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Original Article

Sonographically Assessed Intra-Abdominal Fat And Cardiometabolic Risk Factors in Adolescents with Extreme Obesity

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Key Words

Abstract

Objective: The metabolic and cardiovascular risk of obesity is predominantly defined through the amount of intra-abdominal fat (IAF). Regarding this risk and the benefits of weight reduction gender-specific differences have been described. The aim of this study was to examine the gender-specific relationship between IAF assessed via ultrasound and the cardiometabolic risk profile in extremely obese adolescents before and after weight loss. ***Methods:*** In 107 consecutively admitted adolescents (n = 59 girls, mean age 15.4 ± 2.6 years boys and 15.1 ± 2.1 years girls, mean BMI z-score 3.2 ± 0.6 boys and 3.5 ± 0.6 girls) anthropometric and fasting laboratory chemical parameters were measured before and after an in-patient long-term therapy (mean durance 5.6 ± 2.3 months). IAF was determined by measuring the intra-abdominal depth (IAD) via ultrasound. ***Results:*** IAD was higher in boys as compared to girls (58.0 ± 22.4 mm vs. 51.3 ± 16.0 mm). IAD values were positively associated with BMI-z scores, waist circumferences, HOMA-IR and serum levels of γGT, hs-CRP and IL-6 in both genders. In boys, but not in girls, IAD was significantly correlated with systolic and diastolic blood pressure, serum levels of triglycerides, ALT as well as adiponectin and HDL-cholesterol. After a marked mean weight loss of –27.1 ± 16.2 kg (–20.1 ± 7.9%) in boys and of –20.5 ± 11.5 kg (–17.3 ± 7.1%) in girls, IAD decreased by –20.7 ± 16.2 mm (–-32.4 ± 16.9%) in boys and by –18.4 ± 12,7 mm (–34.3 ± 18.4%) in girls, resulting in more pronounced ameliorations of cardiovascular risk factors in boys than in girls. ***Conclusions:*** The present study indicates that IAF assessed by ultrasound is a good indicator for the cardiometabolic risk factor profile in extremely obese adolescents. Associations between IAF and risk factors are more pronounced in boys than in girls.

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Introduction

The prevalence of childhood obesity increased markedly in the past 30 years, but new reports show a stabilisation or even a decline in recent years in developed countries [1]. However, prevalence rates remain on a high level. Additionally, a worrisome trend emerged in the form of extreme obesity as the fastest growing sub-category of obesity in children and adolescents [2–4].

Even in childhood and adolescence, obesity is associated with a high prevalence of morbidity and mortality and has a major impact on health status in adulthood [5, 6]. Children and adolescents with extreme obesity display a separate risk group which show a more adverse cardiometabolic risk factor profile compared to obese or overweight youth [7–12]. They have a high risk for early onset of obesity-associated mental and somatic co-morbidity, such as disturbed glucose tolerance, insulin resistance, hyperinsulinaemia, and hyperglycaemia, thus leading to an increased risk for diabetes [13–17] as well as lipid abnormalities and hypertension [18–24]. Furthermore, being extremely obese in childhood displays a much stronger risk factor for being obese in adulthood [25].

The distribution of body fat seems to be more important for the development of co-morbidities than overall weight or fat mass [26–29]. Especially abdominal obesity is related to cardiovascular risk factors such as hyperinsulinaemia [30, 31], dyslipidaemia [19, 32, 33] and hypertension [20, 23, 34], already in children and adolescents. Additional distinction between intra-abdominal fat (IAF) or visceral adipose tissue (VAT) and subcutaneous fat reveals a higher morbidity associated with the former in adults [35–37]. Matching this, studies in children showed that fasting insulin and lipid levels are more strongly influenced by visceral than by subcutaneous fat [38–40].

Direct imaging of IAF has proven to be a better predictor of metabolic risk factors than waist circumference [41–43]. Therefore, assessment of IAF might provide an adequate measure for the estimation of metabolic risk factor profile. The gold standard for assessment of IAF is CT or MRI measurement, even in children [44–46]. However, their disadvantages, such as high costs, radiation exposure (for CT) and limited availability, render them impractical for population studies. A relatively new methodological approach is the assessment of IAF by ultrasound sonography. Studies in adults and children have shown a very good correlation of intraabdominal fat measured by sonography and by CT or MRI [47–50].

The aim of this study was to examine cardiometabolic risk factors of severely obese male and female adolescents in relation to IAF assessed by ultrasound before intervention (baseline) as well as to investigate changes in IAF and in cardiometabolic risk factors after a long-term in-patient treatment programme resulting in marked weight loss. We further wanted to elucidate gender-specific differences in the relationship between IAF and cardiometabolic risk factors.

Material and Methods

Study Population

A total of 107 extremely obese adolescents (59 girls) aged 12–23 (15.3 ± 2.3) years with a mean BMI of 41.3 ± 9.3 kg/m^2 and a mean BMI-z score of 3.5 ± 0.6 (girls) or 3.2 ± 0.6 (boys) were consecutively recruited according to their admission within 18 months from the INSULA obesity rehabilitation centre, Bischofswiesen, Germany.

Written informed consent from parents and written assent from adolescents were obtained. The ethics committee of the University of Ulm approved all study proceedings. The trial protocol meets the standards of the Declaration of Helsinki in its revised version of 1975 and its amendments of 1983, 1989, and 1996.

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Anthropometric and Metabolic Measurements

At study entry (baseline t0) and study exit (end of therapy t1) weight and height were determined in lightly apparel with calibrated scales to the nearest 0.1 kg (Soehnle S20/2760; Leifheit AG, Nassau, Germany) and 0.1 centimetres (Seca Mod. 220; Seca GmbH & Co. KG, Hamburg, Germany), respectively. The BMI calculated from weight (kilograms) / height (meters)^2 was used to estimate the degree of obesity. Extreme obesity has been defined as BMI > 99.5th age- and gender-specific percentile. Standard deviation scores of BMI (BMI-z score) were calculated based on the LMS method. BMI reference data for German children were used [51]. Waist circumferences were measured midway between the lower rib margin and the iliac crest with a non-elastic measuring tape. Systolic and diastolic blood pressures were measured twice at the left arm after a 10-min rest in a seated position using a calibrated Omron S2 (OMRON Medizintechnik Handelsgesellschaft mbH, Mannheim, Germany).

Baseline and follow-up blood samples were obtained after a 12-hour overnight fast, followed by a standard oral glucose tolerance test (oGTT). Samples were obtained by venous puncture and processed shortly after withdrawal. All measurements were carried out by two trained nurses.

Biochemical Analyses

Blood glucose from oGTT was measured in a fluoride monovette with Cobas Integra 800 (Roche, Mannheim, Germany). Triglycerides (TG), cholesterol, LDL- and HDL-cholesterol, AST, ALT and γGT were photometrically measured with Cobas 6000 (Roche, Mannheim, Germany). Serum adiponectin was measured using an ELISA (Mercodia, Uppsala, Sweden), serum IL-6 was measured with high sensitive ELISA (R&D Systems, Minneapolis, IN, USA), serum hs-CRP was measured with nephelometry (Siemens, Eschborn, Germany), serum C-peptide and insulin were measured with ELISA (AMP, Obrigheim, Germany). Inter- and intra-assay coefficients of variation did not exceed 10%. Homeostasis model assessment for insulin resistance index (HOMA-IR) was calculated according to the following formula: resistance (HOMA) = (insulin (µU/ml) × glucose (mg/dl)) / 405.

Ultrasound Studies

Ultrasound examinations were performed by a single examiner using a Siemens Sono G 40 (Siemens, Munich, Germany) equipped with a 3.5 MHz curvel-array probe and an 8 MHz linear-array probe. Scans were performed in supine position after an overnight fasting period of patients after inspiration and then bated breath, applying minimal pressure.

The visceral fat mass was estimated by measuring the intra-abdominal depth (IAD), the distance between the internal face of the Musculus rectus abdominis and the anterior wall of the aorta along the Linea alba at the height of the branching of the Arteria mesenterica superior, as described earlier [52]. IAD has been reported to have strong correlations with visceral fat area determined by CT [47, 48, 50, 53]. After sonographic measurements a second independent examiner sized the images three times. The mean value was taken for analysis. As recently reported, these sonographic methods have high validity, good reproducibility and low intra-observer variation [54]. With regard to baseline IAD (mm) and relative changes in IAD (%), three groups were defined for analysing metabolic risk factor profile: group 1: <25th percentile, group 2: >25th to < 75th percentile, and group 3: >75th for percentile of baseline IAD (mm) and of ΔIAD (%).

Treatment Programme

The severely obese adolescents were enrolled in an in-patient weight reduction programme conducted by the Obesity Rehabilitation Centre INSULA (Berchtesgaden, Germany). Therapeutic foreground is solution-oriented psychotherapy with behaviour therapy, exercise training (ET), dietetic treatment as well as an extensive clinical diagnosis and therapy of obesity-associated diseases. Special goals are the long-term modification of physical activity, leisure time and dietary behaviour. An adventure educational approach and discussion rounds with former patients are used. The usual stay in the INSULA centre is 6 months. Within changes of eating behaviour approximately 1,700 kcal were delivered daily. Besides background information

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about healthy foods, the patients participate in practical courses in the in-house teaching kitchen. The ET comprises a regularly strength and endurance training (at least 4 times per week) for the whole therapy duration. Teaching of parents was done by the staff within all therapeutically areas to prevent relapse into old behaviour patterns (*www.dw-hohenbrunn.de/insula/adipositas-rehazentrum*).

Statistical Methods

For statistical analyses all available data (anthropometric and clinical data) of the participants of the INSULA trial were included. For some subjects, levels of fasting blood parameters are missing (TG n = 10; cholesterol n = 10; LDL-cholesterol n = 11; HDL-cholesterol n = 11; AST n = 7; ALT n = 7; γGT n = 7; adiponectin n = 7, IL-6 n = 7, CRP n = 7, HOMA n = 9). Measurement of systolic and diastolic blood pressure is missing for 1 patient. Measurement of waist circumference is missing for 1 patient.

The descriptive statistics summarised the characteristics of the study population. Data are presented as mean and standard deviation for continuous variables. Relative changes were calculated as change in variable divided by baseline variable × 100. Correlations between IAD levels at baseline / Δ levels of IAD and cardiometabolic risk factor concentrations at baseline / Δ levels of cardiometabolic risk factor concentrations were investigated by Spearman's correlations (Spearman's rho). Crude and partially adjusted correlation analyses were conducted. Because gender differences in IAD have been reported in the literature [55–57], all analyses were separately performed for boys and girls. To take into account that the age at baseline and the therapy duration could be different between the participants, these factors were considered as further potential confounders.

A one-way ANOVA was used for between-group comparisons (low, middle and high Δ levels of IAD) on baseline and Δ levels of cardiometabolic risk factor concentrations. Bonferroni post-hoc tests were used to carry out pair-wise comparisons.

All analyses were carried out with the Statistical Analyses System (SAS) version 9.3 (SAS Institute Inc., Cary, NC, USA). We conducted exploratory analyses without formal hypothesis testing and correction for multiple comparisons. Statistical significance was interfered at two-tailed $p < 0.05$.

Results

The 107 adolescents (n = 59 girls) had a mean age of 15.4 ± 2.6 (boys) and 15.1 ± 2.1 (girls) years. Mean treatment duration was 5.6 ± 2.3 months. Anthropometric and metabolic characteristics of the study population at baseline are summarised in table 1a.

Baseline, Cross-Sectional Analysis

As shown in table 1a, male and female study participants were markedly obese with a mean BMI z-score of 3.2 ± 0.6 in boys and 3.5 ± 0.6 in girls ($p < 0.05$) before start of the in-patient treatment programme. Despite the lower baseline BMI z-score, baseline mean IAD was higher in boys as compared to girls (58.0 ± 22.4 mm vs. 51.3 ± 16.0 mm) with concurrently higher mean waist circumference (127.7 ± 20.6 cm (boys) vs. 124.1 ± 16.5 cm (girls)). In addition, boys had markedly higher levels of liver enzymes than girls.

Cardiometabolic Risk Factors in Relation to Baseline IAD

As shown in table 2, measurements of IAD at baseline were significantly ($p < 0.05$) associated with higher BMI z-scores, waist circumferences, IL-6 in both boys and girls as well as with HOMA-IR (girls $p < 0.05$) and serum levels of hs-CRP (boys $p < 0.01$).

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Table 1. Baseline patient characteristics

	Girls (n = 59)		Boys (n = 48)		p values
	mean	SD	mean	SD	
Age, years	15.1	2.08	15.4	2.61	0.6303
BMI-z score	3.5	0.61	3.2	0.56	*0.0087*
Waist circumference, cm	124.1	16.45	127.7	20.59	0.3219
RR systolic, mm Hg	125.9	12.10	126.4	10.91	0.8245
RR diastolic, mm Hg	81.6	8.94	82.4	8.75	0.6431
IAD, mm	51.3	16.00	58.0	22.36	0.0862
TG, mmol/l	1.3	0.61	1.3	0.96	0.9482
Cholesterol, mmol/l	4.3	0.86	4.1	0.88	0.2894
LDL-cholesterol, mmol/l	2.7	0.74	2.6	0.77	0.5771
HDL-cholesterol, mmol/l	1.2	0.30	1.1	0.30	0.2142
AST, U/l	25.2	10.03	31.8	14.72	*0.0117*
ALT, U/l	31.7	20.57	47.3	37.97	*0.0161*
γGT, U/l	21.7	11.52	24.7	12.54	0.2102
Adiponectin, µg/ml	6.7	2.31	6.5	2.37	0.6545
IL-6, pg/ml	3.5	2.35	3.2	2.05	0.4026
hs-CRP, mg/l	5.0	5.11	4.9	5.05	0.9680
HOMA-IR	5.5	3.08	4.8	2.30	0.1958

RR = Riva Rocchi.
$p < 0.05$ = statistically significant between girls and boys.

Initial IAD values in boys, but not in girls, were significantly associated with most of the other cardiometabolic risk factors, as there are systolic and diastolic blood pressure, serum levels of TG, ALT, γGT, as well as adiponectin and HDL-cholesterol (table 2).

Analysis of the cardiometabolic risk factors in the 3 defined groups according to initial IAD (<25th percentile, >25th to <75th percentile, and >75th percentile of baseline IAD) showed differences of mean values between groups which were however not statistically significant (table 3). Boys with the highest baseline IAD were older than boys with lowest IAD (16.6 ± 3.1 vs. 13.8 ± 1.2 years), whereas in girls no difference in age between these IAD groups (15.2 ± 2.3 vs. 15.0 ± 2.2 years) could be seen. Patients with highest baseline IAD had the highest baseline BMI-z-scores, waist circumferences, systolic and diastolic blood pressure, HOMA-IR and IL-6 and hs-CRP levels compared to the other groups, applying for boys and girls. With regard to blood lipids, boys with highest baseline IAD showed markedly higher levels of mean TG, cholesterol, and LDL-cholesterol as well as lower levels of HDL-cholesterol compared with boys with lowest baseline IAD. This was not seen in girls. Additionally, baseline mean γGT levels were found to be highest in boys with the highest amount of baseline IAD. Baseline mean adiponectin levels were lower with the highest baseline IAD as compared to boys in the lower IAD groups in boys only.

Longitudinal Analysis

The mean weight loss was –27.1 ± 16.2 kg (–20.1 ± 7.9%) in boys and –20.5 ± 11.5 kg (–17.3 ± 7.1%) in girls, reducing the mean BMI z-score by 0.8 ± 0.3 (boys) and 0.7 ± 0.4 (girls) as well as the mean waist circumference by 21.8 cm ± 10.7 (boys) and 17.5 cm ± 9.4 (girls) ($p < 0.05$). As expected, the anthropometric and cardiometabolic risk factors improved significantly in both sexes during weight loss (table 1b).

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Table 2. Baseline and follow-up data as well as changes of cardiometabolic risk factors after weight loss

Parameter	Girls (n = 59)								Boys (n = 48)							
	baseline		follow-up		p-values	delta			baseline		follow-up		p-values	delta		
	mean	SD	mean	SD		mean	SD		mean	SD	mean	SD		mean	SD	
BMI-z score	3.5	0.6	2.7	0.7	<0.0001	-0.7	0.4		3.2	0.6	2.4	0.6	<0.0001	-0.8	0.3	
Waist circumference, cm	124.1	16.5	106.6	12.8	<0.0001	-17.5	9.4		127.7	20.6	105.9	16.0	<0.0001	-21.8	10.7	
RR systolic, mm Hg	125.9	12.1	114.2	7.7	<0.0001	-11.7	11.5		126.4	10.9	117.3	8.9	<0.0001	-9.1	11.3	
RR diastolic, mm Hg	81.6	8.9	72.6	8.0	<0.0001	-9.0	9.5		82.4	8.8	73.7	8.7	<0.0001	-8.7	11.2	
IAD, mm	51.3	16.0	32.9	12.0	<0.0001	-18.4	12.7		58.0	22.4	37.3	11.3	<0.0001	-20.7	16.2	
TG, mmol/l	1.3	0.6	1.2	0.4	0.1381	-0.1	0.6		1.3	1.0	1.0	0.6	0.0078	-0.3	0.9	
Cholesterol, mmol/l	4.3	0.9	3.9	0.8	0.0001	-0.4	0.7		4.1	0.9	3.5	0.9	<0.0001	-0.6	0.8	
LDL-cholesterol, mmol/l	2.7	0.7	2.4	0.8	<0.0001	-0.4	0.5		2.6	0.8	2.1	0.7	<0.0001	-0.5	0.5	
HDL-cholesterol, mmol/l	1.2	0.3	1.2	0.4	0.9025	0.0	0.2		1.1	0.3	1.1	0.3	0.0004	0.0	0.2	
AST, U/l	25.2	10.0	23.6	10.4	0.2612	-1.6	11.4		31.8	14.7	23.8	6.0	0.0003	-8.0	13.6	
ALT, U/l	31.7	20.6	28.1	18.7	0.2382	-3.6	22.1		47.3	38.0	26.8	12.5	<0.0001	-20.5	32.8	
GT, U/l	21.7	11.5	17.5	9.5	0.0137	-4.1	11.8		24.7	12.5	15.5	7.2	<0.0001	-9.2	9.7	
Adiponectin, µg/ml	6.7	2.3	7.7	2.1	0.0021	1.0	2.2		6.5	2.4	8.1	2.6	<0.0001	1.6	2.1	
IL-6, pg/ml	3.5	2.3	2.8	2.0	0.0429	-0.7	2.7		3.2	2.0	3.0	2.9	0.7225	-0.2	3.3	
hs-CRP, mg/l	5.0	5.1	2.9	3.4	0.0003	-2.1	4.1		4.9	5.1	3.4	4.7	0.0560	-1.5	5.3	
HOMA-IR	5.5	3.1	3.1	1.4	<0.0001	-2.5	2.7		4.8	2.3	2.4	1.2	<0.0001	-2.4	2.6	
T-duration, months			6.0	2.2							5.4	2.4				

RR = Riva Rocchi.
p < 0.05 = statistically significant.

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Table 3. Correlations (crude and adjusted for age) between measurements of IAD and cardiometabolic risk factors in boys and girls at baseline examination

Parameter	IAD, mm, baseline							
	girls (n = 59)				boys (n = 48)			
	r_{crude}	p values	r_{adj}[a]	p values	r_{crude}	p values	r_{adj}[a]	p values
BMI-z score	*0.46*	*0.0003*			*0.41*	*0.0048*		
Waist circumference, cm	*0.33*	*0.011*	*0.33*	*0.0111*	*0.43*	*0.0200*	0.22	0.1432
RR systolic, mm Hg	0.09	0.4955	0.09	0.4983	*0.43*	*0.0019*	*0.28*	*0.0472*
RR diastolic, mm Hg	0.00	0.97	0.00	0.98	*0.49*	*0.0004*	*0.33*	*0.0225*
TG, mmol/l	0.08	0.551	0.08	0.5669	*0.29*	*0.0479*	0.18	0.2483
Cholesterol, mmol/l	0.09	0.5258	0.10	0.48	0.03	0.8359	0.03	0.8635
LDL-cholesterol, mmol/l	0.02	0.8908	0.02	0.8981	0.04	0.7814	0.03	0.8418
HDL-cholesterol, mmol/l	0.08	0.5919	0.13	0.3503	*−0.48*	*0.0011*	*−0.36*	*0.0185*
AST, U/l	0.07	0.5908	0.07	0.6067	0.13	0.4117	0.05	0.7267
ALT, U/l	0.15	0.2841	0.15	0.2694	*0.35*	*0.0242*	0.22	0.1547
γGT, U/l	0.21	0.1295	0.22	0.1036	*0.34*	*0.0243*	0.17	0.262
Adiponectin, μg/ml	−0.04	0.754	−0.04	0.7892	*−0.33*	*0.0265*	−0.23	0.1386
IL-6, pg/ml	*0.30*	*0.0277*	*0.31*	*0.0243*	0.55	0.0001	*0.45*	*0.0022*
hs-CRP, mg/l	0.23	0.0867	0.25	0.0741	*0.48*	*0.0008*	*0.38*	*0.0105*
HOMA-IR	*0.26*	*0.0498*	*0.26*	*0.0498*	0.30	0.0774	0.27	0.0774

RR = Riva Rocchi.
p < 0.05 = statistically significant.
[a]Adjusted for age.

IAF mass (indicated by IAD) considerably decreased by 20.7 ± 16.2 mm (−32.4 ± 16.9 %) in boys and 18.4 ± 12.7 mm (−34.3 ± 18.4%) in girls (p < 0.05). Concomitant with the decrease in body weight and IAD, marked improvements in blood pressure, serum levels of cholesterol and LDL-cholesterol, γGT, adiponectin as well as in HOMA-IR were observed in both boys and girls (table 1b), being generally more pronounced in boys. In addition, boys showed significant changes in serum levels of TG, HDL-cholesterol, AST and ALT which was not seen in girls.

Patients with the highest baseline IAD (mm) (>75th percentile) showed the largest IAD reduction (%) as a result of the intervention programme (fig. 1). As expected, relative IAD decrease was highest in patients with the longest therapy duration (fig. 2).

Changes in Metabolic Risk Factors in Relation to Changes in IAD
The relative decrease in IAD was significantly correlated with the relative decrease in waist circumference and change in BMI-z-score in both genders (table 4). Furthermore, boys showed significant positive correlations of relative change in IAD with relative changes in blood pressure and serum levels of liver enzymes. In girls, significant positive correlations of ΔIAD could be found with changes in serum levels of liver enzymes and hs-CRP. Overall, therapy duration had a significant impact on changes in metabolic risk factors in both boys and girls (table 5).

Analysis of the changes in metabolic risk factors in the 3 defined groups (<25th percentile, >25th to <75th percentile, and >75th percentile of ΔIAD) showed considerable differences between groups. Between-group comparison analysis using the mean or the median revealed the highest changes in the group with highest relative decrease in IAD. Patients with the highest relative decrease in IAD had the highest change in mean BMI-z-score (−26.8 ± 12.6% (girls) and −29.1 ± 10.7% (boys)) and waist circumference (−18.2 ± 6.0% (girls) and −21.1 ± 6.8% (boys)) compared to patients with lowest relative reduction in IAD (table 6). Although

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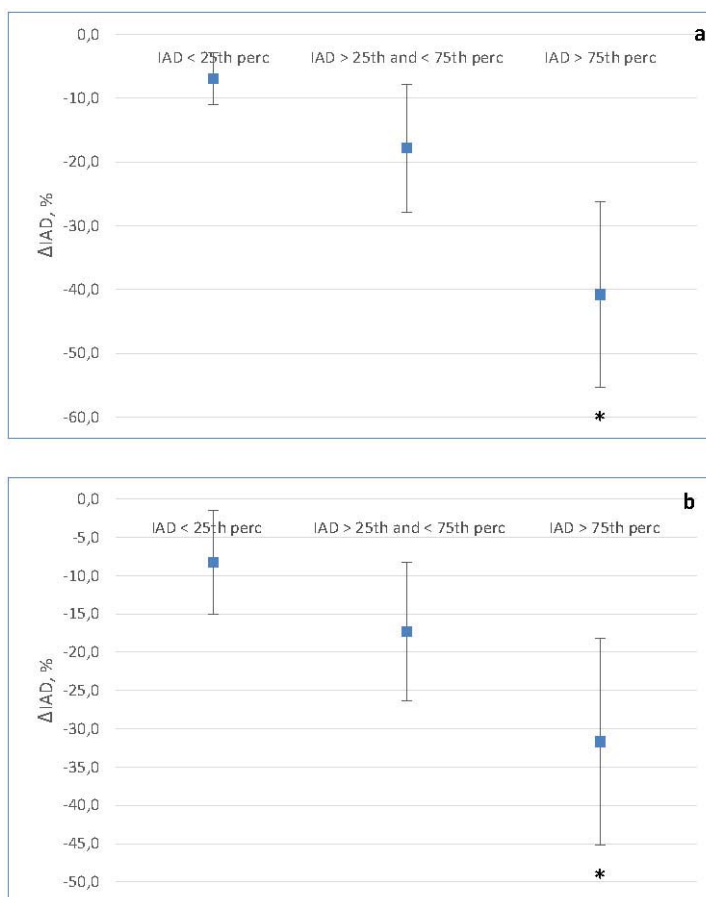

Fig. 1. Relative changes in IAD (ΔIAD, %) in boys (**a**) and girls (**b**) with extreme obesity in dependency on level of IAD at baseline examination. IAD at baseline examination (mm) was classified as low (IAD ≤ 25th internal percentile), middle (IAD > 25th to < 75th internal percentile) or high (IAD ≥ 75th internal percentile). Data are presented as mean ± SD. *p < 0.05 statistically significant between groups (group 1 vs. 3 and 2 vs. 3 boys; group 1 vs. 3 girls).

not statistically significant, mean and median relative decreases in serum levels of IL-6 and hs-CRP were found to be highest in the group with the highest relative mean decrease in IAD in both boys and girls (table 6). Only in boys, the highest increase in adiponectin levels corresponded to the highest relative decrease in IAD. Additionally, mean and median changes in blood pressure were found to be highest in boys with the highest changes in IAD. With regard to blood lipids, boys with highest decrease in IAD showed largest relative changes in the median of serum levels of TG, cholesterol, and LDL-cholesterol (table 6). Mean and median relative changes in ALT, AST and γGT were found to be highest in girls with the highest relative decrease in IAD. This was also true for changes in γGT in boys.

Discussion

The overall aim of the study has been to assess the clinical significance of IAD measured by ultrasound and of cardiometabolic risk factors in severely obese adolescents and to investigate gender-specific differences. Cross-sectional analysis of the data at baseline showed that IAD is an indicator for an adverse cardiovascular risk factor profile in both genders. The associations between IAD and cardiovascular risk factors however have been more pronounced in boys than in girls. The analysis of the longitudinal data showed that a long-term in-patient treatment programme resulting in a marked mean weight loss lead to a marked decrease in
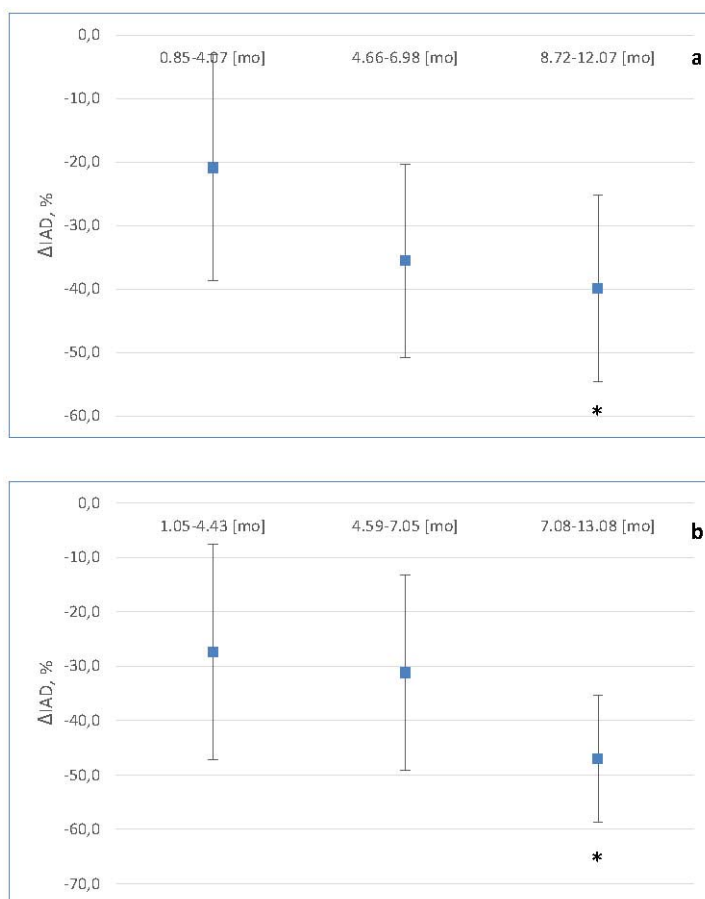
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Fig. 2. Relative changes in IAD (ΔIAD, %) in boys (**a**) and girls (**b**) with extreme obesity in dependency on therapy duration. Therapy duration (months) was classified as low (≤25th internal percentile), middle (>25th to <75th internal percentile) or high (≥75th internal percentile). Data are presented as mean ± SD. *p < 0.05 statistically significant between groups (group 1 vs. 3 boys and girls).

IAF in both genders. The ameliorations of cardiovascular risk factors associated with this decrease were more pronounced in boys than in girls.

For the assessment of IAF CT or MRI were used as gold standard in previous studies, even in children [44, 45, 58]. However, because of their high costs, the radiation exposure (CT) and the limited availability, these methods are not optimal for study purposes. The sonographic estimation of IAF by IAD is a relatively new method, and a good correlation with measurements by CT or MRI for the prediction of abdominal fat mass has been shown both in children and adults [47–50, 53]. As formerly reported this sonographic method has high validity, good reproducibility and low intra-observer variation [54]. Our study shows that IAD measured by ultrasound is an easily assessable parameter with clinical significance reflecting the cardiovascular risk factor profile and its changes during weight loss.

Baseline Analyses

Significant relationships between intra-abdominal fat and several cardiometabolic risk factors have been described in children, adolescents and adults [30, 32–34, 37, 59–62]. Within our baseline analysis, we were able to confirm such relationships in adolescents with extreme obesity – however, in a gender-specific manner. Increased IAF has been shown to be associated with an increased risk of cardiovascular morbidity (i.e. hepatic TG content, elevated ALT, insulin resistance and inflammation markers) [63, 64]. We also could show in our study

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Table 4. Cardiometabolic risk factors in relation to baseline IAD

Parameter	IAD, mm < 25th internal percentile		IAD, mm >25th and <75th internal percentile		IAD, mm > 75th internal percentile	
	mean ± SD	median	mean ± SD	median	mean ± SD	median
Girls						
Age, years	15.0 ± 2.2	14.0	15.2 ± 2.0	15.0	15.2 ± 2.3	15.5
BMI-z score	3.2 ± 0.6	3.2	3.4 ± 0.5	3.3	4.0 ± 0.6	4.0
Waist circumference, cm	119.3 ± 12.0	114.5	119.8 ± 13.7	117.0	137.9 ± 18.7	139.0
RR systolic, mm Hg	126.1 ± 11.9	125.0	124.0 ± 10.9	122.5	130.1 ± 14.7	130.0
RR diastolic, mm Hg	81.6 ± 6.1	80.0	81.3 ± 9.9	82.5	82.5 ± 9.6	80.0
TG, mmol/l	1.2 ± 0.4	1.1	1.4 ± 0.7	1.2	1.3 ± 0.3	1.3
Cholesterol, mmol/l	4.3 ± 0.7	4.1	4.4 ± 1.0	4.2	4.3 ± 0.7	4.5
LDL-cholesterol, mmol/l	2.8 ± 0.7	2.7	2.8 ± 0.8	2.8	2.6 ± 0.8	2.6
HDL-cholesterol, mmol/l	1.2 ± 0.2	1.2	1.2 ± 0.3	1.1	1.2 ± 0.3	1.2
AST, U/l	23.3 ± 5.9	23.0	27.4 ± 12.4	23.0	21.5 ± 4.2	22.0
ALT, U/l	27.1 ± 8.9	27.0	36.0 ± 26.1	28.5	26.0 ± 9.2	27.0
γGT, U/l	17.1 ± 6.2	16.0	24.0 ± 13.3	20.0	21.2 ± 10.6	20.0
Adiponectin, µg/ml	6.5 ± 2.7	5.9	6.8 ± 2.2	6.5	6.7 ± 2.3	6.3
IL-6, pg/ml	2.9 ± 2.3	2.2	3.5 ± 2.4	2.9	4.3 ± 2.1	4.3
hs-CRP, mg/l	3.9 ± 5.4	1.4	4.3 ± 2.5	3.5	8.3 ± 8.4	5.6
HOMA-IR	5.1 ± 2.9	4.2	5.3 ± 2.9	4.8	6.4 ± 3.8	5.4
Boys						
Age, years	13.8 ± 1.2	14.0	15.5 ± 2.6	15.5	16.6 ± 3.1	16.0
BMI-z score	2.8 ± 0.4	3.0	3.2 ± 0.5	3.2	3.3 ± 0.7	3.3
Waist circumference, cm	116.6 ± 16.9	118.5	128.6 ± 17.2	125.0	137.1 ± 25.9	132.5
RR systolic, mm Hg	120.1 ± 9.6	120.0	126.0 ± 10.0	126.3	133.4 ± 10.5	131.3
RR diastolic, mm Hg	76.4 ± 6.2	78.3	83.3 ± 9.5	82.5	86.8 ± 6.1	87.3
TG, mmol/l	1.1 ± 0.8	0.8	1.2 ± 0.6	1.1	1.9 ± 1.5	1.5
Cholesterol, mmol/l	4.0 ± 0.7	4.0	4.1 ± 1.0	4.1	4.5 ± 0.8	4.4
LDL-cholesterol, mmol/l	2.5 ± 0.6	2.5	2.7 ± 0.9	2.5	2.8 ± 0.5	2.9
HDL-cholesterol, mmol/l	1.3 ± 0.3	1.2	1.2 ± 0.3	1.0	1.0 ± 0.2	0.9
AST, U/l	29.6 ± 9.0	29.0	33.5 ± 19.0	28.5	30.8 ± 9.6	26.0
ALT, U/l	32.4 ± 17.4	27.0	56.6 ± 49.0	40.5	44.8 ± 22.6	39.0
γGT, U/l	18.8 ± 9.0	16.0	25.7 ± 13.6	23.5	29.1 ± 12.3	24.0
Adiponectin, µg/ml	7.5 ± 0.8	7.4	6.4 ± 2.7	5.9	5.9 ± 2.6	5.3
IL-6, pg/ml	1.8 ± 0.8	1.7	3.6 ± 2.3	3.0	3.6 ± 1.8	2.7
hs-CRP, mg/l	1.8 ± 1.2	1.2	5.5 ± 5.0	3.6	7.0 ± 6.4	4.5
HOMA-IR	4.7 ± 1.5	4.6	4.1 ± 1.9	3.5	6.6 ± 3.0	6.1

The analysis was performed after dividing the cohort into 3 subgroups according to initial IAD (group 1: < 25th percentile, group 2: > 25th to < 75th percentile, group 3: > 75th percentile of baseline IAD).

that the higher the level of IAD at baseline, the higher the baseline BMI-z score, waist circumference, blood pressure, HOMA-IR, and IL-6 and hs-CRP levels in both genders. However, only boys with highest baseline IAD revealed higher levels of TG, cholesterol, LDL-cholesterol, and γGT as well as lower levels of HDL-cholesterol and adiponectin compared to boys with lower baseline IAD amount. With regard to girls, no comparable trend could be found for blood lipids, liver enzymes and adiponectin.

One possible explanation for these gender-specific observations is that boys had larger baseline amounts of IAD compared to girls. It is well known that body fat distribution is gender-specific, with women having larger stores of subcutaneous fat and men are more likely to have visceral fat [55, 65]. It has also been postulated that these differences contribute

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Table 5. Correlations (crude and adjusted for duration of treatment) between relative changes in measurements of IAD and changes in cardiometabolic risk factors in boys and girls

| Parameter | ΔIAD, % | | | | | | | |
| | girls (n = 59) | | | | boys (n = 48) | | | |
	r_{crude}	p values	r_{adj}[a]	p values	r_{crude}	p values	r_{adj}[a]	p values
ΔBMI-z score, %	0.34	0.0086	0.30	0.0228	0.37	0.0097	0.23	0.1179
ΔWaist circumference %	0.50	<0.0001	0.39	0.0030	0.42	0.0013	0.31	0.0391
ΔRR syst, %	−0.03	0.8463	−0.09	0.5041	0.32	0.0259	0.25	0.0896
ΔRR dias, %	−0.01	0.9637	−0.10	0.4658	0.34	0.0188	0.29	0.0442
ΔTG, %	0.17	0.2269	0.23	0.1002	0.16	0.3108	0.12	0.4306
ΔCholesterol, %	0.16	0.2536	0.25	0.0793	0.16	0.3001	0.10	0.5159
ΔLDL-cholesterol, %	−0.02	0.8958	0.07	0.6170	0.06	0.6890	0.04	0.8160
ΔHDL-cholesterol, %	0.16	0.2676	0.19	0.1740	−0.03	0.8385	−0.04	0.8026
ΔAST, %	0.35	0.0113	0.31	0.0281	0.06	0.7100	−0.02	0.8953
ΔALT, %	0.26	0.0631	0.20	0.1584	0.34	0.0281	0.23	0.1469
$\Delta\gamma$GT, %	0.37	0.0065	0.32	0.0224	0.40	0.0073	0.35	0.0244
ΔAdiponectin, %	0.03	0.8536	0.01	0.9206	−0.16	0.3155	−0.14	0.3728
ΔIL-6, %	0.24	0.0827	0.22	0.1138	0.14	0.3628	0.27	0.0842
Δhs-CRP, %	0.26	0.04833	0.27	0.0475	0.16	0.3010	0.20	0.2076
ΔHOMA-IR, %	−0.02	0.9129	−0.12	0.3980	0.20	0.2081	0.15	0.3422
T-duration	−0.41	0.0013			−0.39	0.0068		

RR = Riva Rocchi.
p < 0.05 = statistically significant.
[a]Adjusted for duration of treatment

to differences in metabolic, endocrine and health consequences attributable to obesity [66, 67]. However, since in our study the differences in IAD as an estimate of IAF between boys (58.0 mm) and girls (51.3 mm) have only been 6.7 mm in mean, we do not think that the difference in the amount of IAF is the main reason for these gender-specific associations with cardiometabolic risk factors. We postulate hormonally (androgen and/or oestrogen) controlled metabolic processes as being the cause for these differences.

Adipose tissue is an important determinant of low-level chronic inflammatory state as reflected by serum levels of IL-6 and CRP [68]. The association of inflammatory markers with adipose tissue is supported by experimental and clinical evidence [69–71]. As shown in earlier studies, inflammation markers are related to BMI, waist circumference and percent body fat in both genders [72–75]. It has been reported that obese children had about 10 times higher hs-CRP concentrations and higher IL-6 levels than controls [76]. hs-CRP correlated with BMI, waist circumference and percent fat mass [76]. The results of our study in extremely obese adolescents confirmed significant baseline correlations between visceral fat as assessed by ultrasound and inflammation proteins (IL-6, hs-CRP) in both genders.

Longitudinal Analyses

In general, weight loss is the appropriate approach to reduce the obesity-related health risk. An improvement of cardiovascular risk factors as a result of weight loss during lifestyle intervention has been reported in several studies in children and adolescents [77, 78].

The mean weight loss in our long-term treatment study was −27.1 ± 16.2 kg (−20.1 ± 7.9%) in boys and −20.5 ± 11.5 kg (−17.3 ± 7.1%) in girls, reducing the mean BMI z-score by 0.8 ± 0.3 and 0.7 ± 0.4, respectively. This marked weight loss is comparable to the amount of

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Table 6. Changes in cardiometabolic risk factors in relation to changes in measurements of IAD

Parameter	ΔIAD, % < 25th internal percentile		ΔIAD, % > 25th and < 75th internal percentile		ΔIAD, % > 75th internal percentile	
	mean ± SD	median	mean ± SD	Median	mean ± SD	median
Girls						
ΔBMI-z score, %	−16.7 ± 13.2	−15.1	−21.9 ± 9.0	−22.6	−26.8 ± 12.6	−24.7
ΔWaist circumference, %	−10.4 ± 4.4	−11.3	−13.2 ± 5.9	−12.6	−18.2* ± 6.0	−18.7
ΔRR systolic, %	−10.0 ± 8.8	−11.7	−7.4 ± 7.9	−7.8	−10.6 ± 8.8	−9.5
ΔRR diastolic, %	−13.4 ± 11.4	−17.0	−9.6 ± 11.6	−10.3	−10.0 ± 10.7	−9.7
ΔTG, %	8.6 ± 35.4	1.1	−8.0 ± 29.3	−9.9	0.2 ± 37.6	−4.1
ΔCholesterol, %	−4.4 ± 16.1	−4.4	−11.5 ± 11.9	−11.6	−6.3 ± 17.5	−9.1
ΔLDL-cholesterol, %	−11.9 ± 22.2	−10.5	−17.9 ± 14.2	−20.0	−7.1 ± 20.1	−10.0
ΔHDL-cholesterol, %	4.0 ± 15.1	5.4	−2.1 ± 16.3	−5.0	0.0 ± 22.3	−7.2
ΔAST, %	9.7 ± 39.6	6.9	−0.6 ± 38.6	−4.2	−16.2 ± 14.1	−14.8
ΔALT, %	17.4 ± 60.9	0.6	1.4 ± 57.9	−10.7	−18.7 ± 24.4	−20.8
ΔyGT, %	−2.2 ± 32.8	2.0	−8.2 ± 34.9	−15.4	−28.6 ± 29.8	−28.0
ΔAdiponectin, %	20.8 ± 41.5	22.4	27.8 ± 46.1	11.7	23.6 ± 50.7	13.2
ΔIL-6, %	−2.0 ± 54.4	−7.5	13.8 ± 88.9	−10.8	−34.0 ± 29.6	−39.9
Δhs-CRP, %	−19.2 ± 59.8	−33.6	1.3 ± 117.3	−53.6	−39.1 ± 60.7	−53.7
ΔHOMA-IR, %	−37.9 ± 33.8	−49.2	−25.8 ± 55.3	−35.8	−33.6 ± 27.6	−36.8
T-duration, months	4.9 ± 1.6	5.6	5.8 ± 2.2	5.9	7.3* ± 2.2	7.1
Age, years	15.3 ± 2.3	15.0	15.0 ± 2.2	14.0	15.2 ± 1.8	15.5
Boys						
ΔBMI-z score, %	−17.5 ± 10.8	−14.2	−26.9 ± 12.0	−26.4	−29.1 ± 10.7	−25.3
ΔWaist circumference, %	−12.5 ± 5.7	−11.9	−16.7 ± 6.6	−17.8	−21.1 ± 6.8	−19.0
ΔRR systolic, %	−2.3 ± 8.0	1.0	−7.4 ± 7.6	−5.9	−8.8 ± 8.3	−6.9
ΔRR diastolic, %	−3.6 ± 11.4	−2.4	−9.6 ± 13.0	−10.6	−15.6 ± 12.3	−13.4
ΔTG, %	−8.3 ± 38.6	−14.3	−17.0 ± 29.6	−19.1	−0.1 ± 103.9	−19.6
ΔCholesterol, %	−14.7 ± 21.6	−7.6	−16.2 ± 10.9	−15.6	−15.8 ± 10.7	−17.2
ΔLDL-cholesterol, %	−16.9 ± 13.3	−18.8	−21.3 ± 15.2	−23.2	−19.0 ± 15.3	−23.5
ΔHDL-cholesterol, %	−1.2 ± 17.2	−0.1	−1.9 ± 17.5	−6.7	−0.6 ± 21.4	−5.9
ΔAST, %	−11.1 ± 19.5	−15.7	−21.7 ± 21.8	−24.1	−18.7 ± 31.1	−24.1
ΔALT, %	−10.8 ± 20.8	−4.3	−41.8* ± 23.7	−43.4	−34.6 ± 33.3	−39.3
ΔyGT, %	−18.0 ± 27.0	−19.9	−31.9 ± 24.8	−36.8	−37.9 ± 33.6	−48.0
ΔAdiponectin, %	29.9 ± 41.8	26.7	24.7 ± 32.5	20.7	41.9 ± 44.5	50.9
ΔIL-6, %	4.9 ± 67.1	−24.3	72.6 ± 233.3	−9.0	−33.8 ± 46.3	−39.4
Δhs-CRP, %	172.1 ± 610.8	−44.2	49.7 ± 373.8	−56.3	−60.5 ± 31.7	−70.8
ΔHOMA-IR, %	−8.8 ± 68.1	−32.8	−49.4 ± 32.9	−60.8	−38.2 ± 40.2	−60.4
T-duration, months	3.5 ± 1.9	3.4	5.9 ± 2.3	5.9	6.3* ± 2.3	5.9
Age, years	14.8 ± 2.3	14.0	15.5 ± 2.8	15.0	15.8 ± 2.7	15.5

The analysis was performed after dividing the cohort into 3 subgroups according to changes in IAD (group 1: < 25th percentile, group 2: > 25th to < 75th percentile, group 3: > 75th percentile of delta IAD).

*$p < 0.05$ statistically significant between groups.

weight loss achieved by bariatric surgery in extremely obese adolescents [79–81]. Weight loss in the present study resulted in significant reductions in IAD assessed by ultrasound being again clearly higher in boys than in girls. Decreases in IAD as a measure of IAF were associated with an improvement in cardiometabolic risk factors. Interestingly, these improvements of metabolic risk factors showed also gender specify, with larger benefits in boys than in girls. These results are in line with results of studies in adults, showing that the improvement of cardiovascular risk factors during weight loss is higher in men than in women [56, 57, 82].

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Finally, we could demonstrate that relative changes in cardiometabolic risk factors were correlated with relative changes in IAD assessed by ultrasound. These data suggest that changes in IAD can predict improvements in cardiovascular risk factors in severely obese adolescents. These findings also confirm results of an earlier study of our group, showing that obese adolescents with an abdominal type of body fat distribution benefit more of a weight reduction programme regarding cardiovascular risk factor reduction than patients with a gluteal-femoral type of body fat distribution [83]. To these data, the present study adds measurements of IAF by ultrasound, demonstrating that the IAF is the clinically relevant organ related to these changes.

Strengths and Limitations

Strengths of this study are the combination of a baseline and follow-up analysis of severely obese adolescents attending a long-term inpatient multimodal obesity programme resulting in a marked amount of weight loss being comparable to that obtained by bariatric surgery. The degree of weight reduction was clinically relevant as demonstrated by an improvement of most cardiometabolic risk factors.

Some potential limitations have to be kept in mind: It must be pointed out that the IAD values assessed via ultrasound depend on the pressure which is applied by the investigator to put the transducer on the abdomen as well as on the patients' respiration. However, the differences in IAD values in this study are likely to be very small because all IAD measurements were conducted by the same experienced investigator.

Conclusions

The results of the present study show that sonographically assessed IAD is a good indicator for the cardiometabolic risk factor profile in the special risk group of adolescents with extreme obesity. Associations between IAF and the risk factors are more pronounced in boys than in girls. Changes of IAF assessed by ultrasound during marked weight loss are associated with an amelioration of the cardiometabolic risk factor profile, with boys having a greater benefit than girls.

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Authorships Section

Conceived and designed the study: AM, MW, WS. Performed the clinical measurements: WS, AS. Analysed the data: AM, SB. Wrote the first draft of the manuscript: AM. Contributed to the writing of the manuscript: AM, MW, SB, KS, WS, AS, WK. Agree with final manuscript and conclusions: AM, MW, SB, KS, WS, AS, WK.

Disclosure Statement

The authors have nothing to disclose.

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