Body composition in children with chronic inflammatory diseases: A systematic review

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Abstract

Background & aims Aberrations in body composition are expected in children suffering from chronic inflammatory conditions. The objective is to examine whether children with inflammatory bowel disease (IBD: Crohn's disease and ulcerative colitis), coeliac disease, asthma and juvenile idiopathic arthritis (JIA) have an altered body composition as compared to healthy children.

Methods A systematic review, registered in Prospero (registration number: CRD42018107645), was conducted according to PRISMA guidelines. We conducted a search of three databases, Pubmed, Cochrane and Scopus. An assessment of the quality of the study was performed.

Results Data from 50 studies, 32 with IBD, 8 with coeliac disease, 2 with asthma and 8 with JIA, involving 2399 children were selected for review after applying the eligibility criteria. In all but 4 studies, children with Crohn's disease exhibited decreased amounts of fat mass and fat free mass. Reductions in fat mass were also evident in studies in children with coeliac disease. It is uncertain whether body composition is altered in children with asthma or JIA.

Conclusions Children with Crohn's disease manifest with lowered adiposity and lean mass and therefore are likely to be at risk for suffering malnutrition-related clinical complications. Apart from Crohn's disease, data examining body composition in children with chronic inflammatory conditions are scarce and there is a paucity of reports examining the relationship between inflammation and body composition. Interpretation of the current study results is hampered by the low quality of the studies and due to the fact that the analyses have been habitually secondary outcomes.

42 Keywords: body composition, children, inflammatory bowel disease, coeliac disease, asthma,
43 juvenile idiopathic arthritis.

1. Introduction

An appropriate nutritional status is of paramount importance for the growth and development of children. Chronic diseases may impair the nutritional status particularly during the rapid phases of growth and development (1) i.e., in early infancy and puberty. The consequences of poor nutritional status may be long-lasting, potentially reducing the adult height (2) as well as likely exerting adverse impacts on quality of life and well-being and the risk of non-communicable diseases in later life. Nevertheless, the extent to which one marker of nutritional status, i.e. body composition, including body adiposity and leanness are affected when a child suffers from the chronic inflammatory conditions, such as inflammatory bowel disease (IBD; Crohn's disease and ulcerative colitis), coeliac disease, asthma and juvenile idiopathic arthritis (JIA), are poorly known.

We hypothesized that the chronic inflammatory conditions, and their treatment (e.g. systemic corticosteroids) in childhood would influence nutritional status through several mechanisms: Firstly, an inadequate or imbalanced dietary intake due to a loss of appetite, nausea or acquired unhealthy dietary habits could result in an inadequate supply of energy and energy-yielding nutrients (3,4,5). Secondly, increased energy requirements due to the actual disease process or the presence of chronic inflammation may predispose children to malnutrition (6,7). Thirdly, a reduced utilization of energy and nutrients may arise from a loss of absorptive properties of the gastrointestinal tract. An example of this final factor is evident in the intestinal inflammation related to untreated coeliac disease (8). All of these potential malnutrition-inducing mechanisms, predisposing children to either undernutrition or overnutrition, may be present in chronic inflammatory conditions in children (Figure 1).

It is noteworthy that the measurement of body composition may confer an advantage in defining the nutritional status and particularly in addressing nutritional impairments in

chronic disease as well as in an evaluation of the success of nutritional and clinical interventions (9,10). This is illustrated in a study where weight loss was related to an increased mortality, whereas loss of fat mass, i.e. a value obtained through measuring body composition, reduced mortality (11). In children, weight and body mass index (BMI) are not ideal ways of interpreting body composition. In a meta-analysis of studies conducted in children and adolescents, a low sensitivity to detect obesity was evident if only BMI cut-off values were used, i.e. about every fourth child with excess body fat was not identified as being obese if assessed by only BMI (12). Thus, the fractions of body fat mass and lean mass contribute to defining body functions beyond body weight, and the measurement of body composition in cases where the weight loss may provide important clinical information also in children (13). Furthermore, if one takes the example of insulin resistance, then the contribution of body composition has been demonstrated to be larger than the body weight itself (14).

The objective of this study was to undertake a systematic literature review to examine whether children with chronic inflammatory diseases, i.e., Crohn's disease, ulcerative colitis, coeliac disease, asthma and JIA, have an altered body composition as compared to healthy children or to the reference values.

2. Material and Methods

2.1 Search strategy

A systematic and comprehensive search of studies published as original research articles involving humans and written in English were searched until 22 July 2016, and subsequently repeated twice (17 May 2018 and 18 March 2019), using the search criteria listed below. Articles were also searched by hand.

- Sources of data: Pubmed, Cochrane and Scopus.
- Search keyword terms: Crohn's disease, colitis ulcerosa, ulcerative colitis, celiac disease, coeliac disease, asthma, juvenile idiopathic arthritis, body composition, fat mass, fat free mass, lean body mass, fat mass proportion, fat free mass proportion, fat mass percent, fat mass percentage, fat mass %, fat free mass percent, fat free mass percentage, fat free mass %, lean body mass percent, lean body mass percentage, lean body %, child, children, youth, adolescent, adolescents
- Participants: Children (less than 20 years or age) diagnosed with Crohn's disease, ulcerative colitis, coeliac disease, asthma or juvenile idiopathic arthritis and controls/healthy children.
- Primary outcomes: Body composition, fat mass, fat free mass, lean body mass, fat percentage, fat free mass percentage, lean body mass percentage.
- Additional outcome: Evaluation of the inflammatory status of the children with chronic inflammatory diseases in cases/studies where body composition had been measured and data was available about dietary intakes.

2.2. Selection of articles

The types of studies which were included were observational studies and also interventional studies, in which case only the data at baseline was utilized.

- Inclusion criteria: Children (< 20 years) diagnosed with Crohn's disease, ulcerative colitis, coeliac disease, asthma or juvenile idiopathic arthritis and English original articles.

- Exclusion criteria: Other disease, older children and adults, babies aged less than 2 years, animal and experimental studies, bone mineral density and skeletal composition, only limbs and their composition reported, and review articles.

2.3. Data extraction

Search hits were exported to RefWorks and duplicates were removed. Two reviewers (NH and KL) analyzed independently the titles and abstracts of the articles retrieved from the search to identify the eligible studies. If eligibility was unclear, the full text was obtained and reviewed. Reasons for exclusion were noted. Unclear articles were discussed prior to coming to a mutual agreement. Full articles were obtained and reviewed by all authors, i.e. at least two authors evaluated each article, considering the inclusion and exclusion criteria. Extracted data included authors, title, year of publications, study design, clinical setting, diagnostic characteristics including body composition measurements in relation to diagnosis, disease severity status, medication and other treatment, number and characteristics of the patients including gender, age, height and weight SDS, inflammation markers measured, availability of the dietary intake data, body composition analysis method, conclusions and limitations. Some articles were also excluded at this point as they were found not to fulfil the eligibility criteria (Figure 2). If multiple articles reported the same or similar data, we included only the article with more relevant data. If the articles were complementary, both references are given in the tables. Studies that reported the results only in figures were not tabulated, but are nevertheless discussed.

2.4. Protocol registration and systematic review guidelines

The protocol of the systematic review was registered in Prospero (registration number: CRD42018107645). We followed Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines in writing this systematic review (15).

2.5 Quality assessment

The Study Quality Assessment Tool published by the National Heart Lung and Blood Institute (16) of cohort and cross-sectional studies and case-controls studies was used to assess the quality of the studies. The studies were classified as good, fair or poor based on 14 criteria for the cross-sectional studies and 12 criteria for the case-control studies, each being scored as yes, no or other (cannot determine, not applicable, not reported). The final score depicting the internal validity and potential bias of the study was based on the overall assessment of these criteria, and the classification poor was given if there were flaws in the several key concepts. Each article was scored by two separate authors and if the scores differed, the scoring was revised and mutually agreed.

3. Results

3.1. Characteristics of the studies

The search resulted in 221 hits and after removing duplicates, 126 articles remained. After reviewing the abstracts, 104 articles were obtained for full text reviewing. Seven additional articles were included after searching by hand. From these 111 articles, including articles identified through database searching and other sources, 61 articles were excluded and thus 50 articles remained for data extraction (Figure 2). Data on inflammation markers were

160 available in 21 studies, data on dietary intake in 10 studies and serum markers of nutritional
161 status in 20 studies. These parameters were variably reported and not analyzed in association
162 with body composition, thus these data were not tabulated and are only dealt with in the
163 discussion.

164 The quality of the studies was evaluated from 43 articles (3 duplicates and 4 articles only
165 presenting the results in figures were excluded from the evaluation) with 14% being rated as
166 good,77% as fair and 9% as poor (Table 1, 2 and 3).

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168 ### 3.3.1 Body composition in children with Crohn's disease and ulcerative colitis

169 We identified 32 studies which met our inclusion criteria, 28 being tabulated (3 articles
170 containing duplicate data from 3 separate articles, shown in the same row in the table 1) with
171 4 having to be excluded because of a lack of exact body composition details i.e. results shown
172 only in figures and thus exact values could not be determined (Table 1). The studies were
173 graded as good (n=3), fair (n=20) and poor (n=2). The 11 studies included 1461 patients with
174 Crohn's disease and a total of 264 patients with ulcerative colitis. There was no single cohort
175 with only ulcerative colitis patients. Body composition and growth had been analyzed within
176 2 weeks of diagnosis in two cohorts (17-19) whereas most of the patients were studied much
177 later after their diagnosis. There were statistically significant changes in growth and body
178 composition of children with Crohn's disease in all but 4 studies (20-23) as compared with
179 either a healthy cohort or reference values of healthy children. Typically, these changes
180 included decreased amounts of fat and fat-free mass and decreased height, loss of weight and
181 reduced BMI in patients with Crohn's disease (Table 1). Children with ulcerative colitis were
182 found to have more mixed results: both decreased (24,25) and similar values (22,26,27) as
183 compared with controls. In addition, ulcerative colitis patients had been analyzed together

184 with Crohn's disease patients as a single cohort in many studies (17,21,28-31) which did not
185 make it possible to analyze body composition and growth separately in these two diseases.

186

187 **3.3.2. Body composition in children with coeliac disease**

188 We found a total of 8 studies with 376 coeliac disease patients and 901 controls (Table
189 2). Two of these studies were graded as good and 6 as fair. The mean age of the cases
190 and controls in these studies ranged from 7 to 16 years of age, but included children as
191 young as 2 years of age as well as young adults aged 18 years. The studies included
192 both gluten-free diet compliant and non-compliant patients with the duration of diet
193 treatment varying from newly diagnosed to more than 10 years. Five studies found
194 lower weight and/or height in coeliac disease patients as compared to controls (32-36)
195 and also a reduction in fat mass was compared to controls (33-37)

196 **3.3.3. Body composition in children with asthma**

197 Two studies in asthma fulfilled the criteria to be included in this review (Table 3). In
198 one report, body composition in 57 children with newly diagnosed, untreated asthma
199 was investigated (38) whereas the other study compared the body compositions of
200 healthy controls and 40 prepubertal children being administered long term inhaled
201 steroids (39). The children with newly diagnosed asthma had a higher body fat percent
202 and a higher frequency of overweight than their healthy peers. The asthmatic children
203 with long term inhaled steroid treatment showed a decreased height, a reduced lean
204 tissue mass, less fat mass and lower bone mineral density as compared to controls.

3.3.4. Body composition in children with juvenile idiopathic arthritis

There were 8 studies with 285 JIA patients and 213 control children (Table 3). Two of these were graded as fair and two as poor. The two publications from Simon et al. (40,41) were confounded by the long-term treatment with high-dose glucocorticoids and therefore no conclusions about the effect of JIA on body composition from these two papers could be drawn.

The results in the rest of the papers were conflicting. Two studies found a higher fat-related compartment in JIA patients as compared to controls (42,43). Van Brussel et al. observed a higher fat mass and Caetano found a higher fat mass percentage, as well as higher truncal fat mass and an elevated BMI z-score in JIA patients as compared to controls. Although no differences in fat mass percentage or fat-free mass compartment were found in the study of Grönlund et al. (44), JIA patients had a larger waist circumference and they tended to have more overweight/obesity than healthy controls.

On the contrary, Więch et al. (45) found a lower muscle mass percentage and a reduced body cell mass percentage in JIA patients as compared to controls. These differences were found only in patients with polyarthritis, not in patients with oligoarthritis. Jednacz et al. (46) reported lower values of body weight, BMI-percentile and a tendency to lower fat mass percentage in JIA patients as compared to controls. Lofthouse et al. (47) reported that JIA patients displayed lower values of both fat mass percentage and fat free mass than controls. When Lofthouse et al. compared the JIA subgroups (polyarticular and oligoarticular disease) to controls, reductions in weight, height, body fat percentage and muscle mass were found in those with polyarticular disease, whereas only the body fat percentage was lower in the oligoarticular group of patients when they were compared to controls.

4. Discussion

Overall, the data examining body composition in children with chronic inflammatory conditions are scarce. The majority of the studies have focused on Crohn's disease, in which reductions in adiposity and lean mass have been detected. With respect to ulcerative colitis, coeliac disease, asthma and JIA, no firm conclusions can be drawn due to the lack or inconsistency of the data.

Children with Crohn's disease seem to have a different body composition than healthy children. An important determinant may be inflammation, which is present both systemically and intestinally in active Crohn's disease. Data considering coeliac disease suggest that patients have a worse body composition than controls; fat-free mass seems to be less affected than fat mass (33-37). However, unlike the situation in IBD, in coeliac disease the changes in body composition are less likely to reflect elevated levels of inflammatory cytokines, but are probably due to autoimmune gluten-induced enteropathy-related malabsorption, which is usually readily ameliorated by the initiation of dietary management. Considering JIA, the results could be grossly divided into two groups; those finding higher adiposity (42-44) and those reporting lower adiposity or lean mass (47) or percentage (45); the latter being especially true in polyarthritis patients. No common explanation behind the division of the results could be identified. All in all, the results are confounded by the fact that the studies had not considered the nature of JIA as a heterogenous group of diseases (48) or taken into account the activity of the rheumatic inflammation. In asthma, data on body composition was

scarce as only two studies, describing conflicting results, were identified. A clear confounding factor is likely to be medication, i.e. inhaled corticosteroids are known to decrease height, lean tissue mass and fat mass. Indeed, newly diagnosed, untreated asthma patients were found to be more often overweight than healthy controls.

The mechanisms behind the potential body compositional alterations in childhood inflammatory disease are thus heterogenic. During periods of active inflammation, the cytokines, especially interleukin (IL)-1, TNF-α and IL-6 (49-51) are considered to be key regulators of metabolism and thus they can influence body composition (52). The proinflammatory cytokines trigger the classical signs of cachexia i.e. anorexia, increased demand of energy, protein losses from skeletal muscles, connective tissue and gut. In particular, the extent of muscle wasting correlates with the levels of proinflammatory cytokines and high sensitivity C-reactive protein (hsCRP). (51,53,54) However, the cachectic changes in the body composition vary in different inflammatory diseases (49). For example, in so-called rheumatoid cachexia, in adult rheumatoid arthritis patients, the BMI is normal or high, the fat mass is increased but the muscle mass is reduced (49,51). Some evidence about similar changes in body composition, as in adult rheumatoid cachexia, has been detected in patients with early JIA (55). In Crohn's disease, an elevated lean mass has been associated with lower inflammation manifested as lower IL-6 levels or an increase in albumin concentrations in plasma (56). Pro-inflammatory cytokines may also cause a loss of fat free mass due to reduced appetite, impaired nutrient utilization and muscle cell atrophy (23).

Biological agents targeting specific cytokines are frequently used to treat children with JIA and IBD (57,58). Catch-up growth has been demonstrated in Crohn's disease patients treated with infliximab, an anti-TNF agent (59-61), with the growth-promoting effects being

associated with CRP normalization and lowered levels of inflammatory parameters (IL-6, TNF-α, CRP and erythrocyte sedimentation rate) (62,63). Despite the promising effects on growth in IBD and JIA patients, the effects of biological agents on body composition are largely unknown (62,63). One small study reported that the lean mass to fat mass ratio increased after 6 months of etanercept plus methotrexate therapy in 10 polyarticular JIA patients (64).

Dietary intake, which is a key contributor to nutritional status, had been analyzed only in six of the reviewed studies, but none of them examined its association with body composition. Lower nutrients intakes, e.g. reduced calcium intake in IBD (22,28,65), but also similar or higher values or those in accordance to that recommended have been reported e.g. in IBD (17) and in JIA (44). Serum or plasma nutritional markers such as albumin (18,19,22,25,30,65-73), 25-hydroxyvitamin D (17,22,25,28,30,44,65,64) and transferrin (25,30,69) or some other markers (18,19,22,33,65,72) were reported in several of the studies. However, only a few articles had examined the association of these markers with body composition. In the publication of Bechtold et al. (25), those children with IBD who had the lowest plasma albumin concentrations, had the lowest muscle cross-sectional area. In another study, lean and fat mass z-scores correlated with the plasma albumin concentration in patients with Crohn's disease (18).

The measurement of body composition may enable a better evaluation of the nutritional status and its changes than can be obtained by measuring growth parameters or BMI. This was demonstrated in patients with ulcerative colitis where the measurement of body composition and subsequent calculation of the body cell mass was shown to be a better indicator of nutritional status than the BMI value (73). Body composition also correlated with

disease severity, whereas no relationship was seen with BMI (73). Despite these benefits, it is surprising that not only has body composition of children with chronic inflammatory conditions been poorly studied in research settings but also in clinical practice. We found that DXA and bioelectrical impedance had been the techniques most commonly used for analyzing body composition. (74). The use of varied methods for measuring body composition is another variable complicating the elucidation of this topic. It is noteworthy that none of the studies applied multicompartment models which might have been advantageous (75,76). A more elaborate definition of the compartmental locations of body fatness might have revealed novel insights, particularly in the identification of metabolic dysregulation. (77)

Along with the potential problems related to the measurement of body composition, there are several other limitations that make it difficult to draw solid conclusions on whether the body composition of children with chronic inflammatory diseases is disturbed. Furthermore, the quality of the majority of the studies was graded as either fair or poor due to several reasons. These included a retrospective study design, a lack of inception cohorts or well-matched controls, heterogeneity with respect to disease duration or time since diagnosis, medication, lack or inadequate documentation of background details such as diet and physical activity, lack of power calculations even with regard to the primary outcomes. Moreover, typically body composition analysis had been a secondary outcome in many of the studies. In those cases, it is very hard to judge whether differences in body composition between healthy children and those with diseases are due to the condition itself or caused by treatment (such as corticosteroids) or other external factors. In addition, gender and pubertal status are known to influence body composition (78), and on the other hand, the chronic disease condition may itself delay the onset of puberty. It is also recommended that the

measurements of fat mass and lean mass should be corrected for height by using the fat mass index or the fat-free mass index, but in general, these have been seldom reported (79).

5. Conclusion

Based on this systematic review, we conclude that the body composition of children with chronic inflammatory diseases may be altered to a variable extent in comparison with either healthy controls or reference values, but several studies also reported no differences. The conditions which have the greatest impacts appear to be Crohn's disease and recently diagnosed coeliac disease, as children with these diseases typically displayed lowered body adiposity. The conclusions with regard to asthma are hampered by the lack of available data. All in all, the body composition in the chronic inflammatory diseases in the paediatric population has been rarely studied, and typically only as a secondary outcome. More studies are needed to draw firmer conclusions on this topic as well as establishing the role of body composition analysis with regard to prognosis, clinical management and also understanding the pathological processes underpinning the chronic inflammatory diseases in children. To achieve these goals, large multicenter, and most likely multinational, trials will be needed.

Conflict of interest

The authors declare no conflicts of interest.

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Figure legends

Figure 1. Different factors predisposing children with chronic inflammatory conditions to malnutrition.

Figure 2. PRISMA flow chart describing the selection of studies through database searching with data evaluating the body composition in children with chronic inflammatory disease

Tables

Table 1. Body composition in children with Crohn's disease and ulcerative colitis.

Table 2. Body composition in children with coeliac disease.

Table 3. Body composition in children with juvenile idiopathic arthritis and asthma.

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Table 1. Body composition in children with Crohn's disease and ulcerative colitis

Author (Year of publication) country	**Overall rating**	**n**	**Age**	**1) Disease duration 2) Medication 3) Disease severity**	**Method used to assess body composition**	**Fat-mass or related compartment**	**Fat-free mass or related compartment**	**Height**	**Weight**	**BMI z score**
Motil (1982 & 1982) (66,67) USA cases: CD controls: healthy age and sex matched friends or relatives as controls	Fair	 6 (6 m) 5 (5 m) mean ± SD	 15.0 ± 1 yr 14.5 ± 1.9 yr mean ± SD	1) 3.3±1.2 yrs (mean ± SD) 2) prednisone (n=4), sulfasalazine (n=5) 3) clinically stable in all	TBK		 29.9 ± 1.7 kg# 42.7 ± 4.3 kg# mean ± SEM	 86.3 ± 4.2 percentage of height for age# 98.2 ± 6.9 percentage of height for age# mean ± SD	 106 ± 20.5 percentage of ideal weight for height 105 ± 26.1 percentage of ideal weight for height mean ± SD	
Varille* (1996) (70) France cases: CD controls: matched children as controls	Fair	 11 (8 m) 11 (8 m) mean ± SD	 14.5 ± 2.5 yr 14.8 ± 2.8 yr mean ± SD	1) 2.5 ± 1.5 yrs (mean ± SD) 2) steroids on alternate days (n=6), azathioprine (n =2), 5-aminosalicylate (n=4), metronidazole (n=2) and sulfasalazine (n=1); night-time nutritional support: central i.v. line (n=8), enteral tube n=3) 3) PCDAI:23.2 ± 12.7 (mean ± SD)	Skinfolds	 21 ± 9 % 16 ± 5 % mean ± SD	 34.2 ± 7.7 kg 41.5 ± 12.1 kg mean ± SD	 4.5 ± 7.9 percentage of height for age# 100.6 ± 6.2 percentage of height for age# mean ± SD	 108 ± 24 percentage of ideal weight for height 98 ±9 percentage of ideal weight for height mean ± SD	
Azcue* (1997) (68) Canada cases: CD	Fair	24 (18 m)	13.1 ± 2.2 yr	1) 2.9 ± 2.0 yrs; 5 newly diagnosed (mean ± SD)	BIA, TBW, TBK	16.8 ± 4.3 %#	TBW: 85.6 (8.1) %, BIA: 86.7 (5.5) %,	151.2 ± 14.9 cm	36.5 ± 10.0 kg#	

controls: "normal controls"		22 (15 m) mean ± SD	13.7 ± 4.2 yr mean ± SD	2) 4 patients on low dose (< 10 mg) alternate day therapy with prednisolone 3) at least moderately active (CDAI > 150)		35.1 ± 12.9 %# mean ± SD	TBK: 87.2 (4.3) %# TBW: 84.6 (17.8) %, BIA: 86.5 (12.9) %, TBK: 64.9 (12.9) %# mean ± SD	154.7 ± 16 cm mean ± SD	47.6 ± 17.3 kg# mean ± SD	
Zoli (1996) (78) UK cases: inactive CD, growing normal controls: healthy, age and gender matched disease controls: inactive CD, growing ceased and matched for disease site and duration	Poor	10 (7 m) 10 (7 m) 9 (6 m) mean ± SEM	17.6 ± 1.4 yr 17.5 ± 1.4 yr 19.0 ± 1.3 yr mean ± SEM	1) cases 6.0 ± 1.1 yrs; disease controls 6.7 ± 1.5 yrs 2) - 3) Simple index of Crohn's disease activity (index was not mentioned but CRP ja IL-6 were normal in all)	Skinfolds	13.2 ± 1.9 %# 20.5 ± 2.4 %# 17.0 ± 2.6 % mean ± SEM	87.0 ± 2.0 % 79.5±2.4 % 84.1 ± 2.7 % mean ± SEM	166.5 ± 2.7 cm 167.2 ± 2.7 cm 169.9 ± 3.5 cm mean ± SEM	51.1 ± 3.7kg# 64.8 ± 2.3 kg# 59.7 ± 3.0 kg# mean ± SEM	19.2 ± 0.6# 23.7 ± 0.6# 20.9 ± 0.7#
Boot* (1998) (27) The Netherlands cases: CD: 22, UC 33 controls: Dutch reference values	Fair	55 (34 m) 0 mean (range)	13 (4–18) yr mean (range)	1) 2.2. (0.1-12) yrs, median (range) 2) all had been on sulfasalazine or mesalazine, 35 had been on prednisolone 3) -	DXA	−0.38 ± 1.11 %#, -0.64 ± 1.02 SD score mean ± SD	−1.04 ± 1.41 SD score# mean ± SD	−0.54 ± 1.25 SD score# mean ± SD		-0.66 (0.85)# mean ± SD
Sentongo (2000) (79) USA cases: CD controls: control subjects of similar age	Fair	132 (84 m) 66 (29 m)	m: 15 ± 4.3 yr, f: 16.4 ± 4.5 yr m: 14.6. ± 6.6 yr, f: 15.1 ± 5.8 yr	1) m: 4.4 ± 0.5 yrs f: 3.9 ± 0.4 yrs (mean ± SD) 2) - 3) PCDAI m: 14.3 ± 9.3, f: 13.1 ± 11.2 (mean ± SD)	DXA	m: 19 ± 8 %, f: 32 ± 9 %# m: 19 ± 7 %, f: 25 ± 8 %#	m: 38.5 ± 12.3 kg, f: 33.2 ± 7.1 kg m: 38.6 ± 16.3 kg, f: 33.2 ± 10.1 kg	m: -0.81 ± 1.14 height for age#, f: -0.46 ± 1.38 height for age m: 0.28 ± 0.93 height for age#, f: -0.16 ± 0.98 height for age	m: -0.66 ± 1.18 weight for age#, f: -0.14 ± 1.19 weight for age m: 0.26 ± 0.95 weight for age#, f: -0.08 ± 0.98 weight for age	

			mean ± SD			mean ± SD	mean ± SD	mean ± SD	mean ± SD	
Burnham (2005 & 2004) (64,64) USA cases: CD controls: healthy controls, results adjusted for age and race	Fair	104 (65 m) 233 (95 m)	15.4 ± 4.3 yr 11.9 ± 5.7 yr mean ± SD	1) 4.0±3.4 yrs 2) mesalazine 86%, sulfasalazine 51%, metronidazole 57%, 6-mercaptopurine 34%, corticosteroid enemas 11% (ever) 3) PCDAI: 12.0 ±11.9 (mean ± SD)	DXA	-0.04 ± 0.86 fat mass-for height-z-score -0.21 ± 0.77 fat mass for age z score 0.00 ± 0.06 fat mass-for height-z-score 0.00 ± 0.95 fat mass for age z score mean ± SD	-0.61 ± 0.92 lean mass-for height z-score# -1.10 ± 1.11 lean mass for age z score# 0.0 ± 0.99 lean mass-for height z-score# 0.00 ± 0.99 lean mass for age z score# mean ± SD	-0.74 ± 1.2 height for age z score# 0.28 ± 1.1 height for age z score# mean ± SD	-0.66 ± 1.1 weight for age z score# 0.36 ± 1.1 weight for age z score# mean ± SD	-0.35 ± 1.0# 0.27 ± 1.12# mean ± SD
Burnham (2007) (80) USA cases: CD controls: healthy controls	Poor	88 (55 m) 128 (51 m)	16.3 ± 4.1 yr 10.7 ± 4.9 yr mean ± SD	1) 3.7 (0.1-16) yrs, median (range) 2) 39% on steroids during study, other medication not mentioned 3) -	DXA		-0.63 ± 0.92 lean mass for height z score# 0 ± 0.99 lean mass for height z score# mean ± SD	-0.59 ± 1.26 height for age z score# 0.31 ± 1.17 height for age z score# mean ± SD		-0.22 ± 1.19 BMI for age z score# 0.42 ± 1.14 BMI for height z score# mean ± SD

Thayu (2007) & Dubner (2009) (18,69) USA <u>cases</u>: CD [&]	Fair	78 (44 m)	12.7 ± 2.8 yr	1) within 2 wks of diagnosis 2) corticosteroids 44%, budesonide 5%, aminosalicylates92% , 6-mercaptopurine/ azathioprine 10%, methotrexate 3%, antibiotics 31%, histamine-2 blockers 8%, proton pump inhibitors 44% 3) PCDAI 38.4±18.0; 4%	DXA	fat mass for height z-score m (nonblack CD): −0.22 ± 0.81 f (nonblack CD): −0.52 ± 0.73#, m (nonblack controls): 0.07 ± 0.93 f (nonblack controls): 0.05 ± 0.97# m (black CD): 1.88 ± 0.29# f (black CD): −1.47 ± 0.98#	lean mass for height z-score m (nonblack CD): −0.71 ± 0.89 #, f (nonblack CD): −1.11 ± 1.16# m (nonblack controls): −0.10 ± 0.98#, f (nonblack controls): −0.14 ± 0.94# m (black CD): 1.23 ± 0.23, f (black CD): −1.17 ± 1.02#	m (all): −0.21 ± 1.06 z score#, f (all): −0.32 ± 1.07 z score#		m (all): -0.35 ± 1.21# f (all): -0.78 ± 1.02#
<u>controls: healthy</u> subsequent comparisons of lean mass for height and fat mass for height z-scores in CD and controls were adjusted for covariates		669 (321 m)	12.1 ± 3.8 yr mean ± SD	inactive; 38% mild; 58% moderate to severe		m (controls): -0.11 ± 1.10# f (black controls): -0.09 ± 1.10# mean ± SD	m (black controls): 0.14 ± 1.03, f (black controls): 0.26 ± 1.06# mean ± SD	m (all): 0.15 ± 0.90 z score#, f (all): 0.23 ± 0.86 z score# mean ± SD		m (all): 0.18 ± 0.97#, f (all): 0.26 ± 0.89# mean ± SD
Bechtold (2010) (24) Germany <u>cases:</u> all CD & UC: 143 newly diagnosed CD: 28 longer disease duration CD: 70 newly diagnosed UC: 13 longer disease duration UC: 32 <u>controls:</u> age and sex matched healthy	Good	143 (84 m) 296	13.9 ± 3.5 yr mean ± SD 5-19 yr	1) newly diagnosed CD: 0.07 ± 0.1 yrs, UC: 0.06 ± 0.1 yrs, longer disease duration CD: 3.4 ± 2.6 yrs, UC: 3.1 ± 2.2 yrs, all 2.4 ± 2.5 yrs 2) nutrition therapy (n=26), azathioprine (n=67), 5-ASA (n=121),	pQTC		-1.12 ± 1.0 z score# -1.61 ± 0.9 z score -1.07 ± 1.0 z score -0.97 ± 1.0 z score -0.85 ± 1.1 z score	-0.82 ± 1.1 SD score# -0.86 ± 0.9 SD score# -0.82 ± 1.1 SD score# -0.30 ± 1.2 SD score -0.96 ± 1.1 SD score#	-0.77 ± 1.0 SD score# -1.12 ± 0.6 SD score# -0.77 ± 1.0 SD score# -0.69 ± 0.6 SD score# -0.50 ± 1.1 SD score#	-0.52 ± 1.2# -0.99 ± 0.9# -0.51 ± 1.3# -0.76 ± 0.6# -0.05 ± 1.4

controls/reference population				infliximab (n=4), glucocorticoids 3) PCDAI: newly diagnosed CD 22.5 (0-52.5), longer duration CD 7.5 (0-57.5); Colitis Index: newly diagnosed UC 8 (0-18), longer duration UC 3.7 (0-16); median (range)			mean ± SD	mean ± SD	mean ± SD	mean ± SD
Ward (2010) (16) Canada <u>cases:</u> CD: 17 UC: 3 <u>controls:</u> results were compared to published normative data	Fair	20 (12 m) 0	14.7 (11.6-16.4) yr median (IQR)	1) within 2 weeks of diagnosis 2) no medication 3) CD (PCDAI): mild disease (12.5-30) (n=6), moderate to severe (> 30) (n=11) UC(PUCAI): mild (n=1), moderate (n=1), severe (n=1)	DXA	-2.0 ± 0.9 z score# mean ± SD		0.04 ± 1.2 z score mean ± SD	-0.5 ± 1.0 z score mean ± SD	
Werkstetter* (2011) (29) Germany <u>cases</u>: CD: 82 & UC: 20 <u>controls:</u> reference values	Fair	102 (67 m)	14.1 (6.9-20.1) median (range)	1) 1.4 (0-7.2) yrs, median (range) 2) 89% had medication (5-ASA 52%, sulfasalazine 20%, azathioprine 35%, infliximab 3%, glucocorticoids 18%) 3) CD: PCDAI 0-60; UC: PUCAI 0-55, range	pQCT		-1.4 (-3.4-2.2) Muscle cross-sectional area# -1.0 (-4.9; 2.0) Muscle cross-sectional area height corrected# median (range)	-0.7 (-3.7-1.6) z score# median (range)	-1.0 (-3.0-1.7) z score# median (range)	-1.0 (-3.6-3.1)# median (range)

Wiskin (2011) (29) UK <u>cases</u>: CD UC <u>controls:</u> reference values	Fair	 37 (26 m) 18 (9 m) median (IQR)	 CD: 14.7 (11.8; 16.3) UC: 12.0 (9.9; 15.3) median (IQR)	1) - 2) - CD: 59% active disease (PCDAI >10); PCDAI 10 (0-60) median (range)	Skinfold thickness	0.04 (-0.43, 0.69) 0.07 (-0.64, 0.81) Triceps z score median (IQR)	-1.32 (-1.81, -0.51)# -0.59 (-1.36, -0.15)# upper arm muscle area z score median (IQR)	-0.65 (-1.47, -0.02) -0.20 (-1.3, 0.31) height z score median (IQR)	-0.74 (-1.57, 0.09) -0.33 (-1.14, 1.21) weight z score median (IQR)	-0.47 (-1.18, 0.44) -0.23 (-0.4, 1.01) median (IQR)
Laakso (2012) (21) Finland <u>cases:</u> CD: 28 UC: 49 Unspecified colitis: 3 <u>controls:</u> age and gender matched healthy controls	Fair	80 (37 m) 80 median (range)	14.9 (5.1-20.1) yr 14.4. (7.4-18.8) yr median (range)	1) 3.4 (0.3-14.5) yrs 2) mesalamine 73%, oral glucocorticoids 30%, azathioprine 18%, infliximab 5%, sulfasalazine 4% 3) PCDAI and PUCAI 65% inactive (PCDAI <10, PUCAI<10), 27% mild (PCDAI 10-29, PUCAI 10-34), 8% moderate-severe (PCDAI ≥30, PUCAI ≥35)	DXA		-0.8 (-3.3-1.0) -0.7 (-2.3-1.0) median (range)		105 (87-156) weight for age 105 (84-192) weight for age median (range)	
Werkstetter (2012) (28) Germany <u>cases</u>: CD: 27 & UC 12 <u>controls:</u> age and gender matched	Fair	39 (24 m) 39 (24) mean ± SD	15.1 ± 2.9 15.2 ± 3.1 mean ± SD	1) 3.5 (0.2–12.6) yrs, median (range) 2) 5-ASA 74%, sulfasalazine 21%, azathioprine 72%, infliximab 23%, nutritional therapy 13%,	BIA		-0.64 (-0.95, -0.34)# 0.09 (-0.16, 0.35)# phase angle α Z-score mean (95% CI)	-0.54 (-0.84, -0.24)# 0.18 (-0.12, 0.47)# height z score mean (95% CI)	-0.75 (-1.04, -0.46)# -0.35 (-0.31, 0.23)# weight z score mean (95% CI)	-0.56 (-0.83, -0.28)# -0.15 (-0.39, 0.10)# mean (95% CI)

				glucocorticoids 3% 3) 66% remission (PCDAI<10, PUCAI<19), 33% mild disease (PCDAI 10-27.5, PUCAI 10-34)						
Gerasimidis* (2012) (81) UK cases: CD controls: z scores according to UK national data	Fair	17 (8) median (range)	12.7 (7-14.8)	1) all but three had newly diagnosed disease 2) immunosuppressant (n=5), aminosalicylates (n=4), antibiotics (n=2), steroids (n=1) 3) all had active disease	BIA	-0.5 z score	-2.1 z score	-0.4 (1.7) z score median (IQR)	-1.3 (2.0) z score median (IQR)	-2.2 (2.3) z score median (IQR)
Hill (2013) (71) Australia cases: CD, altogether 77 repeated measurements controls:	Fair	18 (7 m) 0	8.6-17.1 yrs		TBK		-0.74 ± 1.41# body cell mass z score mean ± SD	0.39 ± 0.96# height z score mean ± SD	0.20 ± 1.08 weight z score mean ± SD	-0.05 ± 1.18 mean ± SD
Tsiountsioura* (2014) (26) Scotland cases: CD UC controls: a contemporary group of local healthy	Fair	53 (29 m) 27 (15 m) 62 (24 m)	14.2 (11.6, 15.4) yr 12.2 (10.7, 14.2) yr 9.8 (6.9-13.8)	1) - 2) - 3) 34% CD and 37% UC patients had active disease, others	BIA	0.1 (-0.7, 0.4) z score& 0.4 (-0.2, 1.7) z score&	-0.1 (-0.9, 0.8) z score 0.4 (-0.3, 1.0) z score -0.3 (-0.9, 0.7) z score	-0.5 (-1.2, 0.3) z score -0.3 (-0.7, 1.0) z score -0.1 (-0.8, -0.6) z score	-0.5 (-1.2, 1.5)#& 0.6 (-0.3, 1.5)& 0.3 (-0.5, 0.9)#	-0.3 (-0.9, 0.4)#& 0.8 (0.0, 1.7)& 0.3 (-0.6, 1.4)#

children with no previous history of chronic gastrointestinal problems			median (IQR)	were in clinical remission		0.4 (-0.4, 1.3) z score median (IQR)	median (IQR)	median (IQR)	median (IQR)	median (IQR)
Costa (2015) (63) Brazil <u>cases:</u> active CD inactive CD <u>controls:</u> first-degree relatives of and in the same age bracket as the CD patients	Fair	 22 (12 m) 29 (16 m) 35 (22 m) mean ± SD	 16.4 ± 2.5 yr, 17.3 ± 2.19 yr 15.5 ± 2.31 yr mean ± SD	1) active: 1.14 ± 1.06 yrs, inactive: 2.83 ± 3.34 yrs (mean ± SD) 3) PCDAI: active: 18.3 ± 10.8 (mild)/26.2 ± 11.4 (moderate), inactive: 7.0 ± 7.1 (mean ± SD)	BIA	 23 ± 0.08 % 21 ± 0.05 % 24 ± 0.04 % mean ± SD	 74 ± 0.08 %#& 79 ± 0.05 %& 76 ± 0.04 %# mean ± SD	 −0.41 ± 0.90 height for age#& −0.15 ± 0.92 height for age#& 0.24 ± 0.99 height for age# mean ± SD		 −1.29 ± 1.64# & 0.01 ± 1.18#& 0.37 ± 1.18# mean ± SD
Callias (2016) (20) Switzerland <u>cases:</u> CD: 16 & UC: 5 <u>controls:</u>	Fair	 21 (10 m) 0 mean ± SD	 14.33 ± 1.33 yr mean ± SD	1) 3 yrs (6 days-6.5 yrs), median (range) 2) 5% 5-ASA, 10% methotrexate, 29% azathioprine, 52% infliximab, 5% adakimumab 3) 19% had mild activity (PCDAI 11-30, PUCAI 10-34), others were in remission (PUCAI <10, PCDAI<10)	DXA	 -1.1 ± 0.4 z score mean ± SD		 -0.7 ± 1.1 z score mean ± SD	 -0.6 ± 1.0 z score mean ± SD	 -0.4 ± 1.1 mean ± SD
DeBoer* (2016) (19) USA <u>cases:</u> CD <u>controls:</u> reference values (921 healthy children)	Fair	 72 0 mean ± SD	 15.1 ± 2.6 yr mean ± SD	1) 1.4 (0.02-12.8) yrs; median (range) 2) 100% anti-TNF-α agent, 85% amino-salicylates, 32% glucocortico-	DXA	 0.30 ± 0.91 z score mean ± SD		 -0.45 ± 1.03 z score mean ± SD	 -0.356 ± 1.04 z score mean ± SD	 -0.17 ± 1.07 mean ± SD

				steroids, 21% mercaptopurine-azathioprine, 19% mercapto-purine 3) PCDAI 25 (15-37); median (IQR)						
Murphy (2017) (82) Australia <u>cases</u>: CD <u>controls</u>: non-matched	Fair	59 (43 m) 108 (55 m)	13.7 ± 2.1 yr 11.3 ± 3.0 yr mean ± SD	1) 1.33 yrs (mean), in 49% less than 6 months 2) not mentioned 3) PCDAI 20.3 (mean); 40% remission, 28% mild, 32% moderate/severe disease	TBK		-1.15 ± 1.36 z score# 0.07 ± 0.93 z score# mean ± SD	-0.40 ± 1.16 z score# 0.40 ± 0.86 z score# mean ± SD	-0.75 ± 1.62 z score# 0.28 ± 0.80 z score# mean ± SD	-0.75 ± 1.61# 0.13 ± 0.75# mean ± SD
Więch (2018) (25) Poland <u>cases:</u> CD: 25 UC: 34 <u>controls:</u> CD-controls UC-controls controls matched for gender and age	Good	59 (34 m) 59 (34 m)	13.8 ± 3.12 yr 13.5 ± 3.41 yr 13.8 ± 3.12 yr 13.5 ±3 .41 yr mean ± SD	1) CD: 10 newly diagnosed, 3 < a year, 12 > a year; UC: 16 newly diagnosed, 4 < a year, 14 > a year 2) - 3) CD (PCDAI): 7 remission, 5 mild, 9 moderate, 4 severe disease; UC (PUCAI): 12 remission, 8 mild, 10 moderate, 4 severe disease	BIA	19.8 ± 6.2 %, 20.9 ± 7.5 % 21.4 ± 8.2 %, 20.4 ± 9.5 % mean ± SD	80.2 ± 6.2 %, 79.1 ± 7.5 %, 35.02 ± 11.70 kg#, 38.10 ± 12.94 kg 78.6 ± 8.2 %, 79.6 ± 9.5 %, 42.93 ± 13.53 kg#, 39.21 ± 13.38 kg mean ± SD			-0.42 ± 0.892# -0.01 ± 0.928, 0.41 ± 1.050# 0.13 ± 0.887 mean ± SD
Altowati (2018) (83) Scotland <u>cases:</u> CD: 8	Fair	8 (6 m)	14.8 (9.0-16.4)	1) 3.3 (0.6-10.1) yrs 2) mercaptopurine /azathioprine (n=4),	DXA	0.04 (-0.6-1.8) z score	-0.8 (-2.4-3.0) z score	-2.4 (-3.3-(-1.4)) z score#		-0.5 (-1.5-0.3)

controls: local reference values of healthy children (n=201)				methotrexate (n=4), glucocorticoids (n=3), 5-ASA (n=2) 3) wPCDAI 17.5 (0, 53); remission (n=4), mild (n=3), moderate (n=1)		mean (range)	mean (range)	mean (range)		mean (range)
Kelly (2018) (84) USA cases: CD: 74 Controls: 1837 healthy individuals from different ethnic groups (multicenter)	Good	74 (47 m)	14.3 (11.8, 16.3) median (IQR)	1) 2.1 (0.02-9.7) yrs 2) remission (n=9), mild (n=28), moderate-severe (n=37); PCDAI 3) 5-ASA (n=59), mercaptopurine-azathioprine (n=27), glucocorticoids (n=24), methotrexate (n=15)	DXA		-1.03 (-1.91, -0.6) z score# -0.15 (-0.68, 0.34) z score# median (IQR)	-0.73 (-1.33, -0.028) z score# 0.13 (-0.42, 0.73) z score# median (IQR)		-0.04 (-0.82, 0.82)# 0.37 (-0.26, 0.96)# median (IQR)

*study design: prospective or RCTs; only baseline data of the studies is presented

&same cases

#sig between cases and controls/reference values, &sig between cases

BCM = body cell mass, metabolically active component of FFM, BIA= bioelectrical impedance, CD = Crohn's disease, DXA = dual-energy X-ray absorptiometry, EEN = Exclusive enteral nutrition, m = males, f = females, MuscleSCA = muscle cross sectional area, PCDAI = Pediatric Crohn's Disease Activity Index, Phase angle α Z-score = Proxy of lean body mass quality, pQCT = peripheral quantitative computed tomography, PUCAI = pediatric ulcerative colitis activity index, TBK = total body potassium, TBW = total body water, UC = ulcerative colitis

Table 2. Body composition in children with celiac disease

Author (Year of publication) country	**Overall rating**	**n**	**Age**	**1) Duration 2) Treatment 3) Diagnostic criteria and assessment of compliance**	**Method used to assess body compositio n**	**Fat-mass or related compartment**	**Fat-free mass or related compartment**	**Height**	**Weight BMI z score[$]**
Scotta (1997) (85) Italy cases: CoD controls: matched for age, sex, ethnic origin and calcium intake	Fair	 66 (33 m) 76 (36 m)	 9.8 (2.3-18.9) yr 9.3 (2.6-18.3) yr median (range)	1) & 2) GFD for 49 months (median, range) (6-221 months); no GFD in 9 (duration?) 3) dg with jejunal biopsy; treated had serological and clinical response	DXA	 19.6 ± 5.6 % 20.6 ± 5.6 % mean ± SD		 m: 134 (88-165) cm f: 134 (91-172) cm m: 135 (91-180) cm f: 133 (84-168) cm median (range)	 m: 30 (11-61) kg f: 30 (13-65) kg m: 28 (13-75) kg f: 28 (12-63) kg median (range)
De Lorenzo (1999) (33) Italy cases: CoD controls: healthy subjects matched for gender and age	Fair	 43 (12 m) 30 mean ± SD	 14.7 ± 2.4 yr 16.0 ± 2.0 yr mean ± SD	1) & 2) GFD for ≥ 12±3 months (mean, SD) 3) dg according to ESPGHAN guidelines; improvement in laboratory parameters and in villous atrophy	DXA	 15.0 ± 6.8 kg 12.9 ± 8.8 kg mean ± SD	 31.6 ± 8.1 kg# 46.3 ± 12.5 kg# mean ± SD	 156.1 ± 10.3 cm# 168.8 ± 11.3 cm# mean ± SD	 48.8 ± 11.4 kg# 62.2 ± 12.0 kg# mean ± SD
Barera* (2000) (32) Italy cases: CoD controls: each patient was matched by sex and chronologic age to a healthy control subject	Fair	 29 (14 m) 29 mean ± SD	 9.5 ± 3.4 yr 9.5 ± 3.4 yr mean ± SD	1) newly diagnosed 2) untreated 3) subtotal villous atrophy and EMAbA +ve	DXA	 17.4 ± 8.3 %# 23.7 ± 8.4 %# mean ± SD	 21.4 ± 8.4 kg 23.4 ± 10.3 kg mean ± SD	 130.7 ± 20.3 cm 134.7 ± 18.8 cm mean ± SD	 28.3 ± 11.0 kg# 34.5 ± 14.1 kg# mean ± SD
Rätsch (2001) (31) Italy cases: CoD controls: all were Saharawi children, randomly selected from the apparently healthy pediatric population	Good	 65 (27 m) 71 (35 m) mean ± SD	 7.7 ± 3.0 yr 7.0 ± 3.7 yr mean ± SD	1) newly diagnosed 2) untreated 3) dg: EMAbA +ve in all plus enteropathy in 16	BIA	 25.8 ± 12.4 % 24.5 ± 9.5 % mean ± SD	 74.9 ± 12.3 % 75.9 ± 9.4 % mean ± SD	 -2.5 ± 1.4 z score# -1.8 ± 1.3 z score# mean ± SD	

and were negative when tested for EMAbA									
Carbone * (2003) (34) Italy cases: CoD controls: healthy children (not matched for age and sex)	Fair	48 (15 m) 30 (23 m)	14.5 ± 2.8 yr 14.9 ± 1.9 yr mean ± SD	1) & 2) GFD for 10 months to 13 years 3) dg according to the ESPGHAN guidelines; 22/48 still had EMAbA +ve	DXA	15.6 ± 7.0 kg 12.9 ± 8.8 kg mean ± SD	32.5 ± 8.5 kg# 46.3 ± 12.5 kg# mean ± SD	156.4 ± 10 cm# 168.8 ± 11.3 cm# mean ± SD	50.5 ± 11.8 kg# 62.2 ± 12 kg# mean ± SD
Pludowski (2007) (35) Poland cases: CoD GFD: normal height: short stature: controls: reference population	Fair	53 29 (27 m) 14 (2 m) 10 (2 m) 562 (284 m)	13.7 ± 2.9 yr 12.6 ± 3.9 yr 12.2 ± 2.9 yr 12.1 ± 3.7 yr mean ± SD	1) newly diagnosed with normal height (n=14), short stature (n=10); 29 patients had been on GFD ≥2 years 2) - 3) total villous atrophy + EMAbA +ve; Compliance was assessed by EMAbA	DXA		frequency of patients in whom lean body mass was below -2.0 SD 3.4 % 7.1 % 30 %	153 ± 17.1 cm& 147±17.5 cm& 134.8 ± 14.4 cm& mean ± SD	45.4 ± 13.3 kg& 40.3 ± 14.9 kg 30.7 ± 10.0 kg& mean ± SD
Tsiountsioura (2014) (26) Scotland cases: CoD controls: contemporary healthy controls	Fair	31 (13 m) 62 (24 m)	9.3 (7.5, 13.6) yr 9.8 (6.9, 13.8) yr median (IQR)	1) - 2) all were probably on GFD since patients were recruited from the outpatient gastroenterology clinics only 3) -	BIA	0.1 (-0.7, 0.6) z score 0.4 (-0.4, 1.3) z score median (IQR)	0.4 (-0.5, 1.0) z score -0.3 (-0.9, 0.7) z score median (IQR)	-0.3 (-0.9, 0.6) z score -0.1 (-0.8, 0.6) z score median (IQR)	0.0 (-0.5, 0.9) z score$ 0.3 (-0.6, 1.4) z score$ median (IQR)
Więch (2018) (36) Poland cases: CoD controls: healthy children and adolescents, strictly matched for gender and age in a 1:1 case-control manner	Good	41 (21 m) 41 (21 m)	10.81 ± 3.96 10.63 ± 4.01	1) compliant to GFD: 74.23 months, Non-compliant to GFD: 26.07 months 2) GFD (n=26) 3) TTG, EmA, GAF-3X, endoscopy	BIA	19.32 ± 7.36 %# 23.34 ± 7.36 %# mean ± SD	80.68 ± 7.36 %# 76.66 ± 7.36 %# mean ± SD		

*study design: prospective or RCTs; only baseline data of the studies is presented

#sig between cases and controls, &sig between cases

BIA=bioelectrical impedance, CoD=coeliac disease, DXA=dual-energy X-ray absorptiometry, dg=diagnosed, EmA=IgA anti-endomysium antibodies, f=females, GFD=gluten free diet, GAF-3X=IgA class anti-deamidated gliadin-analog antibodies, m=males, TTG=IgA class anti-tissue transglutaminase antibodies

Table 3. Body composition in children with juvenile idiopathic arthritis and asthma

Author (Year of publication) Country	**Overall rating**	**n**	**Age**	**1) Duration 2) Medication 3) Disease severity**	**Method used to assess body composition**	**Fat-mass or related compartment**	**Fat-free mass or related compartment**	**Height**	**Weight**	**BMI z score**
Grönlund (2014) (43) Finland cases: JIA (20 oligo, 5 ext.oligo, 14 poly, 1 ERA) controls: healthy age- and sex matched	Fair	40 (19 m) 40 (19 m)	6.4 (3.2-10) yr 6.0 (5.0-7.1) yr median (range)	1) 3.5 (1.7) yrs mean (SD) 2) DMARD n=40, bDMARD n=12, GLC n=4 3) 60% had inactive disease (according to Wallace's preliminary criteria, 2004)	Skinfold thickness at 4 sites (body fat% and mid-upper arm muscle circumference calculated)	17.1 ± 4.7 % 15.4 ± 4.3 % mean ± SD	15.8 ± 1.6 cm 15.2 ± 1.2 cm mean ± SD	-0.10 ± 0.93 SD score 0.04 ± 0.99 SD score mean ± SD	2.9 (11.5) weight-for-height 0.65 (11.2) weight-for-height mean ± SD	
Caetano (2012) (41) Brazil cases: JIA (poly 23, oligo 17, sJIA 2) controls: healthy age and sex matched	Fair	42 (42 f) 35 (35 f) median (range)	13 (6-9) yr	1) 7.0 (0,8-17,9) yrs mean (range) 2) GLC n=7, MTX n=32 3) -	DXA	26.5% (12.7-50)# 16.4% (6.4-37.7)# median (range)		-0.33 (-4.8,1.2) z score -0.59 (-1.9,1.5) z score median (range)		0.17 (-3.8, 2.9)# -0.48 (-1.4, 1.0)# median (range)
Jednacz (2015) (45) Poland cases: JIA (16 oligo, 14 poly) controls: patients from whom rheumatic diseases were excluded	Fair	30 (7 m) 20 (5 m) mean ± SD	14 ± 1.8 yr 14.4 ± 1.8 yr mean ± SD	1) <1 yrs n=6, >1 v n=24 2) Monotherapy or combination: GLC n=8, MTX n=22, SSL n=6, CHQ n=5, Cyc-A n=2, Aza n=1, TNF n=5 3) 37% had inactive disease (according to Wallace's preliminary criteria, 2004)	BIA	19.9 ± 5.8 % 23.0 ± 5.5 % mean ± SD		160.7 ± 8.8 cm 166.0 ± 10.3 cm mean ± SD	48.4 ± 8.6 kg# 55.5 ± 9.0 kg# mean ± SD	37.2 ± 23.6 percentiles # 52.9 ± 25.6 percentiles # mean ± SD
van Brussel (2007) (42) The Netherlands cases: JIA (7 rh+ poly, 29 rh- poly, 11 oligo, 8 ext.oligo, 7 sJIA) controls: age, weight and sex matched children	Fair	62 50	11.9 ± 2.2 yr 12.3 ± 2.5 yr	1) 4.7 (3.2) yrs 2) 15 off-medication, NSAID n=41, DMARD n=28, GLC n=6, biologic agents n=7	Sum of skinfold thicknesses at 7 sites	103.2 ± 46.5 mm# 85.3 ± 35.0 mm#		1.53 ± 0.14 m 1.57 ± 0.14 m	44.5 ± 14.4 kg 45.1 ± 13.4 kg	

			mean ± SD	3) 35 active disease, 12 remission on medication, 15 remission off medication (according to Ruperto and Martini, 2004)		mean ± SD		mean ± SD	mean ± SD	
Więch P (2018) (44) Poland cases: JIA (1 sJIA, 21 poly, 18 oligo) controls: age and sex matched healthy children	Fair	46 46	12.7 ± 3.9 12.7 ± 3.8 mean ± SD	1) 6 new diagnosis, 40 with various stages of treatment (>6 mo) 2) Aza, MTX, SSL, TNF,GLC in monotherapy or combination 3) 38 (83%) inactive disease (according to Wallace's preliminary criteria, 2004)	BIA	26.6 ± 8.5 % 23.9 ± 7.6 % mean ± SD	73.4 ± 8.5 % 76.1 ± 7.6 % mean ± SD	1.49 ± 0.22 m 1.54 ± 0.19 m mean ± SD	45.4 ± 18.1 kg 46.9 ± 15.3 kg mean ± SD	
Lofthouse (2002) (46) UK cases:JIA (7 oligo, 15 poly) controls: children attending the accident and emergency department with no chronic illness, previous surgery or active infection or inflammation, matched for age and sex	Fair	22 (5 m) 22 (5 m)	3-14 yr	1) - 2) 8 patients were treated with GLC, no other medication given 3) -	Skinfold thickness at 4 sites (used to calculate body fat-mass %), BIA (used to calculate total body water as estimate of lean body mass)	15.0 ± 2.3 %# 17.1 ± 2.8 %# mean ± SD	14.3 ± 5.5 kg# 18.6 ± 7.3 kg# mean ± SD	129.6 ± 18.5 cm 140.2 ± 22.3 cm mean ± SD	28.0 ± 9.4 kg 34.6 ± 14.2 kg mean ± SD	
Simon (2003)* (39) France cases: JIA (poly and sJIA) who had GLC therapy controls: French reference values matched for age and sex; reference patients not recruited from the same hospital/area in France and not the same time period	Poor	13 (9 m)	12.5 (8.5-16.3) yr median (range)	1) - 2) median duration of prior GLC therapy 8.2 yrs, median dose 0.39 mg/kg Other medication: MTX n=2, CycA n=4, NSAID n=13 3) disease activity: median ESR 52 (range 10-112)	DXA	8.7 (-2.4, 30.5) SD score median (range) SD score calculated for expected weight for height, not actual weight of the patients	0.45 (-1.4, 1.6) SD score median (range) SD score calculated for expected weight for height, not actual weight of the patients	-4.6 SD score median SD score for chronological age	130.4 % weight-for-height median	1.8 median SD score for chronological age

Simon (2007)* (40) France cases: JIA (6 poly and 24 sJIA). Results divided into 2 groups; those going to receive growth hormone (GH)/those not (no GH) controls: French reference values matched for age and sex	Poor	30 (14 m)	5.6 ± 2.5 yr (GH) 5.7 ± 2.9 yr (no GH) mean ± SD	1) 1.4 yrs 2) Prior GLC therapy 12-15 mo [mean dose at study start 0.5-0.6 mg/kg], many had antirheumatic drugs (not specified) 3) mean ESR 42 (GH)-38 (no GH) , mean CRP 44 (GH) - 57 (no GH)	DXA		-0.1 ± 0.9 SD score (GH) -0.06 ± 0.7 SD score (no GH) mean ± SD SD score calculated for expected weight for height, not actual weight of the patients	-1.1 ± 1.7 SD score (GH) -1.0 ± 1.0 SD score (no GH) mean ± SD SD score for chronological age		1.0 ± 2.3 (GH) 0.9 ± 1.5 (no GH) mean ± SD SD score for chronological age
Boot (1997) (38) cases: asthmatic children using inhaled corticosteroids controls: age and gender matched Dutch reference values	Fair	40 (21 m)	7 (4-11) yr median (range)	1) 4.1 (3-8.2) median (range) 2) inhaled budenoside or beclomethasone ≥0.4 mg/day 3) long-term treatment with moderate to high dose of inhaled corticosteroids over 3 years, no other disease activity given	DXA	-0.34 (-1.92-2.26) SD score # mean (range)	-0.92 (-2.3, 0.60) SD score # median (range)	-0.52 (-2.66, 1.81) SD score # median (range)		0.28 (-1.62, 3.65) median (range)
Vahlkvist (2009) (37) cases: children with newly diagnosed, untreated asthma controls: healthy, age and sex-matched children	Good	57 (32 m) 157 (84 m)	9.6 (9.1-10.1) 9.7 (9.4-10.0) mean (95%CI)	1) newly diagnosed 2) untreated 3) most mild disease; FEV1 90.0% (85.2-94.8) of predicted, mean (95%CI)	DXA	22.8 (19.9-25.6) %# 19.5 (18.2-20.8) %# mean (95%CI)	no difference in lean tissue mass (values not given)	65.8 (58.4-73.2) height percentile 70.1 (66.2-73.9) height percentile mean (95%CI)	68.6 (60.7-76.5) weight percentile# 59.5 (55.3-63.8 weight percentile# mean (95%CI)	28.6%# 12.3%# proportion of overweight children

#sig between cases and controls/reference values, &sig between cases

Aza= azathioprine, bDMARD= biologic drug, eg. TNF-α inhibitors, CHQ=chloroquine, CI= confidence interval, CycA= cyclosporine A, DXA = dual-energy X-ray absorptiometry, DMARD= disease modifying anti-rheumatic drug, GLC= glucocorticoids, ERA=enthesitis related arthritis, GF=growth hormone, ESR= erythrocyte sedimentation rate, ext. oligo= extended oligoarthritis, JIA= juvenile idiopathic arthritis, MTX= methotrexate, NSAID= non-steroidal anti-inflammatory drug, oligo= oligoarthritis, poly= polyarthritis, Rf= rheumatoid factor, SD= standard deviation SSL=sulfasalazine, sJIA= systemic arthritis

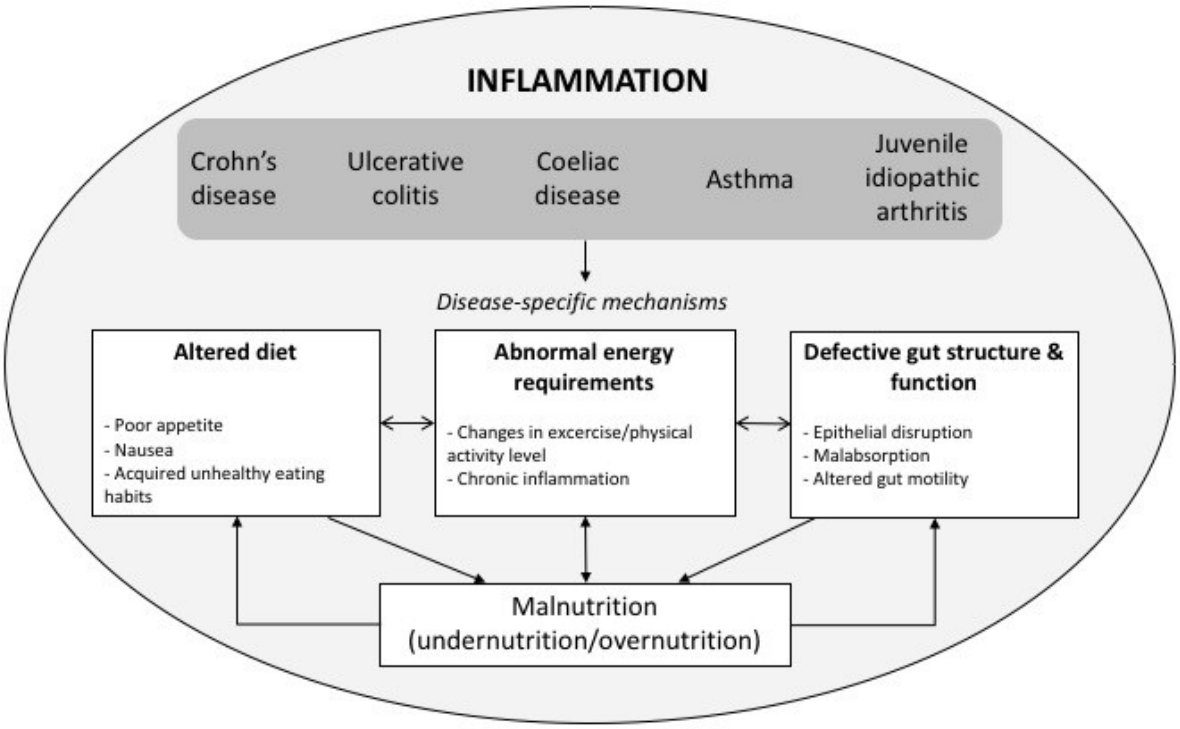
INFLAMMATION
Crohn's disease
Ulcerative colitis
Coeliac disease
Asthma
Juvenile idiopathic arthritis
Disease-specific mechanisms
Altered diet
- Poor appetite
- Nausea
- Acquired unhealthy eating habits
Abnormal energy requirements
- Changes in excercise/physical activity level
- Chronic inflammation
Defective gut structure & function
- Epithelial disruption
- Malabsorption
- Altered gut motility
Malnutrition (undernutrition/overnutrition)

Figure 1.

PRISMA 2009 Flow Diagram

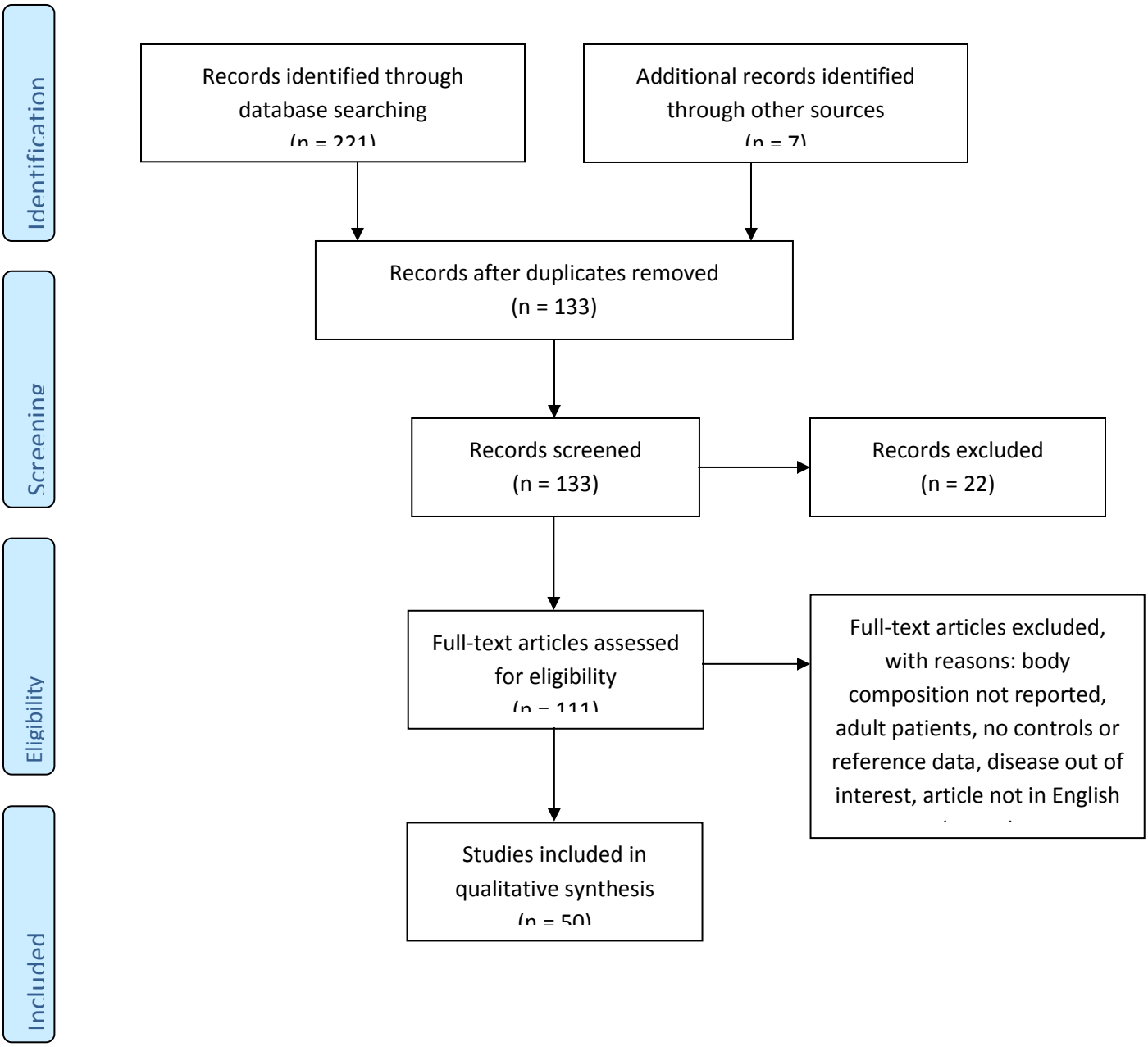

Figure 2.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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