Introduct

The association of increased body weight with elevated levels of triglycerides and diminished high-density lipoprotein (HDL)-cholesterol levels has been described in adults (1). Likewise, alterations on levels of triglycerides and HDL-cholesterol seems to be associated with markers of central obesity, measured with either simple anthropometric indices or with more advance techniques, such as computed tomography (2–4).

Waist circumference and truncal obesity are widely used as surrogates of central and truncal fat depots, respectively, in population studies (5). Waist circumference is a powerful marker of abdominal fat accumulation and visceral adiposity tissue in young people (5,6). Truncal obesity, defined as the ratio of subscapular to triceps skinfold thickness or as the percentage of trunk-to-total skinfolds ratio (TTS%), has also been widely used in population studies (7,8).

The study of the relationship between body fat distribution and dyslipidemia among children and adolescents can be difficult because of the known marked changes in circumferences and skinfold thicknesses (8,9), as well as in the levels of lipids and lipoprotein that occur during growth and development (10,11). Furthermore, the amount of intraabdominal fat, which may have a primary role in adverse cardiovascular profile, is relatively small before adulthood (12,13). In children, subcutaneous fat is the major depot in the abdominal region (14).

Flodmark et al. (15) observed that in obese adolescents, waist circumference was associated with an unfavorable lipoprotein profile, mainly with increased levels of triglycerides and decreased levels of HDL-cholesterol. In children and adolescents from the Bogalusa study (16), waist circumference and waist to hip ratio were related to adverse levels of triglycerides

Truncal and Abdominal Fat as Determinants of High Triglycerides and Low HDL-cholesterol in Adolescents

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We examined whether abdominal and truncal adiposity, assessed with simple anthropometric indices, determines serum triglycerides and high-density lipoprotein (HDL)-cholesterol levels independently of total adiposity amount in adolescents. A total of 547 Spanish adolescents (284 males and 263 females) aged 13–18.5 years were included in this study. Measures of truncal adiposity included subscapular to triceps ratio, and trunk-to-total skinfolds ratio (TTS%). Waist circumference was used as a surrogate of abdominal adiposity, and BMI was used as a measure of total adiposity. The results of the regression models indicated that levels of triglycerides were positively associated with waist circumference and TTS% after controlling for age and Tanner stage in both sexes. Once BMI was entered in the model, these associations remained significant for waist circumference in females. HDL-cholesterol levels were negatively associated with waist circumference in both sexes, and with subscapular to triceps ratio and TTS% in males, after controlling for age and Tanner stage. Once BMI was entered in the model, these associations remained significant for subscapular to triceps ratio and for TTS% in males. The results of this study suggest that in male adolescents, truncal adiposity is negatively associated with levels of HDL-cholesterol, whereas in females, abdominal adiposity is positively associated with levels of triglycerides independently of total adiposity. These findings highlight the deleterious effect of both truncal and abdominal fat depots on the lipid profile already from the first decades of life.
and HDL-cholesterol independently of race, sex, age, weight, and height. Similarly, in school-aged children from Cyprus, waist circumference was the most significant predictor of triglycerides and HDL-cholesterol levels, when compared with BMI and waist to height ratio (17). In prepubertal children, Maffeis et al. (18) observed that waist circumference as well as subscapular and triceps skinfolds were helpful measurements for identifying those with an adverse lipid profile. Morrison et al. (19) observed a positive association between sum of truncal skinfolds (subscapular + suprailiac) and triglycerides levels and a negative association with levels of HDL-cholesterol in White and Black adolescents.

Whether markers of central and truncal fat depots measured with simple anthropometric indices are associated with levels of triglycerides and HDL-cholesterol in Spanish adolescents is not known. Therefore, the aim of our study was to assess whether anthropometric indices of abdominal and truncal adiposity are associated with serum levels of triglycerides and HDL-cholesterol, independently of total adiposity. We used waist circumference as a surrogate of abdominal adiposity, and as a surrogate to truncal adiposity we used the ratio of subscapular to triceps skinfold thickness as well as the trunk-to-total skinfold thickness % (subscapular + suprailiac/(biceps + triceps + subscapular + suprailiac)) (TTS%) (6–8).

**METHODS AND PROCEDURES**

**Study design and subjects**

The subjects were all participants in the AVENA (Alimentación y Valoración del estado Nutricional en Adolescentes) study (20), a population-based cross-sectional multicentre study aiming to assess the nutritional status of the Spanish adolescent population. The study was conducted between 2000 and 2002 in five different geographic locations in Spain. The number of adolescents included in the AVENA study was 2,859 adolescents. Blood samples were randomly obtained from 581 of the subjects. From these, 547 adolescents (284 males and 263 females) had a complete set of Tanner stage, anthropometric, and lipids measurements, and were included in this study. This subsample is considered to be representative of the Spanish adolescent population because we have shown that the variable used to calculate the total sample size of the study (i.e., BMI) was similar between the total AVENA sample and the subsample in which blood samples were obtained (21).

A verbal detailed description of the nature and purpose of the study was given to adolescents, their parents, and school teachers. This information was also sent to parents or adolescents supervisors by letter, and written consents from parents and adolescents were requested. After receiving their written assent, the adolescents were considered for inclusion in the study. Exclusion criteria were type 2 diabetes, pregnancy, alcohol or drug abuse, and non–directly related nutritional medical conditions. The study protocol was performed in accordance with the ethical standards laid down in the 1961 Declaration of Helsinki (as revised in Hong Kong in 1989, and in Edinburgh in 2000), and approved by the Review Committee for Research Involving Human Subjects of the Hospital Universitario Marqués de Valdecilla (Santander, Spain).

**Physical examination**

Identification of pubertal stage (I–V) was assessed according to Tanner and Whitehouse (22). The standard staging of pubertal maturation describes breast and pubic hair development in girls and genital and pubic hair development in boys. In males, distribution by Tanner pubertal stages was stage II, 5.2% (n = 15); stage III, 14.9% (n = 42); stage IV, 40.9% (n = 116); and stage V, 39.0% (n = 111). In females, the corresponding distribution was the following: stage II, 1.6% (n = 4); stage III, 8.5% (n = 22); stage IV, 54.7% (n = 144); and stage V, 35.2% (n = 93).

**Anthropometric method**

Two anthropometrists in each city performed all the measurements; one measured weight, height, and circumferences, and the other one, skinfolds (23). BMI was calculated as body weight (kg) without shoes and with light clothing, divided by height (m) squared. Body weight was measured to 0.05 kg using a standard beam balance.

Skinfold thicknesses were measured at the left side of the body (24) to the nearest 0.1 mm using a Holtain skinfold caliper, at the following sites: (i) triceps, halfway between the acromion process and the olecranon process; (ii) biceps, at the same level as the triceps skinfold, directly above the center of the cubital fossa; (iii) suprailiac, 20 mm below the tip of the scapula, at an angle of 45° to the lateral side of the body; (iv) suprailiac, 20 mm above the iliac crest and 20 mm toward the medial line (23). Intraobserver reliability for skinfold thickness was >95% for almost all the cases, and interobserver reliability for skinfold thickness ranged from 83.05% for biceps skinfold to 96.38% for calf skinfold (23).

Circumferences were measured in cm with an inelastic tape to the nearest mm, with the subject in a standing position. To measure the waist circumference, the tape was applied horizontally midway between the lowest rib margin and the iliac crest about the level of the umbilicus, at the end of gentle expiration. The hip circumference measurement was taken at the point yielding the maximum circumference over the buttocks, with the tape held in a horizontal plane. Intraobserver reliability for circumferences was >95% for almost all the cases; interobserver reliability for waist and hip circumferences were 97.90 and 94.84%, respectively (23).

The complete set of anthropometric measurements was performed three times, but not consecutively. The anthropometric variables were measured in order, and then we repeated the same measurements two more times. For calculations, mean values were obtained from the three measurements.

**Laboratory method**

Blood collection was carried out between 8:00 and 9:00 AM, and after an 8-h overnight fast. The subjects were instructed to abstain from alcoholic beverages for at least 2 weeks before sampling and to refrain from vigorous exercise during the 48 h preceding blood collection. Within 1 h after collection, blood was centrifuged and aliquots of sera were sent refrigerated to a central laboratory (Clinical Biochemistry Service, Granada University Hospital) where all the clinical chemistry tests were performed within 24 h after collection. Total cholesterol, triglycerides, and HDL-cholesterol were measured by enzymatic assay using a Hitachi 911 Analyzer (Roche Diagnostics, Indianapolis, IN). For the HDL-cholesterol assay, precipitation was done using reagents provided by Boehringer (Ingelheim, Germany). Apolipoprotein A-1, and apolipoprotein B were measured by immunonephelometric assay using an Array 306 system (Beckman GMI, Albertville, MN). Low-density lipoprotein cholesterol was calculated with the Friedewald formula (25), and very low-density lipoprotein cholesterol, was calculated as triglycerides divided by 5. The coefficients of variation were <3% and the intraclass coefficients were >0.96% for all blood variables. Quality control of the assays was assured by the Regional Health Authority, as is compulsory for all hospital clinical laboratories in Spain.

**Statistical analysis**

The analyses were performed using the Statistical Package for Social Sciences (SPSS, version 13.0 for WINDOWS; SPSS, Chicago, IL). Intergroups differences among sexes were assessed by either Student’s test (parametric variables) or Mann–Whitney U-test (nonparametric variables). Pearson correlations between anthropometric indices and serum lipids and lipoproteins were calculated in both male and females. Multiple regression models were used to examine the association between indices of body fat distribution and levels of triglycerides and HDL-cholesterol after controlling for age and Tanner stage (model 1), and after further controlling for BMI (model 2). The analyses were
performed separately for males and females. To achieve normality in the residuals, triglycerides and HDL-cholesterol were transformed to the natural logarithm. Each marker of body fat distribution, that is, waist circumference, subscapular to triceps skinfold ratio, and TTS% was examined in a different regression model. Tanner stage was entered as dummy variable. The level of significance was set to 0.05.

**RESULTS**

Anthropometric and lipid and lipoprotein mean values in males and females are shown in Table 1. Waist circumference and the indices of truncal adiposity (subscapular/triceps and TTS%) were significantly higher in males than in females. Levels of triglycerides were higher in males than in females, whereas levels of HDL-cholesterol were lower in males than in females.

Correlations coefficients between anthropometric indices and lipids and lipoproteins are shown in Tables 2 and 3, for males and females, respectively. In males, levels of triglycerides were positively associated with weight, BMI, waist, and hip circumference, and TTS% (all \( P < 0.05 \)). The levels of HDL-cholesterol were negatively associated with the same anthropometric indices, and subscapular to triceps ratio (all \( P < 0.05 \)). In females, levels of triglycerides were positively associated with waist circumference and subscapular to triceps ratio (both \( P < 0.05 \)), whereas levels of HDL-cholesterol were negatively associated with weight, BMI, and waist and hip circumference (all \( P < 0.05 \)).

The results of the regression models with triglycerides and HDL-cholesterol as the outcome variable and anthropometric indices of abdominal and truncal adiposity separated by sex are shown in Table 4. In males, levels of triglycerides were positively associated with waist circumference (\( P < 0.001 \)).

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**Table 1** Anthropometric, lipid, and lipoprotein characteristics of the studied adolescents aged 13–18.5 years

<table>
<thead>
<tr>
<th></th>
<th>Males (n = 284)</th>
<th>Females (n = 263)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>64.54 (13.37)</td>
<td>56.31 (10.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.64 (8.10)</td>
<td>161.47 (6.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.07 (3.86)</td>
<td>21.58 (3.46)</td>
<td>0.064</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>76.98 (9.34)</td>
<td>70.64 (8.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>93.25 (8.67)</td>
<td>93.90 (8.35)</td>
<td>0.374</td>
</tr>
<tr>
<td>Subscapular to triceps ratio</td>
<td>1.03 (0.26)</td>
<td>0.81 (0.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trunk-to-total skinfolds ratio (%)</td>
<td>55.70 (5.09)</td>
<td>50.84 (5.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>156.40 (26.28)</td>
<td>168.59 (26.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>90.84 (23.77)</td>
<td>96.22 (23.26)</td>
<td>0.006</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>51.08 (9.73)</td>
<td>59.21 (11.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VLDL-cholesterol (mg/dl)</td>
<td>14.47 (6.36)</td>
<td>13.16 (6.60)</td>
<td>0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>72.36 (31.80)</td>
<td>65.79 (33.00)</td>
<td>0.001</td>
</tr>
<tr>
<td>Apolipoprotein A-I (mg/dl)</td>
<td>116.75 (19.49)</td>
<td>125.93 (23.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apolipoprotein B (mg/dl)</td>
<td>68.00 (15.43)</td>
<td>70.84 (14.10)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Values are means (±s.d.). HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

**Table 2** Correlation coefficients between anthropometric indices and lipids and lipoproteins in male adolescents

<table>
<thead>
<tr>
<th></th>
<th>Weight</th>
<th>Height</th>
<th>BMI</th>
<th>WC</th>
<th>HC</th>
<th>SST</th>
<th>TTS%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>-0.027</td>
<td>-0.178**</td>
<td>0.070</td>
<td>0.048</td>
<td>0.022</td>
<td>-0.065</td>
<td>-0.017</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>0.027</td>
<td>-0.161**</td>
<td>0.125*</td>
<td>0.080</td>
<td>0.076</td>
<td>-0.027</td>
<td>0.041</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>-0.245**</td>
<td>-0.066</td>
<td>-0.262**</td>
<td>-0.198**</td>
<td>-0.244**</td>
<td>-0.137*</td>
<td>-0.232**</td>
</tr>
<tr>
<td>VLDL-cholesterol</td>
<td>0.159**</td>
<td>-0.036</td>
<td>0.218**</td>
<td>0.198**</td>
<td>0.180**</td>
<td>0.042</td>
<td>0.128*</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.159**</td>
<td>-0.036</td>
<td>0.218**</td>
<td>0.198**</td>
<td>0.180**</td>
<td>0.042</td>
<td>0.128*</td>
</tr>
<tr>
<td>Apolipoprotein A-I</td>
<td>-0.057</td>
<td>-0.018</td>
<td>-0.060</td>
<td>-0.022</td>
<td>-0.078</td>
<td>0.016</td>
<td>-0.050</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>0.005</td>
<td>-0.169**</td>
<td>0.103</td>
<td>0.041</td>
<td>0.024</td>
<td>-0.037</td>
<td>0.055</td>
</tr>
</tbody>
</table>

HC, hip circumference; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SST, subscapular to triceps ratio; TTS%, trunk-to-total skinfolds ratio percentage; VLDL, very low-density lipoprotein; WC, waist circumference.

\(^*P < 0.05, \quad ^{**}P < 0.01.\)

**Table 3** Correlation coefficients between anthropometric indices and lipids and lipoproteins in female adolescents

<table>
<thead>
<tr>
<th></th>
<th>Weight</th>
<th>Height</th>
<th>BMI</th>
<th>WC</th>
<th>HC</th>
<th>SST</th>
<th>TTS%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>0.040</td>
<td>-0.047</td>
<td>0.052</td>
<td>0.081</td>
<td>0.022</td>
<td>0.131*</td>
<td>0.098</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>0.089</td>
<td>-0.093</td>
<td>0.136*</td>
<td>0.137*</td>
<td>0.102</td>
<td>0.140*</td>
<td>0.108</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>-0.128*</td>
<td>0.076</td>
<td>-0.197**</td>
<td>-0.162**</td>
<td>-0.173**</td>
<td>-0.056</td>
<td>-0.052</td>
</tr>
<tr>
<td>VLDL-cholesterol</td>
<td>0.074</td>
<td>0.009</td>
<td>0.077</td>
<td>0.133*</td>
<td>0.030</td>
<td>0.132*</td>
<td>0.108</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.074</td>
<td>0.009</td>
<td>0.077</td>
<td>0.133*</td>
<td>0.030</td>
<td>0.132*</td>
<td>0.108</td>
</tr>
<tr>
<td>Apolipoprotein A-I</td>
<td>-0.035</td>
<td>0.071</td>
<td>-0.087</td>
<td>-0.041</td>
<td>-0.155*</td>
<td>0.042</td>
<td>-0.081</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>0.081</td>
<td>-0.075</td>
<td>0.121</td>
<td>0.101</td>
<td>0.053</td>
<td>0.042</td>
<td>0.079</td>
</tr>
</tbody>
</table>

HC, hip circumference; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SST, subscapular to triceps ratio; TTS%, trunk-to-total skinfolds ratio percentage; VLDL, very low-density lipoprotein; WC, waist circumference.

\(^*P < 0.05, \quad ^{**}P < 0.01.\)
and TTS% \((P = 0.005)\) after controlling for age and Tanner stage (model 1). The association between triglycerides and TTS% was closed to reach the significant level \((P = 0.01)\) after further controlling for BMI (model 2). Levels of HDL-cholesterol were negatively associated with waist circumference \((P = 0.002)\), subcapular to triceps ratio \((P = 0.024)\), and TTS% \((P < 0.001)\) after controlling for age and Tanner stage. These associations remained significant after further controlling for BMI (model 2), for subcapular to triceps ratio \((P = 0.027)\), and TTS% \((P = 0.001)\), but not for waist circumference \((P = 0.164)\).

In females, levels of triglycerides were positively associated with waist circumference \((P = 0.006)\), subcapular to triceps ratio \((P = 0.047)\), and TTS% \((P = 0.048)\) after controlling for age and Tanner stage (model 1). After further controlling for BMI (model 2), levels of triglycerides were positively associated with waist circumference \((P = 0.025)\). Levels of HDL-cholesterol were negatively associated with waist circumference \((P = 0.024)\), however, the association disappeared once BMI was entered in the model (model 2). HDL-cholesterol was not associated with subcapular to triceps ratio or with TTS% in any of the models tested.

**DISCUSSION**

The relationship between body fat distribution and dislipidemia has been previously studied in different cohorts of children and adolescents \((17,26–30)\). Most of these studies have been done in the United States. The majority of the previous studies did not control for potential confounders such as age, pubertal development, and an index of total adiposity. Therefore, covariates that may confound the measures of association in this study were appropriately considered and controlled. In this study we found a negative association between truncal adiposity and levels of HDL-cholesterol in male adolescents, and a positive association between abdominal adiposity and levels of triglycerides in female adolescents after controlling for several potential cofounders including age, pubertal development, and an index of total adiposity, that is, BMI. These findings concur with other studies \((17,30–32)\). Savva et al. \((17)\) observed a significant association of abdominal obesity with levels of triglycerides, as well as with levels of HDL-cholesterol after controlling for age, sex, pubertal development, and BMI. Studies using more advanced techniques to measure abdominal adiposity, such as dual-energy X-ray absorptiometry or magnetic resonance imaging, reported similar results as those found in this study \((30–32)\). In lean and obese children and adolescents, it was observed that the magnitude of the association between serum lipids and trunk fat mass assessed by dual-energy X-ray absorptiometry was similar than the association observed between serum lipids and the sum of trunk skinfolds \((32)\).

Waist circumference correlates well with intraabdominal and subcutaneous fat measured by magnetic resonance imaging in children and adolescents \((5)\). As waist circumference is also related with total body fat \((33,34)\), the relationship between waist circumference and adverse serum lipid profile likely reflect the ability of waist circumference to functions as an index of both fat distribution. Waist circumference has been included in some definitions of the metabolic syndrome in children and adolescents \((35)\), and it has also been considered a good tool for the screening of a clustering of cardiovascular risk factors during childhood \((36)\). That is the reason why to try to establish adequate cutoff values to be used in pediatric populations \((37)\).
A frequent combination of high triglycerides and low HDL-cholesterol levels, called the conjoint trait, has been observed already in young people, being more common in white than in black males (32). Morrison et al. (19) showed that those individuals with the conjoint trait also had the highest mean sum of truncal skinfolds, measured as suscapular + suprailliac skinfolds, and individuals with high levels of triglycerides alone had the second highest mean of truncal adiposity.

Mamalakis et al. (38) observed that, similar to adults, children's fatty acid composition of abdominal adipose tissue is less favorable than that of the buttoc. Abdominal depots have elevated proportions of saturated fatty acids and reduced proportions of monounsaturated and polyunsaturated fat in comparison to buttoc depots. By contributing free fatty acids to the liver, visceral fat leads to increased circulating levels of triglycerides, decreased HDL-cholesterol, increased hepatic glucose production, and decreased hepatic insulin extraction.

Truncal and abdominal adiposity have also been related with inflammatory markers and insulin resistance in pubertal children and adolescents (34,39,40). Findings from the AVENA study revealed that levels of C-reactive protein and complement factors C3 and C4 were associated with central obesity, as measured by waist circumference and total body fat in both male and female adolescents, and with ceruloplasmin in females. After further controlling for BMI, C3 was the only inflammatory marker that remained associated with central obesity.

The main limitation of this study is related with its cross-sectional design, which precludes firm conclusions about whether the variation in body fat distribution may cause any variation in the levels of triglycerides and HDL-cholesterol in adolescents. The associations between abdominal and truncal fat, and levels of triglycerides and HDL-cholesterol were relatively weak; however, the fact that it persisted after further controlling for a measure of total adiposity emphasizes the influence of body fat distribution on the levels of triglycerides and HDL-cholesterol. Also, our study included a moderate number of participants, yet the observed power for the sample size ranged from 0.68 to 0.97.

In conclusion, the results of this study suggest that in male adolescents, truncal adiposity, as measured by subcapular to triceps ratio or TTS%, is negatively associated with levels of HDL-cholesterol after controlling for age, pubertal development, and a measure of overall adiposity such as BMI. In females, abdominal adiposity, as measured by waist circumference, is negatively associated with levels of triglycerides after controlling for age, pubertal development, and BMI. These findings highlight the deleterious effect of both abdominal and truncal fat depots on the lipid profile already from the first decades of life. Direct measurements of visceral adiposity with magnetic resonance imaging or computed tomography may provide further information; however, this cannot be proposed for field studies due to cost and technical difficulties involved (41). Gutin et al. (30) reported that an easily measured anthropometric variable such as waist circumference tended to explain similar proportions of cardiovascular disease risk factors similar to other adiposity indices obtained with more advanced techniques. Thus, according to our finding and those reported by others, waist circumference, and measures of truncal adiposity such as subscapular, suprailiac, biceps, and triceps skinfolds would be helpful to guide clinical work.

The relationship between body fat distribution and dyslipidemia in growing children and adolescents should be studied in longitudinal studies. Moreover, interventions to prevent obesity in children and adolescents (42) and if possible to avoid central (abdominal and truncal) fat depots, and also to decrease these depots in obese children and adolescents (43) should be developed in the future.

AVENA STUDY GROUP

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DISCLOSURE

The authors declared no conflict of interest.

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