SYSTEMATIC REVIEW

Changes in Anthropometric Parameters After Anti-TNFα Therapy in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis

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Abstract

Background Tumour necrosis factor (TNF)-α inhibitors have been widely used for the treatment of moderate-to-severe inflammatory bowel disease (IBD). TNFα also plays an important role in the regulation of weight homeostasis and metabolism and has been linked to variations in anthropometric responses. This relationship in patients with IBD has yet to be determined.

Objectives Our objective was to evaluate the effects of TNFα inhibitors on changes in anthropometric measures in both adults and children with IBD through a systematic review and meta-analysis.

Methods Multiple database searches identified studies involving children and adults with IBD and treated with TNFα inhibitors and reporting at least one primary outcome measure. Where possible, data were combined for meta-analysis. The primary outcomes included weight, body mass index (BMI), waist circumference, height, height/velocity, and fat and lean mass. Secondary outcomes included surrogate markers of disease activity. A random-effects model was used to estimate the standardised mean difference (SMD).

Results In total, 23 cohort studies (total 1167 participants) met the inclusion criteria. Meta-analysis was performed on 13 of these studies. In children, 6–29.3 months of anti-TNFα therapy had a small but statistically significant effect on weight (SMD 0.31; 95% confidence interval [CI] 0.12–0.49; $P = 0.001$) with a mean gain in z score of 0.30 (standard error [SE] 0.12). In adults, 2–22.4 months of treatment had a moderate effect on BMI (SMD 0.72; 95% CI 0.17–1.26; $P = 0.010$; mean gain 1.23 kg/m^2; SE 0.21). A small but statistically significant increase in BMI z score was found in children (SMD 0.28; 95% CI 0.03–0.53; $P = 0.026$; mean change $0.31 \pm$ standard deviation [SD] 0.14) after 12–29.3 months of therapy. A meta-analysis of four studies found a negligible but statistically significant increase in height (SMD 0.16; 95% CI 0.06–0.26; $P = 0.002$; mean change 0.17 z score [SE 0.05]). A negligible effect on fat mass (SMD 0.24; 95% CI −0.19–0.66; $P = 0.272$) was found in a meta-analysis of five studies. Of note, despite the high heterogeneity among the studies that addressed the issue, these results were also consistently supported by findings from studies not included in the meta-analysis and reviewed in the systematic review. Unfortunately, a lack of data meant we were unable to perform moderator analysis on observed heterogeneity.

Conclusion Anti-TNFα treatment appears to be associated with an increase in body weight, BMI, and other anthropometric parameters. Given the differing courses of IBD between children and adults, this association should be considered before initiating biologics for undernourished, overweight, and obese patients.

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1 Introduction

Twenty years ago, infliximab was the first anti-tumour necrosis factor (TNF)-α monoclonal antibody approved for the treatment of moderate-to-severe inflammatory bowel disease (IBD) [1, 2]. Elevated levels of TNFα are causally linked to muscle metabolism and provoke cachexia and sarcopenia [3, 4]. TNFα is also a powerful regulator of lipid and glucose metabolism, exerting complex and diverse effects

Key Points

Our analysis revealed a significant increase in the main anthropometric parameters (body weight, body mass index, and height) among patients with inflammatory bowel disease (IBD) treated with tumour necrosis factor (TNF)-α inhibitors.

Weight gain may be a risk factor for metabolic disorders and increases the likelihood of anti-TNFα therapy failure. The potential effect of TNFα inhibitors on anthropometric measures could be a consideration in the care of overweight and obese adults with IBD.

Weight loss is common during active IBD in children, and anti-TNFα agents could even exert positive improvements in weight and linear growth.

Further prospective studies are warranted to provide stronger evidence of the role of biological therapy on body changes, especially on fat and lean mass, in patients with IBD.

via gluconeogenesis, loss of adipose tissue, and proteolysis through regulation of enzymes involved in lipid metabolism, such as lipoprotein lipase, hormone-sensitive lipase, adipose triglyceride lipase, and acetyl-CoA carboxylase [5].

The inhibition of TNFα and the subsequent reduction of the general inflammatory state may concurrently trigger adipogenesis, which in turn may improve constructive metabolism in muscles. Hence, the control of inflammation improves growth in children and leads to better general clinical conditions in adults.

Many studies have demonstrated statistically significant increases in body mass index (BMI) and/or body weight after anti-TNFα treatment in IBD [1, 2, 6]. Evaluating the impact of anti-TNFα therapy on anthropometric parameter changes in patients with IBD is of particular importance as the increase in lean mass is beneficial (muscle representing the protein reserves of the body and contributing to improved immune function). This is especially true in patients with aggressive IBD in which lower BMI values may result from malnutrition accompanied with severe inflammation [7]. Nevertheless, about 15–40% of patients with IBD are obese, and an additional 20–40% are overweight [9–13], so the potential involvement of adipose tissue in intestinal inflammation and therapeutic outcomes has gained increasing attention [10]. The increase in fat mass can also have significant implications in terms of augmented risk of obesity-related chronic diseases and suboptimal responses

to therapy [8]. Pharmacokinetic studies have identified high body weight as a risk factor for suboptimal response, with the odds of a good response and achieving remission being lower in obese patients with IBD treated with anti-TNFα agents. High body weight is thought to be associated with increased clearance, shorter half-life, and lower serum trough drug concentrations of anti-TNFα agents [14–16].

The relationship between anti-TNFα therapy and changes in anthropometric indices in patients with IBD has not yet been determined. To address this, we performed a systematic review and meta-analysis of studies of anti-TNFα in adult and paediatric patients with IBD that reported changes in anthropometric parameters. We also analysed other clinical outcomes pertinent to the pathophysiology of IBD, such as measurements of body composition and biochemical parameters correlating with disease activity indices.

2 Materials and Methods

2.1 Literature Search

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Table S1 in the electronic supplementary material [ESM]). We submitted our protocol to the International Prospective Register of Ongoing Systematic Reviews (ID: CRD42020163079) [17]. We searched PubMed/MEDLINE, Embase, and the Cochrane database up to 30 September 2019 with no language restriction. Our search strategy for PubMed is described fully in ESM 1 and was adapted as necessary for each database. In brief, we used the following three terms combined with the Boolean operator "AND": TNFα inhibitors, anthropometric parameters, and inflammatory bowel diseases.

2.2 Eligibility Criteria

Inclusion criteria were as follows: any study that assessed at least one anthropometric parameter following anti-TNFα therapy in patients with IBD and reported changes in those measures either for at least two time points (baseline and follow-up) or stratified results by anthropometric cut-off values. Conference proceedings/abstracts with relevant information on body changes were also included.

Studies were excluded if they (1) did not report values for baseline and follow-up, (2) reported the effect of anthropometric measures (e.g. BMI or weight) on treatment outcome rather than vice versa, or (3) included patients treated with parenteral or enteral nutrition or who received pharmacological treatment aimed to treat or prevent metabolic disorders. Case reports, case series, review articles, meta-analysis,

book chapters, and unpublished thesis were not included. Studies in pregnant women were also excluded.

Additional articles were identified through the reference lists of articles included in our systematic review. We did not contact authors for unpublished data.

2.3 Study Selection

The titles and abstracts of retrieved references were imported into EndNote and duplicates eliminated. The titles and abstracts were screened, and papers deemed highly unlikely to be relevant were disregarded. Full-text versions of the remaining articles were obtained and assessed for eligibility based on our prespecified eligibility criteria as described in Sect. 2.2. The entire search process was conducted independently by two reviewers (VB and EI), and discrepancies were resolved by discussion with a third review author (FM) to reach a decision.

Two authors (VB and EI) assessed the risk of bias of studies included in the systematic review using the Newcastle–Ottawa Scale (NOS) [18]. The NOS is divided into three domains evaluating group selection, comparability of the cohort, and ascertainment of the outcome of interest. The scoring sheet allowed a maximum total score of 9 points (highest quality level). Disagreement was resolved by consensus and consultation with the expert group (CC and FM).

2.4 Outcome Measures

Primary outcomes were changes (from baseline) in the following anthropometric measures: weight (kg), BMI (kg/m^2), waist circumference (WC; cm), height (cm), height/velocity (cm/years), fat mass (bioelectrical impedance analysis [BIA]; %), and lean mass (dual-energy X-ray absorptiometry [DXA]; kg).

Secondary outcomes included surrogate markers of disease activity (C-reactive protein [CRP], mg/dL), erythrocyte sedimentation rate (ESR, mm/h), phase angle (PA, degrees °), and disease severity index scores, e.g. the Crohn's Disease Activity Index (CDAI) and the Mayo score.

2.5 Data Extraction and Synthesis

Extracted data from all included studies were compiled into an electronic summary table. The following pertinent information was extracted: change-from-baseline outcomes i.e. weight, BMI, WC, and other anthropometric measures. For paediatric patients, values for weight, BMI, and height were mostly reported as z scores because of their growth variability. Information on the surrogate markers and disease severity index scores was also collected. Further parameters of interest, such as study type (blinding/design), study duration, number of subjects, number of patients naïve to biological

treatment, sex distribution, age, medication type, dose, and concomitant treatment, were also included.

2.6 Statistical Analysis

All statistical analysis was conducted in ProMeta 3 software. For each outcome, change between baseline and follow-up after treatment commencement with a TNFα inhibitor was analysed. Where possible, the effect of anti-TNFα treatment on each different anthropometric measure was assessed in a separate meta-analysis. We considered the mean difference (MD) and their corresponding standard deviations (SDs) if reported in the primary study. If values were available as medians, they were converted to mean ± SD provided they followed a normal distribution. For the missing correlations between baseline and follow-up, a correlation coefficient of 0.7 was imputed, as recommended by Rosenthal [19]. Studies with insufficient information to compute MD were excluded from the meta-analysis, and the main findings of individual studies were summarized separately. Standardised MDs (SMDs) were based on Cohen's d with corresponding 95% confidence interval (CIs) and were considered small ($d = 0.2$), medium ($d = 0.5$), and large ($d \geq 0.8$) as per Cohen's classification scheme [20]. A P value < 0.05 was considered statistically significant. A random-effects model was used to account for both within-group variability and between-study heterogeneity. The between-study heterogeneity index was I^2. Results were considered heterogeneous when homogeneity was unlikely ($P < 0.10$). Forest plots were produced as a means of visualization. Possible publication bias was identified via visual assessment of a funnel plot.

For body weight, BMI, height, and fat mass, the SMD represents the effect estimate between baseline and follow-up. A positive effect estimate indicates that indice(s) was greater after treatment commencement, and a negative effect estimate indicates that indice(s) was lower after TNFα inhibitor commencement.

3 Results

3.1 Study Characteristics

The study selection and screening process is presented in the PRISMA flowchart (Fig. 1). Of the 1016 articles retrieved (340 results were from PubMed, 117 from Cochrane, and 559 from Embase), 23 met the inclusion criteria. Only 13 of the 23 included studies reported pre- and post-treatment changes in anthropometric measures and provided sufficient data to determine effect estimate.

Table 1 summarizes the characteristics of the studies evaluated in the systematic review and meta-analyses. Of the 23

studies, 21 were observational (6 retrospective, 15 prospective) and two were open-label single-arm trials (yielding a total of 1167 patients aged between 1 month and 85 years).

The average age of patients in paediatric studies ($n = 658$) was 13–20 years (range 1 month–20 years). For adults ($n = 509$), the average age was 32–45 years (range 18–85). Of the 1167 patients, 1053 (90.2%) had Crohn's disease (CD); 96 (8.1%) had ulcerative colitis (UC), two (0.16%) had unclassified IBD, and four (0.33%) had indeterminate colitis. With respect to the type of medication used, 22 studies reported data on infliximab ($n = 989$ [84.7%]), seven on adalimumab (n = 159 [13.6%]), and three on certolizumab pegol ($n = 19$ [1.6%]). As concomitant therapy, 79 (6.68%) patients received corticosteroids, 188 (16.1%) received aminosalicylates or nonsteroidal anti-inflammatory drugs, 453 (38.8%) received immunomodulators, and four (0.33%) received antibiotics. Eight studies enrolled paediatric patients (aged < 18 years). The mean percentage of male patients was 51.27%. The period from baseline to the last follow-up varied considerably among the studies, with a mean follow-up period of 15 months (range 1–29.3).

The quality of the included studies was moderate (mean NOS $5.5 \pm$ SD 0.51; Table S2 in the ESM). All the studies
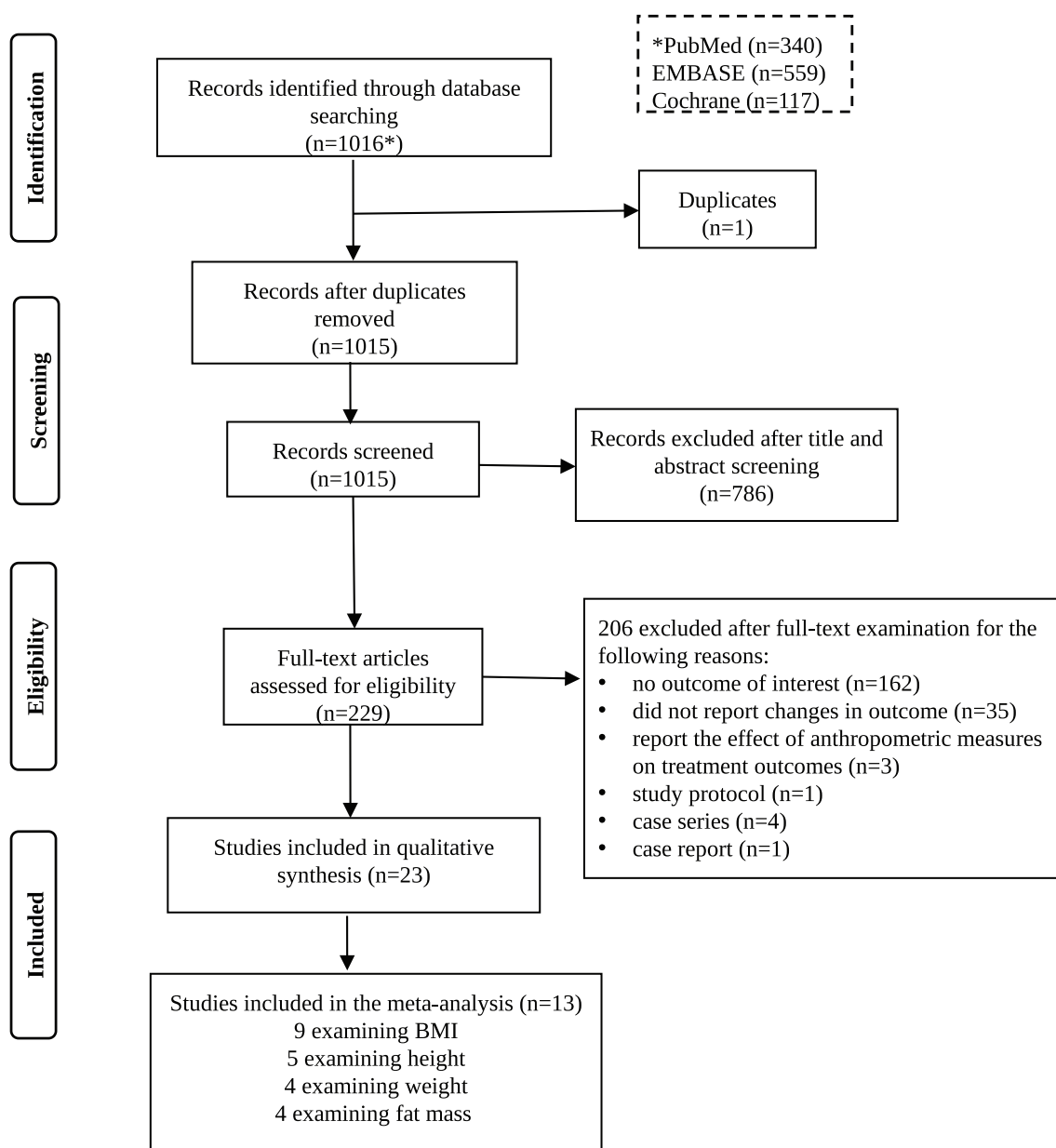

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) flow diagram of process of study selection

Table 1 Characteristics of studies evaluated in the systematic review and meta-analysis

Study	Study design; duration (mo)	Sample characteristics[a]	Disease characteristics	Treatment, n (%)	Dose (mg/kg)	Outcomes	Meta-analysis (Y/N)
Adams et al. [22]	RO; 6	Sample size at baseline: 90 Males: 38 (42%) Median age: 35 (IQR 26–50) Paediatric pts: N	CD 85%; UC 15% Sarcopenic=41 Normal muscle=49 (overweight or obese 34.5%; normal weight 42.2%; underweight 23.3%)	IFX 37 (41); ADA 43 (48); CZP 10 (11)	NA	Primary: Weight Secondary: CRP, ESR, activity (HBI)	N
Amato et al. [23]	RO; mean 22.4 (range 1–95)	Sample size at baseline: 54 Males: 21 (39%) Median age: 45 (range 20–69) Paediatric pts: N	CD 80%; UC 20%	IFX 40 (74); ADA 14 (26)	NA	Primary: BMI[a] Secondary: activity (CDAI, Mayo score)	Y
Assa et al. [32]	RO; 60	Sample size at baseline: 102 Males: 66 (65%) Age: 13.5±3.9 Paediatric pts: Y	CD 100% Disease location at diagnosis (Paris classification): L1 (distal ileum) 40%; L2 (colonic) 33%; L3 (ileocolonic) 27%; L4a/b (upper GI disease) 17% Presence of perianal disease: 35%	IFX 84 (82); ADA 18 (18)	IFX: NA; ADA: induction: 160 mg/1.73; 80 mg/1.73; maintenance: 40 mg/1.73	Primary: BMI Secondary: CRP, ESR	N
Borrelli et al. [33]	PO; 6	Sample size at baseline: 18 Males: NA Median age: 13 (range 6–18) Paediatric pts: Y	CD: 100% 17%: involvement of the upper GI tract	IFX 18 (100)	5	Primary: Weight, height[a] Secondary: CRP, ESR, activity (PCDAI)	Y
Branquinho et al. [34]	PO; 36	Sample size at baseline: 62 Males: 18 (29%) Age: 37.3±13.8 Paediatric pts: N	CD 74%; UC 26% Underweight 16.1%; overweight or obese 12.9%	IFX 62 (100)	NA	Primary: BMI Secondary: NA	N
Csontos et al. [24]	PO; 3	Sample size at baseline: 40 Males: 24 (60%) Age: 33.4±12.9 Paediatric pts: N	CD 82.5%; UC 17.5% CD: disease type (Montreal classification): inflammatory (B1) 57.6%; penetrating (B3) 42.4%; structuring (B2) 0%; Location (Montreal classification): small bowel involvement (L1+L3) 72.7%; colon involvement 27.3% UC: location (Montreal classification): left sided (E1+E2) 14.3%; pancolitis (E3) 85.7%	IFX 16 (40); ADA 24 (60)	IFX: 5; ADA: 160 at week 0, 80 at week 2; maintenance: 40 eow	Primary: weight, BMI, fat mass[a], lean mass Secondary: CRP, activity (CDAI, partial Mayo score)	Y

Table 1 (continued)

Study	Study design; duration (mo)	Sample characteristics[a]	Disease characteristics	Treatment, n (%)	Dose (mg/kg)	Outcomes	Meta-analysis (Y/N)
DeBoer et al. [25]	PO; 12	Sample size at baseline: 72 Males: 42 (58%) Age: 15.1 ± 2.6 Paediatric pts: Y	CD 100% Location of disease: ileal 5.6%; colonic 28.5%; ileocolonic 69.4%; iso-upper 84.7%; perianal 37.5% Tanner stage: II 23.6%; III 25%; IV 30.6%; V 20.8%	IFX 72 (100)	NA	Primary: weight[a], BMI[a], height[a] Secondary: CRP, ESR, activity (PCDAI)	Y
DeBoer et al. [35]	PO; 12	Sample size at baseline: 75 Males: 46 (61%) Age: 14.1 ± 3.3 Paediatric pts: Y	CD: 100% Disease location: ileal 5%; colonic 26%; ileocolonic 69% Disease descriptor: isolated upper 91%; perianal 35% Tanner stage: I 15%; II 23%; III 19%; IV 25%; V 19%	IFX 75 (100)	NA	Primary: BMI[a], height[a], lean mass Secondary: CRP, ESR	Y
Santos et al. [42]	PO; 6	Sample size at baseline: 23 Males: 11 (48%) Age: 42 ± 12 Paediatric pts: N	CD: 100% Location of CD: upper GI tract 7.5%; ileum 26.1%; colon 17.4%; ileum and colon 49% Phenotype of CD: non-stricturing and non-penetrating (B1) 52.2%; stricturing (B2) 30.4%; penetrating (B3) 17.4%	IFX 23 (100)	5	Primary: weight, BMI[a], WC, fat mass[a], lean mass Secondary: activity (HBI), PA	Y
Emerenziani et al. [26]	PO; 3	Sample size at baseline: 12 Males: 7 (59%) Age: 45 ± 8 Paediatric pts: N	CD: 100% Ileal involvement: 75% CDAI 220–450 (moderate disease) 58%; CDAI > 450 (severe disease) 41%	IFX 12 (100)	5	Primary: lean mass, Secondary: PA, CRP	N
Franchimont.et [21]	PO; 1	Sample size at baseline: 20 Males: 12 (60%) Age: NA Paediatric pts: N	CD: 100% Disease location: upper GI tract 15%; ileum only 20%; ileum and colon 35%; colon only 45%; anal 45% Disease type: inflammatory 45%; structuring 10%; fistulizing 45%; extraintestinal manifestations 35%	IFX 20 (100)	NA	Primary: weight, fat mass[a] Secondary: CRP, activity index (CDAI)	Y

Table 1 (continued)

Study	Study design; duration (mo)	Sample characteristics[a]	Disease characteristics	Treatment, n (%)	Dose (mg/kg)	Outcomes	Meta-analysis (Y/N)
Gouldthorpe et al. [36]	RO; median 18	Sample size at baseline: 71 Males: 48 (68%) Median age: 14.4 (range 3.95–20.1) Paediatric pts: Y	CD: 100% Disease classification (Montreal): Location: ileocolonic 63.4%; colonic 31%; ileal 5.63%; +upper GI 57.7% Behaviour: inflammatory 83%; fibrostenotic 7%; penetrating 10%; +perianal 39.4% Children on maintenance IFX (severe disease 55.9%; moderate disease 44.1%)	IFX 71 (100)	5	Primary: weight, height Secondary: NA	N
Griffin et al. [27]	PO; 12	Sample size at baseline: 74 Males: 47 (64%) Median age: 14 (range 5–21) Paediatric pts: Y	CD: 100% Disease location: ileal 5%; colonic 27%; ileocolonic 68% Disease descriptor: isolated upper 84%; perianal 38% Tanner stage: I–II 39%; III–IV 43%; V 18%	IFX 74 (100); of these, 4 switched to ADA, one to CZP	NA	Primary: BMI[a], height[a], lean mass Secondary: CRP, ESR	Y
Haas et al. [8]	RO; median 29.3	Sample size at baseline: 69 Males: 37 (54%) Age: NA Paediatric pts: Y	CD 85%; UC 12%; IC 3% CD: distribution (Paris classification): small intestine (L1) 16.9%; colon (L2) 10.2%; small intestine and colon (L3) 83.1%; isolated upper disease (L4a) 40.7%; inflammatory (B1) 72.3%; stricturing (B2) 10.2%; penetrating (B3) 20.3%; penetrating and stricturing (B2B3) 2.7%; perianal disease (P) 20.3% UC: distribution: proctitis or left sided 2.5%; extensive 12.5%; pancolitis 62.5%	IFX 63 (91); ADA 32 (46); CZP 8 (12)	NA	Primary: weight[a], BMI[a] Secondary: NA	Y
Kierkus et al. [28]	Open-label single-arm trial; 9.3	Sample size at baseline: 33 Males: NA Median age: 14.2 (IQR 12.1–16.5) Paediatric pts: Y	CD: 100%	IFX 33 (100)	5	Primary: weight, BMI, height Secondary: CRP, activity (PCDAI)	N

Table 1 (continued)

Study	Study design; duration (mo)	Sample characteristics[a]	Disease characteristics	Treatment, n (%)	Dose (mg/kg)	Outcomes	Meta-analysis (Y/N)
Kierkus et al. [41]	Open-label single-arm trial; 2.3	Sample size at baseline: 66 Males: 29 (44%) Age: 14.06±3.59 Paediatric pts: Y	CD 100% Involved region: small intestine 43%; colon 91%; upper GI tract 32%	IFX 66 (100)	5	Primary: BMI Secondary: CRP, ESR, activity (PCDAI)	N
Koutroubakis et al. [29]	PO; 3.5	Sample size at baseline: 22 Males: 14 (64%) Age: 38.6 Paediatric pts: N	CD 86%; UC 14% CD: localization: ileum 21.1%; colon 26.3%; ileum and colon 52.6%. Disease type: inflammatory 63.2%; penetrating 36.8%. UC: localization: extensive colitis 100%	IFX 22 (100)	Induction: 5; maintenance: 5–10	Primary: BMI[a] Secondary: CRP, activity (CDAI, SCCAI)	Y
Malik et al. [37]	PO; 12	Sample size at baseline: 36 Males: 22 (61%) Age: 14.7 Paediatric pts: Y	CD 100% Disease location: most commonly panenteric (ileocolonic and upper GI tract, L3+L4 42%;+perianal disease 42% Tanner stage: I 19%; II 14%; III 14%; IV 6%; V 25%; NA 22%	ADA 36 (100)	18 pts: 80 at wk 0+40 at wk 2; 9 pts 24/m²; 2 pts: 160 at wk 0+80 at wk 2; 7 pts: other regimens; maintenance: 33 pts: 40 eow; 3 pts: 24/ m² eow	Primary: height velocity Secondary: activity (PCDAI)	N
Miranda-Bautista et al. [30]	RO; 36	Sample size at baseline: 128 Males: 64 (50%) Age: 43.55±12.82 Paediatric pts: N	CD 72%; UC 25%; IC 3% CD localization (Montreal classification): ileal (L1) 32.3%; colonic (L2) 9.7%; ileocolonic (L3) 58.1%; upper GI tract infection (L4+) 13.8%. Behaviour (Montreal classification): non-stricturing and non-penetrating (B1) 39.8%; stricturing (B2) 17.2%; penetrating (B3) 43%; perianal disease 36.2% UC: extension (Montreal classification): proctitis (E1) 3.1%; proctosigmoiditis (E2) 12.5%; left colitis (E3) 40.6%; pancolitis (E4) 43.8%	IFX 104 (81); ADA 10 (8); IFX+ADA: 14 (11)	IFX 5; ADA 160 at wk 0+80 at wk 2	Primary: BMI Secondary: NA	N
Parmentier-Decrucq et al. [38]	PO; 2	Sample size at baseline: 21 Males: 8 (38%) Age: 32±8 Paediatric pts: N	CD 100%	IFX 21 (100)	5	Primary: BMI[a], fat mass Secondary: NA	Y

Table 1 (continued)

Study	Study design; duration (mo)	Sample characteristics[a]	Disease characteristics	Treatment, n (%)	Dose (mg/kg)	Outcomes	Meta-analysis (Y/N)
Vadan et al. [39]	PO; 13.5	Sample size at baseline: 30 Males: 17 (57%) Age: 33.3 ± 13.87 Paediatric pts: N	CD 100% Disease location: ileum 3.3%; colon 63.3%; ileum + colon 33.3% Disease behaviour: inflammatory 60%; structuring 40% 30 patients (100%) with moderate/severe flares of disease 43.3% of patients with severe nutritional risk defined by the NRI[a]	IFX 30 (100)	5	Primary: weight, BMI Secondary: NA	N
Van Hoeve et al. [40]	PO; 12	Sample size at baseline: 42 Males: 21 (50%) Age: NA Paediatric pts: Y	CD 62%; UC 38% CD (Paris classification): disease location: L1 19%; L2 19%; L3 62%. Upper GI involvement: L4a 62%; L4b 4%. Disease behaviour: B1 81%; B2 19%. Perianal disease modifier: 12%. Growth: G0 69%; G1 31% UC (Paris classification): disease extent: E1 6%; E2 25%; E3 19%; E4 50%. Disease severity: S0 69%; S1 31%	IFX 42 (100)	8	Primary: weight[a], BMI[a], height[a] Secondary: CRP, ESR	Y
Wiese et al. [31]	PO; 6	Sample size at baseline: 7 Males: 1 (14%) Age: 41.1 Paediatric pts: N	CD 100% (ileal or ileocolonic) Of the 7 patients, 5 had active disease defined by CRP > 1.0 and 6 had active disease defined by HBI > 5	IFX 7 (100)	5	Primary: BMI, fat mass[a], lean mass Secondary: CRP, activity (HBI)	Y

ADA adalimumab, *BMI* body mass index, *CD* Crohn's disease, *CDAI* Crohn's Disease Activity Index, *CRP* C-reactive protein, *CZP* certolizumab pegol, *eow* every other week, *ESR* erythrocyte sedimentation rate, *GI* gastrointestinal, *HBI* Harvey Bradshaw index, *IC* indeterminate colitis, *IFX* infliximab, *IQR* interquartile range, *mo* months, *NA* not available, *NRI* Nutritional Risk Index, *PA* phase angle, *PCDAI* Paediatric Crohn's Disease Activity Index, *PO* prospective observational, *pts* patients, *RO* retrospective observational, *SCCAI* Simple Clinical Colitis Activity Index, *UC* ulcerative colitis, *WC* waist circumference, *wk* week(s)

[a] Age is presented as mean ± standard deviation (years) unless otherwise indicated

[b] Primary outcomes analysed using meta-analysis methodology

included in the review were rated as of moderate quality (NOS score 5–6). The most common quality issue was in the comparability domain.

3.2 Primary Outcomes

3.2.1 The Effect of Tumour Necrosis Factor (TNF)-α Inhibitors on Body Weight

Of the 23 studies, 11 reported information on body weight changes. Of these, six involved paediatric patients (164 participants) [8, 25, 33, 35, 36, 40] and five involved adults [21, 22, 24, 39, 42]. For paediatrics, SMD calculation was possible for four of the six studies; these four studies were included in the meta-analysis [8, 25, 33, 40]. The analysis revealed that patients' weight was significantly increased in children (SMD 0.31; 95% CI 0.12–0.49; $P=0.001$) after the commencement of anti-TNFα therapy (duration range 6–29.3 months). Figure 2 illustrates the effects of anti-TNFα pre- and post-treatment on weight in paediatrics. The weighted pooled mean increase in weight z score was 0.30 (standard error [SE] 0.12). The between-study heterogeneity was significant ($P=0.096$; $I^2=52.74\%$). A funnel plot (Fig. 1a in the ESM) showed no potential publication bias. The remaining two studies that were excluded from analysis supported these findings (Table 2). Briefly, in one study, children with CD following maintenance therapy of infliximab significantly increased weight z score by 0.51 ($P<0.001$) [36]. Similarly, Kierkus et al. [28] reported a significant increase in body weight of 5.6 kg after 50 weeks of treatment.

We were unable to calculate SMDs for the adult populations, because of insufficient information: values for change in body weight for at least two time points were not reported. Although there was marked heterogeneity in the way in which the studies included patients with physical frailty, all the studies nevertheless reported a significant increase in body weight following anti-TNFα treatment (Table 2). Adams et al. [22] found a trend toward statistical difference for body weight change among patients with normal muscle mass ($\Delta 1.86$ kg, $P=0.07$) but not in those with sarcopenia ($\Delta 1.14$ kg, $P=0.4$) after 6 months of anti-TNFα therapy. Vadan et al. [39] reported that undernourished patients had a significantly higher increase in body weight than well-nourished patients at the 30th and 54th week after anti-TNFα treatment. A significant increase in body weight was also found in the other three prospective studies after a mean duration of treatment of 3.33 months (range 1–6) [21, 24, 42].

3.2.2 The Impact of TNFα Inhibitors on Body Mass Index (BMI)

In total, 19 studies examined the effect of anti-TNFα on BMI. Of these, nine were eligible for meta-analysis. For paediatrics, the analysis of five studies (281 participants) [8, 25, 27, 35, 40] revealed a significant effect of anti-TNFα on BMI (SMD 0.28; 95% CI 0.03–0.53; $P=0.026$), with a weighted pooled mean change in BMI z score of 0.31 ± 0.14 (Fig. 3a). The duration of anti-TNFα therapy ranged from 12 to 29.3 months (mean 15.46). Significant between-study heterogeneity was detected ($I^2=85.04$; $P<0.001$). Funnel plots showed potential publication bias (Fig. 1b in the ESM).

For adults, four studies with 120 participants were included in the meta-analysis [23, 29, 38, 42]. The duration of anti-TNFα therapy in included studies ranged from 2 to 22.4 months (mean 8.47). The overall effect was nonsignificant (SMD 0.72; 95% CI 0.17–1.26; $P=0.1$), with an average BMI gain of 1.23 kg/m^2 (SE 0.21) (Fig. 3b). Statistically significant between-study heterogeneity was observed ($I^2=90.56$; $P<0.001$). Funnel plots indicate potential publication bias (Fig. 1c in the ESM). We explored sources of heterogeneity using stratification and repeated the analysis using a random-effects model as an additional sensitivity analysis. A sensitivity analysis was conducted by excluding the conference abstract [23]. The gain in BMI remained significant (SMD 0.93; 95% CI 0.42–1.43; $P<0.0001$) with considerable unexplained heterogeneity ($I^2=79.53$; $P=0.008$).

Table 2 summarizes the main findings for the remaining ten studies not included in the meta-analysis. Concerning children, in the study by Assa et al. [32], the clinical response was associated with an improvement in BMI z scores (-0.8 to -0.4; $P=0.04$). Likewise, Kierkus et al. [28, 41] reported a significant increase in BMI in children with severe CD treated with infliximab. For adults, Csontos et al. [24] reported significant BMI gain (from 23.81 ± 7.19 at baseline to 24.52 ± 7.34 kg/m^2 after 3 months; $P<0.001$). In a retrospective cohort of 128 patients who received at least three doses of infliximab or two doses of adalimumab, a significant increase in mean BMI was observed (0.74 and 1.44 kg/m^2 at 1- and 3-year follow-up, respectively) [30]. Vadan et al. [39] evaluated 30 patients with CD undergoing infliximab therapy and observed a significant increase in BMI among underweight subjects (from 17.31 ± 1.2 to 21.46 ± 1.61 kg/m^2) and normal-weight subjects (from 23.24 ± 2.27 to 23.51 ± 2.22 kg/m^2) after 54 weeks of treatment. In the study by Wiese et al. [31], seven patients experienced a gain in BMI of 2.21 kg/m^2 ($P=0.03$) after 6 months of infliximab treatment. Branquinho et al. [34] reported no significant change in BMI after induction treatment with infliximab, whilst an increase was noted at the 1-year follow-up (from 21.4 to 22.7 kg/m^2; $P=0.049$), which became

statistically significant after 3 years of therapy (from 21.4 to 22.8 kg/m^2; $P = 0.026$).

3.2.3 The Impact of TNFα Inhibitors on Height

For children, eight studies reported data on changes in height. Five of these, with 269 patients, were included in the meta-analysis (Fig. 4) [25, 27, 33, 35, 40]. The overall effect was significant (SMD 0.16; 95% CI 0.06–0.26; $P = 0.002$). The weighted pooled mean increase in height z score was 0.17 (SE 0.05). The between-study heterogeneity was nonsignificant ($I^2 = 11.19$; $P = 0.342$). The funnel plot showed no significant publication bias (Fig. 1d in the ESM). Findings from other paediatric studies not included in the meta-analysis confirmed a considerable increase in height after a treatment duration ranging from 9.3 to 18 months (Table 2) [28, 36, 37].

3.2.4 The Impact of TNFα Inhibitors on Fat Mass

Five studies reported changes in fat mass in adults [21, 24, 31, 38, 42]; of these, four were eligible for inclusion in the meta-analysis (Fig. 5). We found an overall increase in fat mass (%) (SMD 0.24; 95% CI − 0.19 to 0.66; $P = 0.272$), with considerable heterogeneity ($I^2 = 81.97$; $P = 0.001$). The funnel plot indicated a risk of publication bias (Fig. 1e in the ESM).

Other related reported outcomes were the body fat mass index (BFMI; kg/m^2), the visceral fat area (cm^2), and the total abdominal fat (cm^3); however, findings among studies were not consistent (Table 2). Parmentier et al. [38] reported a significant increase in total abdominal fat (212 ± 47 vs. 251 ± 50 cm^3; $P = 0.027$) after 8 weeks of induction treatment with infliximab, whereas Csontos et al. [24] found that fat parameters had not changed significantly at week 12 (visceral fat area 95.65 vs. 85.00 cm^2; $P = 0.730$; BFMI: 4.57 vs. 4.76 kg/m^2; $P = 0.120$). Santos et al. [42] reported a significant increase in fat mass index (fat mass [kg]/squared height: 5.5 ± 2.3 vs. 6.8 ± 2.3; $P = 0.000$).

3.2.5 The Impact of TNFα Inhibitors on Lean Mass

Six studies, with 231 patients, examined the effect of anti-TNFα treatment on lean mass [24, 26, 27, 31, 35, 42]. Information was insufficient to compute the SMD, and the main findings of individual studies are summarised here.

Data on changes in lean mass were available in six paediatric studies (n = 231 patients) [24, 26, 27, 31, 35, 42] not eligible for inclusion in the meta-analysis. Briefly, the period of observation ranged from 3 to 12 months. Csontos et al. [24] found a significant increase in skeletal mass index ($P = 0.003$) and fat-free mass index (FFMI) at week 12 ($P < 0.00$), along with a significant increase in food intake. Similarly, a significant increase in lean mass index (LMI) was also reported by Santos et al. [42] (17.5 ± 2.2 vs. 18.1 ± 2.3 kg/m^2; $P < 0.001$). Emerenziani et al. [26] reported a nonsignificant increase in FFMI among patients started on infliximab compared with patients on conventional treatment (41.7 ± 3.7 vs. 44.6 ± 4.2 kg; $P < 0.05$). Similarly, Griffin et al. [27] reported that Paediatric Crohn's Disease Activity Index (PCDAI) scores decreased after 10-week induction treatment, with subsequent gains in muscle area after 12 months (z scores $- 0.81 \pm 1.10$ vs. $- 0.35 \pm 1.10$; $P < 0.01$).

All studies observed lean body mass (LBM) values after anti-TNFα therapy in a period of observation ranging from 3 to 12 months. In brief, Csontos et al. [24] found a significant increase in both food intake and skeletal mass index ($P = 0.003$) and the FFMI ($P < 0.00$) in patients with IBD at week 12. Similarly, a significant increase in LMI was also reported by Santos et al. [42] (17.5 ± 2.2 vs. 18.1 ± 2.3 kg/m^2; $P < 0.001$). Emerenziani et al. [26] reported a nonsignificant increase in FFMI in patients on infliximab therapy compared with patients on conventional therapy (41.7 ± 3.7 vs. 44.6 ± 4.2 kg; $P < 0.05$). Similarly, Griffin et al. [27] reported that PCDAI scores decreased during the 10-week induction, with subsequent gains in muscle area z scores after 12 months ($- 0.81 \pm 1.10$ vs. $- 0.35 \pm 1.10$ mm^2; $P < 0.01$). In a prospective cohort study of 75 patients aged 5–21 years with CD, leg lean mass score increased significantly following 12 months of anti-TNFα therapy ($- 0.76 \pm 1.04$ vs. $- 0.27 \pm 1.01$ kg; $P < 0.001$) [35]. In contrast, no significant change in the LBM per DXA value was observed by Wiese et al. [31] (from 39.16 at baseline to 40.03 kg; $\Delta 0.87$ kg; $P = 0.44$) after 6 months of infliximab treatment in seven patients with CD.

3.2.6 The Impact of TNFα Inhibitors on Waist Circumference

Only one study examined change in WC after commencement of anti-TNFα therapy [42]. A significant increase in WC (from 88.1 ± 6.7 at baseline to 93.9 ± 7.7 cm; $P < 0.05$) was found in adults with moderate-to-severe CD after 6 months of anti-TNFα therapy.

3.3 Secondary Outcomes

In total, 21 studies reported secondary outcomes, i.e. laboratory markers of disease activity, disease severity index scores, and changes in PA (Table 3 in the ESM). In all studies, the efficacy of treatment in reducing disease activity was confirmed by a significant reduction in both surrogate markers of disease activity (i.e. ESR and CRP) and severity index scores, regardless of IBD type (CD or UC) and population (children or adults). A limited number of studies reported on the effect of anti-TNFα treatment on PA.

Only two studies examined the influence of anti-TNFα treatment on PA in IBD, but the findings were conflicting. PA remained unchanged (6.2 vs. 6.8; $P = 0.94$) in the study by Santos et al. [42], whereas Emerenziani et al. [26] found a significant increase in mean PA scores (from 4.6 ± 0.3 to 6.2 ± 0.4; $P < 0.05$) (Table 2).

4 Discussion

Evidence addressing the relationship between anti-TNFα agents and variations in body composition is of primary importance in the assessment of safety and efficacy outcomes with this pharmacological approach. Previous studies revealed contradictory results concerning the effects of anti-TNFα therapy on body composition in rheumatological patients [44–46].

This is the first systematic review aimed at evaluating the impact of anti-TNFα therapy on anthropometric variations in adult and paediatric patients with IBD. In doing so, we took care to consider all aspects that were revealing of disease activity indices. The goal was to determine whether the weight gain was due to an increase in fat or muscle mass and to improve knowledge on any potential effect related to anti-TNFα therapy. To maximize comparability and minimize potential bias, we excluded studies with the possible confounding effect of parenteral or enteral nutrition or in patients receiving pharmacological treatment to control or prevent metabolic disorders.

We found evidence for a statistically significant impact of TNFα inhibitors on BMI in both adults (SMD 0.72; 95% CI 0.17–1.26; $P = 0.010$) and children (SMD 0.28; 95% CI 0.03–0.53; $P = 0.026$). The SMD was larger for adults than for children. Furthermore, there was a small but statistically significant effect on body weight (SMD 0.31; 95% CI 0.12–0.49; $P = 0.001$) and height (SMD 0.16; 95% CI 0.06–0.26; $P = 0.002$).

Relatedly, and of note, despite the high heterogeneity among studies that addressed the issue, these results were also consistently supported by findings from studies not included in the meta-analysis and reviewed in the systematic review. Unfortunately, because of the lack of data, we could not perform moderator analysis on observed heterogeneity. Such heterogeneity might be attributed to variations in study patients, sex, disease severity, type of anti-TNFα, and concomitant treatment as well as the remitting and relapsing nature of IBD.

BMI and body weight changes were the main outcomes most commonly reported. There was a meaningful increase in BMI from baseline in all studies; this effect was more evident in studies dealing with long-term follow-up, especially after 3 years of therapy, showing an increase in BMI of 1.4 kg/m² [30, 34]. In line with this, we found an overall increase in BMI of 1.23 ± 2.3 kg/m² from baseline after a therapy duration ranging from 2 to 22.4 months. Similarly, we noted an increase in weight in both adults and children after a mean duration of 6 and 12.4 months of treatment, respectively. In line with this, increased WC was evident after infliximab therapy (88.1 ± 6.7 vs. 93.9 ± 7.7 cm; $P < 0.05$) in adults with moderate-to-severe CD [42].
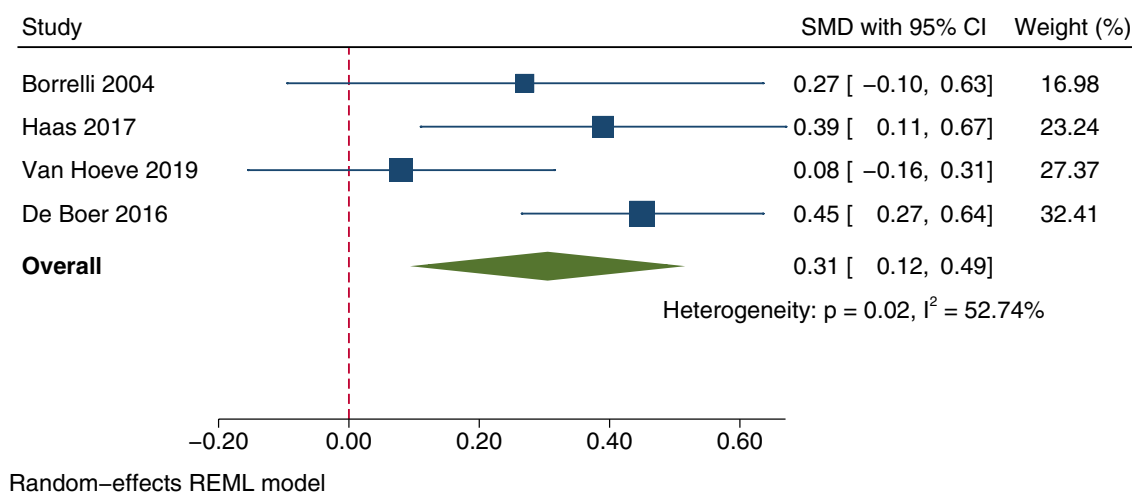

Fig. 2 Forest plot showing the change in body weight between baseline and after treatment commencement with a tumour necrosis factor (TNF)-α inhibitor in paediatric patients. Standardized mean difference (SMD) estimates were based on Cohen's d with corresponding 95% confidence intervals (CIs) and were considered small ($d = 0.2$), medium ($d = 0.5$), and large ($d \geq 0.8$) as per Cohen's classification scheme [20]. A P value < 0.05 was considered statistically significant

Table 2 Summary of post anti-tumour necrosis factor-α treatment changes in anthropometric measures in studies excluded from meta-analysis

Outcome	Study	Baseline	Endpoint	Variation[a]	Duration of anti-TNF therapy
Body weight (kg)	Adams et al. [22]	NR	NR	Entire cohort: 1.5 ($P = 0.06$) Sarcopenic: 1.14 ($P = 0.4$) Normal muscle: 1.86 ($P = 0.07$)	6 months (IFX, ADA, CZP)
	Csontos et al. [24]	63.4 (58.82–79.40)[b]	63.7 (58.49–82.65)[b]	Overall: NR; Significant increase ($P < 0.001$) Stratified by disease severity: Mild 3.54 ± 3.59 Moderate 1.87 ± 2.60 Severe 0.98 ± 2.67	3 months (IFX, ADA)
	Santos et al. [42]	62.6 ± 9.5	68.4 ± 13.2	NR; significant increase ($P = 0.006$)	6 months (IFX)
	Franchimont et al. [21]	63.6 (3.6)[c]	64.4 (3.5)[c]	NR; significant increase ($P = 0.013$)	1 month (IFX)
	Gouldthorpe et al. [36]	Weight-for-age SDS: $- 0.77$[b]	Weight-for-age SDS: $+ 0.48$[b]	NR; significant increase ($P < 0.05$)	44 months (IFX)
	Kierkus et al. [28]	43 (36.2–50.7)[d]	48.6 (42–53.5)[d]	NR	10 months (IFX)
	Vadan et al. [39]	NR	NR	Stratified by BMI category: Baseline BMI < 18.5: 11.2 ± 3.58 ($P = 0.002$) Baseline BMI > 18.5: 6.58 ± 2.32	13.5 months (IFX)
BMI (kg/m^2)	Assa et al. [32]	BMI for age and sex SDS, z scores: $- 0.8$[e]	BMI for age and sex SDS, z scores: $- 0.4$[e]	NR; significant increase ($P = 0.04$)	60 months (IFX, ADA)
	Branquinho et al. [34]	21.4 ± 3.07	22.8[e]	NR; nonsignificant increase at 1 year, significant increase at 3 years ($P = 0.026$)	36 months (IFX)
	Csontos et al. [24]	21.75 (19.20–26.55)[b]	22.5 (20.17–27.02)[b]	Overall: NR; significant increase ($P < 0.001$) Stratified by disease severity Mild 1.16 ± 1.19 Moderate 0.63 ± 0.88 Severe 0.34 ± 0.91	3 months (IFX, ADA)
	Kierkus et al. [41]	17.9 (16.4–19.5)[d]	18.9 (16.9–20)[d]	NR; significant increase	10 months (IFX)
	Kierkus et al. [28]	17.5 (15.4–19.4)[b]	18 (16.7–20)[b]	NR; significant increase	2.5 months (IFX)
	Miranda-Bautista et al. [30]	23.9 ± 4.6	NR	1.44 ± 3.5 ($P < 0.001$)	36 months (IFX, ADA)
	Vadan et al. [39]	Baseline BMI < 18.5: 17.31 ± 1.22 Baseline BMI > 18.5: 21.03 ± 2.1	Baseline BMI < 18.5: 21.46 ± 1.61 Baseline BMI > 18.5: 23.51 ± 2.22	NR; significant increase ($P = 0.01$)	13.5 months (IFX)
	Wiese et al. [31]	24.45[e]	26.66[e]	2.21 ($P = 0.03$)[e]	6 months (IFX)

Table 2 (continued)

Outcome	Study	Baseline	Endpoint	Variation[a]	Duration of anti-TNF therapy
Height (cm)	Gouldthorpe et al. [36]	Height-for-age SDS: −0.33[b]	Height-for-age SDS: 0.86[b]	NR; significant increase ($P < 0.05$)	44 months (IFX)
	Kierkus et al. [28]	154.3 (142–164.5)[d]	158.5 (152–168.5)[d]	NR; significant increase	10 months (IFX)
Height velocity (cm/y)	Malik et al. [37]	2 (0–5.8)[f]	4.2 (0–10.3)[f]	NR; nonsignificant increase ($P = 0.11$)	12 months (ADA)
Fat mass	Parmentier-Decrucq et al. [38]	TAF (cm³): 212 ± 47	TAF (cm³): 251 ± 50	NR; significant increase ($P = 0.027$)	2 months (IFX)
	Csontos et al. [24]	Visceral fat area: 95.65 cm³ BFMI: 4.57 kg/m²	Visceral fat area: 85.00 cm³ BFMI: 4.76 kg/m²	NR; nonsignificant increase	
	Santos et al. [42]	BFMI: 5.5 ± 2.3 kg	BFMI: 6.8 ± 2.3 kg	NR; significant increase	
Lean mass	Csontos et al. [24]	FFMI: 17.64 ± 3 SMI (kg/m²): 9.81 ± 1.83	FFMI: 18.14 ± 3.08 SMI: 10.05 ± 1.90	NR; significant increase ($P < 0.001$) Stratified by disease severity (FFMI): Mild 1.02 ± 0.74 Moderate 0.46 ± 0.68 Severe −0.05 ± 0.61 Differences within mild and severe disease activity subgroups ($P = 0.005$)	3 months (IFX, ADA)
	DeBoer et al. [25]	LegLM: −0.76 ± 1.04	LegLM: −0.27 ± 1.01	NR; significant increase ($P < 0.001$)	12 months (IFX)
	Santos et al. [42]	LMI: 17.5 ± 2.2	LMI: 18.1 ± 2.3	NR; significant increase ($P = 0.000$)	6 months (IFX)
	Emerenziani et al. [26]	FFM: 41.7 ± 3.7	FFM: 44.6 ± 4.2	NR; significant increase	3 months (IFX)
	Griffin et al. [27]	Muscle CSA (mm²), z score: −0.81 ± 1.10	Muscle CSA (mm²), z score: −0.35 ± 1.06	Muscle CSA (mm²), z score: 0.46 ± 0.78 ($P < 0.01$)	12 months (IFX, ADA, CZP)
	Wiese et al. [31]	DXA (kg): 39.16[e]	DXA (kg): 40.03[e]	DXA (g): 872.33 ($P = 0.4$)[e]	6 months (IFX)
WC (cm)	Santos et al. [42]	88.1 ± 6.7	93.9 ± 7.7	NR; significant increase ($P = 0.002$)	6 months (IFX)

Data are presented as mean ± SD unless otherwise indicated

NRI = 1.519 × serum albumin (g/L) + 41.7 × (current/usual body weight)

ADA adalimumab, *BFMI* body fat mass index, *BMI* body mass index, *CSA* cross-sectional area, *CZP* certolizumab, *DXA* dual-energy X-ray absorptiometry, *FFM* fat-free mass, *FFMI* Fat-Free Mass Index, *IFX* infliximab, *IQR* interquartile range, *LegLM* leg lean mass, *LMI* lean mass index, *NR* not reported, *NRI* Nutritional Risk Index, *SD* standard deviation, *SDS* standard deviation scores, *SEM* standard error of the mean, *SMI* Skeletal Muscle Mass Index, *TAF* total abdominal fat, *TNF* tumour necrosis factor, *WC* waist circumference

[a]Presented as change (Δ) unless otherwise specified

[b]Median (IQR)

[c]Mean (SEM)

[d]Median (range)

[e]Mean ± SD

[f]Median (10th–90th centiles)

Importantly, responders had significant improvements in body weight and BMI compared with nonresponders, which may reflect early discontinuation of treatment in nonresponders and a switch to an alternative treatment. Factors such as age, disease duration, smoking, or other medication did not appear to have a significant association with BMI, suggesting that anti-TNFα therapy may play a significant
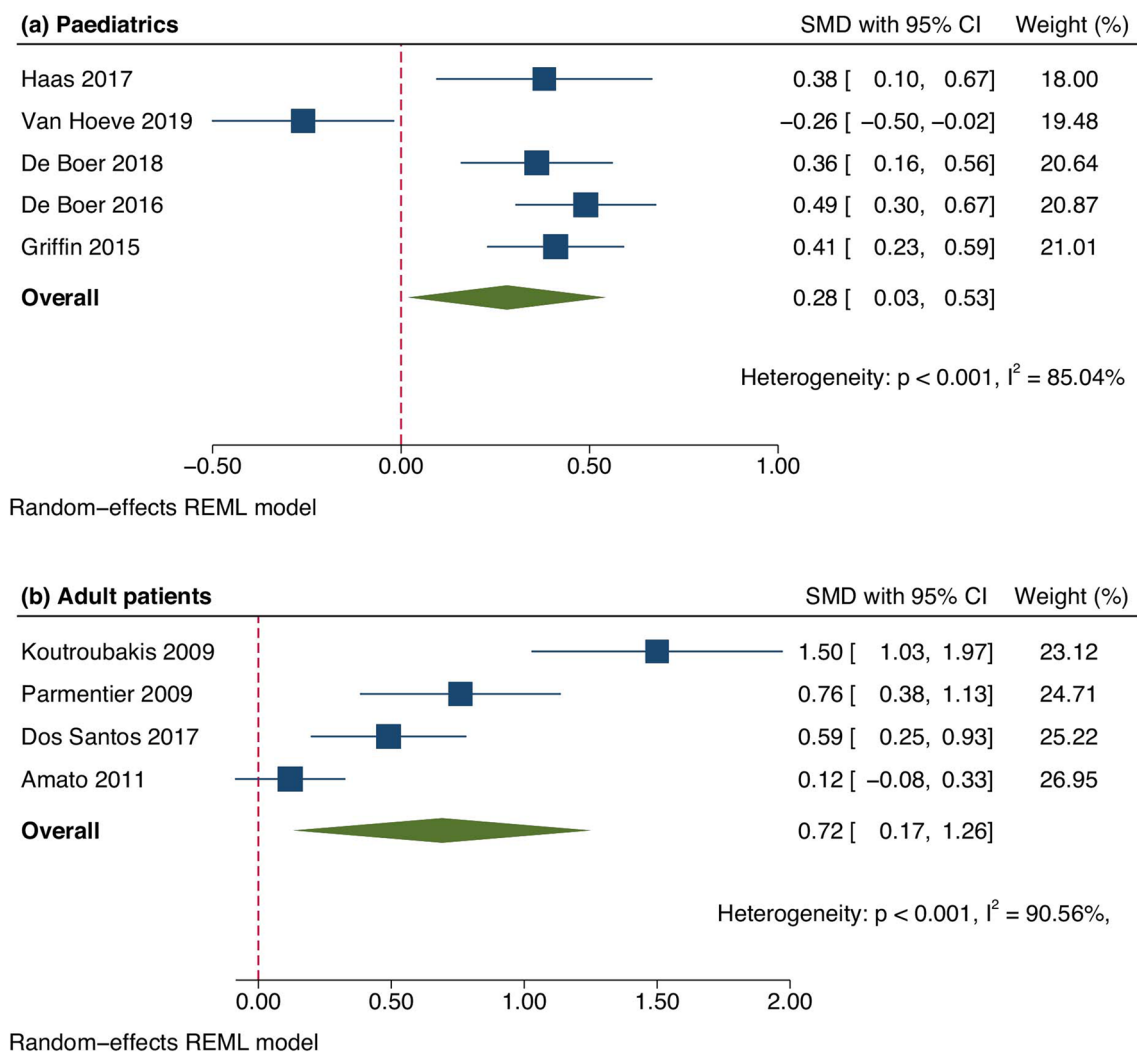
(a) Paediatrics

	SMD with 95% CI	Weight (%)
Haas 2017	0.38 [0.10, 0.67]	18.00
Van Hoeve 2019	−0.26 [−0.50, −0.02]	19.48
De Boer 2018	0.36 [0.16, 0.56]	20.64
De Boer 2016	0.49 [0.30, 0.67]	20.87
Griffin 2015	0.41 [0.23, 0.59]	21.01
Overall	0.28 [0.03, 0.53]	

Heterogeneity: $p < 0.001$, $I^2 = 85.04\%$

Random–effects REML model

(b) Adult patients

	SMD with 95% CI	Weight (%)
Koutroubakis 2009	1.50 [1.03, 1.97]	23.12
Parmentier 2009	0.76 [0.38, 1.13]	24.71
Dos Santos 2017	0.59 [0.25, 0.93]	25.22
Amato 2011	0.12 [−0.08, 0.33]	26.95
Overall	0.72 [0.17, 1.26]	

Heterogeneity: $p < 0.001$, $I^2 = 90.56\%$,

Random–effects REML model

Fig. 3 Forest plot showing the change in body mass index (BMI) between baseline and after treatment commencement with a tumour necrosis factor (TNF)-α inhibitor in **a** paediatric and **b** adult patients. Standardized mean difference (SMD) estimates were based on Cohen's *d* with corresponding 95% confidence intervals (CIs) and were considered small ($d = 0.2$), medium ($d = 0.5$), and large ($d \geq 0.8$) as per Cohen's classification scheme [20]. A *P* value < 0.05 was considered statistically significant

role in body changes by ameliorating the disease status [24, 30, 32, 34].

The adult patients in our analysis were of normal weight (BMI ranged from 21.9–24.4 kg/m^2), except for three studies in which < 30% of the cohort were underweight [32, 34, 38]; therefore, the increase in body parameters from the baseline raises concerns over cardiometabolic diseases and the inferior response of anti-TNFα treatments in patients with IBD [43]. Conversely, paediatric patients were underweight (BMI *z* scores ranged from − 1 to − 0. 1), suggesting that the beneficial impact of the increase in these parameters was limited to the paediatric clinical setting.

At the end of follow-up (range 6–36 months), all included studies reported significant increases in both weight and height in children. It would have been interesting to understand whether the weight and height gain was only anti-TNFα dependent or the normal growth of children over time. Reported data suggest that patients aged < 10 years had the most weight gain; this may reflect the faster growth velocity seen in early puberty and/or a greater impact of anti-TNFα agents in this population. Additional studies with a larger cohort may help clarify these issues.

Although the observed increase in weight and BMI during anti-TNFα treatment can probably be attributed to the decline in intensity of the inflammatory response and improved nutrient absorption and utilization, an intrinsic anti-TNFα therapy effect cannot be ruled out. Anti-TNFα therapy itself may increase abdominal fat tissue in patients with IBD, likely through blockade of the TNFα-induced lipolytic effect, a mechanism that may contribute to the

weight and BMI gain we detected. Moreover, as an activator of nuclear factor (NF)-κB, TNFα has a remarkable effect on metabolic pathways. As a consequence, anti-TNFα therapy may prevent the activation of NF-κB [47], influencing both nutritional status and body composition.

Skeletal muscle and adipose tissue produce cytokines and thus play an important role in the maintenance of metabolic homeostasis [48, 49]. As nutritional status assessments based on BMI and body weight do not provide sufficient information concerning body composition, we attempted to examine changes from baseline in fat and lean mass. However, only eight studies reported body composition changes, suggesting that the effect of anti-TNFα treatments on body composition in patients with IBD still lacks adequate attention.

We found no significant increase in fat mass (SMD 0.24; 95% CI − 0.19 to 0.66; $P = 0.272$), likely because of the overall short period of observation (mean 6 months; range 1–6), which probably did not allow the detection of substantial changes, with highly significant heterogeneity between studies ($I^2 = 81.97$; $P = 0.001$). Although not all studies reached statistical significance, findings from data not included in the meta-analysis showed an overall increase in total abdominal fat ($P = 0.027$) [38] in BFMI (5.5 ± 2.3 vs. 6.8 ± 2.3 kg/m^2; $P = 0.00$ [42]; 4.57 vs. 4.76 kg/m^2; $P = 0.120$) and in visceral fat area (95.65 vs. 85.00 cm^2; $P = 0.730$) [24].

While some results in terms of the effects of anti-TNFα therapy on fat mass were partially conflicting, data on changes in lean mass in paediatric studies [24, 26, 27, 31, 35, 42] consistently showed a significant increase after anti-TNFα therapy. Investigating these studies further, all but one reported a significant increase in LBM values from baseline, as confirmed by skeletal mass ($P = 0.003$), FFMI ($P < 0.00$), LMI, muscle area z scores ($P < 0.001$), and leg lean mass score ($P = 0.001$) in observation periods ranging from 3 to 12 months. Importantly, FFMI was significantly increased in patients on infliximab therapy compared with patients on conventional therapy in the study by Emerenziani et al. [26]. Only one study reported no significant change in LBM value, in patients with CD after 6 months ($P = 0.44$), and this was likely because of the small sample size, i.e. seven patients [31].

A significant proportion of children with CD has growth impairment at diagnosis [50, 51]. Whereas TNFα is known to be implicated in the suppression of the growth hormone axis and long bone growth [52–54], evidence regarding growth benefits during anti-TNFα therapy is still wanting [55], with no systematic data available yet. We now describe a small but statistically significant overall increase in height (SMD 0.16; 95% CI 0.06–0.26; $P = 0.002$) from baseline in paediatric patients with CD (along with an improvement in BMI and weight). All studies confirmed this substantial increase, after a treatment duration ranging from 9.3 to 18 months. The finding that growth (including height velocity) was more likely to improve in responders suggests that growth improves as a result of better disease control with anti-TNFα therapy [32, 37].

Some studies have suggested that, in different chronic conditions, PA can be considered a promising tool to assess nutritional status [56–58]; reduced PA values are indeed associated with unfavourable disease progression
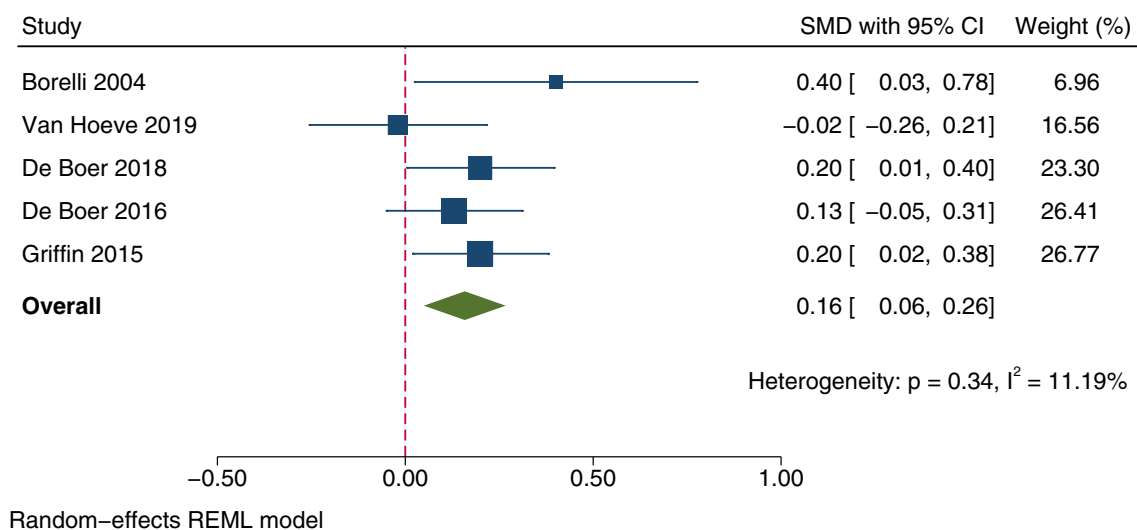

Study	SMD with 95% CI	Weight (%)
Borelli 2004	0.40 [0.03, 0.78]	6.96
Van Hoeve 2019	−0.02 [−0.26, 0.21]	16.56
De Boer 2018	0.20 [0.01, 0.40]	23.30
De Boer 2016	0.13 [−0.05, 0.31]	26.41
Griffin 2015	0.20 [0.02, 0.38]	26.77
Overall	0.16 [0.06, 0.26]	

Heterogeneity: p = 0.34, I^2 = 11.19%

Random−effects REML model

Fig. 4 Forest plot showing the change in height between baseline and after treatment commencement with a tumour necrosis factor (TNF)-α inhibitor in paediatric patients. Standardized mean differences (SMDs) were based on Cohen's d with corresponding 95% confidence intervals (CIs) and were considered small ($d = 0.2$), medium ($d = 0.5$), and large ($d \geq 0.8$) as per Cohen's classification scheme [20]. A P value < 0.05 was considered statistically significant
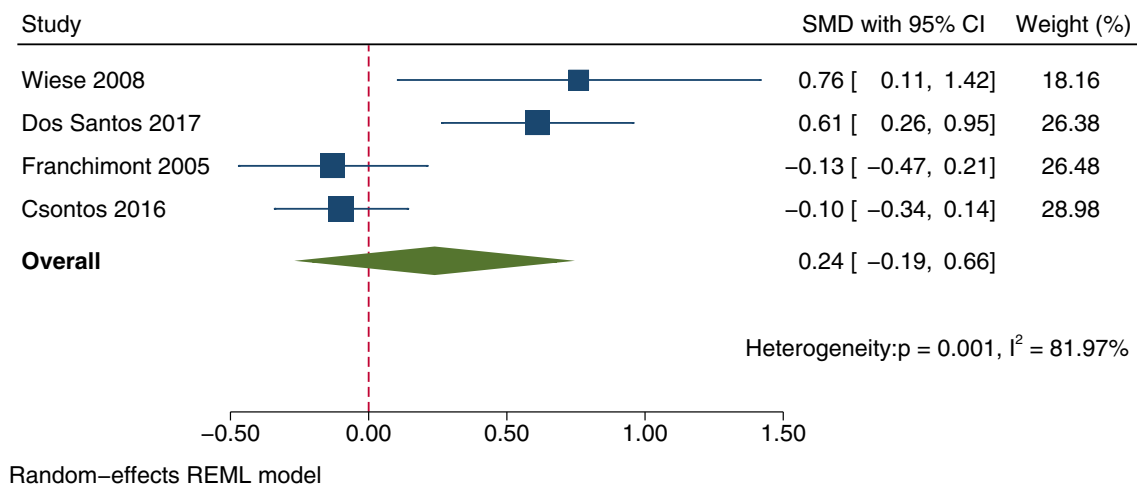
Fig. 5 Forest plot showing the change in fat mass between baseline and after treatment commencement with a tumour necrosis factor (TNF)-α inhibitor in adult patients. Standardized mean differences (SMDs) were based on Cohen's *d* with corresponding 95% confidence intervals (CIs) and were considered small ($d = 0.2$), medium ($d = 0.5$), and large ($d \geq 0.8$) as per Cohen's classification scheme [20]. A *P* value < 0.05 was considered statistically significant

and poor prognosis. More recently, PA has been assessed in paediatric patients with IBD during clinical remission [59]. Unfortunately, data on PA changes from the baseline were limited for our analysis, and findings from the only two studies reporting PA values were conflicting. Emerenziani et al. [26] found a significant increase in PA (from 4.6 ± 0.3 to 6.2 ± 0.4; $P < 0.05$), along with a substantial increase in FFMI, whereas PA remained unchanged (6.2 vs. 6.8; $P = 0.94$) in the study by Santos et al. [42] after 24 weeks of infliximab therapy. The lack of substantial improvement may be because PA decreases when fat mass increases and lean mass decreases; although patients gained both fat mass and lean mass, fat mass gain was more substantial.

4.1 Limitations

The main limitation of this study was that we could only include 13 of the 23 identified studies in the meta-analysis as the remaining studies did not report the required data. The absence of published randomised controlled trials on this issue forced us to include only observational studies. The limited data on potential covariates such as disease duration, disease severity, other medications, smoking, physical activity, and dietary changes prevented us conducting meta-regressions to explore in more detail the effects of TNFα inhibitors on body changes. Moreover, the vast majority of patients included in the study (90.2%) had CD, and only a few patients had UC. This could be an additional bias for the interpretation of the results. CD is more often associated with weight loss and growth impairment than UC, so it would be interesting to understand whether having a higher

proportion of patients with UC would have elicited the same results.

5 Conclusion

Our analysis revealed an increase in the main anthropometric parameters (body weight, BMI, and height) among patients with IBD treated with TNFα inhibitors. These increases were also greater with longer follow-up and in responders compared with non-responders. The potential effect of TNFα inhibitors on anthropometric measures could be a consideration in the care of overweight and obese adults with IBD given the concerns that weight gain may be a risk factor for developing metabolic disorders and increase the likelihood of anti-TNFα therapy failure. In contrast, IBD was associated with impaired weight gain in children, in whom anti-TNFα agents could exert positive improvements in weight and linear growth. Further prospective studies are warranted to provide stronger evidence for the role of biological therapy on body changes, especially on fat and lean mass in patients with IBD.

Declarations

have no conflicts of interest that are directly relevant to the content of this article.

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