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**Author contributions:** AMS formulated the search strategy, conducted the initial search, assimilated the results into table form, designed the Crohn's disease nutrition assessment flow chart and contributed to the writing of the manuscript. CLW updated the literature search, conducted the literature on dietary intake, re-formulated the table of results and contributed to the writing and review of the manuscript throughout. MCEL provided leadership and critical comment on the intellectual content of the manuscript. All authors approved the final version of the manuscript pre-submission.

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1 **Title of the manuscript:** A narrative review of nutrition assessment in Crohn's disease using  
2 anthropometric, biochemical and dietary indices.

3

4 **Research Snapshot**

5 *Research question:* What is the existing evidence to inform a comprehensive nutrition  
6 assessment of patients with Crohn's disease?

7 *Key findings:* There were heterogeneous findings on nutrition status in Crohn's disease.  
8 Significant deficits in fat mass, fat-free mass and muscle strength were observed. Lower serum  
9 micronutrient levels, micronutrient intakes and fruit and vegetable intakes were reported in  
10 patients with Crohn's disease compared with healthy controls. The findings from this narrative  
11 review have informed the development of a practical clinical guide for comprehensive nutrition  
12 assessment of patients with Crohn's disease.

13 **Abstract**

14 Malnutrition is common in patients with Crohn's disease and negatively impacts immunity and  
15 quality of life. The optimal tools for nutrition assessment in patients with Crohn's disease are  
16 not clearly defined and lead to variations in practice. This review aims to appraise the existing  
17 evidence for nutrition assessment of patients with Crohn's disease compared with healthy  
18 controls and provide a comprehensive guide with relevant measures applicable to clinical  
19 practice. A literature search using Medline, Embase and Scopus from inception to 1<sup>st</sup> October  
20 2018 was conducted. Forty-one papers which assessed body composition, muscle strength,  
21 micronutrient status and/or dietary intake in adults with Crohn's disease compared with an age  
22 and sex-matched healthy population were included. There were heterogeneous findings on  
23 nutrition status in Crohn's disease compared with healthy controls. Only one paper reported a  
24 clinically significant difference for BMI; however significant deficits in fat mass, fat-free mass  
25 and muscle strength were observed in Crohn's disease compared with healthy controls, with  
26 more pronounced differences with increasing disease activity and length of diagnosis. Most  
27 research reported significantly lower serum micronutrients in Crohn's disease compared with  
28 healthy controls. Half of studies measuring micronutrient intake reported lower intakes in  
29 Crohn's disease compared with healthy controls. Fruit and vegetable intake was also lower in  
30 Crohn's disease. Difficulties characterising the type and prevalence of malnutrition exist due  
31 to the heterogeneous nature of Crohn's disease and warrants continued investigation. This  
32 review advocates that a nutrition assessment should include more parameters than weight and  
33 body mass index.

34 **Introduction**

35 Malnutrition is a significant issue in Crohn's disease with an estimated prevalence between 20-  
36 85%, depending on the criteria used.<sup>1</sup> It is associated with increased susceptibility to infections,  
37 gastrointestinal barrier dysfunction, post-operative complications and reduced quality of life.<sup>2-  
38 4</sup>

39 Reasons for malnutrition in Crohn's disease are multifactorial. More than 80% of people with  
40 Crohn's disease experience problems with food<sup>5</sup> and 72% alter their diet as a result,<sup>6</sup> often  
41 leading to insufficient nutrient intakes.<sup>7</sup> Active disease is associated with reduced appetite, low  
42 mood and abdominal pain<sup>1</sup> and mucosal inflammation causes malabsorption due to damaged  
43 intestinal microvilli<sup>8</sup> and increased diarrhea, leading to a loss of electrolytes and fluids.<sup>9</sup>  
44 Systemic inflammation elevates nutrient requirements due to catabolism causing weight loss.<sup>1</sup>  
45 The inflammatory response produces cell-damaging free radicals; micronutrients act as  
46 antioxidants to reduce damage therefore, prolonged inflammation eliminates micronutrients  
47 via excessive utilization.<sup>10</sup> Pharmacological side effects also contribute to malnutrition.  
48 Corticosteroids increase adiposity and are associated with reduced bone mineral density.<sup>11</sup>  
49 Micronutrient deficiencies in Crohn's disease are a further healthcare burden. Inflammation  
50 and suboptimal vitamin D levels are associated with impaired bone mineral density, making  
51 osteoporosis common in Crohn's disease.<sup>12</sup> Dietary deficits in zinc reduce muscle mass and  
52 strength<sup>13</sup> which has deleterious consequences on functional ability and activities of daily  
53 living.<sup>14</sup> Suboptimal circulating concentrations of folic acid, vitamin B12, vitamin C and  
54 selenium in Crohn's disease have also been reported.<sup>15, 16</sup> The risk of malnutrition persists  
55 during the remission phase of the disease; whilst 86% of patients with active disease avoid  
56 certain foods during flare ups, 77% of patients continue to avoid certain foods during remission  
57 to prevent disease relapse.<sup>7</sup>

58

59 In clinical practice, nutrition assessment in patients with Crohn’s disease remains challenging  
60 and most frequently is measured using weight and body mass index (BMI).<sup>17</sup> Weight and BMI  
61 are inadequate measures of malnutrition in Crohn’s disease as systemic inflammation alters  
62 body composition meaning BMI may mask deficits in lean mass due to increased fat mass.<sup>18</sup>  
63 However, there are no guidelines on what components should be included in a comprehensive  
64 nutrition assessment of patients with Crohn’s disease.

65

66 Accurate quantification of nutrition status in Crohn’s disease is essential to enable diet and  
67 nutritional therapy to be targeted to address specific deficits. However, in a study on nutrition  
68 assessment in patients with Crohn’s disease, body composition was measured in only 3%,  
69 hand-grip strength in only 4% and dietary micronutrient intake in 16% of patients, suggesting  
70 that current assessments are limited.<sup>17</sup>

71

72 This narrative review comprehensively appraises the existing evidence for nutrition assessment  
73 of patients with Crohn’s disease, in comparison to a healthy population. It aims to provide a  
74 comprehensive guide with relevant measures applicable to clinical practice.

75

## 76 **Methods**

### 77 Search strategy and study selection

78 The PICOT framework (population, intervention, comparison, outcomes and type of study)<sup>19</sup>  
79 was used to inform the criteria needed to answer the research question “*what evidence exists*  
80 *on the nutrition status of patients with Crohn’s disease and how can this evidence inform*  
81 *nutrition assessment in clinical practice?*”. The search strategy included studies of patients  
82 with Crohn’s disease aged 18 to 64 years using validated assessment methods available in  
83 clinical practice to establish nutrition status compared with a healthy age and sex matched

84 control (HC) group sampled from the same population as those with Crohn's disease. Studies  
85 which reported nutrition status outcomes including body composition, muscle strength and  
86 function, micronutrient status and/or dietary intake were included if they were in the English  
87 language and primary research or systematic reviews.

88 Limiting the search in this way allowed the literature review to establish a 'typical' nutrition  
89 status in healthy people without Crohn's disease and facilitated the comparative quantification  
90 of nutrition status in Crohn's disease. Whilst anthropometric reference ranges for the healthy  
91 population have been developed, these vary depending on assessment methods used.<sup>20</sup>

92 Recruiting a HC group ensures comparisons are made using identical methods to those used  
93 with Crohn's disease patients. Three databases were searched (Medline®, Embase® and  
94 Scopus®) on 1<sup>st</sup> October 2018. Multiple search terms were combined with the Boolean  
95 functions 'and' and 'or' to focus the search.<sup>21</sup> The medical library subject heading terms or  
96 keywords included were [Crohn's disease OR inflammatory bowel disease] AND [nutrition\*  
97 assessment, body composition, body fat, fat mass, anthropometry, lean body weight,  
98 malnutrition, protein energy malnutrition, muscle strength, hand grip, grip strength, trace  
99 element, nutrition\* status, nutrition\* deficiency, vitamin deficiency, mineral deficiency,  
100 dietary intake, diet OR micronutrient]. Filters (English, human and adult aged 18 – 64 years)  
101 were applied to target the search results.

102  
103 Following removal of duplicates, the titles, and where applicable abstracts, were screened for  
104 relevance. Abstracts of relevant titles were reviewed and if a HC group was described the full  
105 text was examined against the inclusion and exclusion criteria.

106

107 Data extraction and synthesis



108 Eligible studies for data synthesis were critically appraised using the ‘assessing methodological  
109 quality’ question checklist in Greenhalgh (2006) and the ‘Critically appraising papers’ chapter  
110 process in Hickson (2008) to assess quality of individual studies.<sup>22, 23</sup> Data were summarized  
111 in a data extraction spreadsheet according to anthropometric, biochemical and dietary  
112 assessment techniques (as per the Nutrition Care Process structure). The Nutrition Care Process  
113 was developed by the Academy of Nutrition and Dietetics and is used by nutrition professionals  
114 to ensure systematic, evidence-based nutrition care.<sup>24</sup> Outcome data was only extracted if  
115 available and clinically relevant. Anthropometric outcomes included: assessment of body  
116 composition using direct anthropometry, bioelectrical impedance analysis (BIA), dual energy  
117 X-ray absorptiometry (DEXA), computed tomography (CT) or magnetic resonance imaging  
118 (MRI) and muscle strength or function measurements. Biochemical outcomes included: plasma  
119 or serum markers of nutrition status including folic acid, vitamin B12, vitamin C, vitamin D,  
120 zinc, copper and selenium. Iron status and albumin were not collected as these are acute phase  
121 reactants and results are difficult to compare with a HC population. Dietary intake outcomes  
122 included: macronutrient and micronutrient intake, food group intake or exclusions of specific  
123 food groups. Where possible the anthropometric, biochemical and dietary assessment methods  
124 and results were compared and critiqued across studies.

125

## 126 **Discussion**

127 To our knowledge, this is the first review appraising the evidence for methods of nutrition  
128 assessment in patients with Crohn’s disease relevant to clinical practice. There were 41 eligible  
129 papers (Figure 1) including 2370 Crohn’s disease patients and 4450 healthy controls. All  
130 studies were cross-sectional in design. The Crohn’s disease cohorts included patients with  
131 active disease and/or disease in remission. Most studies included males and females with the  
132 exception of two studies which reported body composition data of only males<sup>25</sup> or only

133 females.<sup>26</sup> Nevertheless, compared with HC, there were significant differences in body  
134 composition and dietary intake as well as deficits in muscle strength and serum micronutrients.  
135 The findings follow the Nutrition Care Process (anthropometric, biochemical and dietary  
136 assessment structure) and include recommendations for clinical practice (Figure 2).

137

### 138 Anthropometric Outcomes

139 Clinically relevant, and commonly available, anthropometric assessments methods were  
140 reviewed.

141

#### 142 *Body Mass Index*

143 In the majority of studies (n=18) BMI was not significantly different between patients with  
144 Crohn's disease and HC (Table 1)<sup>11, 13, 15, 16, 25, 27-39</sup> but in eight of these studies, significant  
145 differences in body composition were observed.<sup>11, 15, 16, 25, 29, 30, 34, 39</sup> Where significant  
146 differences in BMI existed (n=12), it was always lower in patients with Crohn's disease  
147 compared with HC.<sup>40-51</sup> However, studies rarely assessed clinically significant differences in  
148 BMI, as BMI tended to be reported as a mean rather than as the proportion of patients that had  
149 a clinically underweight BMI (less than 18.5kg/m<sup>2</sup>).<sup>52</sup> Only one study assessed this, and the  
150 prevalence of underweight BMI was 21% in Crohn's disease and 2-4% in HC.<sup>38</sup>

151

#### 152 *Dual Energy X-ray Absorptiometry (DEXA)*

153 Seven studies used DEXA to determine body composition (Table 1).<sup>11, 28-30, 34, 43, 48</sup> DEXA  
154 studies most frequently found no difference in fat mass (FM) between patients with Crohn's  
155 disease and HC<sup>28, 29, 34, 43, 48</sup> but a trend of fat-free mass (FFM) depletion in patients with  
156 Crohn's disease.<sup>11, 34, 48</sup> Superior FFM was observed in patients with newly diagnosed Crohn's  
157 disease compared with HC.<sup>28, 29</sup> The only study to include patients with longstanding Crohn's

158 disease (>5 years) found they had significantly lower FFM compared with HC.<sup>30</sup> These  
159 findings suggest that lean mass depletion in Crohn's disease occurs over time. One study  
160 recruited patients with active Crohn's disease and showed that BMI was significantly lower in  
161 the active disease group as was FFM and FM was non-significantly different when compared  
162 with HC.<sup>48</sup> DEXA scans have ethical and practical limitations. Small amounts of radiation are  
163 absorbed by bone and tissue and increasing exposure to radiation is linked to an increased  
164 cancer risk.<sup>53</sup> Additionally, whole body DEXAs are conducted by specialist radiographers<sup>54</sup>  
165 which presents a practical barrier for routine clinical use.

166

### 167 *Bioelectrical Impedance (BIA)*

168 Eleven studies used BIA to determine body composition (Table 1).<sup>13, 15, 16, 25, 39, 41, 42, 44-47</sup> In  
169 contrast to DEXA, the majority of BIA studies observed a lower FM in patients with Crohn's  
170 disease compared with HC<sup>15, 39, 45-47, 55</sup> but, as Table 1 demonstrates, the results were not  
171 consistent.<sup>13, 16, 25</sup> For FFM, there were no consistent differences between groups.

172 A study from India in patients with active Crohn's disease detected significant deficits in FM  
173 and FFM.<sup>45</sup> However, it lacks external validity to non-Indian populations as recent data  
174 demonstrates significant ethnic disparities in body composition, especially in South Asians.<sup>56</sup>

175 Another study in patients with active Crohn's disease reported lower FM compared with HC.  
176 <sup>39</sup> Thus, there are body composition deficits in active Crohn' disease, highlighting the  
177 importance of considering disease activity in the clinical assessment section of the Nutrition  
178 Care Process.

179

### 180 *CT and MRI*

181 Three studies used medical imaging techniques to further explore body composition.<sup>25, 26, 37</sup>

182 One study undertook umbilicus CT scanning to determine body fat distribution alongside

183 BIA.<sup>25</sup> They found intraabdominal fat was significantly higher in Crohn's disease versus HC.  
184 Furthermore, using MRI, visceral adipose tissue was significantly higher in patients with CD  
185 in remission compared with HC.<sup>26</sup> In another study, CT scans were used to characterise muscle  
186 size.<sup>37</sup> Quadricep muscle cross-sectional area was 14% lower in Crohn's disease compared  
187 with HC however, this was not statistically significant.

188

### 189 *Muscle Strength and Function*

190 Eight studies assessed muscle strength and function.<sup>13, 16, 28, 29, 36, 39, 44, 57</sup> Limited studies have  
191 reported on the potential effect of disease duration on muscle strength or function.<sup>16, 36</sup> In  
192 patients with newly diagnosed Crohn's disease, muscle strength is similar to HC;<sup>29</sup> whereas at  
193 least five years after diagnosis, the literature suggests a reduction in muscle strength and  
194 increased muscle fatigue in active disease or disease in remission.<sup>16, 28, 36, 57</sup> However, disease  
195 activity may impact upon muscle strength.<sup>39, 44</sup>

196

197 There are no reports of change in muscle strength over time in patients with Crohn's disease  
198 compared with HC. It is unknown if reduced muscle strength during active disease is a  
199 temporary reduction in strength associated with a disease flare and if, or how quickly, muscle  
200 strength improves once the disease is in remission. One study found no difference in hand grip  
201 strength but reduced muscle endurance between patients with Crohn's disease in remission for  
202 at least three months compared with HC.<sup>13</sup> Longitudinal research on muscle strength during  
203 periods of active disease and disease remission would provide further understanding on the  
204 impact of acute and chronic inflammation on muscle strength and function. Muscle wasting  
205 and weakness in Crohn's disease results in fatigue and reduced quality of life;<sup>13</sup> both of which  
206 are prevalent in people living with Crohn's disease.<sup>58, 59</sup>

207

208 *Direct Anthropometry*

209 Five studies report the use of direct anthropometry in their methods,<sup>16, 28, 40, 46, 47</sup> however, three  
210 do not report their data.<sup>16, 46, 47</sup> The authors cite strong correlations between their direct  
211 anthropometry results and BIA/DEXA as a justification for presenting only the results of the  
212 latter. However, critics may argue this preferential inclusion of BIA/DEXA results at the  
213 expense of omitting anthropometric data represents reporting bias.<sup>60</sup> Direct anthropometry is  
214 the most frequently used body composition assessment method in clinical practice because of  
215 its low cost and feasibility.<sup>61</sup> Therefore, there is a missed opportunity for this unreported  
216 anthropometric data to be available to clinicians.

217

218 One study calculated body FM percentage using composite measures of skin fold thickness  
219 from the bicep, tricep, subscapular and suprailiac.<sup>28</sup> FM percentage and muscle mass did not  
220 differ significantly between patients with Crohn's disease and HC. This finding that the body  
221 composition of Crohn's disease patients is not inferior to HC is surprising; especially  
222 considering 47% of the group had active disease (CDAI >150). In another study, lower tricep  
223 skin fold thickness was reported in males with Crohn's disease compared with HC males,  
224 whilst there was no difference between females, suggesting there may be sex differences.<sup>40</sup>

225

226 *Summary for Anthropometric Outcomes*

227 The majority of studies found no significant difference in BMI between Crohn's disease and  
228 HC groups<sup>11, 13, 15-17, 25, 27-34, 36, 37, 39, 41</sup> confirming that using BMI alone provide limited data for  
229 an optimal nutrition assessment. Only 14 studies examined FFM and FM, half of which suggest  
230 that FFM is decreased in Crohn's disease<sup>11, 16, 29, 30, 34, 45, 48</sup> and two studies suggests that intra-  
231 abdominal FM is greater in Crohn's disease than HC.<sup>25, 26</sup> A reduction in muscle endurance in  
232 Crohn's disease, and reduced muscle strength during active or longstanding Crohn's disease

233 has been reported.<sup>13, 16, 28, 36, 39, 44, 57</sup> BIA is a more feasible and less invasive measure of body  
234 composition than CT or DEXA scans.<sup>61</sup> However, the routine use of BIA in clinical practice  
235 may be time intensive and financially challenging; thus, mid-arm anthropometry and HGS are  
236 measures that can be readily and cheaply assimilated into clinical practice<sup>61</sup> (Figure 2). As body  
237 composition fluctuates over the disease course, anthropometric assessments should be repeated  
238 to monitor change.

239

#### 240 Biochemical Outcomes

241 Comprehensive plasma micronutrient studies are arguably lacking, with most papers only  
242 quantifying two or three micronutrients.<sup>50, 62-67</sup> Geerling *et al* are the only research group to  
243 measure an extensive range of micronutrients.<sup>28, 29</sup> A major limitation of the 18 micronutrient  
244 studies (Table 2 and Table 3)<sup>27-29, 31-33, 49-51, 57, 62-70</sup> is that only two<sup>15, 16</sup> report deficiency  
245 prevalence for micronutrients other than vitamin D. In clinical practice, patients are not treated  
246 for low micronutrient levels unless they are deficient,<sup>71</sup> thus it would be more clinically relevant  
247 to report the prevalence of micronutrient deficiency rather than mean micronutrient levels.

248

249 Disease activity was reported in all but three of the studies.<sup>63, 65, 66</sup> The remaining studies  
250 reported micronutrient concentrations in either patients with Crohn's disease in remission<sup>28, 62</sup>  
251 or in a heterogenous patient group.<sup>29, 50, 62, 63, 65-67</sup> There were no studies comparing  
252 micronutrient differences between active and remission Crohn's disease, although the validity  
253 of measuring micronutrients in active disease is questionable. In clinical practice, and in the  
254 included studies, micronutrients are quantified in the plasma fraction of blood. However,  
255 inflammatory responses in active Crohn's disease have been found to decrease plasma  
256 micronutrient concentrations by decreasing albumin, independent of their actual body stores.<sup>72</sup>  
257 Micronutrients on circulating erythrocytes provide a more accurate marker of micronutrient

258 stores, particularly for zinc, copper, selenium, vitamin B2 and vitamin B6, but this analysis is  
259 not available in routine clinical practice. Indeed, the transport protein for copper increases in  
260 the acute phase response, which may explain one study's finding of significantly higher serum  
261 levels of copper in patients with Crohn's disease compared with HC.<sup>65</sup>

262

### 263 *Summary for Biochemical Outcomes*

264 The majority of studies reported lower mean levels of circulating micronutrients in patients  
265 with Crohn's disease compared with HC; including folic acid, vitamin B12, vitamin C, vitamin  
266 D, zinc, and selenium.<sup>28, 29, 50, 62, 63, 65, 66</sup> The majority of studies reported higher prevalence of  
267 vitamin D deficiency in patients with Crohn's disease compared with HC.<sup>28, 31, 33, 49, 51, 69</sup> Whilst  
268 the review findings do not support the routine measurement of vitamin B6 and thiamine in all  
269 Crohn's disease patients, consideration must be given to their jejunal absorption site. For  
270 patients with small bowel disease or previous resection, it is common practice to measure  
271 micronutrients absorbed at the jejunum every 3-6 months.<sup>73</sup> See Figure 2 for key micronutrients  
272 that should be measured in Crohn's disease in clinical practice, and their accuracy in reflecting  
273 body stores during the acute phase response.

274

### 275 Dietary Assessment Outcomes

276 Eleven studies assessed dietary intake and the main findings are summarised in Table 4.<sup>15, 16,</sup>  
277 <sup>25, 27-29, 38, 40, 45, 46, 62</sup> Energy intake was similar between patients with Crohn's disease and HC  
278 in eight studies<sup>15-17, 25, 27-29, 62</sup> and lower in the other three studies,<sup>40, 45, 46</sup> especially in patients  
279 with a lower BMI.<sup>40, 45</sup> Although nine studies<sup>15, 25, 28, 29, 38, 40, 45, 46, 62</sup> measured protein intake,  
280 seven of these found no significant differences in intakes between groups (Table 4).<sup>15, 28, 29, 38,</sup>  
281 <sup>40, 46, 62</sup> Patients with Crohn's disease tended to consume a high percentage of total energy from  
282 carbohydrate compared with HC,<sup>29, 40, 45</sup> similar sugar intake<sup>28, 40</sup> and similar fat intake,<sup>15, 17, 25,</sup>

283 <sup>28, 62</sup> with the exception of two studies where the percentage of total energy from fat was lower  
284 in patients with Crohn's disease.<sup>45, 46</sup>

285

286 Six studies measured dietary micronutrient intake; three found no difference between patients  
287 with Crohn's disease and HCs<sup>27-29</sup> whereas another three found lower intakes of beta-carotene,  
288 vitamin B1, vitamin B6, vitamin C, vitamin D, vitamin E, vitamin K, calcium and zinc.<sup>15, 17, 40</sup>

289

290 In two studies, patients with Crohn's disease consumed less fruit and vegetables compared with  
291 HC<sup>16, 40</sup> and this lower intake was associated with a low vitamin C intake. Another study  
292 showed that fiber intake was significantly lower in patients with Crohn's disease compared  
293 with HC, and none of the Crohn's disease group met the recommended fiber intake.<sup>28</sup>  
294 Interestingly, no studies assessed whether low fruit and vegetable intake in Crohn's disease  
295 was associated with a reduction in fiber intake.

296

### 297 *Summary for Dietary Assessment Outcomes*

298 Macronutrient intake is similar between patients with Crohn's disease and HC, however  
299 micronutrient and fiber intakes may be impaired; whether this is due to temporary food  
300 exclusions during active disease or longer-term food exclusion is not described in the literature.

301 Dietary intake assessment is an essential component of nutrition assessment (Figure 2). The  
302 most appropriate dietary assessment is dependent on the patient care setting. If using a diet  
303 history of usual intake, it is important to ask about food exclusion behaviors and frequency of  
304 consumption of key food groups high in micronutrients and fiber to identify the potential for  
305 inadequate nutrient intake.

306

### 307 Limitations of studies in this area.



308 The heterogeneity may be due to underpowered studies, small sample sizes and inadequate  
309 characterization of disease activity. Only three studies report a sample size calculation.<sup>36, 38, 49</sup>  
310 Furthermore, results of no significance may be attributed to type II error secondary to small  
311 sample groups.<sup>74</sup> For example, one study used small Crohn's disease groups of n=5 and n=7.  
312 <sup>41</sup> Limited standardization for disease activity is evident; in 22 studies, the Crohn's disease  
313 group comprised patients with active disease or disease in remission. Sixteen studies analysed  
314 the Crohn's disease group in remission only,<sup>13, 15-17, 27, 28, 31, 32, 34, 40, 43, 45-47, 57, 62</sup> with merely  
315 three studies recruiting a distinct active Crohn's disease group.<sup>44, 45, 48</sup> Nutrition status in active  
316 disease is more likely to be compromised compared with disease in remission due to increased  
317 malabsorption, inflammation and oxidative stress.<sup>75</sup> Evidently, there is a paucity of literature  
318 exploring this. Of the studies that did specifically assess active Crohn's disease, significant  
319 deficits were seen in body composition and dietary intake, warranting more investigation into  
320 the effect of disease activity. The majority of evidence is for patients in remission, thus  
321 potentially underestimating the prevalence of malnutrition in Crohn's disease.

322

323 Efforts were made to counteract the heterogeneity of the included studies. Only studies  
324 comparing Crohn's disease with an age and sex matched HC were included. Limiting the search  
325 in this way allowed the literature review to establish a 'typical' nutrition status in healthy  
326 people without Crohn's disease and facilitated the comparative quantification of nutrition status  
327 in Crohn's disease. The inclusion of a HC group ensures comparisons are drawn using identical  
328 methods to those used in patients with Crohn's disease. Additionally, the use of a local  
329 population increases internal validity of the results. For example, vitamin D status is highly  
330 dependent on latitude<sup>76</sup> so recruiting HC from the local population reduces this confounder.

331

332 Implications for Clinical Practice

333 This review has important implications for clinical practice. The UK IBD Standards (2013),<sup>77</sup>  
334 Gastroenterological Society of Australia Clinical guidelines (2018)<sup>78</sup> and European Society for  
335 Clinical Nutrition and Metabolism guidelines (ESPEN, 2017)<sup>79</sup> all state that all IBD patients  
336 should have access to a dietitian; however, there is a paucity of evidence-based  
337 recommendations on how clinicians should assess malnutrition in Crohn's disease. Guidelines  
338 from the British Society of Gastroenterology (2004)<sup>80</sup> recommend weighing IBD patients as a  
339 minimum requirement for a nutrition assessment and the American Gastroenterological  
340 Association management of Crohn's disease guidelines (2018) recommend routine laboratory  
341 testing to screen for malnutrition.<sup>81</sup> The British Dietetic Association guidelines (2014) on  
342 Crohn's disease do not contain advice on nutrition assessment, but state this should be included  
343 as a priority in future guidelines.<sup>80, 82</sup> Even the most recent ESPEN guidelines (2017)<sup>79</sup> do not  
344 advise specific components that should be included in a nutrition assessment. The absence of  
345 recommended measures that should be included in a nutrition assessment have led to variations  
346 in practice.<sup>17</sup> The creation of an evidence-based nutrition assessment tool (Figure 2), based on  
347 the findings of this narrative review, provides clinicians with recommendations which can be  
348 assimilated into the Nutrition Care Process.

349

350 This review highlights that alternative methods can detect differences in nutrition status where  
351 BMI cannot. If using BMI alone, malnutrition does not appear to be an issue in Crohn's disease.  
352 However, deficits were identified in body composition, muscle strength and serum  
353 micronutrients in Crohn's disease compared with HC. This is of concern as a survey of UK  
354 dietitians found the most frequently used methods for nutrition assessment in Crohn's disease  
355 were weight (98%) and BMI (89%). Only 3% of patients had their body composition measured

356 and 16% had their micronutrient intake quantified as part of their nutrition assessment.<sup>17</sup> Thus,  
357 based on current practice, there is a risk malnutrition in Crohn's disease remains undetected.

358

359 The findings from this review challenge the traditionally held view that malnutrition in Crohn's  
360 disease always presents as underweight with dietary protein-energy deficits.<sup>83</sup> Insignificant  
361 differences in protein and energy consumption was commonly reported<sup>15, 17, 28, 45, 62</sup> and  
362 increased intraabdominal fat was observed in the imaging studies included in this review. The  
363 clinical importance of central obesity is its etiological link to cardiovascular disease.<sup>84</sup> Long-  
364 term conditions involving inflammatory pathophysiology have been associated with  
365 overweight and obesity. This is due to sustained activation of pro-inflammatory cytokines  
366 TNF- $\alpha$  and IL-6 over time leading to increased adipocytes.<sup>85</sup> Moreover, recent findings have  
367 demonstrated a high prevalence of obesity in IBD in remission;<sup>6</sup> however, further metabolic  
368 studies are required before conclusions can be drawn on whether FM accretion occurs in  
369 Crohn's disease in remission.

370

### 371 Need for Future Research

372 Future studies should include a sample size calculation to ensure studies are adequately  
373 powered. Clearly defined Crohn's disease activity groups, with a distinction between active  
374 disease and remission are also important. Furthermore, research quantifying nutrition status in  
375 active disease, remission and pre-surgical Crohn's disease is needed to characterize nutrition  
376 deficits across the spectrum of Crohn's disease to prioritize appropriate nutrition assessment  
377 provision in healthcare. There is insufficient evidence to determine if Crohn's disease  
378 phenotype (inflammation location, presence of strictures or penetrating disease)<sup>86</sup> has a  
379 definitive impact on nutrition status. With research priorities moving towards precision

380 medicine,<sup>87</sup> future studies should investigate Crohn's disease phenotype, and this may facilitate  
381 a personalized prediction of nutrition risk.

382

383 Novel methods of measuring body composition via imaging should be explored. Abdominal  
384 CT and MRI scans can precisely locate specific deficits in muscle and FM and are routinely  
385 conducted in Crohn's disease patients for clinical monitoring,<sup>88</sup> but it is expensive to extend  
386 this method to HC.<sup>61</sup> This limitation is highlighted by the authors of one study without a power  
387 calculation and a comparison of 24 MRI scans in Crohn's disease patients with only 11 HC  
388 scans.<sup>26</sup> Indeed there have been several recent publications reporting CT body composition in  
389 Crohn's disease patients<sup>89-91</sup> but none in comparison with a HC group. Further studies should  
390 explore readily available CTs and MRIs conducted in the clinical setting and assess their  
391 feasibility for use in body composition assessments.

392

393 Once the evidence-base has comprehensively characterized nutrition deficits between active  
394 Crohn's disease and remission, further research must explore how best to correct these deficits.  
395 For active Crohn's disease patients this may involve lifestyle advice on increasing muscle  
396 strength with the use of nutritional supplements, thus reducing post-operative morbidity.<sup>92</sup> In  
397 addition to the historical issue of muscle wasting in Crohn's disease,<sup>83</sup> attention is needed to  
398 better manage overweight and obesity in remission.<sup>6</sup> Consequently, future research questions  
399 may address whether active Crohn's disease patients require a different nutrition management  
400 approach from patients in remission.

401

## 402 **Conclusion**

403 Malnutrition is a significant issue in Crohn's disease with deleterious consequences. However,  
404 as this narrative review demonstrates difficulties characterizing the type and prevalence of

405 nutrition deficits in this population exist due to the heterogeneous nature of Crohn's disease.  
406 This review advocates that a nutrition assessment should include more than weight and BMI.  
407 As a result of the findings from this narrative review, an evidence-based comprehensive  
408 nutrition assessment tool for Crohn's disease has been developed and will help guide clinician  
409 practice.

410

411 Further research is required to elucidate the metabolic mechanisms for the deficits in nutrition  
412 status observed and how to correct them with medical and lifestyle management.

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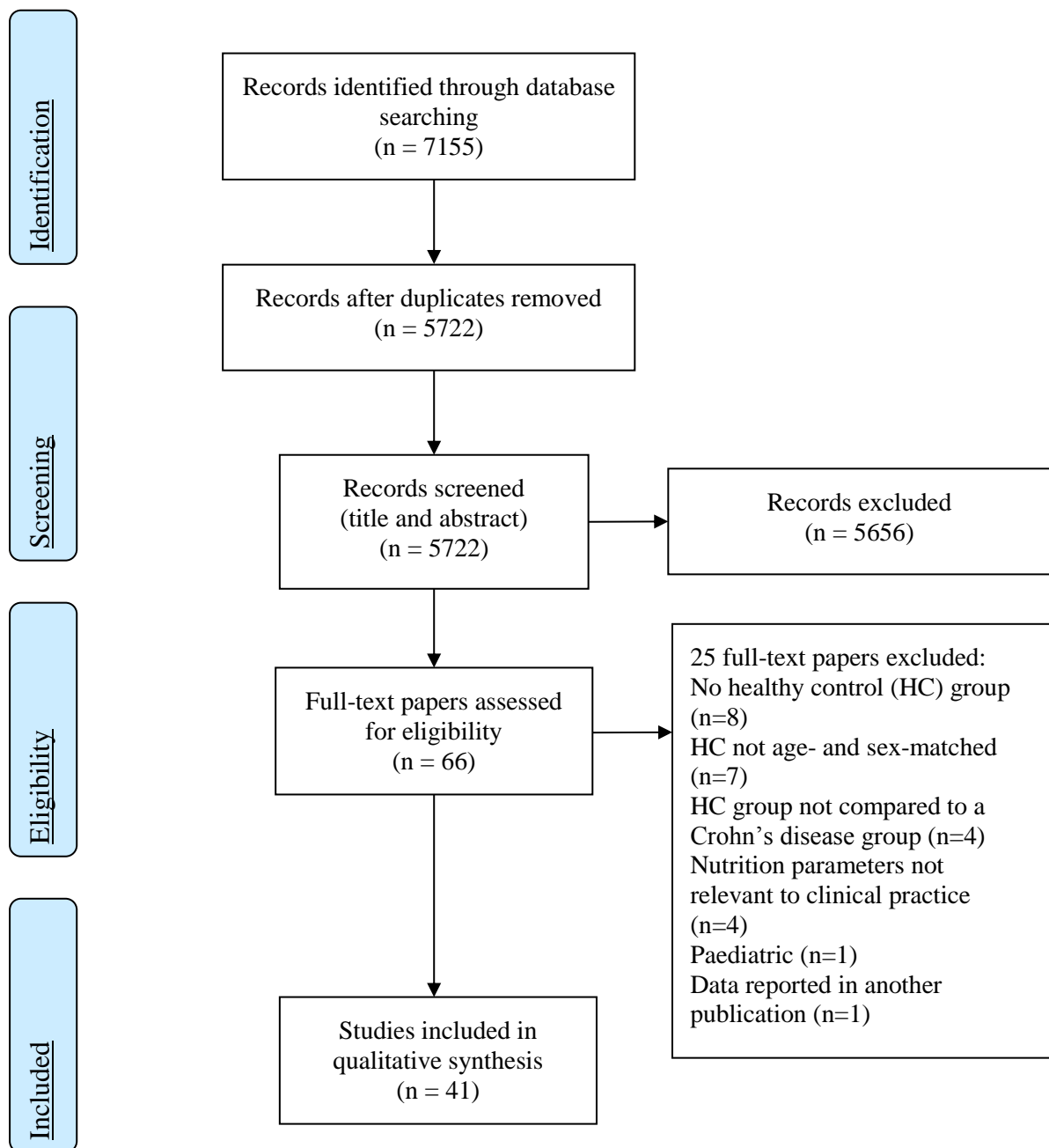
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**Figure 1:** PRISMA flow diagram for studies included in the narrative review on nutrition assessment in Crohn's disease.

Anthropometry		
Measure	Methods	Reference ranges
<b>Hand-grip strength (HGS)</b> <sup>13,16,44</sup> Reliable measure of muscle strength and muscle reserve.	Different methods exist for HGS; the most important consideration is to use the same method consistently at each measure to improve reliability. The following method is recommended by the American Society of Hand Therapists. Measure the non-dominant arm with the patient sitting with their elbow at 90° and gripping the dynamometer with their greatest effort, as shown below. <sup>95</sup>	If the highest of three readings is <85% of the population reference then this is classified as 'protein malnutrition'. <sup>100</sup> If using reference ranges from your HGS manufacturer, then ensure you also follow the method provided by your manufacturer for accurate interpretation.
<b>Mid-upper arm circumference (MUAC)</b> <sup>16,30,42,48,49</sup> Compared to body mass index (BMI), MUAC is less affected by fluid status and so is a more sensitive marker of nutritional depletion in those with oedema and ascites.	MUAC measurement, taken from the non-dominant arm to the nearest 0.1 cm using plastic tape as shown below. <sup>94</sup> Inaccuracies in measurement can be minimised with adherence to a standardised protocol, such as that shown below. There is a risk of poor inter-rater reliability in mid-arm anthropometry, <sup>97</sup> ideally patients should have follow-up anthropometry conducted by the same clinician at each review.	Mid-arm anthropometry values ≤5 <sup>th</sup> percentile of the population reference range for age and sex are categorised as malnourished. <sup>101</sup>
<b>Tricep skin fold (TSF)</b> <sup>16,28,40,46,47</sup> Skinfold anthropometry has been validated in chronic diseases and is a more reliable predictor of body adiposity than BMI.	Measure the non-dominant arm. The method is shown below is recommended by The World Health Organisation. <sup>73</sup>	TSF values >95 <sup>th</sup> percentile are categorised as high. <sup>101</sup>
<b>Mid-arm muscle circumference (MAMC)</b> <sup>16,28,40,46,47</sup> Derived from MUAC and TSF, this measure has high predictive validity; greater morbidity and mortality are observed in those with malnourished MAMC readings.	MAMC is a composite measure of MUAC and TSF and is calculated using the equation below: $MAMC (cm) = MUAC (cm) - (TSF (mm) \times (\pi/10))^{96}$	Mid-arm anthropometry values ≤5 <sup>th</sup> percentile of the population reference range for age and sex are categorised as malnourished. <sup>101</sup>
<b>Bioelectrical impedance (BIA)</b> <sup>13,15,16,25,39,41,42,44,45,46,47</sup> BIA is a portable, non-invasive method for assessing body composition including fat free mass (FFM) and fat mass (FM).	Electric flow is passed through the body which determines the electrical resistance (impedance) of different tissues. BIA estimates total body water (TBW) from electrical impedance. Thereafter, FFM and FM are estimated. The determination of TBW is affected by hydration status; therefore, participants should be instructed to urinate prior to the test to improve test validity. <sup>97</sup> Follow the manufacturer's guide when conducting BIA. There are clinical guidelines which consider the different types of BIA machines. <sup>98,99</sup>	Depleted FFM and FM are characterised by readings ≤5 <sup>th</sup> percentile for age and sex. High FM is >25.6% body fat in men and >35.7% in women. <sup>20</sup>
<b>Novel imaging methods</b> <sup>25,26,37</sup> e.g. computerised tomography (CT) or magnetic resonance imaging (MRI).	Images collected as part of clinical monitoring could be interpreted by radiographers to calculate abdominal fat mass.	No reference ranges have been developed for abdominal fat mass using CT or MRI. However, reference ranges using dual energy X-ray absorptiometry (DEXA) in healthy 20-30 year olds may provide an interpretation guide. <sup>102</sup>

Anthropometry techniques		
Mid-upper arm circumference (MUAC)	Tricep skin fold (TSF)	Hand-grip strength (HGS)
 <ol style="list-style-type: none"> <li>1. With elbow of the non-dominant arm at 90°, the length from the acromion (in the shoulder) to the olecranon process (elbow) is measured. Mid-point marked (as shown above).</li> <li>2. Measure the circumference at the mid-point mark. Repeat this measure three times.</li> </ol>	 <ol style="list-style-type: none"> <li>1. With the non-dominant arm relaxed, a vertical pinch of the skin is made at the mid-point using the thumb and index finger of the left hand.</li> <li>2. The caliper is applied at a 90° angle to 1cm below the skinfold.</li> <li>3. Release the tension of the caliper and take the reading. Steps 2-3 should be repeated three times.</li> </ol>	 <ol style="list-style-type: none"> <li>1. The position for HGS test. The reading is generated following maximal static force to the dynamometer.</li> </ol>

Micronutrients		Dietary	
Measure	Interpretation	Method	Interpretation
Thiamine <sup>73</sup>	Serum levels can be rapidly depleted after 10 days of poor oral intake. Therefore, interpret with caution if acutely malnourished. Evidence from this review does not support the routine measurement of thiamine but consideration must be given to its jejunal absorption site. For patients with small bowel disease or previous resection, measure every 3-6 months.	24-hr recall <sup>45</sup>	Method determines intake for the preceding day only, which increases recall reliability as no reliance on long term memory. However, variability in daily dietary patterns is not captured in a 24-hr recall, limiting inferences to habitual dietary intake. <sup>103</sup> Method well-suited to inpatients to measure day-to-day changes in portion sizes consumed, and energy and protein intake. <sup>103</sup>
Vitamin B6 <sup>73</sup>	Low levels indicative of chronic poor food intake and malabsorption. Evidence from this review does not support the routine measurement of vitamin B6, but consideration must be given to its jejunal absorption site. For patients with small bowel disease or previous resection, measure every 3-6 months.	Diet history of usual intake <sup>45</sup>	Diet history highlights major nutrition issues, such as food group exclusion/restriction and irregular food patterns <sup>103</sup> which are common in Crohn's disease. <sup>7</sup> Restricted food groups will give some information as a proxy to micronutrient intake. For example, a low dairy and dairy-alternative intake may be indicative of inadequate calcium intake. Method is used as standard dietary assessment method in clinical practice. <sup>103</sup> However, patient recall bias is a limitation of verbal diet histories <sup>104</sup> , if concerned about under- or over-reporting, consider validating diet history against another dietary assessment technique, for example, food records. <sup>103</sup>
Folate <sup>28,29,50,67</sup>	Low levels indicative of malabsorption. Sulfasalazine impairs folate absorption.	3 to 7-day food record <sup>45,25,38,46</sup>	Well-suited to an outpatient setting to measure specific nutrients, e.g. fiber and sugar intake, if inputted into a dietary software package and analysed. <sup>103</sup> Can be used alongside a symptom diary to identify trigger foods. Consider which patients this method is suitable for, anxious patients with a high level of stress related to food may not benefit from this method. Patients need a high level of motivation and literacy to record household measures and portion sizes. <sup>103</sup> The gold standard method for recording dietary intake and quantifying nutrient intake is a 7-day food diary. <sup>103</sup> However, this can be burdensome for patients. Only 3-days of food records are required for accurate quantification of energy intake <sup>106</sup> so Nutrients with greater variability in intakes may require a longer recording period <sup>103</sup> , so careful consideration of the diary's purpose should be considered before instructing a patient to complete a food diary.
Vitamin B12 <sup>28,29,50,67</sup>	Consider measuring more regularly in patients with ileocaecal resection as this is the main site of vitamin B12 absorption. Consider measuring more regularly in patients avoiding meat and dairy as major source of vitamin B12.	Food frequency questionnaire (FFQ) <sup>6,27,28,29,40,62</sup>	An FFQ contains a list of foods for patients to record how often they consume each food. This method is useful for highlighting if certain food groups are being excluded (e.g. fruit and vegetables), which could be a proxy marker for micronutrient intake. It also establishes patterns of food choice. <sup>103</sup> The benefit of this method is that it can be completed outside of clinic time by the patient. Results can also encourage patient-clinician discussions on the overall balance of the diet. <sup>103</sup> Response validity to FFQs is limited if food lists are too long and complex. <sup>107</sup>
Vitamin C <sup>28,29,66</sup>	Reduced during periods of oxidative stress (such as intestinal inflammation). Also assess if fruit and vegetables are being restricted via a diet history.		
Vitamin D <sup>27,28,31,32,33,40,51,57,68,69,70</sup>	Consider seasonal variation in readings.		
Zinc <sup>28,29,62,64,65</sup>	Decreased in acute phase response (due to reduction in carrier protein albumin). Also decreased via gastrointestinal losses of chronic diarrhoea.		
Copper <sup>28,29,64,65</sup>	May increase during active disease in acute phase response. Therefore, measure when disease stable.		
Selenium <sup>16,28,29,63,65,66</sup>	Decreased in acute phase response (due to reduction in carrier protein albumin).		

**Figure 2:** Components of a comprehensive nutrition assessment tool in Crohn's disease  
Components are based on evidence from studies included in the narrative review.

Table 1. Assessment of body composition in patients with Crohn's disease (CD) compared with an age and sex-matched healthy control group (HC).

Author, Year, Country	Participants (n)		Disease activity	Tech- nique	BMI <sup>a</sup> (kg/m <sup>2</sup> )		FM <sup>c</sup> (kg)		%FM <sup>d</sup>		FFM <sup>e</sup> (kg)		VAT <sup>f</sup> (cm <sup>2</sup> or mL) mean (SD <sup>b</sup> )	
	CD	HC			CD	HC	CD	HC	CD	HC	CD	HC	CD	HC
Capristo <i>et al.</i> 1998 <sup>46</sup> Italy	43	60	Remission	BIA <sup>g</sup>	21.5*	23.7	12.2*	17.0	20.4***	25.5	49.2	50.4		
Capristo <i>et al.</i> 1998 <sup>47</sup> Italy	18	20	Remission	BIA <sup>g</sup>	20.5*	23.6	12.6*	17.4	22.0*	26.4	45.6	49.5		
Mingrone <i>et al.</i> 1999 <sup>55</sup> Italy	18	12	Mixed	BIA <sup>g</sup>	21.6*	23.8	13.8***	19.0			48.0	47.7		



Wiroth <i>et al.</i> 2005 <sup>13</sup>	41	25	Remission	BIA <sup>g</sup>	22.1	24.0	13.0	16.4	18.3	21.7	56.2	58.0
France	24F <sup>i</sup>	15F <sup>i</sup>			22.1	21.4	15.3	16.0	25.8	27.5	42.9	41.0
Filippi <i>et al.</i> 2006 <sup>15</sup>	54	25	Remission	BIA <sup>g</sup>	22.1	22.1	14.4*	16.6			49.2	46.7
France												
Valentini <i>et al.</i> 2008 <sup>16</sup>	94	61	Remission	BIA <sup>g</sup>	22.3	23.7	12.7	15.2			58.5**	67.4
Austria, Germany & Italy	61F <sup>i</sup>	41F <sup>i</sup>			22.1	21.8	18.1	16.6			*	44.1
											43.9	
Benjamin <i>et al.</i> 2011 <sup>45</sup>	80	100	Remission	BIA <sup>g</sup>	21.6**	23.9	13.4	14.1	21.9	21.5	43.3**	48.9
India	43		Active		18.8*	21.6	8.2*	14.1	15.7*	21.5	40.7*	48.9

Rizzi <i>et al.</i>	78	75	Mixed	BIA <sup>g</sup>										
2012 <sup>39</sup>	42M <sup>h</sup>	41M <sup>h</sup>			22	22	12 <sup>**</sup>	22			53	49		
Italy	36F <sup>i</sup>	34F <sup>i</sup>			21	22	15 <sup>*</sup>	21			37	40		
Lu <i>et al.</i>	150	256	Mixed	BIA <sup>g</sup>										
2016 <sup>44</sup>	109	115M <sup>h</sup>			19.8 <sup>***</sup>	23.9	9.9 <sup>***</sup>	16.8						
China	M <sup>h</sup>	139F <sup>i</sup>			19.1 <sup>***</sup>	22.1	12.7 <sup>***</sup>	17.2						
	41F <sup>i</sup>													
Katznelson <i>et al.</i> 2003 <sup>25</sup>	20M <sup>h</sup>	20M <sup>h</sup>	Mixed	BIA <sup>g</sup> & CT <sup>j</sup>	24.2	23.3			21.0 <sup>*</sup>	17.7			115 <sup>***</sup>	69
USA														
Buning <i>et al.</i> 2015 <sup>26</sup>	31F <sup>i</sup>	19F <sup>i</sup>	Mixed	MRI <sup>k</sup>	25.9	23.8							1185 <sup>*</sup>	941
Germany														
Geerling <i>et al.</i> 1998 <sup>28</sup>	32	32	Remission	DEXA <sup>l</sup>	23.2	24.6	17.6	19.7	26.1	28.7	48.6	49.7		
	14M <sup>h</sup>	14M <sup>h</sup>			22.8	26.4	13.2	18.4	18.4 <sup>*</sup>	23.5	56.4	60.5		

The Nether- lands	18F <sup>i</sup>	18F <sup>i</sup>			23.4	23.3	20.9	20.7	32.1	32.7	42.6	41.2
Tjellesen <i>et al.</i> 1998 <sup>34</sup>	31	88	Remission	DEXA <sup>1</sup>	23.5	23.9	20.3	19.2	27.8*	23.1	51.8*	62.2
Denmark	18F <sup>mi</sup>	69F <sup>i</sup>			21.1	22.0	21.6	21.3	38.8*	32.8	34.9*	42.4
Geerling <i>et al.</i> 1999 <sup>30</sup>	20 <sup>n</sup>	20	Mixed	DEXA <sup>1</sup>	22.7	23.0	19.4	19.5	28.3	29.2	49.2*	46.8
	40 <sup>o</sup>	40	Mixed		22.8	24.0	17.7	18.9	26.7	27.7	47.1*	49.9
The Nether- lands												
Geerling <i>et al.</i> 2000 <sup>29</sup>	23	23	Mixed	DEXA <sup>1</sup>	22.2	22.7	18.5	19.0	27.5	28.7	48.9*	46.9
The Nether- lands												
Jahnsen <i>et al.</i> 2003 <sup>11</sup>	60	60	Mixed	DEXA <sup>1</sup>	23.3	23.4	20.8	20.0	31.4	29.2	44.5*	48.8
	24M <sup>h</sup>	24M <sup>h</sup>			23.2*	24.8	16.7	18.1	23.1	22.6	54.2**	61.0
Norway	36F <sup>i</sup>	36F <sup>i</sup>			23.4	22.5	23.5	21.3	37.0	33.6	*	40.7

											38.0**	
Cuoco <i>et al.</i>	13	20	Active	DEXA <sup>l</sup>	19.8**	23.4	21.1	19.6			35.8**	49.6
2008 <sup>48</sup>											*	
Italy												
Schneider <i>et al.</i>	82	50	Remission	DEXA <sup>l</sup>	21.1*	22.2	16.2	16.1	25.7	25.9	43.8	46.7
2008 <sup>43</sup>												
France												

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<sup>a</sup> BMI body mass index, <sup>b</sup> SD standard deviation, <sup>c</sup> FM fat mass, <sup>d</sup> %FM percentage fat mass, <sup>e</sup> FFM fat free mass, <sup>f</sup> VAT visceral adipose tissue, <sup>g</sup> BIA bioelectrical impedance analysis, <sup>h</sup> M male, <sup>i</sup> F female, <sup>f</sup> CT computed tomography, <sup>k</sup> MRI magnetic resonance imaging, <sup>l</sup> DEXA dual energy X-ray absorptiometry, <sup>m</sup> weighted mean reported, <sup>n</sup> newly diagnosed, <sup>o</sup> longstanding disease > 5 years.

CD versus HC \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ .

Table 2. Blood markers of nutrition status in patients with Crohn's disease (CD) compared with an age and sex-matched healthy control group (HC).

Author, Year, Country	Participants		Disease activity	Folic acid (nmol/L)		Vitamin B12 (pmol/L)		Vitamin C ( $\mu$ mol/L)		Zinc ( $\mu$ mol/L)		Copper ( $\mu$ mol/L)		Selenium ( $\mu$ mol/L)	
	CD	HC		Mean (SD <sup>a</sup> )	Mean (SD <sup>a</sup> )	Mean (SD <sup>a</sup> )	Mean (SD <sup>a</sup> )	Mean (SD <sup>a</sup> )	Mean (SD <sup>a</sup> )	Mean (SD <sup>a</sup> )	Mean (SD <sup>a</sup> )				
Kallel <i>et al.</i> (2011) <sup>5</sup> <sup>0</sup> Tunisia	89	103	Mixed	19.3 (6.9)	18.4 (7.0)	218 <sup>**</sup> *	279 (125)								
Yakut <i>et al.</i> (2010) <sup>67</sup> Turkey	45	53	Mixed	17.4 (12.0)	22.4 (7.5)	207 (122)	252 (132)								

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Geerling	20 <sup>b</sup>	20	Remission							12.4	13.0				
<i>et al.</i>	32 <sup>c</sup>	32	Mixed							12.0*	13.1				
(1999) <sup>62</sup>															
The															
Nether-															
lands															
Geerling	23 <sup>b</sup>	23	Mixed	10.7	12.4	225*	270	47.6	54.5	12.3	12.9	23.6	22.2	0.92	0.99
<i>et al.</i>				(9.1)	(5.6)	(60.7)	(88.2)	(17.7)	(22.9)	(3.0)	(1.3)	(8.9)	(7.4)	(0.16)	(0.16)
(2000) <sup>29</sup>															
The															
Nether-															
lands															

Geerling	32	32	Remission	14.4	13.4	403	263	35.3**	57.8	12.0**	13.4	19.1	20.1	0.86**	1.30
<i>et al.</i>				(13.4)	(5.88)	(282)	(91.5)	*	(22.3)	(1.7)	(2.2)	(4.6)	(6.9)	*	(0.15)
(1998) <sup>28</sup>								(25.8)						(0.14)	
The															
Nether-															
lands															
Hinks <i>et</i>	11	22	Active							12.7	12.9	17.3	16.3		
<i>al.</i>										(1.8)	(1.7)	(3.3)	(2.6)		
(1988) <sup>64</sup>															
UK <sup>d</sup>															
Ringstad	47 <sup>b</sup>	123	Not stated												
<i>et al.</i>	27 <sup>e</sup>	76 <sup>e</sup>								14.4	12.7	20.8**	15.8	1.31**	1.45
(1993) <sup>65</sup>	20 <sup>f</sup>	47 <sup>f</sup>								13.5	12.9	*	18.1	*	1.37
Norway												23.8 <sup>†</sup>		1.24 <sup>†</sup>	

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Gentsche	351	853	Not stated			1.37**	1.41
<i>w et al.</i>						*	(0.01)
(2012) <sup>63</sup>						(0.01)	
New Zealand							
Wendlan	37	37	Mixed	64.0**	78.4	0.81	0.80
<i>d et al</i>				(4.6)	(2.9)	(0.04)	(0.04)
(2001) <sup>66</sup>							
Canada							

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<sup>a</sup> SD standard deviation, <sup>b</sup> newly diagnosed Crohn's disease, <sup>c</sup> diagnosed Crohn's disease for more than 5 years, <sup>d</sup> UK United Kingdom, <sup>e</sup> M male,

<sup>f</sup> F female.

CD versus HC \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$



Table 3. Vitamin D concentration and prevalence of deficiency in patients with Crohn's disease (CD) compared with an age and sex-matched healthy control group (HC).

Author, Year	Country	Participants		Disease activity	Vitamin D nmol/L		Vitamin D 25(OH)D <sub>3</sub> ng/mL		Suboptimal micronutrient level		Suboptimal criteria
		(n)			mean (SD <sup>a</sup> )		mean (SD <sup>a</sup> )		n (%)		
					CD	HC	CD	HC	CD	HC	
Geerling <i>et al.</i> (1998) <sup>28</sup>	The Netherlands	32	32	Remission					18 <sup>**</sup> (56.0)	9 (28.0)	< 70 nmol/L (summer and autumn) or < 25 nmol/L (winter)
Ardizzone <i>et al.</i> (2000) <sup>68</sup>	Italy	51	30	Mixed			19.5 (7.5)	18.1 (7.9)			
Duggan <i>et al.</i> (2004) <sup>27</sup>	Ireland	44	44	Remission	75.0* (28.7)	105.3 (55.5)			3 <sup>‡</sup> (6.8)	2 (4.5)	< 40 nmol/L

Tajika <i>et al.</i> (2004) <sup>51</sup>	Japan	33	15	Mixed		15.2 (6.5)	16.9 (5.2)	9 (27.3)	1 (6.7)	< 10 ng/mL
Gilman <i>et al.</i> (2006) <sup>31</sup>	Ireland	47	47	Remission	71.6*** (33.0)	113 (69.2)		9* (19.1)	2 (4.3)	< 40 nmol/L
Joseph <i>et al.</i> (2009) <sup>49</sup>	India	34	34	Mixed		16.3* (10.8)	22.8 (11.9)	27* (79.0)	17 (50.0)	< 20 ng/mL
Suibhne <i>et al.</i> (2012) <sup>33</sup>	Ireland	81	70	Mixed	47.8 (27.3)	51.9 (24.5)		51 (63.0)	36 (51.0)	< 50 nmol/L
Grunbaum <i>et al.</i> (2013) <sup>32</sup>	Canada	34	48	Remission	71.1 (31.1)	68.3 (26.2)		10 <sup>‡</sup> (29.4)	11 (22.9)	< 50 nmol/L

Salacinski <i>et al.</i> (2013) <sup>57</sup>	USA	19	19	Remission	32.0 (9.1)	35.3 (11.1)	2 <sup>‡</sup> (10.5)	1 (5.3)	< 20 ng/mL
Dumitrescu <i>et al.</i> (2014) <sup>69</sup>	Romania	14	94	Mixed	23.0* (10.0)	31.0 (13.0)	5 <sup>‡</sup> (36.0)	19 (20.0)	< 20 ng/mL
Tan <i>et al.</i> (2014) <sup>70</sup>	China	107	122	Mixed	11.6* (5.0)	12.9 (4.4)			

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<sup>a</sup> SD standard deviation, <sup>‡</sup> no statistical test reported comparing CD and HC. CD versus HC \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$

Table 4. Characteristics and outcomes of studies which assessed dietary intake of patients with Crohn's disease (CD) compared with an age and sex-matched healthy control group (HC).

Study, Country	Assessment method	Participants (n)	Disease activity	Outcome measures	Differences compared with HC
Capristo <i>et al.</i> 1998 <sup>46</sup> , Italy	7-day food record	CD n=43 HC n=60	Remission	Macronutrient intake	CD consumed less energy and less %TE <sup>a</sup> from fat than HC.
Geerling <i>et al.</i> 1998 <sup>28</sup> , The Netherlands	FFQ <sup>b</sup>	CD n=32 HC n=32	Remission	Macro- and micronutrient intake	Macro- and micronutrient intake similar except fibre and phosphorus intake lower in CD.
Geerling <i>et al.</i> 1999 <sup>62</sup>	FFQ <sup>b</sup> & diet history	CD n=20 <sup>c</sup> CD n=32 <sup>d</sup> HC n=52	Remission Mixed	Macronutrient intake	Newly diagnosed CD had higher total carbohydrate and mono and disaccharide intake

The Netherlands					than controls. Those with longstanding CD dietary intake was similar to HC.
Geerling <i>et al.</i> 2000 <sup>29</sup> , The Netherlands	FFQ <sup>b</sup>	CD n=23 <sup>c</sup> HC n=23	Active n=4 Remission n=19	Macro- and micronutrient intake	CD %TE <sup>a</sup> from CHO <sup>e</sup> higher, lower intake of alcohol and PUFA <sup>f</sup> than HC. Micronutrient intake not different. CD with active disease had higher %TE <sup>a</sup> from CHO <sup>e</sup> than CD in remission.
Katznelson <i>et al.</i> 2003 <sup>25</sup> , USA	5-day food record	CD n=20 (male only) HC n=20	Mixed	Macronutrient intake	%TE <sup>a</sup> from protein lower in CD.
Duggan <i>et al.</i> 2004 <sup>27</sup> , Ireland	FFQ <sup>b</sup>	CD n=44 HC n=44	Remission	Calcium & vitamin D intake	Dietary intake not different.

Lomer <i>et al.</i> 2004 <sup>38</sup> , UK	7-day food record	CD n=91 HC n=91	Remission	Macronutrient and iron, vitamin C intake	Macronutrient intake similar. Lower intake of iron, non-haem iron, iron from breakfast cereals and vitamin C. Similar intake of iron from animal tissue.
Filippi <i>et al.</i> 2006 <sup>15</sup> , France	3-day food record	CD n=54 HC n=25	Remission	Macro- and micronutrient intake, RDA	Macronutrient intake not different, CD had lower intake of beta-carotene, vitamin C and female CD had lower intake of vitamins B1, B6 and Mg <sup>g</sup> compared with HC females. Significantly less CD met RDA <sup>h</sup> for Zn <sup>i</sup> , Mg <sup>g</sup> , Vitamins C, B6, E, B1, B-carotene compared with HC.
Guerreiro <i>et al.</i> 2007 <sup>40</sup> , Portugal	FFQ <sup>b</sup>	CD n=87 HC n=80	Remission	Macro- and micronutrient intake, food exclusion behaviours	Lower energy (also lower BMI <sup>j</sup> ) and fibre intake. %TE <sup>a</sup> from CHO <sup>e</sup> higher and from fat lower than HC. Lower calcium, vitamins C, D, E, K, PUFA <sup>f</sup> intakes in CD (not controlled for energy

intake). Fruit and vegetables exclusion associated with low vitamin C & E intakes.

Valentini <i>et al.</i> 2008 <sup>16</sup> , Austria, Germany & Italy	FFQ <sup>b</sup>	CD n=94 HC n=61	Remission	Food group intake	CD eat less fruit, vegetables, milk products, fish and alcoholic drinks than HC. Similar intake of meat, sweets, snacks, fast food, oils/fats.
Benjamin <i>et al.</i> 2011 <sup>45</sup> , India	24hr-food recall	CD n=123 HC n=100	Active n=43 Remission n=80	Macronutrient intake	Macronutrient intake of active and remission CD not different. CD energy and protein intake lower than in HC, higher %TE <sup>a</sup> from CHO <sup>e</sup> and less from fat.

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<sup>a</sup> %TE percentage of total energy, <sup>b</sup> FFQ food frequency questionnaire, <sup>c</sup> newly diagnosed Crohn's disease, <sup>d</sup> longstanding Crohn's disease > 5 years, <sup>e</sup> CHO carbohydrate, <sup>f</sup> PUFA polyunsaturated fatty acids, <sup>g</sup> Mg magnesium, <sup>h</sup> RDA recommended daily allowance, <sup>i</sup> Zn zinc, <sup>j</sup> BMI body mass index