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Research Snapshot

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

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

Abstract

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

Introduction

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

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

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

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

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

Methods

Search strategy and study selection

The PICOT framework (population, intervention, comparison, outcomes and type of study) [19] was used to inform the criteria needed to answer the research question "*what evidence exists on the nutrition status of patients with Crohn's disease and how can this evidence inform nutrition assessment in clinical practice?*". The search strategy included studies of patients with Crohn's disease aged 18 to 64 years using validated assessment methods available in clinical practice to establish nutrition status compared with a healthy age and sex matched

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

Limiting the search in this way allowed the literature review to establish a 'typical' nutrition status in healthy people without Crohn's disease and facilitated the comparative quantification of nutrition status in Crohn's disease. Whilst anthropometric reference ranges for the healthy population have been developed, these vary depending on assessment methods used.[20] Recruiting a HC group ensures comparisons are made using identical methods to those used with Crohn's disease patients. Three databases were searched (Medline®, Embase® and Scopus®) on 1st October 2018. Multiple search terms were combined with the Boolean functions 'and' and 'or' to focus the search.[21] The medical library subject heading terms or keywords included were [Crohn's disease OR inflammatory bowel disease] AND [nutrition* assessment, body composition, body fat, fat mass, anthropometry, lean body weight, malnutrition, protein energy malnutrition, muscle strength, hand grip, grip strength, trace element, nutrition* status, nutrition* deficiency, vitamin deficiency, mineral deficiency, dietary intake, diet OR micronutrient]. Filters (English, human and adult aged 18 – 64 years) were applied to target the search results.

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

Data extraction and synthesis

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

Discussion

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

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

Anthropometric Outcomes

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

Body Mass Index

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

Dual Energy X-ray Absorptiometry (DEXA)

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

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

Bioelectrical Impedance (BIA)

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

A study from India in patients with active Crohn's disease detected significant deficits in FM and FFM.[45] However, it lacks external validity to non-Indian populations as recent data demonstrates significant ethnic disparities in body composition, especially in South Asians.[56] Another study in patients with active Crohn's disease reported lower FM compared with HC.[39] Thus, there are body composition deficits in active Crohn' disease, highlighting the importance of considering disease activity in the clinical assessment section of the Nutrition Care Process.

CT and MRI

Three studies used medical imaging techniques to further explore body composition.[25, 26, 37] One study undertook umbilicus CT scanning to determine body fat distribution alongside

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

Muscle Strength and Function

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

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

Direct Anthropometry

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

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

Summary for Anthropometric Outcomes

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

233 has been reported.[13, 16, 28, 36, 39, 44, 57] BIA is a more feasible and less invasive measure of body
234 composition than CT or DEXA scans.[61] 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[61] (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.[50, 62-67] Geerling *et al* are the only research group to
243 measure an extensive range of micronutrients.[28, 29] A major limitation of the 18 micronutrient
244 studies (Table 2 and Table 3)[27-29, 31-33, 49-51, 57, 62-70] is that only two[15, 16] 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,[71] 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.[63, 65, 66] The remaining studies
250 reported micronutrient concentrations in either patients with Crohn's disease in remission[28, 62]
251 or in a heterogenous patient group.[29, 50, 62, 63, 65-67] 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.[72]
257 Micronutrients on circulating erythrocytes provide a more accurate marker of micronutrient

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

Summary for Biochemical Outcomes

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

<u>Dietary Assessment Outcomes</u>

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

[28, 62] with the exception of two studies where the percentage of total energy from fat was lower in patients with Crohn's disease.[45, 46]

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

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

Summary for Dietary Assessment Outcomes

Macronutrient intake is similar between patients with Crohn's disease and HC, however micronutrient and fiber intakes may be impaired; whether this is due to temporary food exclusions during active disease or longer-term food exclusion is not described in the literature. Dietary intake assessment is an essential component of nutrition assessment (Figure 2). The most appropriate dietary assessment is dependent on the patient care setting. If using a diet history of usual intake, it is important to ask about food exclusion behaviors and frequency of consumption of key food groups high in micronutrients and fiber to identify the potential for inadequate nutrient intake.

<u>Limitations of studies in this area.</u>

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

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

Implications for Clinical Practice

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

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

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

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

<u>Need for Future Research</u>

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

medicine,[87] future studies should investigate Crohn's disease phenotype, and this may facilitate a personalized prediction of nutrition risk.

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

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

Conclusion

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

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

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

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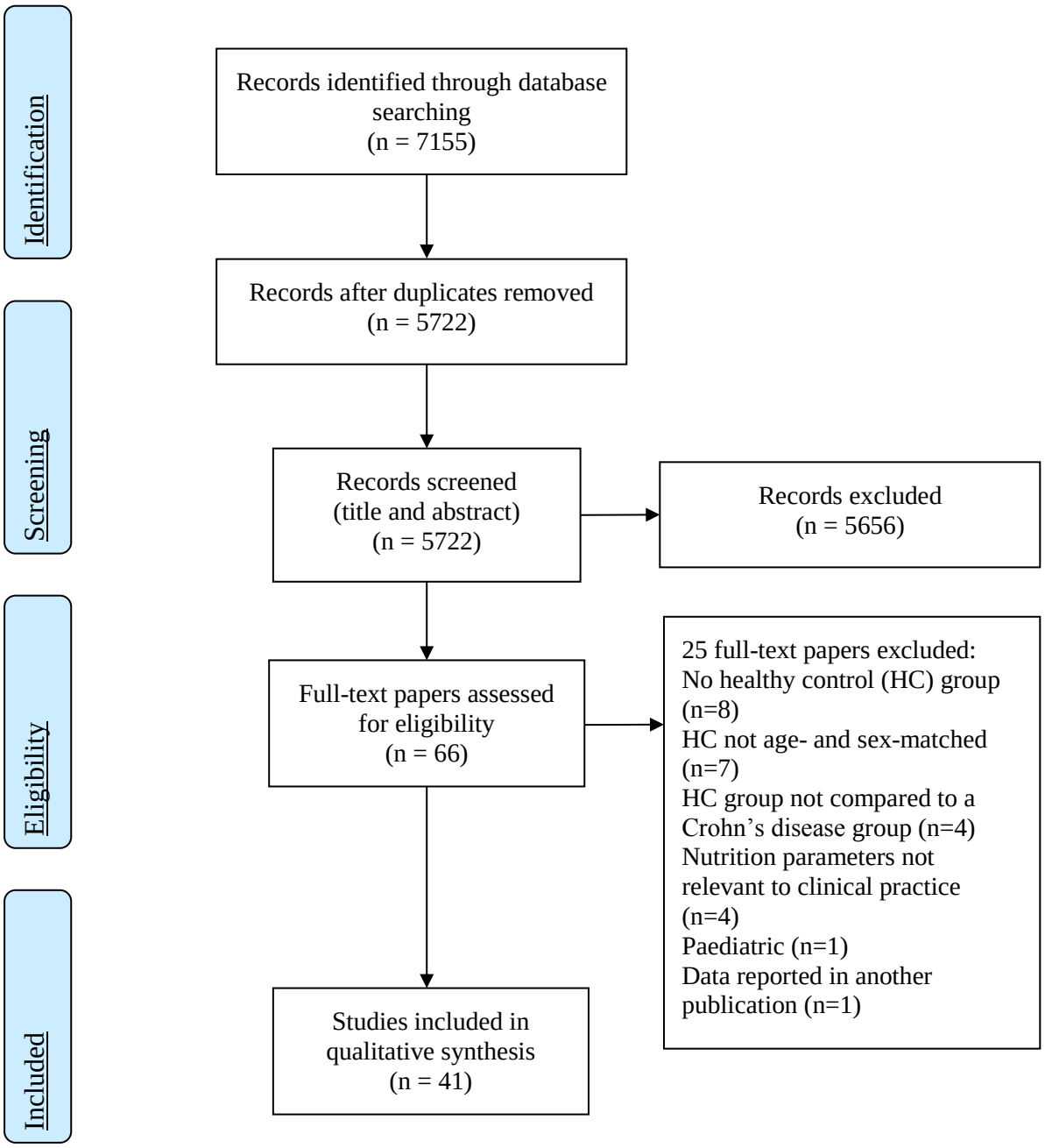


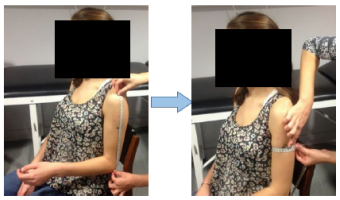
Figure 1: PRISMA flow diagram for studies included in the narrative review on nutrition assessment in Crohn's disease.

Anthropometry

Measure	Methods	Reference ranges
Hand-grip strength (HGS)[13, 16, 44] 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 dynometer with their greatest effort, as shown below.[93]	If the highest of three readings is <85% of the population reference then this is classified as 'protein malnutrition'.[100] If using reference ranges from your HGS manufacturer, then ensure you also follow the method provided by your manufacturer for accurate interpretation.
Mid-upper arm circumference (MUAC)[16, 30, 42, 48, 49] 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 0.1cm using plastic tape as shown below.[96] 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,[97] ideally patients should have follow-up anthropometry conducted by the same clinician at each review.	Mid-arm anthropometry values ≤5th percentile of the population reference range for age and sex are categorised as malnourished.[101]
Tricep skin fold (TSF)[16, 28, 40, 46, 47] 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.[52]	TSF values >95th percentile are categorised as high.[101]
Mid-arm muscle circumference (MAMC)[16, 28, 40, 46, 47] 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) x (π/10))[96]	Mid-arm anthropometry values ≤5th percentile of the population reference range for age and sex are categorised as malnourished.[101]
Bioelectrical impedance (BIA)[13, 15, 16, 25, 39, 41, 42, 44, 45, 46, 47] 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.[97] Follow the manufacturers guide when conducting BIA. There are clinical guidelines which consider the different types of BIA machines.[98, 99]	Depleted FFM and FM are characterised by readings ≤5th percentile for age and sex. High FM is >25.6% body fat in men and >35.7% in women.[20]
Novel imaging methods[25, 26, 37] 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.[102]

Anthropometry techniques

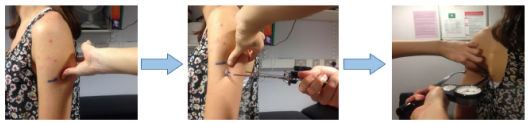
Mid-upper arm circumference (MUAC)



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).

2. Measure the circumference at the mid-point mark. Repeat this measure three times.

Tricep skin fold (TSF)



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.

2. The caliper is applied at a 90° angle to 1cm below the skinfold.

3. Release the tension of the caliper and take the reading. Steps 2-3 should be repeated three times.

Hand-grip strength (HGS)

1. The position for HGS test. The reading is generated following maximal static force to the dynamometer.

Micronutrients

Measure	Interpretation
Thiamine[73]	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.
Vitamin B6[73]	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.
Folate[28, 29, 50, 67]	Low levels indicative of malabsorption. Sulfasalazine impairs folate absorption.
Vitamin B12[28, 29, 50, 67]	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.
Vitamin C[28, 29, 66]	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[27, 28, 31, 32 33, 49, 51, 57, 68, 69, 70]	Consider seasonal variation in readings.
Zinc[28, 29, 62, 64, 65]	Decreased in acute phase response (due to reduction in carrier protein albumin). Also decreased via gastrointestinal losses of chronic diarrhoea.
Copper[28, 29, 64, 65]	May increase during active disease in acute phase response. Therefore, measure when disease stable.
Selenium[16, 28, 29, 63, 65, 66]	Decreased in acute phase response (due to reduction in carrier protein albumin).

Dietary

Method	Interpretation
24-hr recall[45]	Method determines intake for the proceeding 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.[103] Method well-suited to inpatients to measure day-to-day changes in portion sizes consumed, and energy and protein intake.[103]
Diet history of usual intake[62]	Diet history highlights major nutrition issues, such as food group exclusion/restriction and irregular food patterns[103] which are common in Crohn's disease.[7] 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.[103] However, patient recall bias is a limitation of verbal diet histories[104]; if concerned about under- or over-reporting, consider validating diet history against another dietary assessment technique; for example, food records.[103]
3 to 7-day food record[15, 25, 38, 46]	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.[103] 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.[103] The gold standard method for recording dietary intake and quantifying nutrient intake is a 7-day food diary.[105] However, this can be burdensome for patients. Only 3-days of food records are required for accurate quantification of energy intake.[106] Nutrients with greater variability in intakes may require a longer recording period[103], so careful consideration of the diary's purpose should be considered before instructing a patient to complete a food diary.
Food frequency questionnaire (FFQ)[16, 27, 28, 29, 40, 62]	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.[103] 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.[103] Response validity to FFQs is limited if food lists are too long and complex.[107]

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 [a] (kg/m^2) mean (SD^b)		FM[c] (kg) mean (SD^b)		%FM[d] mean (SD^b)		FFM[e] (kg) mean (SD^b)		VAT[f] (cm^2 or mL) mean (SD^b)	
	CD	HC			CD	HC	CD	HC	CD	HC	CD	HC	CD	HC
Capristo *et al.* 1998[46] Italy	43	60	Remission	BIA[g]	21.5*	23.7	12.2*	17.0	20.4***	25.5	49.2	50.4		
Capristo *et al.* 1998[47] Italy	18	20	Remission	BIA[g]	20.5*	23.6	12.6*	17.4	22.0*	26.4	45.6	49.5		
Mingrone *et al.* 1999[55] Italy	18	12	Mixed	BIA[g]	21.6*	23.8	13.8***	19.0			48.0	47.7		

Wiroth *et*	41	25	Remission	BIA[g]								
al. 2005[13]	17M[h]	10M[h]			22.1	24.0	13.0	16.4	18.3	21.7	56.2	58.0
France	24F[i]	15F[i]			22.1	21.4	15.3	16.0	25.8	27.5	42.9	41.0
Filippi *et al.*	54	25	Remission	BIA[g]	22.1	22.1	14.4[*]	16.6			49.2	46.7
2006[15]												
France												
Valentini *et*	94	61	Remission	BIA[g]								
al. 2008[16]	33M[h]	20M[h]			22.3	23.7	12.7	15.2			58.5[**]	67.4
Austria,	61F[i]	41F[i]			22.1	21.8	18.1	16.6			[*]	44.1
Germany &											43.9	
Italy												
Benjamin *et*	80	100	Remission	BIA[g]	21.6[**]	23.9	13.4	14.1	21.9	21.5	43.3[**]	48.9
al. 2011[45]	43		Active		18.8[*]	21.6	8.2[*]	14.1	15.7[*]	21.5	40.7[*]	48.9
India												

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

The Nether-	18F[i]	18F[i]			23.4	23.3	20.9	20.7	32.1	32.7	42.6	41.2
lands												
Tjellesen *et*	31	88	Remission	DEXA[l]								
al. 1998[34]	13M[h]	19M[h]			23.5	23.9	20.3	19.2	27.8[*]	23.1	51.8[*]	62.2
Denmark	18F[mi]	69F[i]			21.1	22.0	21.6	21.3	38.8[*]	32.8	34.9[*]	42.4
Geerling *et*	20[n]	20	Mixed	DEXA[l]	22.7	23.0	19.4	19.5	28.3	29.2	49.2[*]	46.8
al. 1999[30]	40[o]	40	Mixed		22.8	24.0	17.7	18.9	26.7	27.7	47.1[*]	49.9
The Nether-												
lands												
Geerling *et*	23	23	Mixed	DEXA[l]	22.2	22.7	18.5	19.0	27.5	28.7	48.9[*]	46.9
al. 2000[29]												
The Nether-												
lands												
Jahnsen *et*	60	60	Mixed	DEXA[l]	23.3	23.4	20.8	20.0	31.4	29.2	44.5[*]	48.8
al. 2003[11]	24M[h]	24M[h]			23.2[*]	24.8	16.7	18.1	23.1	22.6	54.2[**]	61.0
Norway	36F[i]	36F[i]			23.4	22.5	23.5	21.3	37.0	33.6	[*]	40.7

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

[a] BMI body mass index, [b] SD standard deviation, [c] FM fat mass, [d] %FM percentage fat mass, [e] FFM fat free mass, [f] VAT visceral adipose tissue, [g] BIA bioelectrical impedance analysis, [h] M male, [i] F female, [f] CT computed tomography, [k] MRI magnetic resonance imaging, [l] DEXA dual energy X-ray absorptiometry, [m] weighted mean reported, [n] newly diagnosed, [o] 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 (n)		Disease activity	Folic acid (nmol/L) Mean (SD[a])		Vitamin B12 (pmol/L) Mean (SD[a])		Vitamin C (µmol/L) Mean (SD[a])		Zinc (µmol/L) Mean (SD[a])		Copper (µmol/L) Mean (SD[a])		Selenium (µmol/L) Mean (SD[a])	
	CD	HC		CD	HC	CD	HC	CD	HC	CD	HC	CD	HC	CD	HC
Kallel *et al.*(2011)[50] Tunisia	89	103	Mixed	19.3 (6.9)	18.4 (7.0)	218** * (118)	279 (125)								
Yakut *et al.* (2010)[67] Turkey	45	53	Mixed	17.4 (12.0)	22.4 (7.5)	207 (122)	252 (132)								

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

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

Gentschew *et al.* (2012)[63] New Zealand	351	853	Not stated			1.37** * (0.01)	1.41 (0.01)
Wendland *et al* (2001)[66] Canada	37	37	Mixed	64.0** (4.6)	78.4 (2.9)	0.81 (0.04)	0.80 (0.04)

[a] SD standard deviation, [b] newly diagnosed Crohn's disease, [c] diagnosed Crohn's disease for more than 5 years,[d] UK United Kingdom, [e] M male, [f] 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 (n)		Disease activity	Vitamin D nmol/L mean (SD[a])		Vitamin D 25(OH)D_3 ng/mL mean (SD[a])		Suboptimal micronutrient level n (%)		Suboptimal criteria
		CD	HC		CD	HC	CD	HC	CD	HC	
Geerling *et al.* (1998)[28]	The Nether-lands	32	32	Remission					18[**] (56.0)	9 (28.0)	< 70 nmol/L (summer and autumn) or < 25 nmol/L (winter)
Ardizzone *et al.* (2000)[68]	Italy	51	30	Mixed			19.5 (7.5)	18.1 (7.9)			
Duggan *et al.* (2004)[27]	Ireland	44	44	Remission	75.0[*] (28.7)	105.3 (55.5)			3[≠] (6.8)	2 (4.5)	< 40 nmol/L

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

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

[a] SD standard deviation, [≠] 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 *et al.* 1998[46], Italy	7-day food record	CD n=43 HC n=60	Remission	Macronutrient intake	CD consumed less energy and less %TE[a] from fat than HC.
Geerling *et al.* 1998[28], The Netherlands	FFQ[b]	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 *et al.* 1999 [62]	FFQ[b] & diet history	CD n=20[c] CD n=32[d] 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 *et al.* 2000[29], The Netherlands	FFQ[b]	CD n=23[c] HC n=23	Active n=4 Remission n=19	Macro- and micronutrient intake	CD %TE[a] from CHO[e] higher, lower intake of alcohol and PUFA[f] than HC. Micronutrient intake not different. CD with active disease had higher %TE[a] from CHO[e] than CD in remission.
Katznelson *et al.* 2003[25], USA	5-day food record	CD n=20 (male only) HC n=20	Mixed	Macronutrient intake	%TE[a] from protein lower in CD.
Duggan *et al.*2004[27], Ireland	FFQ[b]	CD n=44 HC n=44	Remission	Calcium & vitamin D intake	Dietary intake not different.

Lomer *et al.* 2004[38], 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 *et al.* 2006[15], 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[g] compared with HC females. Significantly less CD met RDA[h] for Zn[i], Mg[g], Vitamins C, B6, E, B1, B-carotene compared with HC.
Guerreiro *et al.* 2007[40], Portugal	FFQ[b]	CD n=87 HC n=80	Remission	Macro- and micronutrient intake, food exclusion behaviours	Lower energy (also lower BMI[j]) and fibre intake. %TE[a] from CHO[e] higher and from fat lower than HC. Lower calcium, vitamins C, D, E, K, PUFA[f] intakes in CD (not controlled for energy

					intake). Fruit and vegetables exclusion associated with low vitamin C & E intakes.
Valentini *et al.* 2008[16], Austria, Germany & Italy	FFQ[b]	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 *et al.* 2011**[45]**, 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[a] from CHO[e] and less from fat.

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