low certainty of evidence) (Fig. 4). As compared with CS, there were twelve fewer (22 fewer to 2 more) relapse events per 100 patients followed in



Study, Year	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Mucosal healing:					
Pigneur 2019	●	?	●	●	?
Borelli 2006	?	●	●	?	●
Remission:					
Pigneur 2019	●	?	●	?	●
Borelli 2006	?	●	●	?	●
Terrin 2002	?	●	●	?	●
Weight after induction therapy:					
Borelli 2006	?	●	●	●	●
Microbiota diversity:					
Pigneur 2019	●	?	●	●	●
Adherence:					
Terrin 2002	?	●	●	?	●
Borelli 2006	?	●	●	?	●
Adverse events:					
Terrin 2002	?	●	●	?	●
Borelli 2006	?	●	●	?	●

Legend: low risk- ● some concerns- ? high risk- ●

Fig. 2. Risk of bias summary of included randomised controlled trials.

the EEN intervention group (Table 3). Subgroup analysis for newly diagnosed *v.* all active CD found no statistically significant effect ($P=0.23$) between the two groups. Substantial heterogeneity was still present in the newly diagnosed CD group, and significant heterogeneity for the overall effect ($I^2=56\%$) was not well explained (Fig. 4). No RCT evidence was available for this outcome.

Nutritional status. One RCT reported on post-treatment weight for thirty-two children⁽⁴²⁾. The SMD in post-treatment weight was 0.74 SD units lower in the EEN group (SMD -0.74, 95% CI (-1.46, -0.02), very low certainty of evidence) than the CS group (Fig. 4). When the MD was described as a weighted MD, the EEN group achieved a 2.40 kg lower post-treatment weight compared with the CS group (MD -2.40, 95% CI (-4.59, -0.21)). Among the four cohort studies with 183 children reporting on post-treatment weight^(30,52,53,57), we found a lower SMD of 0.26 SD units in the EEN group compared with the CS group (SMD -0.26, 95% CI (-0.54, 0.04); $I^2=1\%$, very low certainty of evidence) (Table 3). When the MD was described as a weighted MD in two cohort studies ($n=62$)^(30,52), the EEN group achieved a 5.20 kg lower post-treatment weight compared with CS group (MD -5.20, 95% CI (-14.11, 3.71)). When the MD was described as a weighted MD for Z-score in another two cohort studies ($n=121$)^(53,57), the EEN group achieved 0.22 lower post-treatment weight compared with CS group (MD -0.22, 95% CI (-0.74, 0.31)).

Faecal calprotectin. Two cohort studies considered our outcome measuring FC levels^(31,54). Meta-analyses were not feasible as data were available as medians accompanied by a range. Both

studies simply reported non-significant differences in FC values at week 8 since diagnosis of CD (Levine *et al.*, (1736 (617–2000) $\mu\text{g/g}$ in EEN group and 558 (162–1848) $\mu\text{g/g}$ in CS group)⁽⁵⁴⁾; Scarpato *et al.*, 291.5 (15–1470) $\mu\text{g/g}$ in EEN group and 435 (20–610) $\mu\text{g/g}$ in CS group⁽³¹⁾). No forest plots were generated from the FC studies due to limited data.

Adherence (withdrawal rate). The outcome of adherence to the intervention was reported in two RCT with fifty-seven participants^(42,47) and two cohort studies with 168 participants^(29,50). In two RCT, we calculated a RR of 0.95 (95% CI (0.15, 6.03), very low certainty of evidence), which in absolute effects means no more (0) children had withdrawal per 100 children receiving EEN (from 6 fewer to 36 more) (Table 3). In two cohort studies, we calculated a RR of 3.06 (95% CI (0.36, 26.23), very low certainty of evidence), which in absolute effects means no more (0) children will have withdrawal per 100 children receiving EEN as there were no events in the control group (Table 3). No significant heterogeneity was present for this outcome ($I^2=0\%$). The reasons for withdrawal in EEN group were inability to introduce the formula, intolerance of the nasogastric tube feeding and development of an enterovesical fistula. The reason for two withdrawal events in the steroid therapy group was the worsening of disease activity.

Adverse events. We found two RCT ($n=52$)^(42,47) and two cohort studies ($n=75$) reported on this outcome^(48,58). When considering RCT evidence, we found a RR of 0.32 (95% CI (0.13, 0.80), low certainty of evidence) (Table 3). In absolute effects, when compared with CS, there were thirty fewer (38 fewer to 9 fewer) patients with adverse events per 100 patients in the EEN group

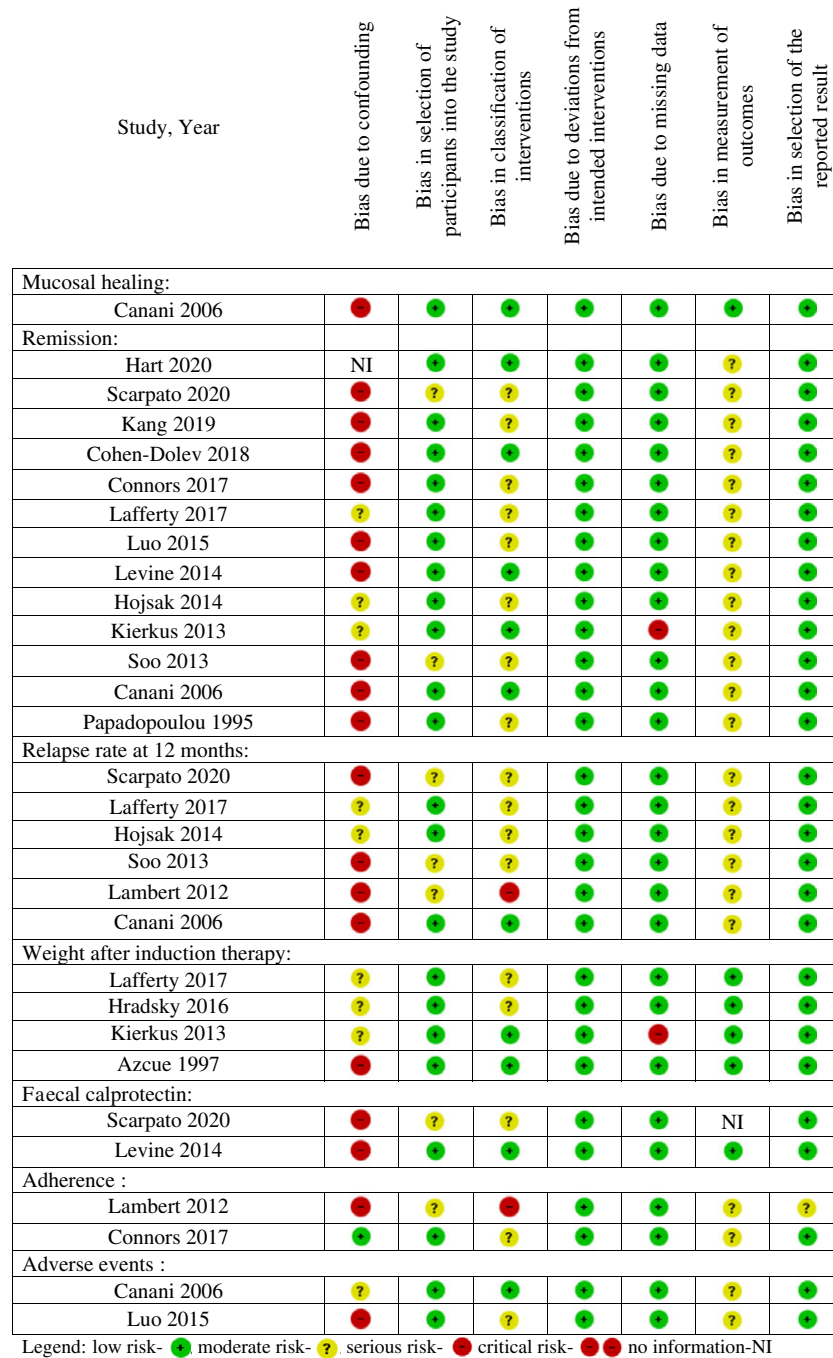


Fig. 3. Risk of bias summary of included cohort studies.

(Table 3). When considering cohort studies, as compared with CS, there was a RR of 0.19 (95 % CI (0.02, 2.26), very low certainty of evidence), which means sixty-four fewer (77 fewer to 99 more) patients with adverse events per 100 patients in the EEN group (Table 3). Significant heterogeneity for the overall effect ($I^2 = 71\%$) was not explained, and subgroup analyses were not feasible due to a limited number of studies (Fig. 4).

Adverse events described in the EEN group are abdominal pain/discomfort, nausea, vomiting, flatulence, diarrhoea and insomnia, whereas, in the CS group, adverse events described

include abdominal pain, nausea and/or vomiting, flatulence, insomnia, cushingoid appearance, acne, skin striae, hirsutism, myopathy/muscle weakness, headache, depression, hyperglycaemia and osteoporosis. No serious adverse event was reported.

Health-related quality of life. No studies that met our eligibility criteria reported on the HRQL outcome, and no forest plots were generated due to limited data. A list of important excluded studies (e.g. abstract only) can be found in online Supplementary



Table 2. The results of the microbiota outcome before and after treatment in EEN and CS groups

Study	α -diversity index (Shannon)	β -diversity index	Bacterial abundance at the genus level	Bacterial abundance at the species level
Pigneur <i>et al.</i> , 2019 ⁽⁸⁾ (RCT)	EEN (n 4): ↑ from 3.82 to 5.0; CS (n 4): ↑ from 5.39 to 5.75 (minimal change)	EEN or CS: significant clustering before and during treatment (P = 0.049)	EEN (n 4): ↑ <i>Clostridium XIVa</i> ; ↓ <i>Faecalibacterium</i> and <i>Roseburia</i> CS (n 4): ↑ <i>Ruminococcus</i> ↓ <i>Roseburia</i>	EEN (n 4): ↑ <i>Clostridium symbiosum</i> , <i>C. ruminantium</i> , <i>Ruminococcus torques</i> , <i>Ruminococcus gnavus</i> and <i>Clostridium hathewayi</i> CS (n 4): ↑ <i>Bacterium M62</i> , <i>A186</i> , <i>Roseburia intestinalis</i> , <i>Eubacterium</i> and <i>Bifidobacterium bifidum</i>
Hart <i>et al.</i> , 2020 ⁽⁴⁾ (Cohort)	EEN (n 16): ↑ CS (n 4): ↑	EEN (n 16) and CS (n 4): tighter and greater clustering	EEN (n 16): ↓ <i>Fusobacterium</i> , <i>Escherichia/Shigella</i> and <i>Veillonella</i> CS (n 4): ↓ <i>Alistipes</i> , <i>Veillonella</i> and <i>Fusobacterium</i>	

RCT, randomised controlled trial; EEN, exclusive enteral nutrition; CS, corticosteroids.

Table 2. Based on the published abstracts, one prospective cohort study of thirty-one children reported a small but significant difference in generic HRQL (KIDSCREEN-10 index) between the children on CS (higher HRQL) *v.* those on EEN (MD 2.24 points, 95 % CI (0.34, 4.15))⁽⁵⁹⁾. The MD and 95 % CI in the abstract were lower than the minimal important difference estimate of 4.53 obtained from parental ratings of KIDSCREEN-10 index⁽⁶⁰⁾. Another prospective cohort study (n 64) did not find a significant difference in the disease-specific HRQL score between children receiving either EEN or CS⁽⁶¹⁾.

Discussion

Summary of main results and certainty of evidence

Our systematic review found three RCT and sixteen cohort studies having evaluated enteral nutrition in children with CD. Among two RCT (n 56)^(8,42) based on low certainty of evidence, at 4–12 weeks after induction EEN may result in an increase in mucosal healing in 40 per 100 children followed (from 6 more to 100 more) when compared with CS. Based on three RCT (n 76)^(8,42,47), eighteen more children had clinical remission per 100 children receiving EEN (from 1 fewer to 43 more), based on very low certainty of evidence. In one RCT (n 32)⁽⁴²⁾, we found that children on EEN experienced 2.40 kg lower post-treatment weight as compared with CS alone (4.59 lower to 0.21 lower), based on very low certainty evidence. Among two RCT (n 52) on EEN therapy^(42,47), thirty fewer children per 100 followed (38 fewer to 9 fewer) were likely to experience adverse events based on low certainty evidence. On the basis of very low certainty of evidence, no significant effect on adherence outcome was detected^(42,47). With respect to intestinal microbial signatures described in one RCT⁽⁸⁾, a narrative synthesis was completed due to limited available data. Although the effect on the Shannon diversity seems to indicate a trend towards EEN, it is not possible to conclude the efficacy of treatment based on the very limited sample size.

When reviewing cohort studies (n 1104 participants), twelve more children had clinical remission per 100 children receiving EEN (from 1 more to 24 more), but the certainty of evidence is

very low^(4,28,31,43,48–56). In addition, the evidence is very uncertain for the effect of EEN on mucosal healing⁽⁴⁸⁾, relapse at 12 months^(29,31,43,48,53,56), post-treatment weight^(30,52,53,57), and adherence^(8,50), and adverse events^(48,58). With regard to intestinal microbial signatures, HRQL and FC^(4,31,54), a narrative synthesis was completed due to a lack of available data, and the potential effects were unclear.

Strengths and limitations

Strengths of our systematic review included a comprehensive search of five databases as well as the use of internationally recognised tools to assess RoB and certainty of evidence^(38,39). We also considered two study designs and nine outcomes to provide a more comprehensive understanding of the literature on enteral nutrition therapy in paediatric CD. This is the first systematic review to compare stool microbiome and HRQL between enteral nutrition and CS in paediatric CD. However, limitations to the data presented are important to consider. First, for most included studies with limited sample size, especially observational studies, important baseline confounding factors such as disease severity, concomitant medications and anthropometric measurements are important to consider^(31,43,54,57,62). Sixteen cohort studies were at serious risk due to a lack of measurement/control of these important confounders. Therefore, the results from the cohort studies should be interpreted with caution, although underpowered and small studies should still be used as the best available evidence⁽⁶³⁾. Second, our review did not address the cost-effectiveness analysis of EEN *v.* CS in patients with CD, which may have important clinical considerations when assigning patients to the induction therapy⁽⁶⁴⁾. Finally, although the authors were contacted, we were not able to obtain complete information on microbiota signatures from two studies, which may have provided additional data for our quality assessment and meta-analysis.

Meaning of the study and relation to previous studies

Treatments for induction of remission in children with active CD include enteral nutrition, CS and biologic agents⁽³⁾. Recently, enteral nutrition has been recommended as primary therapy

Table 3. Summary of findings (95 % confidence intervals)

Certainty assessment							No. of patients (%)				Effect				95 % CI	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EEN	CS	Relative	95 % CI	Relative	95 % CI	Absolute				
Mucosal healing (RCT) 2 ^(8,42)	Randomised trials	Serious*	Not serious	Not serious	Serious†	None	22/32	68.8	7/24	29.2	RR 2.36	1.22, 4.57	40 more/100 (from 6 more to 100 more)		⊕⊕○○	Low	IMPORTANT
Mucosal healing (cohort studies) 1 ⁽⁴⁸⁾	Observational studies	Serious‡	Not serious	Not serious	Very serious§	None	26/37	70.3	4/10	40.0	RR 1.76	0.80, 3.86	30 more/100 (from 8 fewer to 100 more)		⊕○○○	Very low	IMPORTANT
Remission (RCT) 3 ^(8,42,47)	Randomised trials	Serious*	Not serious	Not serious	Very serious§	None	37/42	88.1	22/34	64.7	RR 1.28	0.99, 1.67	18 more/100 (from 1 fewer to 43 more)		⊕○○○	Very low	IMPORTANT
Remission (cohort studies) 13 ^(4,28,31,43,48–56)	Observational studies	Serious‡	Serious	Not serious	Not serious	Publication bias strongly suspected¶	375/476	78.8	314/482	65.1	RR 1.18	1.02, 1.38	12 more/100 (from 1 more to 25 more)		⊕○○○	Very low	IMPORTANT
Relapse at 12 months (cohort studies) 6 ^(29,31,43,48,53,56)	Observational studies	Serious‡	Serious	Not serious	Very serious§	None	99/231	42.9	82/164	50.0	RR 0.76	0.56, 1.03	12 fewer/100 (from 22 fewer to 2 more)		⊕○○○	Very low	IMPORTANT
Weight after induction therapy (RCT) 1 ⁽⁴²⁾	Randomised trials	Serious**	Not serious	Not serious	Very serious†	none	17		15		–		SMD 0.74 SD lower (1.46 lower to 0.02 lower)		⊕○○○	Very low	IMPORTANT
Weight after induction therapy (cohort studies) 4 ^(30,52,53,57)	Observational studies	Serious‡	Not serious	Not serious	Very serious§	None	83		100		–		SMD 0.26 SD lower (0.55 lower to 0.04 higher)		⊕○○○	Very low	IMPORTANT
Adherence withdrawal (RCT) 2 ^(42,47)	Randomised Trials	Serious*	Not Serious	Not Serious	Very Serious§	None	2/29	6.9	2/28	7.1	RR 0.95	0.15, 6.03	0 fewer/100 (from 6 fewer to 36 more)		⊕○○○	Very low	IMPORTANT
Adherence withdrawal (cohort studies) 2 ^(29,50)	Observational studies	Serious‡	Not serious	Not serious	Very serious§	None	4/107	3.7	0/61	0.0	RR 3.06	0.36, 26.23	0 fewer/100 (from 0 fewer to 0 fewer)		⊕○○○	Very low	IMPORTANT

Z. Ding *et al.*

Table 3. (Continued)

Certainty assessment							No. of patients (%)				Effect					
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EEN		CS		Relative	95 % CI	Absolute	95 % CI	Certainty	Importance
Adverse events (RCT) 2 ^(42,47)	Randomised trials	Serious*	Not serious	Not serious	Serious††	None	4/27	14.8	11/25	44.0	RR 0.32	0.13, 0.80	30 fewer/100 (from 38 fewer to 9 fewer)		⊕⊕○○ Low	IMPORTANT
Adverse events (cohort studies) 2 ^(48,58)	Observational studies	Serious‡	Serious‡‡	Not serious	Very serious§	None	12/47	25.5	22/28	78.6	RR 0.19	0.02, 2.26	64 fewer/100 (from 77 fewer to 99 more)		⊕○○○ Very low	IMPORTANT

EEN, exclusive enteral nutrition; CS, corticosteroids; RCT, randomised controlled trial; RR, risk ratio; SMD, standardised mean difference.

* Serious concerns around the randomisation process (particularly with lack of allocation concealment) and issues around blinding of the outcome assessors in studies with more weight suggest some serious risk of bias.

† With a small number of sample size or total events, fragility exists within the results. Furthermore, the optimal information size threshold is not met, and the effect estimate overlaps the GRADE recommended threshold for appreciable benefit, suggesting imprecision.

‡ When considering the included study/studies bias due to confounding, which is an important domain in the risk of bias tool, was not fully addressed. At least one important baseline confounder (e.g. disease severity, disease location, co-morbidities, concomitant medications, anthropometric measurements) was not measured or controlled for studies that hold more weight within the meta-analyses.

§ With a small number of sample size or total events, fragility exists within the results. Furthermore, CI include the possibility of a small or no effect and important benefit or harm, suggesting imprecision.

|| There is a significant level of heterogeneity that subgroup analyses cannot explain. This suggests some serious inconsistencies exist between studies.

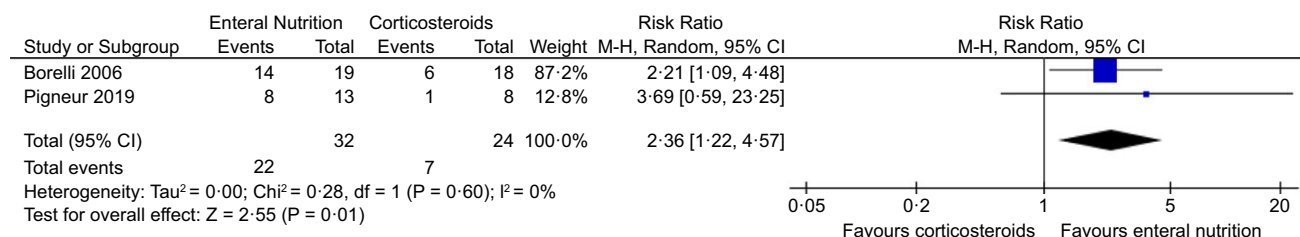
¶ Begg's plot was suggestive of publication bias ($P = 0.005$).

** Serious concerns around the randomisation process (particularly with lack of allocation concealment) suggest some serious risk of bias.

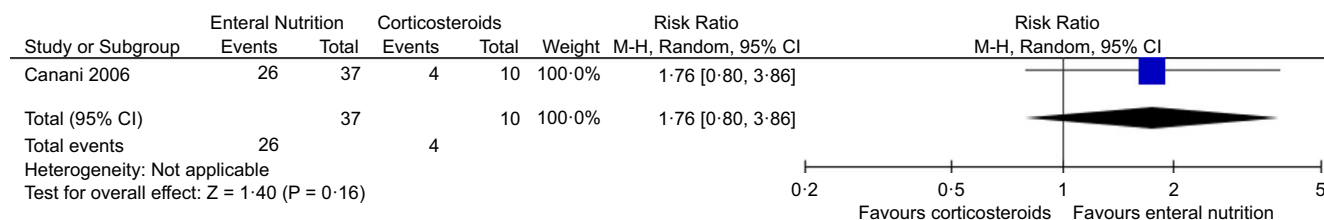
†† With a small number of sample size and total events, fragility exists within the results.

‡‡ There is unexplained heterogeneity that exists. Subgroup analyses were not feasible due to a limited number of studies.

Mucosal healing (Randomised controlled trials)



Mucosal healing (Cohort studies)



Clinical remission (Randomised controlled trials)

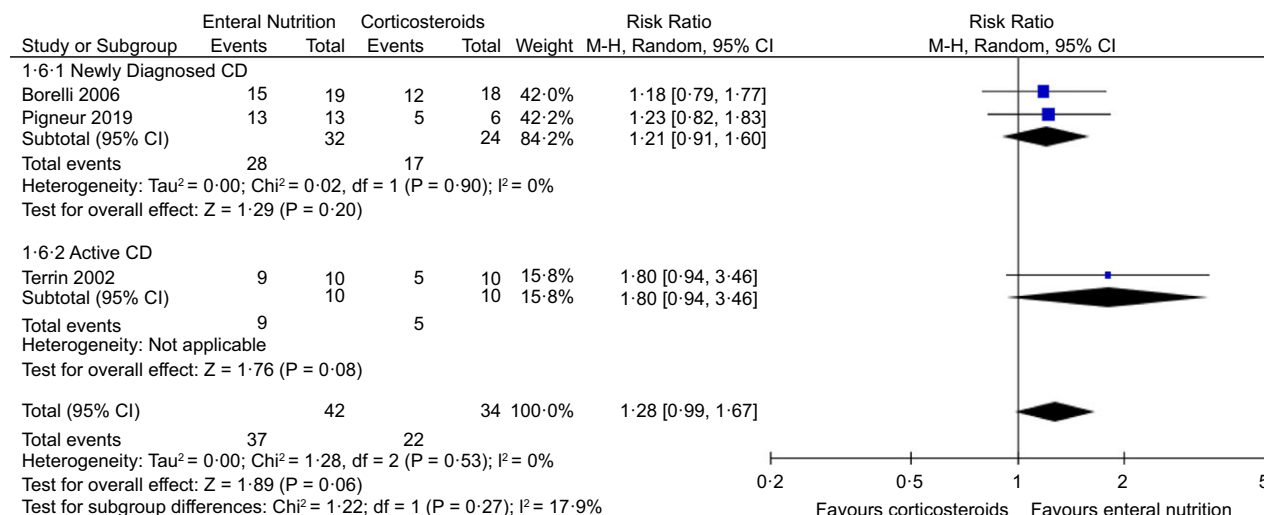
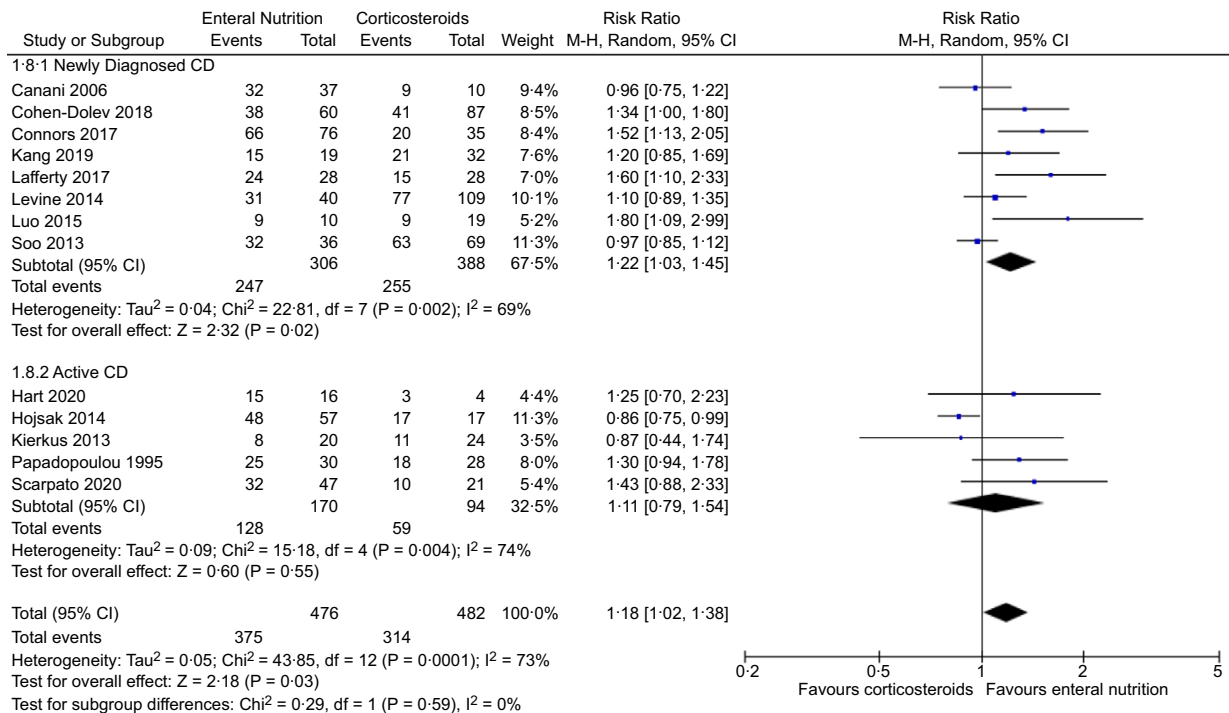


Fig. 4. Forest plots for comparison of outcomes between enteral nutrition v. corticosteroids in children with Crohn's disease (CD).

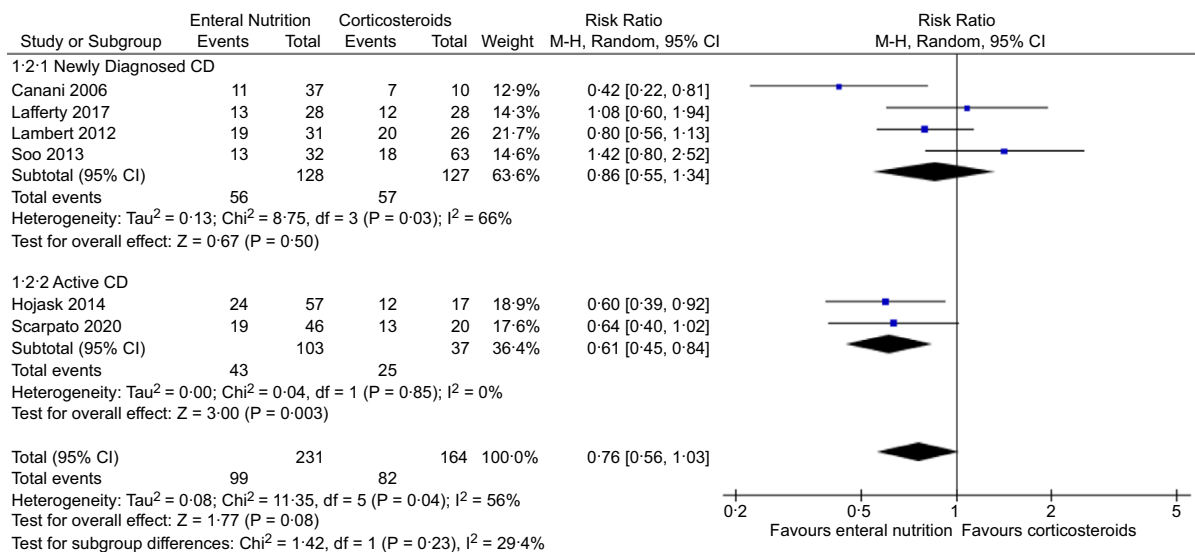
in children with active CD due to the remission induction efficacy^(3,6). Similar to our study's conclusions from RCT evidence, three previous systematic reviews determined no significant differences between EEN and CS in clinical remission in the paediatric population^(7,21,22). However, our conclusion based on cohort studies is different and suggests that EEN seems to be beneficial in clinical remission, but the evidence is uncertain. Similar to another systematic review, the evidence on 1-year relapse rates between EEN and CS remains uncertain but trends towards lower relapse rates in the EEN group⁽²¹⁾. In addition to clinical symptoms, therapeutic goals have changed with a recent focus on targeting objective improvement, including mucosal/histological healing^(6,20). Although patients treated with CS may achieve similar clinical remission and HRQL outcomes, they may fail to induce mucosal healing^(7,59,61,65). Similar to recent systematic reviews^(7,21,22), outcomes of mucosal healing based on two RCT in our review showed that children on EEN were more

likely to achieve endoscopic verified mucosal healing than children administered CS. Despite low certainty of evidence, the potential advantage of enteral nutrition over CS treatment may be clinically appealing when weighing the therapeutic options for treating paediatric CD. Furthermore, recent studies indicated that EEN might have a therapeutic impact on the microbiota diversity and inflammation marker levels, although conflicting results exist among paediatric and adult studies^(8–10). From two related studies, we found only one RCT that reported on microbial diversity values as measured through the Shannon index in just four children in each group⁽⁸⁾. In another cohort study of twenty patients with CD, there were incomplete microbiota values with respect to microbiota diversity and bacterial abundance⁽⁴⁾. Regarding microbiota indices, sparse data and heterogeneity exist between the two studies, although the effect on the Shannon diversity index seems to indicate a trend in favour of EEN in the RCT (Table 2).

Clinical remission (Cohort studies)



Relapse rate at 12 months (Cohort studies)



Post-treatment weight (Randomised controlled trials)

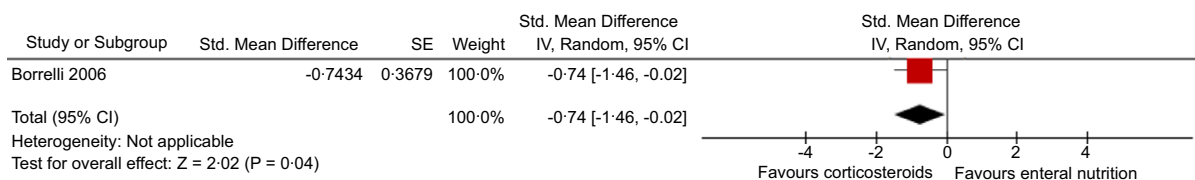
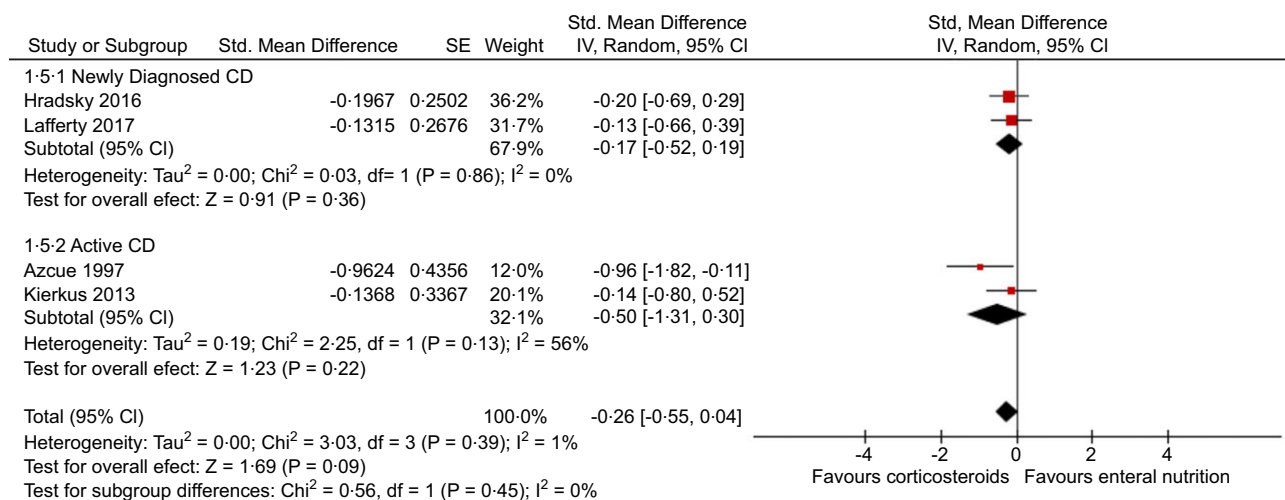
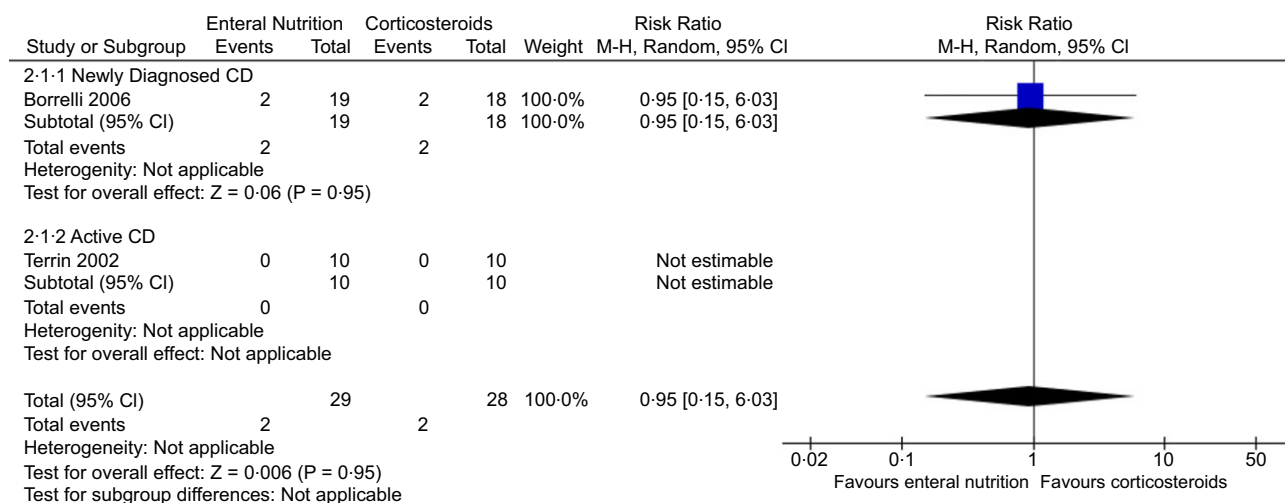


Fig. 4. (Continued)

Post-treatment weight (Cohort studies)



Adherence-withdrawal (Randomised controlled trials)



Adherence-withdrawal (Cohort studies)

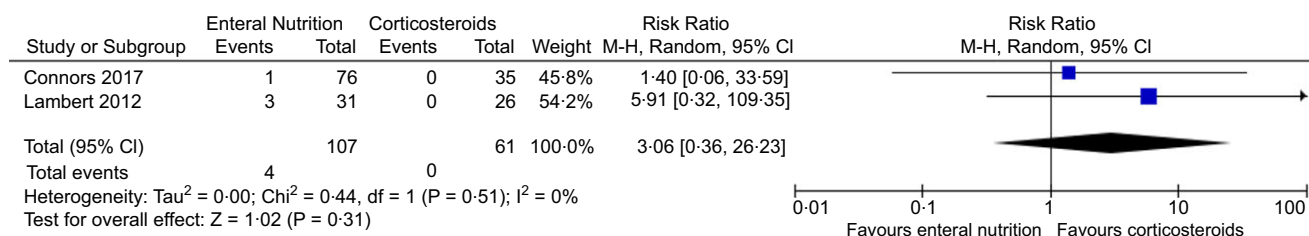
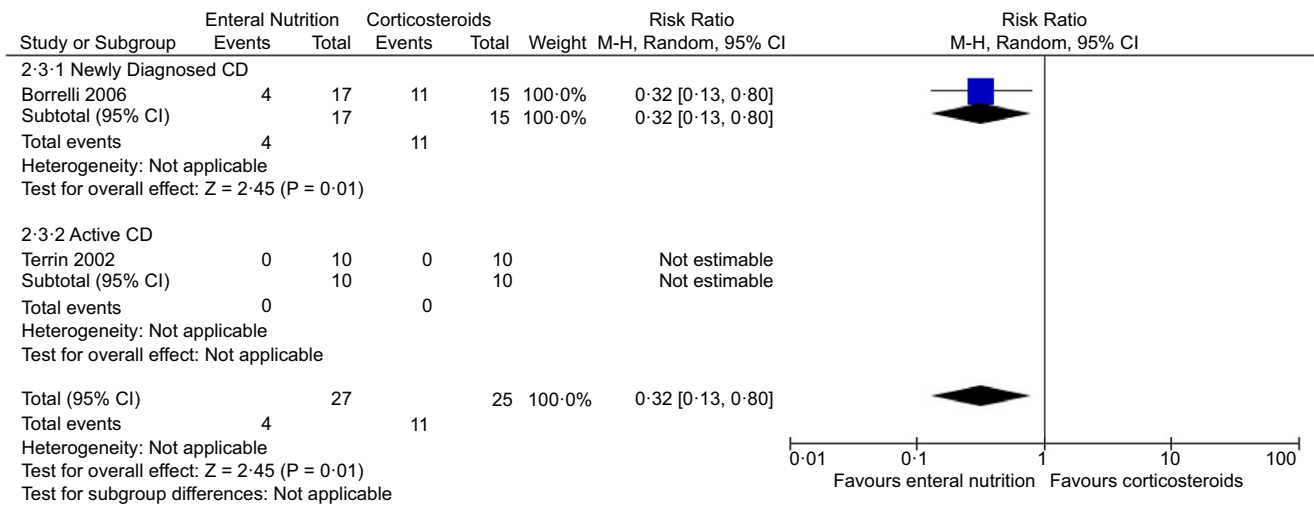


Fig. 4. (Continued)



Adverse events (Randomised controlled trials)



Adverse events (Cohort studies)

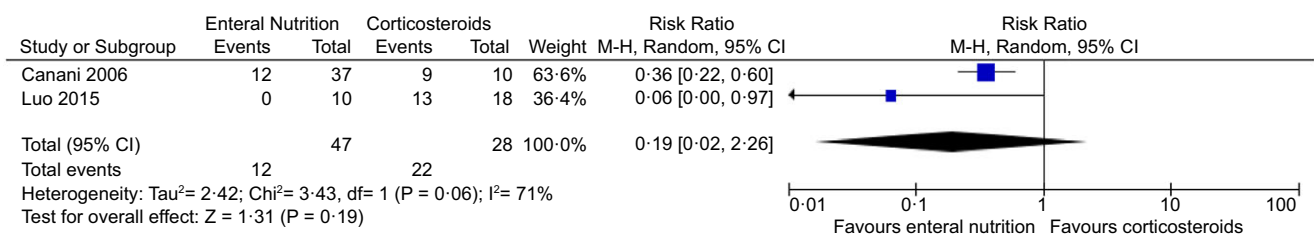


Fig. 4. (Continued)

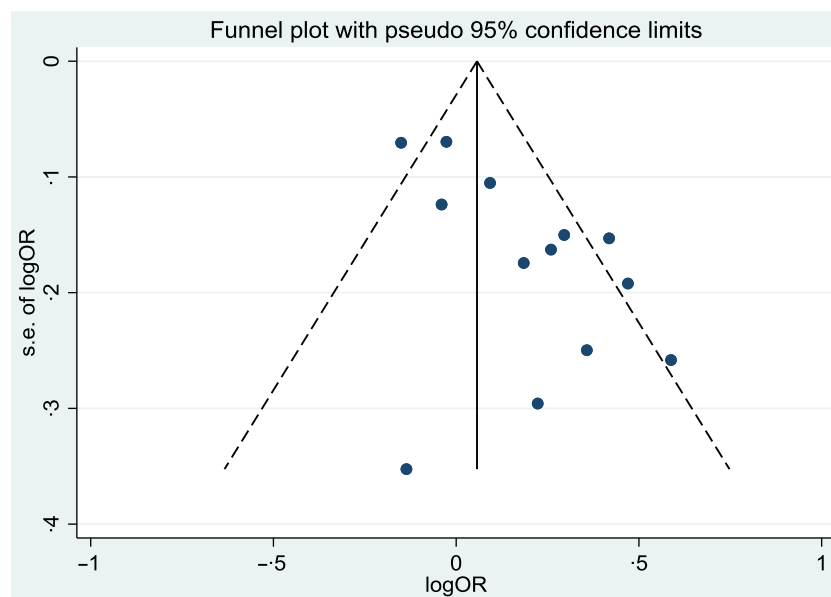


Fig. 5. Funnel plot for cohort studies of clinical remission.



With regard to the weight changes after treatment, a previous systematic review showed that weight gain in the EEN group was higher than the CS group but was not statistically significant⁽²¹⁾. One RCT in our review reported that the post-treatment weight was lower in the EEN group *v.* the CS group⁽⁴²⁾. However, weight and BMI may provide an inaccurate and misleading assessment of body composition analysis which divides the body into fat-free mass (lean mass) and fat mass. CS may lead to an increase in fat mass and a decrease in lean mass, so the misinterpretation of clinical parameters of nutrition may mask potential deficits in lean mass and malnutrition after steroid treatment^(66–69). For HRQL, unfortunately, no RCT or cohort studies met our eligibility criteria. While authors of the related studies were contacted for more information based on the published conference abstracts, the full-text articles with additional data were not successfully obtained to conduct a meta-analysis and generate forest plots. However, one prospective cohort study in Canada (abstract only) reported a higher generic HRQL score in the CS group compared with the EEN group and indicated a trend towards CS. To interpret the magnitude of the HRQL effect, the anchor-based minimal important difference estimate was used according to available data and published evidence^(70–72). Although the result was statistically significant, the MD did not meet the minimal important difference estimate⁽⁵⁹⁾. Another prospective cohort Canadian study (abstract only) found that for children receiving either EEN or steroids for induction therapy, disease-specific HRQL scores were similar over time⁽⁶¹⁾. Regarding FC, there is no single standard cut-off value to implicate the presence of mucosal inflammation⁽⁷³⁾. Due to this potential controversy, we did not use the dichotomous FC data for meta-analysis⁽⁵⁴⁾. Similar to the previous systematic reviews^(7,21), our review indicated that children on EEN were less likely to experience adverse events when compared with steroid therapy in paediatric IBD, although the withdrawal rates do not differ between two groups. The findings may be clinically useful when assessing the risks and benefits of EEN and CS.

Implications for practice and research

The study results may help inform clinical practices and provide guidance for the design of future research. Our findings may be useful when assessing the clinical risks and benefits of EEN and CS in children with active CD, especially for mucosal healing, clinical remission, relapse, adherence and adverse events. However, meta-analyses and determining the certainty of evidence were not feasible for the following outcomes: microbiota signatures, HRQL and FC. Our systematic review may provide valuable inferences and implications for future research areas in paediatric IBD treatment. Further RCT and cohort studies are required to better understand the applicability of EEN when considering these outcomes, especially microbiota diversity, growth parameters and FC. Crohn's specific HRQL is also an important patient-centred metric to be evaluated and compared with anchor-based minimal important differences. Moreover, further RCT and cohort studies regarding PEN *v.* CS may expand the available literature and provide important insight into the management of paediatric IBD.

Conclusions

Our study suggests that based on low certainty of evidence, EEN may be more beneficial than CS for mucosal healing at 4–12 weeks after induction therapy with fewer adverse events. However, the impact on clinical remission, relapse at 12 months post-induction therapy, post-treatment weight and adherence is uncertain based on very low certainty of evidence. Furthermore, the evidence on the effect of EEN compared with CS on microbiota signatures, FC and HRQL remains unclear due to limited available data, although there seems to be a trend in favour of EEN regarding gut microbiota. Additional sufficiently powered RCT are required to better assess the impact of enteral nutrition *v.* CS on paediatric CD.

Acknowledgements

The authors would like to extend sincere thanks to Denise Smith, MLIS, Health Sciences Library, McMaster University, for assistance in developing the search strategies.

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

M. Z., B. C. J., M. S. and P. M. contributed to the study idea, study design, study supervision, data interpretation and critical review of the manuscript. Z. D. and K. N. contributed to literature search, study design, data collection, data analysis, data interpretation and manuscript writing. All authors have approved the final version of the manuscript and the authorship list.

The authors declare no conflicts of interest.

Supplementary material

For supplementary material referred to in this article, please visit <https://doi.org/10.1017/S0007114523000405>

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