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Predictive fat mass equations for children with inflammatory bowel disease

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Abstract

Objective: Evaluate accuracy of skinfold thicknesses and body mass index (BMI) for the prediction of fat mass percentage (FM%) in pediatric inflammatory bowel disease (IBD) and to develop population specific formulae based on anthropometry for estimation of FM%.

Methods: IBD children (n=30) and healthy controls (HCs, n=144) underwent anthropometric evaluation and Dual-energy X-ray absorptiometry (DEXA) scan, as the clinical reference for measurement of body composition. Body FM% estimated with skinfolds thickness was compared with FM% measured with DEXA. By means of four prediction models, population specific formulae for estimation of FM% were developed.

Results: No significant difference in terms of FM% measured by DEXA was found between IBD population and HCs (FM% 29.6% vs 32.2%, p=0.108). Triceps skinfold thickness (TSF, Model 2) was better than BMI (Model 1) at predicting FM% (82% vs. 68% of variance). The sum of two skinfolds (biceps + triceps; SF2, Model 3) showed an improvement in the prediction of FM% as compared to TSF, Model 2 (86% vs. 82% of variance). The sum of

four skinfolds (biceps + triceps + suprailiac + subscapular; Model 4) showed further improvement in the prediction of FM% as compared to SF2 (88% vs. 86% of variance).

Conclusion: The sum of 4 skinfolds is the most accurate in predicting FM% in paediatric IBD. The sum of 2 skinfolds is less accurate but more feasible and less prone to error. The newly developed population specific formulae could be a valid tool for estimation of body composition in IBD population and an alternative to DEXA measurement.

What Is Known

- Monitoring of nutritional status and body composition is important to prevent malnutrition and improve disease outcome in patients with inflammatory bowel disease.
- Dual-energy X-ray absorptiometry (DEXA), the clinical gold standard for body composition analysis, is not always available in clinical practice.

What Is New

- In this study we developed population specific formulae based on anthropometry for estimation of fat mass percentage (FM%) in pediatric inflammatory bowel disease (IBD) as an alternative to DEXA.
- The sum of 4 skinfolds is the most accurate in predicting FM%, the sum of 2 skinfolds is less accurate but more feasible in clinical practice because less prone to inter-operator error.

Introduction

Inflammatory bowel disease (IBD) is a group of disorders characterized by chronic and relapsing inflammation of the gastrointestinal tract. The etiopathogenesis is multifactorial involving genetic predisposition and environmental factors (1,2). Nutrition is a key element in the pathogenesis of disease but also as an important factor influencing disease course; nutritional approach with exclusive enteral nutrition (EEN) and more recently specific diets such as Crohn's Disease Exclusion Diet (CDED) have been demonstrated to be effective for induction of remission in pediatric CD (3, 4).

Weight loss, growth restriction, malnutrition and bone mass deficit have been well described in pediatric IBD (5). Data on body composition in children and adolescents with IBD is scarce and discordant (6). Dual-energy X-ray absorptiometry (DEXA), the clinical gold standard for assessment of body composition, is not always available in clinical practice. Simple, reliable, rapid and cost effective methods are needed for estimation of body composition in clinical practice. Prediction formulas for the estimation of FM % are

available. These formulas have been created for the general population but are not disease specific. Callias et al. (7) evaluated the level of agreement between some plicometric equations (Deurenberg, Slaughter, Weststrate, Durnin and Rahman, Johnston, Brook) and DEXA in a population of children and adolescents with IBD, concluding that although Durnin and Rahman was found to have the best agreement with DEXA, none of the plicometric equations used was accurate enough to predict the amount of FM from plicometric measurements in pediatric IBD.

The objectives of the present study are:

1) Compare body composition of patients with IBD with healthy controls (HCs);
2) Evaluate accuracy of skinfold thicknesses and body mass index (BMI) for the prediction of FM% in children and adolescents with IBD by comparing results with FM% measured with DEXA.
3) Develop population specific formulae based on anthropometry for estimation of FM% in pediatric IBD.

Methods

Thirty patients affected by IBD were prospectively recruited between September 2019 and May 2020 from the Gastroenterology Unit of "Vittore Buzzi" Children's Hospital, Milan, Italy. IBD patients were recruited at any time of their disease course. Inclusion criteria were: a) Age: 6-18 years old; b) Diagnosis of Crohn's disease (CD), ulcerative colitis (UC) or unclassified IBD (IBDU). Exclusion criteria were: a) Age less than 6 or greater than 18 years old; b) Diagnosis under definition. All subjects enrolled in the study underwent a complete nutritional assessment through clinical and instrumental evaluation, as described below. Informed consent was obtained from parents or legal guardian prior to participation in the study. At the moment of enrollment, data on disease location at diagnosis, disease activity and medical treatment were collected. To define disease activity, the pediatric ulcerative colitis activity index (PUCAI score) (8) and the short pediatric crohns disease activity index (sPCDAI) (9) was used respectively for UC and CD.

Healthy controls (HCs, n=144) were children and adolescents aged 6-18 years attending the International Center for the Assessment of Nutritional Status (ICANS, University of Milan) for screening of nutritional status. All control children and adolescents underwent anthropometric measurement and DEXA. To be eligible for the study, they had to be free of known acute (e.g., influenza) and chronic disease (e.g., diabetes). Informed consent was obtained from each patient's and healthy control's legal guardian before enrollment.

Anthropometric evaluation

In IBD patients the following parameters were measured: weight, height, pubertal stage, BMI, body circumferences (waist, abdomen, hips) and skinfold thicknesses (biceps, triceps, suprailiac and subscapular skinfolds). Body weight was measured to the nearest 100 g with a beam scale, and body height to the nearest 0.1 cm using a vertical stadiometer. For pubertal

stages, we considered Prepubertal stage=Tanner Stage 1; Middle puberty = Tanner Stage 2-3; Late puberty=Tanner Stage 4-5 (10,11). BMI was calculated as weight (kg)/height (m^2). The standard deviation scores (SDS) of weight, height, and BMI were calculated using WHO reference data (12). Nutritional status was defined using the IOTF reference (13). Skinfold thicknesses were measured using a professional mechanical skinfold caliper (GIMA). Each skinfold was measured three times, and the mean value was considered and recorded to the nearest 0,1 mm. Measurements were collected by trained dietitians using a standardized technique (14).

• Estimation of body fat mass percentage (FM %)

Predictive equations based on skinfold thicknesses were used for estimation of body FM %.

The following formulas were used to calculate body density:

- **Brook** (1-9 years old): (15)

  - Girls: Body Density = 1.2063 - 0.0999 * (log Σ of the 4 skinfolds)

  - Boys: Body Density = 1.1690 – 0.0788 * (log Σ of the 4 skinfolds)

- **Johnston** (8-14 years old): (16)

  - Girls: Body Density = 1.144 - 0.06 * (log Σ of the 4 skinfolds)

  - Boys: Body Density = 1.166 - 0.07 * (log Σ of the 4 skinfolds)

- **Durnin and Rahman** (13-15 years old): (17)

  - Girls: Body Density = 1.1369 - 0.0598 * (log Σ of the 4 skinfolds)

  - Boys: Body Density = 1.1533 - 0.0643 * (log Σ of the 4 skinfolds)

- **Durnin and Womersley** (16-19 years old): (18)

  - Girls: Body Density = 1.1549 - 0.0678 * (log Σ of the 4 skinfolds)

  - Boys: Body Density = 1.162 - 0.063 * (log Σ of the 4 skinfolds)

The value of body density (D) obtained, which is inversely related to fat content of the body, was used to estimate the FM (Fat Mass) through Siri predictive equation (19):

- Siri Equation: FM (%) = 495/D – 450

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Body composition evaluation with DEXA (Dual X-ray Absorptiometry) technique

Within four weeks from the nutritional assessment, all subjects with IBD underwent a body composition study with DEXA technique at the Pediatric Bone Densitometry Unit, San Raffaele Scientific Institute, using the Lunar Prodigy Advance DEXA System - GE Medical Systems LUNAR (software version 16). In IBD patients, FM% estimated with the above mentioned available predictive formulae (Brook, Johnston, Durnin and Rahman, Durnin and Womersley) was compared with FM% measured with DEXA scan.

Statistical Analysis

Most continuous variables were not Gaussian-distributed, and all are reported as 50th (median), 25th and 75th percentiles. Discrete variables are reported as the number and proportion of subjects with the characteristic of interest. Between-group comparisons were performed with the Wilcoxon Mann-Whitney test for continuous variables and with the Pearson's Chi-squared test for discrete variables. We evaluated the contribution of body mass index (BMI), triceps skinfold (TSF), the sum of 2 skinfolds (triceps + biceps), and the sum of 4 skinfolds (triceps + biceps + subscapular + suprailiac) to percent fat mass (FM%), i.e. fat mass (FM, kg) / body mass (BM, kg) using 2 prespecified linear regression models. The response variable of both models was FM% (%). The predictors of Model 1 were logeBMI (mm), logeTSF (mm), loge2SF (mm) or loge4SF (mm), IBD status (discrete, 0= CTR; 1 = IBD) and their interaction (continuous X discrete). All the predictors were loge transformed to ensure homoskedasticity (20). If the interaction of Model 1 was not significant, i.e. the regression lines of CTR and IBD were parallel, we evaluated Model 2, i.e. Model 1 without the interaction term. Model 2 test the hypothesis that the parallel regression lines detected by Model 1 are superimposed. To control for potential confounding factors, both models were adjusted for sex (discrete; 0=female, 1=male) and age (continuous). The linearity of the predictor X IBD interaction was checked using plots and multivariable fractional polynomials (21). Standard diagnostic plots were used to evaluate model fit. The adjusted coefficient of determination (R2adj) and the root mean squared error of the estimate (RMSE) were used as measures of model fit (22). The 95% confidence intervals (95% CI) of the regression coefficients, R2adj and RMSE were calculated using bootstrap on 1,000 random samples of 174 subjects, i.e. the whole sample (23). The bootstrap offers an efficient way of correcting for overoptimism and is presently considered the best method for performing internal cross-validation (24).

With regards to comparison between FM% estimated with predictive formulae and FM% measured with DEXA, Bland and Altman's method was used to calculate the limits of agreement (LOA) between predicted and measured FM%. Bias was calculated as (predicted FM% – measured FM%) and percentage bias as [(predicted FM% – measured FM%)/measured FM%] *100. Pitman's test was used to evaluate proportional bias. Statistical analysis was performed using Stata 15.1 (Stata Corporation, College Station, TX, USA).

Results

Demographic, anthropometric and body composition data of our study population are shown in Table 1. Of all the IBD patients, 16 had Crohn's Disease (CD, 53.3%), 12 ulcerative colitis (UC, 40%), 2 unclassified IBD (IBD-U, 6.6%). In IBD patients, median age at recruitment was 14 years (interquartile range 11; 16). F:M ratio was 10:20. Pubertal stage was pre-pubertal in 16.6% (5/30), middle puberty in 33.3% (10/30), late puberty in 50% (15/30). Mean duration of disease at the moment of enrollment was 21 months (+ 9 months). Data on disease location, activity and treatment of IBD patients are shown in Supplementary table, http://links.lww.com/MPG/C366. According to the International Obesity Task Force (IOTF) growth charts for BMI, 2 (6.7%) of IBD children had grade 1 thinness, 21 (70%) were normal weight, 4 (13.3%) were overweight and 3 (10%) were obese.

At the moment of recruitment, the control group (HCs=144) had a median age of 15 years (interquartile range 14; 17 years), a F:M ratio of 25:119. Pubertal stage was pre-pubertal in 18.7% (27/144), middle puberty in 9.7% (14/144) and late puberty in 71.5% (103/144). According to the IOTF growth charts for BMI, 5 (3.5%) had grade 1 thinness, 107 (74.3%) were normal weight, 17 (11.8%) were overweight and 15 (10.4%) were obese.

The regression models used to predict FM% from anthropometry are given in Table 2. Triceps skinfold thickness (TSF, Model 2) was much better than BMI (Model 1) at predicting FM%, explaining 82% vs. 68% of its variance and being associated with a RMSE of 3.8% vs. 4.9%. The sum of two skinfolds (biceps + triceps, SF2- Model 3) offered a marginal improvement in the prediction of FM% as compared to TSF (Model 2), explaining 86% vs. 82% of the variance of FM% and being associated with a RMSE of 3.2% vs 3.8%. The sum of four skinfolds (triceps + biceps + subscapular + suprailiac, SF4- Model 4) offered an even more modest improvement in the prediction of FM% as compared to SF2 (Model 3), explaining 88% vs. 86% of the variance of FM% and being associated with a RMSE of 3.0 % vs 3.2%. Figure 1 gives the scatterplots of FM% *vs.* logeBMI, logeTSF, logeSF2 and logeSF4. All the relationships were linear and the predictor X IBD interaction was not significant in any model (data not shown).

Population specific formulae per estimation of FM% based on anthropometry

On the basis of the four prediction models, the proposed population specific formulae for estimation of FM% based on anthropometry in pediatric patients with IBD are the following:

1. Formula based on BMI (derived from Model 1)
   FM%= -8.6*sex(female=0; male=1) - 1.5*age(years) + 2*IBD(yes=1, no=0) + 36.7*Log_eBMI - 58.4
2. 2.Formula based on triceps skinfold (derived from Model 2)
   FM%= -1.2*sex(female=0; male=1) - 0.8*age(years) - 0.7*IBD(yes=1, no=0) + 15.6*Log_eTSF - 1.4

- Formula based on two skinfolds (biceps + triceps; derived from Model 3)

FM%= -2.5*sex(female=0; male=1) - 0.8*age(years) + 2.1*IBD(yes=1, no=0) + 16.1*Log_eSF2 -13.0

- 4. Formula based on four skinfolds (biceps, triceps, subscapular + suprailiac; derived from Model 4)
  FM%= -2.6*sex(female=0; male=1) - 0.7*age(years) + 3.6*IBD(yes=1, no=0) + 16.0*Log_eSF4 - 25.1

When we compared predicted FM% using previous predictive equation, we found that in IBD patients, the Durnin & Womersley equation had the highest median (25th, 75th percentile) percentage bias [-26.4% (-36.7; -16.4%)], followed by Johnston equation [-23.3% (-29.8; -13.6)], Durnin & Rahman equation [-14.2% (22.3; -6.4%) and Brook equation [-5.6% (-17.5; 3.3)]. Figure 2 shows Bland and Altman plots for each FM% predictive equation compared with measured FM%, revealing a proportional bias affecting all equations (Pitman test $p<0.05$).

Discussion

Considering the values of FM% obtained with DEXA technique, no significant differences in terms of FM% was observed between subjects with IBD and HCs (FM% 29.6% vs 32.2%, p=0.108). Five studies evaluated fat free mass (FFM) in patients with Crohn's Disease (CD, n=255) (25-29). Deficits of FFM were described in three studies (n=221). Sentongo et al. (25) described deficits in FFM between CD patients (n=132) and HCs, using DEXA technique and skinfold measurements after adjustment for age in both males and females. Varille et al. (26) also showed deficits in FFM in a cohort patients with CD (n=11) with stricturing refractory disease phenotype, prior to surgery. Thayu et al. (27) assessed whole body composition (FFM and FM) using DEXA technique in 78 CD subjects and 669 HCs, aged 5-21 years. FFM was significantly lower in females with CD compared to controls ($p< 0.01$). Within the males, FFM was significantly lower in the nonblack subjects with CD compared with controls ($p < 0.001$).

Zoli et al. (28) showed no difference in FFM between CD and controls in a small study (n=10), the patients in this cohort were in remission and skinfold thicknesses were used for estimation of body composition. Azcue et al (29) characterised body composition and resting energy expenditure (REE) in 24 children with CD and compared data with HCs and with female subjects with anorexia nervosa. Body weight, ideal body weight and FFM were lower in patients with CD than in HCs (29). A possible explanation for reduced FFM is hyper-catabolism caused by acute inflammation mediated by circulating pro-inflammatory cytokines but also by medications such as glucocorticoids (30, 31).

There are few studies reporting on FM in children with IBD (n=611, CD 502, UC 109) (25, 32-38). The majority of studies used DEXA technique for measurement of FM (n=516) (28-33), only two studies used bioelectrical impedance (n=95) (37, 38). No significant difference was found in terms of FM between IBD patients and healthy controls (HCs) except for two studies conducted by Thayu et al. and Boot et al. respectively (27, 34). In the first study,

Authors found gender related differences in body composition deficits at diagnosis in patients with CD. In females, CD was associated with significantly lower FM (p=0.001), adjusted for age, race and Tanner stage, compared to HCs. All patients included in the study had moderate to severe disease activity. Boot et al. (34) evaluated bone mineral density and body composition with DEXA technique of 55 patients with IBD (22 CD and 33 UC). Decreased FM was found in patients with longer disease duration (mean 2.2 years).

In Model 1 we evaluated the contribution of continuous predictors expressed as loge, discrete variables (IBD yes, IBD no) and their interaction in the prediction of FM. The continuous variables that were considered were: body mass index (logeBMI), triceps skinfold (logeTSF), sum of two skinfolds (triceps + biceps loge2SF) and sum of four skinfolds (triceps + biceps + subscapular + suprailiac loge4SF).

Figure 1 shows four scatter plots that display data of FM in function of the predictors and the interaction between the continuous and discrete variables.

We used four prediction models based on anthropometry, for estimation of FM%. Results are shown in table 3. As determined by R2adj (adjusted coefficient of determination) and RMSE (root mean square error), Model 1 was the less accurate (R2adj 0.68, RMSE 4.94%) confirming that BMI is a poor predictor of body composition. Model 3, obtained by incorporating the sum of two skinfolds (biceps + triceps) demonstrated a slight improvement in predicting FM % compared to applying only the single triceps fold in Model 2, (R2adj 0.86, RMSE 3.23% vs R2adj 0.82, RMSE 3.75%). Model 4, obtained by incorporating the sum of four skinfolds (biceps + triceps + suprailiac + subscapular) revealed an additional improvement in prediction of FM% compared to Model 3 (R2adj 0.88, RMSE 3.03% vs R2adj 0.86, RMSE 3.23%). We reckon that the proposed method based on skinfold thickness measurements for estimation of FM% is feasible in clinical practice and acceptable for patients as it is a non invasive procedure. The only critical aspect is that skinfold thicknesses should be measured by trained dietitians that are not always present in all clinical settings.

Our study has some limitations, in first instance the low numerosity of subjects included did not permit to evaluate differences in body composition between patients with CD and UC. In literature, the available studies show no difference in deficits of FFM between CD and UC, however FM is lower in CD than UC. There is a discrepancy between age and pubertal stage between the two groups (IBD and HCs) due to the fact that the groups were comparable for range of age but not matched for age and gender. This could have influenced results on FM%. For this reason we have performed adjustment for age and sex in the statistical analysis.

Furthermore, an association between body composition and disease activity and treatment has not been performed. There are studies reporting on patients with active disease (n=160, CD 153, UC 7) (25, 33, 36, 37) with LM deficits. However, in two of these studies, patients were receiving systemic steroids at the time of study and thus this may contribute to these findings. Indeed there is increasing evidence on the effects of anti-TNFα treatment on body weight and body composition (39-41). This aspect is extremely important because increased body weight

is also a risk factor for loss of response to anti-TNF therapy (infliximab and adalimumab). Future studies should attempt to differentiate between the effects of therapy and the disease process itself.

Conclusions

Despite the results of our study haven't found significant differences in FM% using DEXA technique between subjects with IBD and HCs, it is known that patients with IBD are at incresed risk of having altered body composition due to several risk factors including malnutrition secondy to the underlying gastrointestinal disease but also pharmacological treatment (corticosteroids, anti-TNFα therapy). Given the importance of nutritional status in these patients, when DEXA scan is not available, it is possible to use skinfold thicknesses to estimate FM%. In fact, we have shown that the sum of 4 skinfolds (triceps + biceps + subscapular + suprailiac) is the most accurate in predicting FM % in children and adolescents with IBD. The sum of 2 skinfolds (triceps + biceps) is similarly accurate, in addition, the measurement of 2 skinfolds vs 4 skinfolds could be less prone to measurement error. The newly developed population specific formulae with the sum of 2 or 4 skinfolds could be a valid tool for estimation of body composition in children with IBD and valid alternative to DEXA measurement. Further prospective studies are needed in order to confirm our data and validate the specific formulae.

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Figure legend

Figure 1. Scatterplots of FM% vs. LogeBMI, LogeTSF, LogeSF2 and LogeSF4.

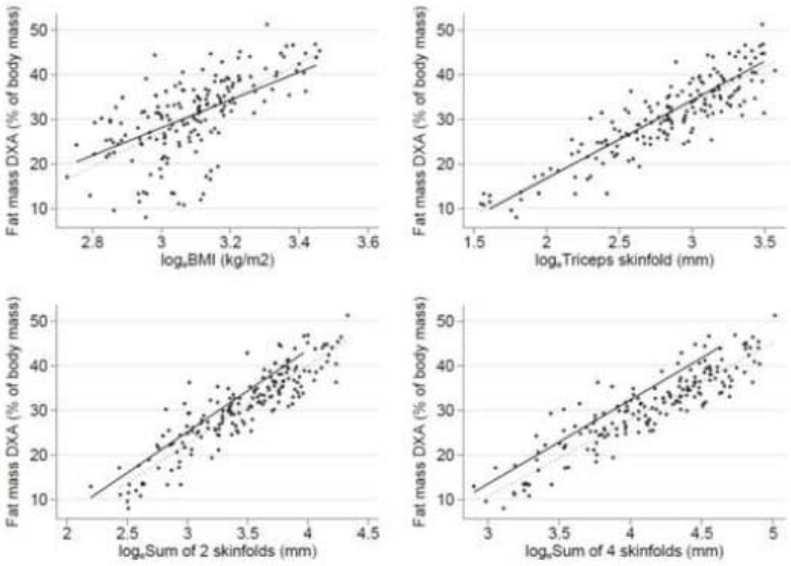

Figure 2. Bland and Altman plots for each FM% predictive equation compared with measured FM% (DEXA)

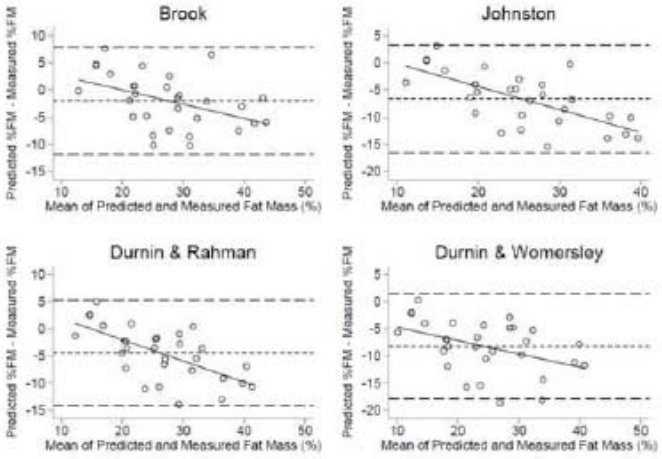

Table 1. Demographic, anthropometric and body composition data of IBD patients and HCs. Continuous variables. BMI= body mass index, FM= fat mass, DEXA= Dual-energy X-Ray absorptiometry.

	Total	**HC**	**IBD**	
	N=174	N=144	N=30	
	median (IQ)	median (IQ)	median (IQ)	p value
Age (year)	15 (13;16)	15 (14;17)	14 (11;16)	0.23
Weight (kg)	59.8 (50.6; 66.2)	60.5 (52.6; 66.6)	51 (40.8; 63.1)	0.004
Height (m)	1.63 (1.56; 1.69)	1.63 (1.58; 1.69)	1.59 (1.45; 1.69)	0.077
Height (SDS WHO)	0.245 (-0.273; 0.819)	0.249 (-0.243; 0.867)	0.195 (-0.501; 0.697)	0.43
BMI (kg/m^2)	22.1 (19.9; 24)	22.4 (20.3; 24.1)	20.1 (17.5; 22.4)	0.002
BMI (SDS WHO)	0.588 (-0.118; 1.053)	0.61 (-0.083; 1.052)	0.483 (-0.167; 1.088)	0.503
Fat mass DEXA (kg)	17.1 (12.6; 22.7)	18.3 (13.5; 23.4)	12.4 (8.6; 17)	0.002
Fat mass DEXA (% of body mass)	31.6 (25.4; 36.5)	32.2 (25.8; 36.7)	29.6 (21.7; 34.9)	0.108
Biceps skinfold (mm)	9.8 (6.6; 13)	9.9 (6.7; 13.1)	9.2 (5.4; 12.8)	0.541
Triceps skinfold (mm)	18.1 (12.8; 24)	19.5 (13.8; 24.1)	14 (11.2; 18)	0.026
Subscapular skinfold (mm)	13.6 (9.8; 21.6)	14.8 (10.6; 22.4)	8.7 (6.8; 13)	<0.001
Supraliac skinfold (mm)	22.9	26.6	10.6	<0.001

	(13.6; 33)	(16.6;35)	(7.8; 15)	
Sum of 2 skinfolds (mm)	33.1	35.5	23.1	<0.001
	(22.5; 44.2)	(24.9; 45.1)	(17.6; 33)	
Sum of 4 skinfolds (mm)	64.9	71.6	42.8	<0.001
	(43.4; 90.6)	(48.9; 92.6)	(31.4; 55.6)	