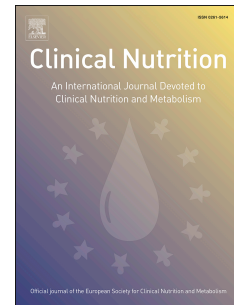


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Effect of Fat Composition in Enteral Nutrition for Crohn's Disease in Adults: A Systematic Review

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1 **Effect of Fat Composition in Enteral Nutrition for Crohn's Disease in Adults: A**
2 **Systematic Review**

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29 **Abstract**

30 **Background & Aims:** The role of enteral nutrition (EN) fat composition in regulating
31 inflammation in Crohn's disease (CD) is not clear. There is, moreover, insufficient evidence
32 to guide the choice of EN in CD with any confidence. We have reanalysed the findings of
33 previous studies in a systematic review focusing on the relationship between EN fat content
34 and remission rates (RR).

35 **Methods:** A systematic search with no language restriction was undertaken in Medline and
36 Embase databases supplemented by a manual search in the reference lists of identified
37 studies. The selection criteria were: clinical trial, exclusive EN, adults and CD. Data on the
38 type of EN, its fat composition, achieved RR, and study design were extracted. An
39 established assessment tool was used to assess the quality of the studies.

40 **Results:** A total of 29 clinical trials are included in this review. The quality of the studies was
41 highly variable. No fewer than 27 formulations of enteral feed were identified including 4
42 elemental and 23 non-elemental preparations.

43 There was a positive correlation between the total n-6 fatty acid content and response rates,
44 which was significant when expressed as the ratio between n-6 and n-3 fatty acids ($r = 0.378$,
45 $p = 0.018$). A non-significant positive trend was founded ($r = 0.072$; $p = 0.643$) between
46 medium chain triglycerides (MCT) delivery as a percentage of the total energy provision and
47 RR. While a non-significant negative trend was reported for the delivery of monounsaturated
48 fatty acids (MUFA) ($r = -0.23$, $p = 0.13$). A qualitative advantage to regimens based on
49 safflower oil suggest that optimised therapeutic approaches are within reach.

50

51 **Keywords:** Crohn's disease, Enteral nutrition, Lipid, Fatty acid, Dietary fat, and
52 Inflammatory bowel disease

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56 **Abbreviations**

57 EN: Enteral nutrition

58 CD: Crohn's disease

59 RR: Remission rate

60 TGF- β : Transforming growth factor- β

61 MCT: Medium chain triglycerides

62 LCT: Long chain triglycerides

63 MUFA: Monounsaturated fatty acid

64 PUFA: Polyunsaturated fatty acid

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77 Introduction

78 Crohn's disease (CD) remains an incompletely understood, inflammatory condition of
79 the intestine. Although there are important genetic components to its origins, there are also
80 undoubted environmental elements, amongst which dietary factors are clearly identifiable.
81 As well as having a probable role in pathogenesis, nutrition has been identified as a key
82 mediator in established disease, such that, in paediatrics at least, defined enteral nutrition
83 (EN) is the treatment of first choice for many patients. However, as is often the case in
84 clinical nutrition, the evidence base is not as strong as might be wished. Several meta-
85 analyses have been conducted, but it remains difficult to judge the true effectiveness of EN in
86 patients with CD. The collected evidence supports a superior effect of corticosteroids over
87 EN in adults with CD, but many adult clinicians and most paediatricians believe that EN is an
88 appropriate and evidence-based primary therapy in CD. This belief rests on the positive
89 results from studies of paediatric and malnourished CD patients, which confirm beneficial
90 effects of EN in improving growth and nutritional status, but which also indicate mucosal
91 healing, and of course a favourable risk profile compared to pharmacological options.

92 Enteral nutrition comprises, however, a broad range of options, and the limited
93 comparative evidence prevents confidence that the best choice(s) can currently be made.
94 Polymeric, protein-based feeds with high fat content have been compared with low fat,
95 glucose and amino acid-based feeds, and with oligomeric peptide-based feeds [1-4], but
96 without compelling evidence that one is better than another [4]. At present a single EN
97 formula is licenced and marketed specifically for inflammatory bowel disease in adults. This
98 is a casein-based polymeric feed rich in transforming growth factor- β (TGF- β), but there is
99 little evidence to support any particular efficacy [5, 6].

100 Meta-analysis shows a weak and non-significant positive association between the
101 protein content of feeds and their associated clinical response rates (RR). One meta-analysis

102 found a negative correlation between long chain triglyceride (LCT) content and RR [7], and a
103 second found comparable but non-significant trends favouring low LCT and low overall fat
104 content [4]. Given the potential aetiopathogenic relevance of lipids to Crohn's disease (more
105 disease in populations on high fat Western diets) and the curious phenomenon of fat
106 wrapping (almost pathognomonic of Crohn's), further investigation in this area appears
107 readily justifiable despite and partly because of the inability of the other meta-analyses to
108 provide a verdict on this issue.

109 The aim of this systematic review has been to reanalyse the findings of the older
110 studies and to combine these with the findings of those more recently published, specifically
111 to evaluate the relationship between nutrient fat content and response rates in the treatment of
112 patients with CD. Conscious that currently reported evidence is inconclusive and aware that
113 many authorities consider the case for EN so weak as to argue robustly against it in the
114 treatment of CD, we have approached this in a different and we hope more exploratory
115 fashion than previous reviews. We focus on specific fatty acids, not just on lipid class, and
116 on the ratios of individual fatty acids to each other, as well as to other macronutrients and to
117 their relative contributions to energy provision.

118 **Materials and methods**

119 The PRISMA checklist and guidelines were used for this systematic review (see
120 supplementary data in **Appendix A**). The study is registered with the PROSPERO database
121 of systematic reviews, registration number: CRD42016033857.

122 **Search strategy**

123 A computer-based systematic search was undertaken using the Medline database
124 (1946 to present) and the Embase database via OVID. The search strategy was customized
125 for each database and applied to titles and abstracts of papers. For text terms related to
126 enteral nutrition we used: “enteral”, “elemental”, “polymeric”, “whole protein”, “amino acid

127 based”, “peptide based”, “low fat”, or “high fat”; these terms were all combined with
128 “nutrition”, “feeding”, “diet”, or “feed”. For disease-related text terms we used “Crohn’s
129 disease”, or “inflammatory bowel disease”. Also, we searched “enteral nutrition” and “Crohn
130 disease” as index terms (MeSH) and exploded them as appropriate. The searches were
131 limited to studies that involved humans, adults (18-plus years), clinical trials, controlled
132 clinical trials, randomized controlled trials, meta-analyses, and systematic reviews. The
133 searches were not restricted to the English language. In addition, a manual search of the
134 reference lists of previously published papers was carried out, looking specifically for clinical
135 trials investigating the effect of EN in adult patients with active CD.

136 **Selection criteria**

137 The selection of studies was determined by two reviewers following set criteria. The
138 studies included were required to be prospective clinical trials in adults with CD (including
139 controlled and uncontrolled trials). The EN intervention was to have been given exclusively
140 for a defined period of time without any food intake (only water and sugar/milk-free
141 beverages were allowed). The response rate must have been measured as a primary or
142 secondary outcome, according to clearly stated criteria. The enteral feed used had to be
143 clearly defined (i.e. name and type of feed, oil source, and fatty acid composition). Studies
144 were removed from consideration if EN was given together with oral food intake, the study
145 was retrospective, or performed in a paediatric population. Trials that did not provide a
146 defined RR for CD, and trials that investigated the effect of EN in combination with other
147 medical therapies (e.g. with non-absorbable antibiotics or with erythropoietin) were also
148 excluded. Studies where the full identity of the lipid content was not published were
149 excluded only after application to researcher and/or manufacturer had failed to provide this
150 information. When studies were published initially as interim reports our analysis used data
151 only from the later full article.

152 Data extraction

153 For each eligible study, a detailed review was undertaken using a report form, looking
154 for the type and quantity of fatty acids in the enteral feeds, the RR achieved by EN, which
155 was calculated on the basis of a “per protocol” analysis, and selected characteristics related to
156 study design (e.g. duration of intervention, criteria for remission, geographical location,
157 number of patients). The gender and age of patients, and the anatomical location and
158 duration of their disease were recorded. Any apparent discrepancies in the data extracted
159 were discussed and resolved between the two reviewers.

160 Most papers did not provide sufficient detail of the fat composition in the enteral
161 feeds for our purposes. These deficits have been addressed as follows. Where the formula
162 was described by a proprietary name the manufacturer’s data sheet has been interrogated.
163 Where no proprietary name was provided a query was sent to the primary investigator of the
164 study concerned. In each case our analysis was based on the fatty acid content of the feed
165 used. In the great majority of cases this information was not provided either by authors or by
166 manufacturers. However, the nature and proportion of the oils in the feeds was generally
167 available or possible to estimate from the information given. The fatty acid profile of each
168 oil was then drawn from a thorough published analysis [8]. One additional and unexpected
169 problem arose from the fact that the composition of some feeds has been modified within the
170 last fifteen years. Care was therefore taken to ensure that the analysis of the lipid content
171 referred to that of the feed available at the time of the study.

172 Quality assessment

173 The quality of the included studies was judged according to the Downs and Black
174 quality checklist on reporting, external validity, internal validity (study bias), and
175 confounding (selection bias) [9], with Livingston’s amendment for assessment of power [10].

176 This is considered a reliable assessment tool for both randomized and non-randomized
177 clinical trials: the higher the score the better the quality of the methods.

178 **Data synthesis and statistical analysis**

179 The primary aim of this review has been to review and interpret the available
180 evidence in order to test the potential correlation between the fat composition of enteral feeds
181 and the resultant RR. Scatter plots were used to identify trends. The significance of possible
182 relationships was tested by the Pearson correlation test (SPSS Statistics for Windows,
183 Version 22.0, released 2013. IBM Corp., Armonk, NY, USA). Subgroup analysis was also
184 conducted which stratified RR by the different levels of fats in EEN feeds (e.g. low vs.
185 moderate vs. high MCT) and by the different levels of response rate (i.e. low RR <70% vs.
186 high RR >70% response rate).

187 **Results**

188 **Literature search**

189 The electronic searches yielded 63 articles and the manual search from previous meta-
190 analyses and reviews identified an additional 14 articles. Initial screening of the 77 articles
191 comprised examination of title and abstract in the context of our selection criteria. Forty
192 articles were judged relevant and were further assessed for eligibility. In each case the full
193 paper was read (professionally translated if necessary) and checked against our selection
194 criteria. Joint decisions on selection were made by the two reviewers, following discussion if
195 any initial discrepancy arose. Ultimately our systematic review was based on 29 pertinent
196 papers (Fig. 1).

197 **Study characteristics**

198 From the total of 29 studies, 24 were controlled trials and 5 were uncontrolled.
199 Among the controlled trials: 10 compared the efficacy of EN against drug therapy; 2

200 compared EN with PN; and 8 investigated the effect of the type of EN by comparing
201 elemental feeds with non-elemental feeds (which include polymeric and semi-elemental,
202 oligomeric feeds). Only 4 trials specifically addressed the effect of fat composition; these
203 trials compared similar types of feeds but with different fat composition. The study design,
204 patient characteristics, and criteria used to measure RR in the papers considered by this
205 review are provided in Appendix B.

206 **Quality of studies**

207 The quality of the included studies was highly variable. The study with the highest
208 quality [11] scored 26 (out of 28) by the assessment tool [9, 10], while the lowest quality
209 study scored only 10 [12]. Poor (or unknown) representativeness of study subjects and the
210 lack of power calculations were the commonest defects overall, and in the controlled trials,
211 there were high risks of performance and detection bias due to the lack of blinding, and high
212 risk of selection bias due to the lack of allocation concealment during randomization
213 (Appendix B).

214 **Characteristics of identified enteral feeds**

215 No fewer than 29 distinct enteral feeds have been used in the published studies. We
216 have excluded one study [13], and therefore data on two formulae, because patients who were
217 randomized to receive polymeric feeding were prescribed one or other of the two formulae
218 depending on availability, but the RR was provided only as a combined rate for the two
219 formulae. Therefore, the final number of reviewed formulae is 27: 4 elemental formulae and
220 23 non-elemental preparations. The fatty acid composition of these formulae with reference
221 to RR is demonstrated in Table 1. More detailed fat composition data are provided in
222 Appendix B.

223 **Correlation between fat composition and remission rate**

224 ***Total amount of fat***

225 Eight studies have compared a pair of feeds with different nutrient composition (e.g.
226 polymeric versus elemental or semi-elemental versus elemental). It is difficult to determine
227 the effect of fat content from these comparisons, as their composition for other nutrients was
228 not standardised. Only two studies have specifically examined the effect of the amount of
229 total fat. High and low fat feeds (fat mainly in the form of LCT) were compared. The earlier
230 study showed that the feed with a low percentage of fats (15.6% of total calories) achieved a
231 higher RR (92%), than the high fat feed (35.6% of total calories), which achieved a RR of
232 55% [7]. The later study indicated that a very low fat feed (1.15% of total calories) achieved
233 a significantly higher RR (80%) than a modest fat feed (11.27% of total calories), which
234 achieved a RR of (25%) [14]. It will be noted that the amount of fat in this higher fat feed
235 was barely distinguishable from that of the low fat feed of the earlier study and yet the
236 clinical effects were hugely different. Overall we find no significant correlation or trend
237 between total fat content and RR ($r=0.176$, $p=0.252$) (Fig. 2A).

238 *Medium chain triglycerides (MCT)*

239 Varying MCT content does not have a consistent strong effect. A single study which
240 compared a feed with added MCT against a feed with no MCT, generated significantly
241 different RRs of 77% and 67% respectively [15]. However, the high MCT feed was semi-
242 elemental and the low MCT feed was elemental, which precludes any firm conclusions about
243 the contribution of the lipid to the observed differences. Our quantitative analysis, which is
244 based on results from all studies, finds a weak non-significant positive trend between MCT
245 delivery as a percentage of the total energy provision and RR ($r=0.072$; $p=0.643$) where the
246 range was from 0 to 30% of total energy supply (Fig. 2B). The apparent outlier to the upper
247 left of the plot comes from Leiper's study [16] in which there was a particularly high
248 concentration of MCT (>86% of all fat) with a high proportion of MUFA (29%) and a low n-
249 6:n-3 ratio (see below) amongst the fats that were LCTs.

250 Long chain triglycerides

251 The effect of undifferentiated LCTs has been addressed by comparing feeds with
252 similar amounts of total fat but with different percentages of LCT. One study (already
253 mentioned above) compared four feeds: elemental, elemental with added LCT, elemental
254 with added MCT, and semi-elemental [7]. The feed with high LCT was associated with the
255 lowest RR (55%), while the elemental feed with added MCT performed best, with a RR of
256 92%. However, a second study found no significant difference in RRs between use of feed
257 with 5% LCT and an isocaloric feed with 30% LCT [16]. Our quantitative analysis of all the
258 reported studies of all feedings reveals a non-significant negative trend between LCT
259 provision and RR ($r = -0.254$; $p = 0.096$) where the range was from 4 to 35% of total energy
260 supply and where in most cases the predominant lipids were of the n-6 class (where not, the
261 relative excess came from n-9 lipid which we also consider disadvantageous (Fig. 2C and see
262 below).

263 Saturated fats

264 No single study has directly compared feeds with different levels of saturated fatty
265 acids. We found no significant correlation or trend between the amount of saturated fat and
266 the RRs ($r = -0.007$, $p = 0.964$) where the range was from trace amounts to over 30% of total
267 energy supply (Fig. 2D).

268 Olive oil/MUFA

269 Only a single study has compared two feeds with the same amount of total fat but
270 with different amounts of oleic acid (balanced by linoleic acid) [11]. The feed with higher
271 oleic acid content (79% of total fat) was significantly less effective (RR = 27%) than the feed
272 with lower oleic acid (28%) and higher linoleic acid (45%), which achieved a RR of 63%.
273 Although there are no other specific studies addressing MUFAs, our overall quantitative
274 analysis is concordant, showing disadvantage from monounsaturated fatty acids (MUFA)

275 with no statistical significance ($r = -0.23$, $p = 0.13$) with a range from trace amounts to about
276 25% of total energy supply (Fig. 2E).

277 *n-6 and n-3 PUFAs*

278 Only the study by Gassull et al. has directly investigated the effect of an n-6-rich feed
279 (specifically linoleic acid), in which a significantly higher RR was achieved than with a lower
280 n-6 content [11]. No study of non-elemental formulae readily allows assessment of the
281 individual effects of an n-3-rich approach.

282 In our quantitative analysis a very weak non-significant negative correlation was
283 found between the amount and proportion of PUFA (of all types) and the response rates from
284 all feeds ($r = -0.157$, $p = 0.308$) (Fig. 2F) as was also the case for n-3 fatty acids ($r = -0.166$, p
285 $= 0.313$) (Fig. 2H).

286 However, there was a weak positive correlation between the total n-6 fatty acid
287 content and response rates ($r = 0.253$, NS) (Fig. 2G), statistical significance ($r = 0.378$, $p =$
288 0.018) which remained significant after correction for multiple tests (Fig. 2I). In the subgroup
289 analysis (TABLE 2), when RR was stratified by the level of n-6:n-3, significant difference (p
290 $= 0.011$) was reported in the pooled RR between EEN feeds with moderate n-6:n-3 (58.94%
291 RR) (95% CI 48.99, 68.9) versus feeds with high n-6:n-3 (79.91% RR) (95% CI 72.31,
292 87.51).

293 When patients exposed to only a single oil are considered (informal subgroup
294 analysis) then the use of safflower oil is favoured, with a mean (median) response rate of
295 83.6% (84%) compared to the overall average response of 68.1% and mean (median) values
296 for isolated exposure to soybean or arachis oil of 63.7% (68.5%) and 68.6% (75%)
297 respectively.

298 Discussion

299 The wide range of patient characteristics, the low number of participants in each
300 study, and varying study designs obstruct the route to confident and generalizable
301 conclusions. We deliberately used results taken from observations on patients who followed
302 treatment protocols (rather than intention to treat), but although biologically justifiable this
303 will be of limited clinical value if a future “optimal” formula is not tolerated and thus the
304 treatment plan is not completed. Fortunately the compliance/acceptance of the many
305 different formulae did not appear systematically different according to the particular lipid
306 profiles. This may have been obscured however by the range of duration of the intended
307 therapies. The duration of intervention in most of the trials examined was between 3 and 8
308 weeks, 12 weeks in one trial [17], and only 2 weeks in 3 studies [18-20].

309 No fewer than eight different sets of criteria have been utilised to define response.
310 Some were strict and binary (e.g. complete steroid withdrawal) and associated with relatively
311 low response rates [21, 22], while others were more qualitative (subjective). It should not
312 have had a major effect on our interpretations since a full analysis performed on this basis
313 provides the same qualitative results (data not shown).

314 Our methods may not have been sufficient to overcome bias introduced by the
315 differing anatomical location of the CD (small bowel, large bowel, or both). The trials with
316 the highest proportions of patients with small bowel CD (50% and 52%) also had amongst
317 the highest RRs (86% and 75% respectively)[21, 23], a linkage already well recognized in the
318 literature, and perhaps a confounder despite apparently well-matched controls.

319 It has been thought that EN is more effective in those with early, purely inflammatory
320 disease. Although not all evaluated studies provided the duration of the disease, the shortest
321 and longest mean disease durations (1.3 and 18 years) were associated with similar and very

322 respectable RRs of 90% and 80% respectively, suggesting that this effect is not profound [18,
323 24].

324 Considerable differences were observed in respect of sex ratio (0-89% male [15],
325 [25]), but although prognosis of CD may differ between the sexes [25] a systematic bias
326 could not be detected within our analysis [26].

327 The divergence between the different types of unsaturated LCTs (n-3, n-6 and n-9)
328 and outcome appear at first surprising, but are fully consistent with the negative results from
329 supplementary fish oil in CD [27]. In terms of specific oil content, interpretation is clouded
330 by the number of feeds which contain multiple oils. However the numerical advantage to
331 safflower oil is very much in line with the overall conclusion that high n-6:n-3 ratio is
332 advantageous and low proportion of MUFA could be relatively effective as well, given the
333 relative paucity of MUFA in safflower oil (13.9% compared to 23.9% in soy and 56% in
334 arachis oil) and its n-6:n-3 ratio, which, at over 90, is the highest of all the dietary oils. It has
335 been more difficult still to link interpretation to individual fatty acids, but linoleic acid is
336 favoured, and oleic acid as the only n-9 fatty acid in artificial feeds is targeted for avoidance.

337 There is a little supportive evidence also for our hypothesised complementary
338 combination of safflower oil and MCT. One of the highest response rates in the literature
339 (92% [7]) was in patients on this combination, and only the study of Lindor *et al* appears to
340 point in the opposite direction, this being a small study in which the comparator was steroid
341 therapy [28].

342 **Conclusions**

343 The fat content of EN formulae and its influence on controlling the inflammation of
344 CD has generated interest, but its true role has remained unclear. Given its potential
345 importance it is surprising that most authors have not thought it worthwhile or necessary to
346 disclose the lipid analysis of the formulae used in their study. This systematic review has

347 dissected the previously very broad classification of lipids in order to try to assess the effects
348 of individual dietary oils and their fatty acids. It is recognised that definitive analysis is not
349 possible given, on the one hand, the incomplete comparative information available, and, on
350 the other, the inevitable complexity introduced by the replacement of one lipid with another
351 and/or by different total fat content in different feeds. We manifestly lack sufficiently robust
352 clinical trials in this area [29].

353 However, our results expose significant results from individual studies, and, as well as
354 several suggestive trends, support significant advantage from a high n-6 to n-3 ratio and
355 perhaps from avoidance of MUFA. The various trends are, moreover, not mutually exclusive
356 despite the considerable variation in study design and response rates. Aiming for a relatively
357 low total LCT content and proportionately high MCT content, with a relative low MUFA and
358 high n-6:n-3 fatty acid ratio can now be argued to offer an optimised approach. This might
359 most easily and effectively be achieved by development of feeds based on a combination of
360 safflower oil and MCT.

361

362

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367 provided additional information as required. Thanks also to the companies marketing enteral
368 nutritional products who provided additional information about their composition.

369 The authors' responsibilities were as follows - both of the authors have contributed to
370 the protocol design, data collection/analysis, and writing of this systematic review. AF has
371 recently undertaken speaker engagements for B Braun and Fresenius-Kabi, but there are no

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ACCEPTED MANUSCRIPT

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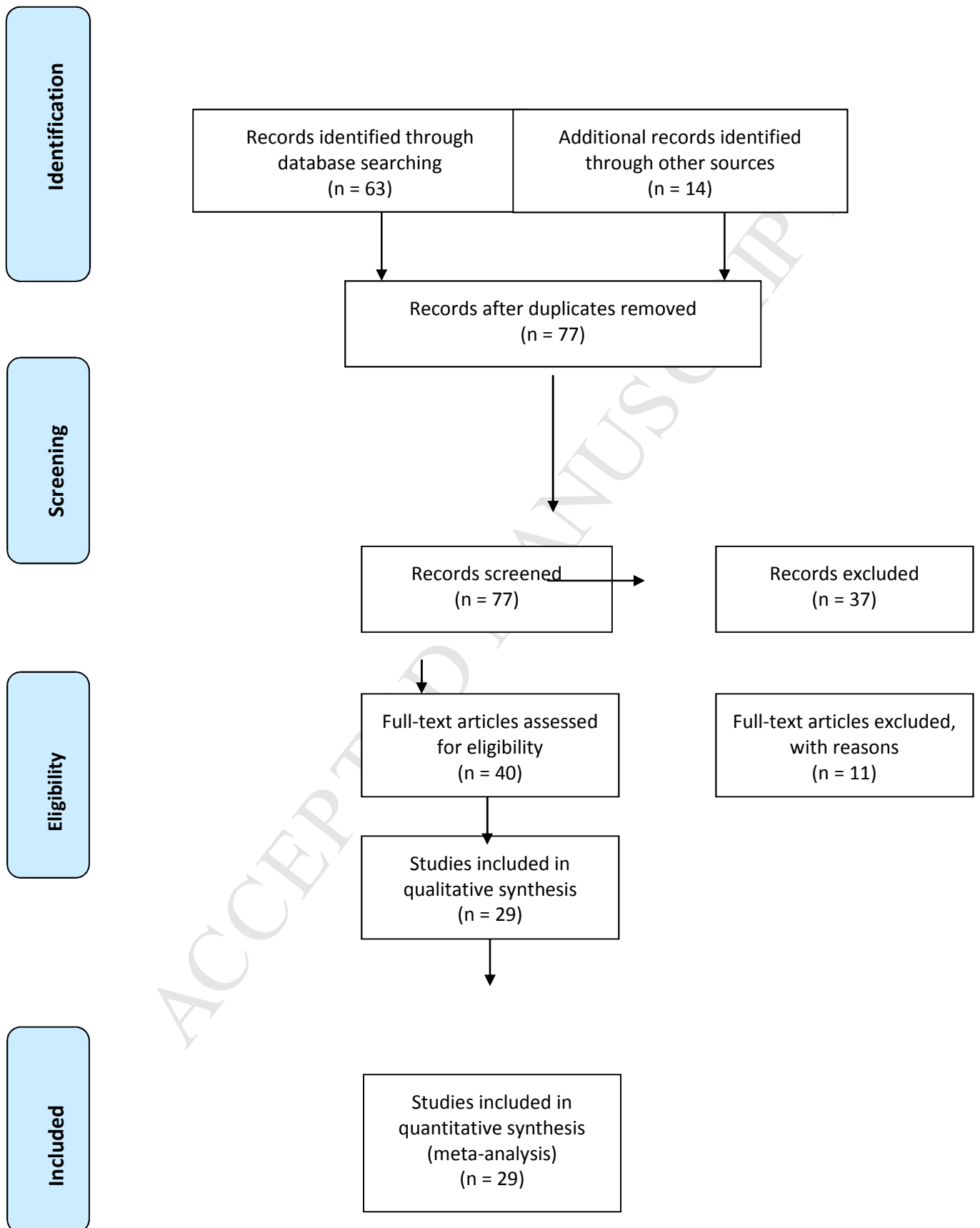
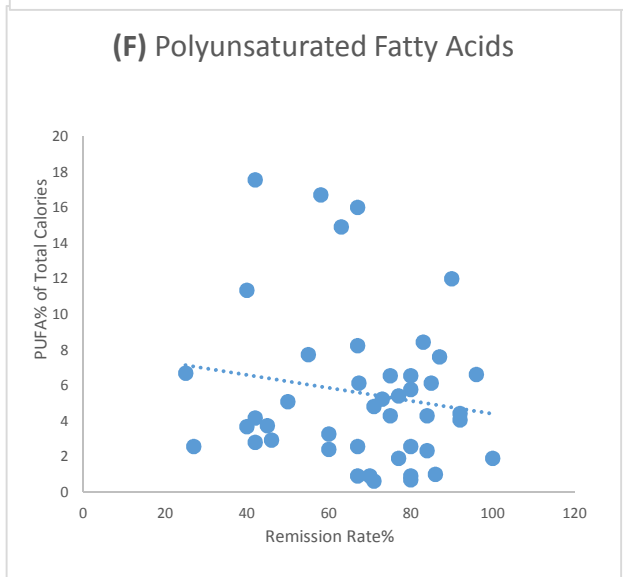
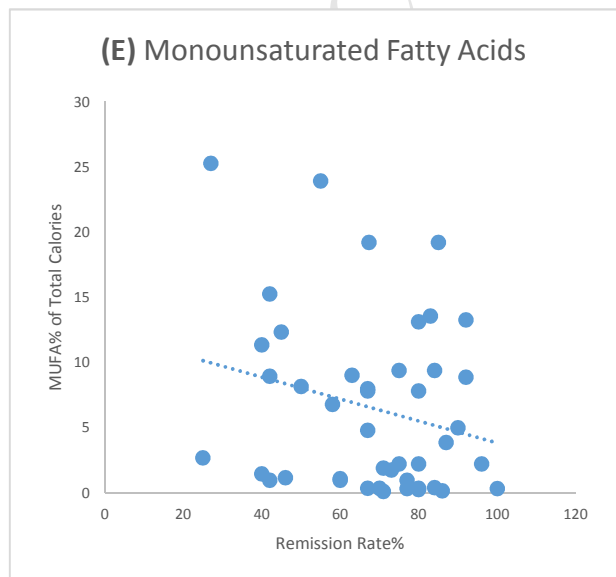
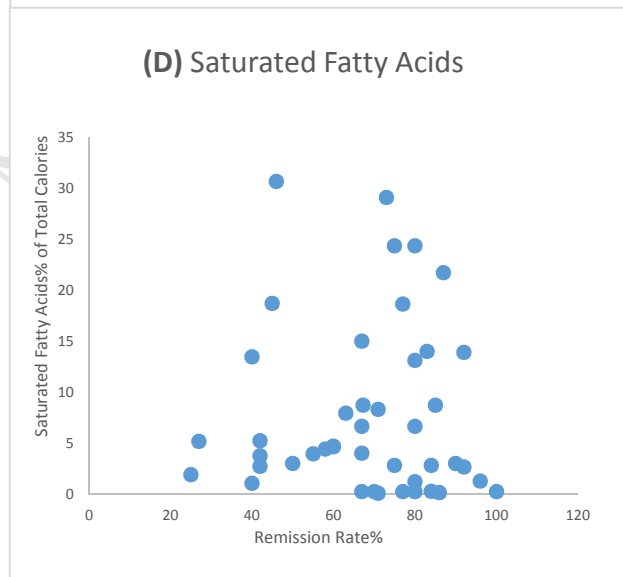
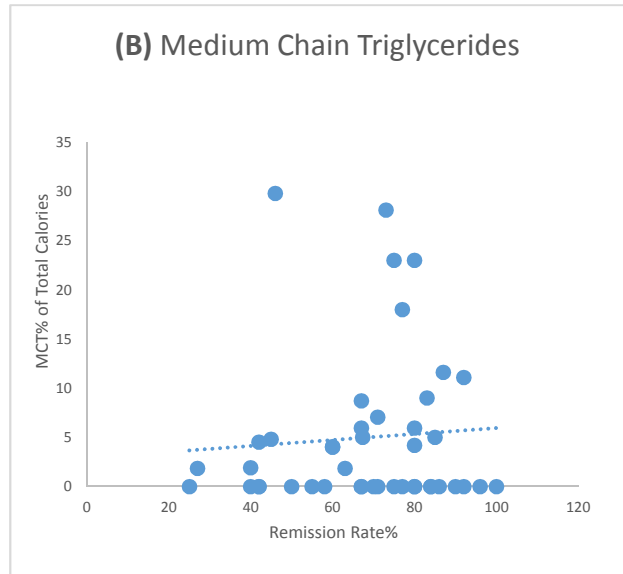
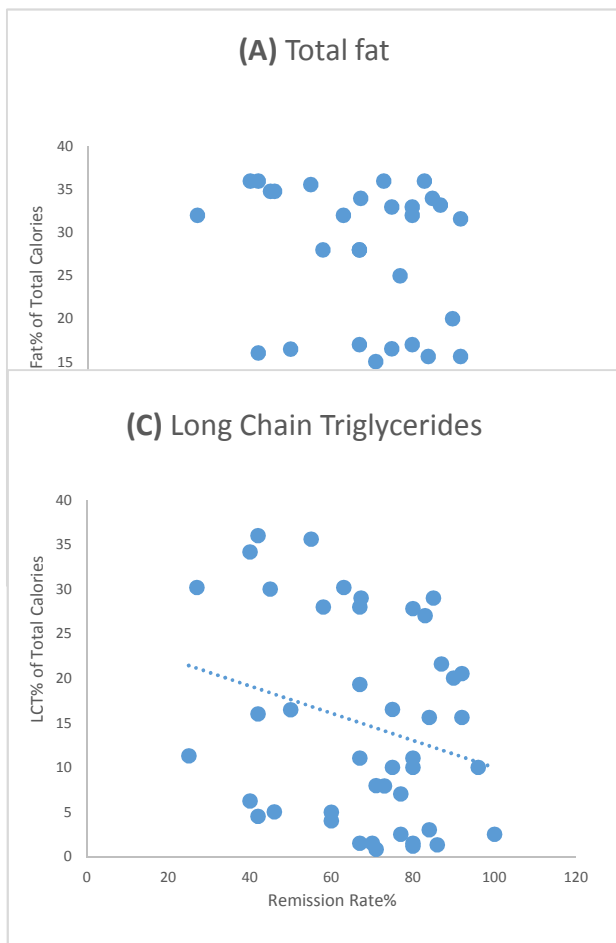


FIGURE 1: PRISMA 2009 flow diagram demonstrating the search and selection strategy. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.



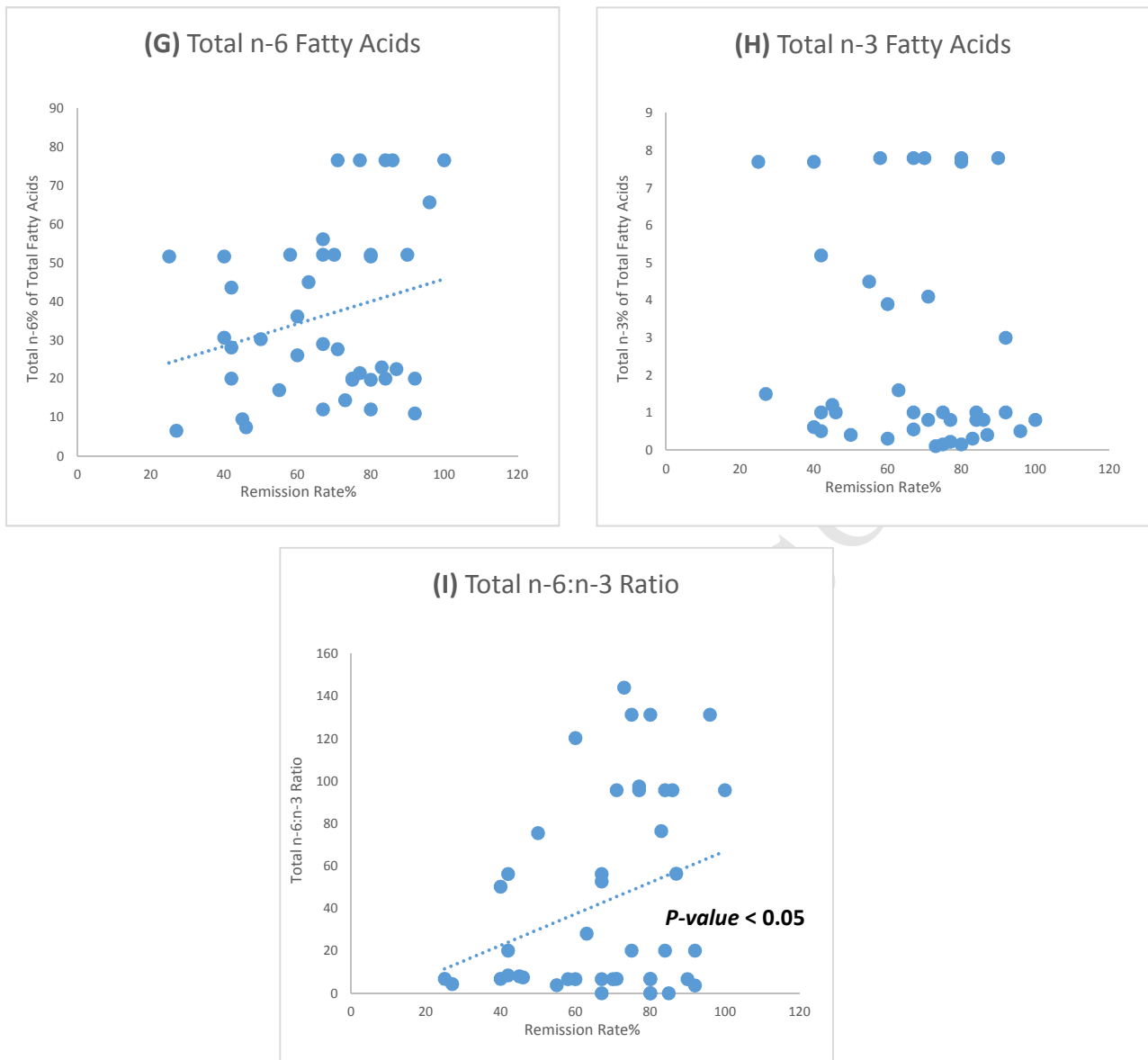


FIGURE 2: The association between fat composition of enteral nutritional feeds and remission rates (calculated based on per protocol analysis) in patients with Crohn's disease. Pearson correlation test was used to measure the strength of the correlation. (A) Total fat percentage ($r = -0.176$, $P\text{-value} = 0.252$). (B) Medium chain triglycerides (MCT) percentage ($r = 0.072$, $P\text{-value} = 0.643$). (C) Long chain triglycerides (LCT) percentage ($r = -0.254$, $P\text{-value} = 0.096$). (D) Saturated fatty acids (SFA) percentage ($r = -0.007$, $P\text{-value} = 0.964$). (E) Monounsaturated fatty acids (MUFA) percentage ($r = -0.23$, $P\text{-value} = 0.13$). (F) Polyunsaturated fatty acids (PUFA) percentage ($r = -0.157$, $P\text{-value} = 0.308$). (G) Total linoleic acid (n-6) percentage ($r = 0.253$, $P\text{-value} = 0.110$). (H) Total linolenic acid (n-3) percentage ($r = -0.166$, $P\text{-value} = 0.313$). (I) Total n-6:n-3 ratio ($r = 0.378$, $P\text{-value} = 0.018^*$).

TABLE 1: Fat composition and remission rate for enteral nutritional formulas

Reference	Type of enteral nutrition	Energy Kcal/day	Fat% of total calories	Source of oil	LCT% of total calories	LCT% of total fat	MCT% of total calories	MCT% of total fat	SFA% of total calories	SFA% of total fat	MUFA% of total calories	MUFA% of total fat	PUFA% of total calories	PUFA% of total fat	Total n-6% of total fatty acids	Total n-3% of total fatty acids	n-6:n-3 Ratio	RR%
Bamba <i>et al.</i> (2003)[14]	Elemental, Low fat (6 packs of Elental + 6 packs of dextrin)	2400	1.15	Soybean oil	1.15	100	0	0	1.19	16.8	0.27	23.9	0.68	59.3	0	7.7	6.70	80
	Elemental, Medium fat (6 packs of Elental + 3 packs of dextrin+ 3 packs of C-1 dextrin)	2400	6.21	Soybean oil	6.21	100	0	0	1.04	16.8	1.48	23.9	3.68	59.3	51.6	7.7	6.70	40
	Elemental, High fat (6 packs of Elental + 6 packs of C-1 dextrin)	2400	11.27	Soybean oil	11.27	100	0	0	1.89	16.8	2.69	23.9	6.68	59.3	51.6	7.7	6.70	25
Gassull <i>et al.</i> (2002)[11]	Polymeric, high in n-9 MUFA	2307	32	Synthetic Trioleate	30.17	94.28	1.83	5.71	5.16	16.11	25.28	79	2.56	8	6.5	1.5	4.33	27
	Polymeric, high in n-6 PUFA	2266	32	Corn oil	30.17	94.28	1.83	5.71	7.94	24.8	9.02	28.2	14.91	46.6	45	1.6	28.13	63
Glafter <i>et al.</i> (1990)[21]	Elemental (Vivonex)	2500	1.3	Safflower oil	1.3	100	0	0	0.12	9.1	0.18	13.9	1	77.3	76.5	0.8	95.63	86
	Polymeric (Fortison)	2500	36	Vegetable oil (canola & sunflower)	36	100	0	0	3.74	10.4	15.26	42.4	17.55	48.75	43.6	5.2	8.38	42
Léper <i>et al.</i> (2001)[16]	Polymeric, 5% LCT	-	34.8	Soybean & coconut oils	5	13.8	29.8	86.2	30.69	88.2	1.18	3.4	2.92	8.4	7.4	1	7.40	46
	Polymeric, 30% LCT	-	34.8	Palm, Canola, and coconut oils	30	84.7	4.8	15.3	18.72	53.8	12.35	35.5	3.72	10.7	9.5	1.2	7.92	45
Mansfield <i>et al.</i> (1995)[22]	Elemental (E028)	2250	16	Arachis oil	16	100	0	0	2.72	17	8.96	56	4.16	26	20	1	20.00	42
	Semi-elemental (Pepti-2000 LF liquid)	2250	9	Corn (50%) & MCT oils	4.5	50	4.5	50	5.22	58	0.99	11	2.79	31	28.05	0.5	56.10	42
Middleton <i>et al.</i> (1995)[7]	Elemental (E028)	-	15.6	Arachis oil	15.6	100	0	0	2.65	17.1	8.88	56.9	4.06	26	20	1	20.00	92
	Elemental (E028), High LCT	-	35.6	Safflower & canola oils	35.6	100	0	0	3.95	11.1	23.92	67.2	7.73	21.7	17	4.5	3.78	55
	Elemental (E028), High MCT	-	31.6	Safflower, canola, and coconut oils	20.5	64.9	11.1	35.1	13.9	44	13.27	42	4.42	14	11	3	3.67	92
	Semi-elemental (Peptide 2+)	-	33.2	Corn & coconut oils	21.6	65	11.6	34.9	21.71	65.4	3.88	11.7	7.6	22.9	22.5	0.4	56.25	87
Park <i>et al.</i> (1991)[25]	Elemental (E028)	2266	16.47	Arachis oil	16.47	100	0	0	3.01	18.3	8.17	49.6	5.07	30.8	30.2	0.4	75.50	50
	Polymeric (Enteral 400)	2289	36	Arachis (75%) & MCT oils	27	75	9	25	14	38.9	13.57	37.7	8.42	23.4	22.9	0.3	76.33	83
Raouf <i>et al.</i> (1991)[30]	Elemental (E028)	-	16.5	Arachis oil	16.5	100	0	0	2.82	17.1	9.39	56.9	4.29	26	20	1	20.00	75
	Polymeric (Tiosorb)	-	36	Sunflower (22%) & MCT oils	7.9	22	28.1	78	29.09	80.8	1.76	4.9	5.22	14.5	14.4	0.1	144.00	73
Rigaud <i>et al.</i> (1991)[13]	Elemental (Vivonex HN)	2286	0.8	Safflower oil	0.8	100	0	0	0.07	9.1	0.11	13.9	0.62	77.3	76.5	0.8	95.63	71
Royall <i>et al.</i> (1994)[23]	Elemental (Vivonex-TEN)	-	3	Safflower oil	3	100	0	0	0.27	9.1	0.42	13.9	2.32	77.3	76.5	0.8	95.63	84
	Semi-elemental (Peptamen)	-	33	Sunflower (30%) & MCT oil	10	30.3	23	69.7	24.37	73.84	2.22	6.72	6.53	19.8	19.68	0.15	131.20	75
Sakurai <i>et al.</i> (2002)[15]	Elemental, Low fat (Elental)	-	1.5	Soybean oil	1.5	100	0	0	0.24	15.7	0.36	24.2	0.9	59.8	52.1	7.8	6.68	67
	Semi-elemental, High MCT (Twinline)	-	25	Safflower & MCT oil (tricapritin)	7	28	18	72	18.64	74.54	0.97	3.89	5.41	21.64	21.42	0.22	97.36	77
Verma <i>et al.</i> (2000)[31]	Elemental	2500	17	NS	11.05	65	5.95	35	6.63	39	7.82	46	2.55	15	12	-	-	80
	Polymeric	2500	17	NS	11.05	65	5.95	35	6.63	39	7.82	46	2.55	15	12	-	-	67
Gonzalez-Huix <i>et al.</i> (1993)[32]	Polymeric (Edanec HN)	2800	32	Olive oil (55%) & milk fat	27.8	87	4.2	13	13.12	41	13.12	41	5.76	18	-	-	-	80
Lindor <i>et al.</i> (1992)[28]	Semi-elemental (Vital HN)	-	9	Safflower (55%) & MCT (45%)	4.95	55	4.05	45	4.68	52.04	1.1	12.32	3.26	36.3	36.08	0.3	120.27	60
Lochs <i>et al.</i> (1991)[33]	Semi-elemental (Peptisorb)	-	8	Soybean oil (50%) & MCT	4	50	4	50	4.62	57.85	0.97	12.1	2.39	29.9	26.05	3.9	6.68	80
Malchow <i>et al.</i> (1990)[34]	Semi-elemental (Survimed)	-	10	Sunflower	10	100	0	0	1.28	12.8	2.24	22.4	6.6	66	65.6	0.5	131.20	96
Greenberg <i>et al.</i> (1988)[35]	Polymeric (Precision-Isotonic)	-	28	Soybean oil	28	100	0	0	4.4	15.7	6.8	24.2	16.7	59.8	52.1	7.8	6.68	58
Kobayashi <i>et al.</i> (1998)[36]	Elemental (Elental)	-	1.5	Soybean oil	1.5	100	0	0	0.24	15.7	0.36	24.2	0.9	59.8	52.1	7.8	6.68	70
	Polymeric (Clinimel)	-	28	Corn & coconut oils	19.3	69	8.7	31.15	15	53.7	4.8	17.1	8.23	29.5	28.95	0.55	52.64	67
Mantzaris <i>et al.</i> (1996)[12]	Polymeric (Nutrison HE)	-	36	Corn, palm, & coconut oils	34.17	94.92	1.9	5.27	13.45	37.41	11.35	31.54	11.35	31.24	30.63	0.61	50.21	40
O'morain <i>et al.</i> (1984)[37]	Elemental (Vivonex)	-	2.5	Safflower	2.5	100	0	0	0.23	9.1	0.35	13.9	1.9	77.3	76.5	0.8	95.63	100
Gorard <i>et al.</i> (1993)[38]	Elemental (Vivonex TEN)	2100	2.5	Safflower	2.5	100	0	0	0.23	9.1	0.35	13.9	1.9	77.3	76.5	0.8	95.63	77
Okada <i>et al.</i> (1990)[24]	Elemental (Elental)	-	1.5	Soybean	1.5	100	0	0	0.24	15.7	0.36	24.2	0.9	59.8	52.1	7.8	6.68	80
Bodemar <i>et al.</i> (1991)[18]	Polymeric (Semper lowfat)	-	20	Soybean	20	100	0	0	3	15.7	5	24.2	12	59.8	52.1	7.8	6.68	90
Coyle and Sladen (1989)[39]	Polymeric (Enteral 250)	2000-3000	28	Corn oil	28	100	0	0	4	14.8	8	28.1	16	57.1	56.1	1	56.10	67
Ricordan <i>et al.</i> (1993)[19]	Elemental (E028)	-	15.6	Arachis oil	15.6	100	0	0	2.82	17.1	9.39	56.9	4.29	26	20	1	20.00	84
Guo <i>et al.</i> (2013)[40]	Polymeric (Nutrison Fiber)	1500-2000	34	Sunflower, canola, & MCT oils	29	84.6	5	15.4	8.7	25.6	19.2	56.4	6.12	18	-	-	-	85

Zoli <i>et al.</i> (1997)[20]	Semi-elemental (Peptamen)	-	33	Sunflower (30%) & MCT oil	10	30.3	23	69.7	24.37	73.84	2.22	6.72	6.53	19.8	19.68	0.15	131.20	80
Hu <i>et al.</i> (2014)[17]	Semi-elemental (Peptisorb liquid)	-	15	Soy oil % MCT oil	7.95	53	7.05	47	8.3	55.3	1.9	12.8	4.8	31.7	27.6	4.1	6.73	71
Zhu <i>et al.</i> (2013)[41]	Polymeric (Nutrison Fibre)	2037	34	Sunflower, canola, & MCT oils	29	84.6	5	15.4	8.7	25.6	19.2	56.4	6.12	18	-	-	-	67

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TABLE 2: Subgrouping analysis for the effect of fat composition of enteral nutritional feeds on CD remission rate stratified by the level of lipid class

Factor assessed	Subgroup	Number of comparisons (compared enteral feeds)	Pooled RR (95% CI)
Total fat level	Low fat	11	74.09 (63.63, 84.56)
	Moderate fat	21	66.9 (57.53, 76.28)
	High fat	12	64.86 (53.34, 76.38)
MCT level	No MCT	22	69.59 (60.59, 78.59)
	Moderate MCT	10	56.93 (43.8, 70.06)
	High MCT	12	74.83 (67.32, 82.35)
LCT level	Low LCT	11	74.27 (64.1, 84.45)
	Moderate LCT	22	70.55 (62, 79.09)
	High LCT	11	57.21 (45.35, 69.07)
SFA level	Low SFA	11	77.36 (66.55, 88.18)
	Moderate SFA	22	62.83 (54.36, 71.31)
	High SFA	11	69.55 (57.47, 81.62)
MUFA level	Low MUFA	11	77.45 (70.25, 84.65)
	Moderate MUFA	21	65.29 (56.53, 74.05)
	High MUFA	12	64.61 (50.74, 78.48)
PUFA level	Low PUFA	12	76.83 (70.03, 83.63)
	Moderate PUFA	20	65.17 (56.02, 74.31)
	High PUFA	12	64.42 (50.46, 78.37)
Total n-6 level	Low n-6	11	65.45 (52.23, 78.68)
	Moderate n-6	18	61.11 (51.29, 70.93)*
	High n-6	12	78.83 (70.7, 86.97)*
Total n-3 level	Low n-3	10	72.3 (60.26, 84.34)
	Moderate n-3	19	67.84 (58.07, 77.62)
	High n-3	10	60.7 (45.96, 75.44)
n-6:n-3 level	Low n-6:n-3	10	67.9 (54.06, 81.74)
	Moderate n-6:n-3	18	58.94 (48.99, 68.9)*
	High n-6:n-3	11	79.91 (72.31, 87.51)*

-Low level (lower quartile range); moderate level (interquartile range); high level (upper quartile range).

-RR (remission rate); MCT (medium chain triglycerides); LCT (long chain triglycerides); SFA (saturated fatty acids); MUFA (monounsaturated fatty acids); PUFA (polyunsaturated fatty acids).

-One-way ANOVA with multiple correction test have been used to test the significance of difference in RR between the subgroups.

*Difference between subgroups is significant (P-value<0.05).

TABLE 3: Subgrouping analysis for the correlation between the fat composition of enteral nutritional feeds and CD remission rate stratified by the level of remission rates achieved

Factor assessed	Subgroup	Number of comparisons (compared enteral feeds)	r (95% CI)	P-value
RR for total fat correlation	Low RR < 70%	20	-0.03 (-0.46, 0.42)	0.91
	High RR ≥ 70%	24	-0.00 (-0.41, 0.40)	0.99
RR for MCT correlation	Low RR < 70%	20	0.05 (-0.39, -0.48)	0.83
	High RR ≥ 70%	24	-0.28 (-0.62, 0.14)	0.18
RR for LCT correlation	Low RR < 70%	20	-0.05 (-0.49, 0.39)	0.81
	High RR ≥ 70%	24	0.27 (-0.15, 0.60)	0.21
RR for SFA correlation	Low RR < 70%	20	-0.00 (-0.44, 0.44)	>0.99
	High RR ≥ 70%	24	-0.21 (-0.57, 0.21)	0.32
RR for MUFA correlation	Low RR < 70%	20	-0.16 (-0.56, 0.31)	0.51
	High RR ≥ 70%	24	0.23 (-0.19, 0.58)	0.29
RR for PUFA correlation	Low RR < 70%	20	0.13 (-0.33, 0.54)	0.57
	High RR ≥ 70%	24	0.24 (-0.18, 0.59)	0.26
RR for n-6 correlation	Low RR < 70%	19	0.19 (-0.29, 0.59)	0.44
	High RR ≥ 70%	22	0.19 (-0.26, 0.56)	0.41
RR for n-3 correlation	Low RR < 70%	18	-0.08 (-0.53, 0.39)	0.74
	High RR ≥ 70%	21	-0.13 (-0.53, 0.32)	0.59
RR for n-6:n-3 correlation	Low RR < 70%	18	0.30 (-0.19, 0.67)	0.22
	High RR ≥ 70%	21	-0.01 (-0.44, 0.43)	0.98

-r (Pearson correlation coefficient)

-RR (remission rate); MCT (medium chain triglycerides); LCT (long chain triglycerides); SFA (saturated fatty acids); MUFA (monounsaturated fatty acids); PUFA (polyunsaturated fatty acids).