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# Intima-Media Thickness in Obese Children Before and After Weight Loss

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## ABSTRACT

**OBJECTIVE.** Obesity in childhood is related to increased intima-media thickness, a noninvasive marker for early atherosclerotic changes. The objective of this study was to analyze the changes of intima-media thickness in obese children with weight loss.

**METHODS.** We analyzed the changes of intima-media thickness and, as markers of cardiovascular risk factor profile, systolic and diastolic blood pressure, triglycerides, high-density lipoprotein cholesterol, glucose, insulin, and insulin resistance index (homeostasis model analysis) in 56 prepubertal obese children (median: 9 years old) before and after a 1-year outpatient intervention program. The control group consisted of 10 nonobese children of the same age and gender. We determined the carotid intima-media thickness by B-mode ultrasound with a 14-MHz linear transducer. Substantial weight loss was defined by a reduction of overweight of at least 0.5 standard deviation scores in BMI.

**RESULTS.** Obese children demonstrated a significantly thicker intima-media compared with the control group. Furthermore, blood pressure, triglycerides, insulin, and insulin resistance index were significantly higher in obese children, whereas high-density lipoprotein cholesterol was significantly lower. In the 24 obese children with substantial weight loss, intima-media thickness, blood pressure, triglycerides, insulin, and insulin resistance index decreased significantly, whereas high-density lipoprotein cholesterol increased significantly. In the 32 obese children without substantial weight loss, there were no significant changes apart from an increase of insulin and insulin resistance index.

**CONCLUSIONS.** Because obese children demonstrated a thicker intima-media, vascular changes seemed to occur already in childhood obesity. Paralleling the improvement of the cardiovascular risk factor profile, intima-media thickness decreased in obese children with substantial weight loss, suggesting the reversibility of early atherosclerotic changes.

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### Key Words

obesity, carotid arteries, ultrasound, weight loss, children

### Abbreviations

HDL—high-density lipoprotein  
 IMT—intima-media thickness  
 SDS-BMI—SD score of BMI  
 SBP—systolic blood pressure  
 DBP—diastolic blood pressure  
 HOMA—homeostasis model analysis  
 CI—confidence interval

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**O**BESITY IN CHILDHOOD is an increasing phenomenon.<sup>1</sup> Childhood obesity has a wide range of serious complications and increases the risk of early illness and death in later life. As in adulthood, obesity in childhood contributes to an increased prevalence of cardiovascular risk factors, such as hypertension, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, and impaired glucose metabolism.<sup>1-4</sup>

Exposure to these cardiovascular risk factors in early life may induce changes in the arteries contributing to the development of atherosclerosis in adulthood.<sup>5</sup> Measurement of the intima-media thickness (IMT) of the common carotid artery is an acknowledged noninvasive marker for early atherosclerotic changes and is a feasible, reliable, valid, and cost-effective method.<sup>5-9</sup> Increased carotid IMT was shown to be predictive and is related to the severity and extent of coronary artery disease and strokes in adults.<sup>10,11</sup> Studies in adults and children revealed associations between IMT, obesity, and cardiovascular risk factors such as hypertension, dyslipidemia, and insulin resistance.<sup>10,12-14</sup>

The appropriate approach to reduce the obesity-related health risks is weight loss. Weight reduction has a beneficial effect on several cardiovascular risk factors such as dyslipidemia, insulin resistance, and hypertension, even in obese children.<sup>15-18</sup> However, the association between reduction of body weight and carotid atherosclerosis has not yet been clearly established. Some studies showed decreasing IMT in weight loss,<sup>19,20</sup> although one study revealed stable IMT in obese adults losing weight.<sup>21</sup> The only study in obese children reported decreasing IMT in weight loss.<sup>22</sup> Because the findings in the few existing studies are controversial, we performed this study to analyze the relationships between changes of weight status, cardiovascular risk factors, and carotid IMT in obese children participating in a 1-year outpatient long-term intervention program.

## MATERIALS AND METHODS

We collected the clinical data (age, gender, and degree of overweight) and the cardiovascular risk factor profile of 63 prepubertal, nonsyndromally obese white children participating in the 1-year obesity intervention program "Obeldicks" between 2004 and 2005 at baseline and 1 year later, and compared the profiles with those of 10 prepubertal nonobese healthy children in a prospective study. Children with endocrine or metabolic disorders, smokers, and children taking any kind of medication including oral contraceptives were excluded from the study. Patients who dropped out during the intervention period were also excluded from the study.

Obesity was defined according to the BMI 97th percentile using the definition of the International Task Force of Obesity in Childhood and population-specific data.<sup>23,24</sup> The weight status was recorded as BMI. Because the BMI is not normally distributed in childhood, we

used Cole's least mean square method, which normalizes the BMI skewed distribution and expresses BMI as a standard deviation score (SDS-BMI) by the formula  $SDS-BMI = [BMI/M(t)^{L(t)-1}]/[L(t) \times S(t)]$ .<sup>25</sup> The  $M$  and  $S$  curves correspond to the median and coefficient of variation in BMI for German children at each age and gender, whereas the  $L$  curve allows for the substantial age dependent skewness in the distribution of BMI.<sup>23,25</sup>

Blood pressure was measured by 1 investigator using a validated protocol.<sup>26</sup> Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice at the right arm after a 10-minute rest in the supine position by using a calibrated sphygmomanometer, then the 2 measurements were averaged. The cuff size, which was based on the length and circumference of the upper arm, was chosen to be as large as possible without having the elbow skin-crease obstruct the stethoscope.<sup>26</sup>

Serum triglyceride, HDL cholesterol, glucose, and insulin concentrations were measured in the fasting state using commercially available test kits (HDL-C- Plus, Roche Diagnostics, Mannheim, Germany; Vitros analyzer, Ortho Clinical Diagnostics, Neckargemuend, Germany; and MEIA, Abbott, Wiesbaden, Germany). The children and their parents were carefully instructed to fast for at least 10 hours before testing. Intra-assay and interassay variations for the concentrations of these variables were <5%. Homeostasis model assessment (HOMA) was used to detect the degree of insulin resistance<sup>27</sup>: The resistance can be assessed from the fasting glucose and insulin concentrations by the formula: resistance (HOMA) = (insulin [mU/L] × glucose [mmol/L])/22.5.

We measured carotid IMT by B-mode ultrasound using a 14-MHz linear transducer following a standardized protocol. The measurement was performed at the common carotid artery near the bifurcation at the far wall after a 10-minute rest. We measured 4 values on each side and took the maximum value for statistical purposes, because the strongest association between the different measurements of IMT and coronary risk factors in otherwise healthy individuals is achieved by applying the maximum and not the mean value of IMT.<sup>28</sup> The patients were examined in the supine position with the head turned slightly to the side. The same sonographer, who was blinded to the participants' cardiovascular risk factor status and to the weight changes during the 1-year period, performed all examinations.

The obesity intervention program Obeldicks, which has been described in detail elsewhere,<sup>16,17,29-31</sup> was based on physical exercise, nutrition education, and behavior therapy, including the individual psychological care of the child and his/her family. An interdisciplinary team of pediatricians, diet assistants, psychologists, and exercise physiologists was responsible for the training. The children were divided into groups according to their gender and age. The 1-year program was divided into 3 phases: In the intensive phase (3 months), the children took part

in a nutritional course and eating-behavior course in 6 group sessions, each lasting for 1.5 hours. At the same time, parents were invited to attend 6 parents' evenings. In the establishing phase (6 months), individual psychological family therapy was provided (30 minutes per month). In the last phase of the program (accompanying the families back to their everyday lives; 3 months), additional individual care was possible, if and when necessary. Exercise therapy took place once a week during the entire year and consisted of ball games, jogging, trampoline jumping, and instructions in physical exercise as part of everyday life and in reduction of the amount of time spent watching television. The nutritional course was based on the prevention concept of the "optimized mixed diet." This diet was fat- and sugar-reduced and contained 30% fat, 15% protein, and 55% carbohydrates, including 5% sugar.<sup>30</sup>

Substantial weight loss during the 1-year intervention was defined as a decrease in the SDS-BMI  $\geq 0.5$ , because with a reduction of  $<0.5$  SDS-BMI, no improvement of insulin resistance and cardiovascular risk factors could be measured in obese children.<sup>16,17</sup>

### Statistical Analysis

All variables tested by the Kolmogorov-Smirnov test revealed normal distribution apart from insulin, HOMA, and IMT. Differences were tested with  $\chi^2$  tests, *t* tests for paired and unpaired observations, Mann-Whitney *U* tests, and Wilcoxon tests as appropriate. Confidence limits for means were calculated based on the *t* distribution.

Changes of parameters were demonstrated as  $\delta$  variable defined by variable at the end of intervention – variable at baseline. Relative changes of IMT were calculated as change in IMT divided by baseline IMT  $\times 100$ . Unadjusted associations between potential predictors, confounders, and IMT were estimated with linear regression models and ordinal regression models considering the precision limit of IMT measures. Dummy-coding (divided at quartiles) for nonnormally distributed explanatory variables was used because of not-defined logarithms among negative difference values. Backward multivariate linear and ordinal logistic regression models were used to assess adjusted effects of potential predictors on IMT in the entire study group. All variables were considered for final models. Outliers (data points that do not seem to follow the characteristic distribution of the rest of the data) were excluded from the analysis to minimize the impact of measurement errors or other anomalies. For each individual outcome measurement, we tested whether its exclusion changed the standard deviation of the outcome variable by  $>10\%$ . Any observation fulfilling this criterion was excluded as an outlier. Regression diagnostics also included examination of residuals, nonconstant error of variance (heteroscedasticity), and nonlinearity. Multicollinearity of respective covariates was identified by a variance inflation factor

$>10$ .<sup>32</sup> A *P* value of  $<.05$  was considered statistically significant. All calculations were conducted with Winstat for Excel (Fitch Software, Bad Krozingen, Germany), the statistical software package SAS 9.1.3 (SAS Institute, Inc, Cary, NC), and R 2.2.1 (available at [www.r-project.org](http://www.r-project.org)).

The local ethics committee of the University of Witten/Herdecke approved this study. Informed consent was obtained from all subjects and their parents.

### RESULTS

Seven (11%) of the 63 participants in the intervention program dropped out and were excluded from the study. They did not differ from the children completing the intervention program in respect to age, gender, degree of overweight (SDS-BMI), cardiovascular risk factor profile, and IMT values at baseline. The 56 obese children completing the intervention program and their parents participated regularly at all sessions.

The obese children demonstrated significantly increased carotid IMT, lower HDL cholesterol levels, higher triglyceride concentrations, higher insulin values and insulin resistance index (HOMA), and higher systolic and DBP compared with the nonobese children (see Table 1). The obese children did not significantly differ from the normal weight children in age or gender.

Twenty-four obese children reduced their degree of overweight substantially. In these children, IMT (mean change:  $-0.10$  mm), SBP (mean change:  $-7$  mm Hg), DBP (mean change:  $-8$  mm Hg), insulin (mean change:  $-7$  mU/L), insulin resistance index (mean HOMA change:  $-1.6$ ), and triglyceride concentrations (mean change:  $-19$  mg/dL) decreased significantly, whereas HDL cholesterol levels (mean change:  $+4$  mg/dL) increased significantly (see Table 2). The mean relative decrease of IMT was 11% (95% confidence interval [CI]: 7%–15%). Eight (33%) children with substantial weight loss entered into puberty during the study period.

In the 32 obese children without substantial weight loss, there were no significant changes in IMT (mean change: 0 mm), SBP (mean change:  $+1$  mm Hg), DBP (mean change:  $+2$  mm Hg), triglycerides (mean change:  $+7$  mg/dL), and HDL cholesterol concentrations (mean change:  $+2$  mg/dL), whereas insulin (mean change:  $+3$  mU/L) and insulin resistance index (mean change of HOMA:  $+0.8$ ) increased significantly (see Table 2). Eleven (34%) children without substantial weight loss entered into puberty during the study period.

The 24 obese children with substantial weight loss did not differ significantly from the 32 children without substantial weight loss in respect to age ( $P = .379$ ), gender ( $P = .936$ ), degree of overweight (SDS-BMI,  $P = .654$ ), IMT ( $P = .120$ ), SBP ( $P = .087$ ), DBP ( $P = .874$ ), glucose ( $P = .229$ ), insulin ( $P = .336$ ), insulin resistance index (HOMA,  $P = .371$ ), or lipids (triglycerides,  $P = .569$ ; HDL cholesterol,  $P = .496$ ) at baseline.

Univariate linear regression analysis showed that the

**TABLE 1 Clinical Characteristics, Lipids, Glucose, Insulin, Insulin Resistance Index, and IMT of Obese and Nonobese Children**

	Obese	Nonobese	P
Number	56	10	
Age, mean (95% CI), y	8.7 (8.3–9.1)	8.9 (8.1–9.6)	.701 <sup>a</sup>
Gender, % male	34	30	.810 <sup>b</sup>
Weight, mean (95% CI), kg	50.0 (46.9–53.1)	34.7 (30.7–38.7)	<.001 <sup>a</sup>
BMI, mean (95% CI), kg	24.8 (24.1–25.5)	18.2 (17.6–19.0)	<.001 <sup>a</sup>
SDS-BMI, mean (95% CI)	2.4 (2.3–2.5)	0.7 (0.5–0.9)	<.001 <sup>a</sup>
HDL cholesterol, mean (95% CI), mg/dL	46 (43–49)	59 (47–71)	.033 <sup>a</sup>
Triglycerides, mean (95% CI), mg/dL	117 (103–131)	84 (61–107)	.015 <sup>a</sup>
SBP, mean (95% CI), mm Hg	113 (110–116)	102 (96–108)	.015 <sup>a</sup>
DPB, mean (95% CI), mm Hg	60 (58–62)	53 (48–58)	.020 <sup>a</sup>
Glucose, mean (95% CI), mg/dL	86 (84–92)	87 (84–90)	.376 <sup>a</sup>
Insulin, mean (95% CI), mU/L	14 (10–17)	7 (5–9)	.011 <sup>c</sup>
Insulin resistance index (HOMA), mean (95% CI)	3.0 (2.3–2.3)	1.6 (1.0–2.2)	.015 <sup>c</sup>
IMT, mean (95% CI), mm	0.60 (0.58–0.62)	0.47 (0.42–0.55)	<.001 <sup>c</sup>

<sup>a</sup> *t* test.

<sup>b</sup>  $\chi^2$  test.

<sup>c</sup> Mann-Whitney *U* test.

**TABLE 2 Changes of Weight Status, IMT, Lipids, Glucose, Insulin, and Insulin Resistance Index in Obese Children With and Without Substantial Weight Loss**

	Substantial Weight Loss <sup>a</sup>			No Substantial Weight Loss <sup>b</sup>			
	Baseline	1 y Later	P <sup>c</sup>	Baseline	1 y Later	P <sup>c</sup>	P <sup>d</sup>
BMI, kg/m <sup>2</sup>	24.6 (23.5–25.7)	22.4 (21.4–23.4)	<.001 <sup>e</sup>	24.9 (24.1–25.8)	25.4 (24.5–26.3)	.084 <sup>e</sup>	<.001 <sup>f</sup>
SDS-BMI	2.4 (2.2–2.6)	1.7 (1.5–1.9)	<.001 <sup>e</sup>	2.3 (2.1–2.5)	2.2 (2.0–2.4)	.006 <sup>e</sup>	<.001 <sup>f</sup>
HDL cholesterol, mg/dL	46 (42–50)	50 (46–54)	.048 <sup>e</sup>	46 (42–50)	48 (44–52)	.145 <sup>e</sup>	.783 <sup>f</sup>
Triglycerides, mg/dL	111 (92–130)	92 (78–107)	.049 <sup>e</sup>	120 (100–140)	125 (102–148)	.592 <sup>e</sup>	.030 <sup>f</sup>
SBP, mm Hg	116 (111–121)	108 (104–112)	.006 <sup>e</sup>	110 (106–124)	111 (107–115)	.747 <sup>e</sup>	.463 <sup>f</sup>
DBP, mm Hg	62 (58–66)	55 (52–58)	.036 <sup>e</sup>	60 (57–63)	62 (59–65)	.451 <sup>e</sup>	.005 <sup>f</sup>
Glucose, mg/dL	87 (83–91)	85 (83–87)	.347 <sup>e</sup>	85 (83–87)	84 (82–86)	.121 <sup>g</sup>	.279 <sup>f</sup>
Insulin, mU/L	16 (10–22)	8 (5–11)	.021 <sup>g</sup>	13 (10–16)	17 (14–20)	.016 <sup>e</sup>	<.001 <sup>h</sup>
Insulin resistance index (HOMA)	3.5 (1.9–5.1)	1.9 (1.3–2.5)	.040 <sup>g</sup>	2.8 (2.3–3.3)	3.5 (2.9–4.1)	.041 <sup>e</sup>	<.001 <sup>h</sup>
IMT, mm	0.62 (0.58–0.68)	0.55 (0.51–0.59)	<.001 <sup>g</sup>	0.59 (0.56–0.62)	0.62 (0.59–0.63)	.072 <sup>g</sup>	.006 <sup>h</sup>

Data shown are mean (95% CI).

<sup>a</sup> *n* = 24, age 8.6 (8–9.2), 33% male.

<sup>b</sup> *n* = 32, age 8.7 (8.2–9.2), 34% male.

<sup>c</sup> Baseline compared with 1 year later.

<sup>d</sup> Comparison of subgroups at end of intervention.

<sup>e</sup> *t* test for paired observation.

<sup>f</sup> *t* test for unpaired observation.

<sup>g</sup> Wilcoxon test.

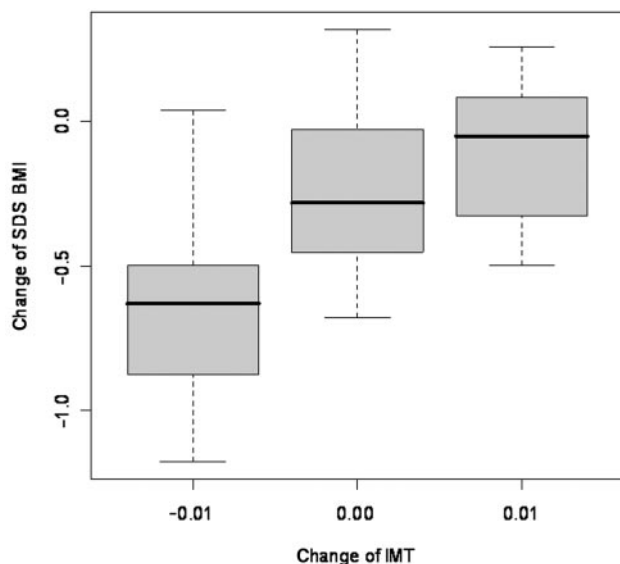
<sup>h</sup> Mann-Whitney *U* test.

changes of IMT in the 56 obese children were significantly associated with changes of weight status (SDS-BMI,  $P < .001$ ; see Fig 1) and DBP ( $P = .045$ ), whereas changes of SBP, HDL cholesterol, glucose, triglycerides, insulin, and insulin resistance index (HOMA) were not significantly associated with changes of IMT. Multicollinearity was assumed for insulin and insulin resistance index (HOMA) because of variance inflation factors  $>100$ . Therefore, only the insulin resistance index (HOMA) was considered in the final regression model. Changes of IMT were significantly related to changes of SDS-BMI (coefficient: 0.15 mm; 95% CI: 0.09–0.21;  $P < .001$ ;  $r^2 = 0.45$ ) but not to changes of SBP and DPB, HDL cholesterol, glucose, triglycerides, and insulin resistance index (HOMA) in the final multivariate model. A com-

parison between the crude estimate of change of SDS-BMI for change of IMT and the estimate adjusted for systolic and DBP showed a change in estimate of  $-4.7\%$  for change of SDS-BMI and IMT. All results could also be observed by ordinal logit regression models.

## DISCUSSION

Our study demonstrated the relationships between changes of IMT and changes of weight status, as well as the changes of the cardiovascular risk factors hypertension, dyslipidemia, and impaired glucose metabolism in obese children losing weight. IMT and cardiovascular risk factors were significantly increased in obese children compared with nonobese children of similar age in agreement with most other studies in childhood,<sup>13,33–38</sup>



**FIGURE 1**  
Changes of weight status (SDS-BMI) in relation to changes of IMT (change of variable defined by variable at end of the 1-year intervention variable at baseline) in the course of 1 year in 56 obese children participating in a 1-year intervention program ( $P < .001$  derived from linear and ordinal logit regression).

allowing us to analyze the impact of weight loss on these factors. These findings also emphasize the early age at which arterial abnormalities can be demonstrated in obese children.

Reduction of body weight in our obese children because of a fat-reduced diet and an increase in physical activity resulted in an improvement of the atherogenic risk-factor profile, as shown in previous studies.<sup>16,17,30,39,40</sup> Substantial weight loss was also associated with a decrease in IMT demonstrating the reversibility of this early atherogenic vascular damage. This observation suggests a link between cardiovascular risk factors and carotid IMT as previously described in cross-sectional analyses of obese children.<sup>13,14</sup> Accordingly, studies in adults reported a regression of IMT in intervention studies with lipid-lowering therapy.<sup>41,42</sup> Conversely, the changes of lipids, blood pressure, and insulin resistance were not related to changes of IMT in our study if the correlation was adjusted for changes in weight status. These findings suggest that weight loss is the main determinant of changes in IMT.

Our finding of decreased IMT in substantial weight loss is in concordance with the majority of the few existing studies concerning IMT in weight loss,<sup>19,20,22</sup> whereas only 1 study reported no change of IMT in weight loss.<sup>21</sup> This difference may be caused by a smaller degree of weight loss, failure to have sustained the achieved weight loss, or different analyses of IMT measurements. A temporary weight reduction over weeks was not associated with a decrease of IMT in contrast with weight loss over months.<sup>19</sup> In previous studies, we demonstrated that the achieved weight loss and the improvement of cardiovascular risk factors were sustained over years after the end of obesity

intervention.<sup>30,31</sup> Many studies, including the study showing that weight loss was not associated with a decrease in IMT,<sup>21</sup> have used the mean value of the measurements of IMT. The strongest association between the different measurements of IMT and coronary risk factors in otherwise healthy individuals is achieved by applying the maximum and not the mean value of IMT.<sup>28</sup> This confirms the findings that atherosclerosis is not equally distributed in all the blood vessels, but that the extent of the thickening of the arterial wall differs in the various regions.

In contrast to a study in adults,<sup>20</sup> IMT did not increase significantly but demonstrated a tendency of progression in obese children without substantial weight loss. The smaller number of our obese patients and the shorter period of observation might explain this difference, and the increased physical activity in the children without substantial weight loss probably prevented, in part, the reported annual progression of IMT in obese subjects.<sup>20</sup>

This study has a few potential limitations. First, BMI percentiles were used to classify overweight. Although BMI is a good measure for overweight, one needs to be aware of its limitations as an indirect measurement of adiposity. Second, the HOMA model is only an assessment of insulin resistance; insulin-clamp studies are the gold standard to analyze insulin resistance. Because the HOMA model correlates to clamp studies, it is a good method to study insulin resistance in field studies.<sup>43</sup> Third, IMT measurements were performed in our study by 1 investigator. Therefore, the reproducibility of IMT measurements by multiple investigators has to be studied for clinical applicability. Fourth, the multiple regression analysis explained only 45% of the variance in changes of IMT, suggesting that besides changes of weight status and cardiovascular risk factors other variables are involved in determining IMT. For instance, physical activity and the way of dieting may influence IMT independently of weight status. This has to be analyzed in additional studies. Finally, although most reports presume that IMT is related to an initial atherosclerotic process,<sup>10,12,28</sup> an increased IMT was also discussed to reflect a nonatherosclerotic adaptive response to changes in shear stress and tensile stress.<sup>44</sup> Furthermore, the ultrasound measurement of IMT does not allow to differentiate between IMT attributable to an atherosclerotic process or medial hypertrophy (smooth muscle growth) caused by the hemodynamic stimulation of a progressive increase in SBP, pulse pressure, or arterial diameter over time.<sup>45</sup> However, moderate hypertension in obese children seems to have little effect on IMT, because a comparison between the crude estimate of change of SDS-BMI for change of IMT and the estimate adjusted for blood pressure showed a decrease in estimate of only 4.7% for change of SDS-BMI and IMT.

## CONCLUSIONS

Obese children demonstrated a significantly increased IMT compared with a healthy-weight control group. Substantial weight loss because of an obesity intervention program led to decrease of IMT, which demonstrated the reversibility of the early atherogenic changes. Therefore, intervention in obese children may prevent cardiovascular diseases in later life. Additional prospective research in obese children with weight loss is necessary to study the long-term effect on cardiovascular diseases.

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#### WHEN YOUNG PEOPLE USE, PARENTS SELDOM KNOW

“Parents consistently and substantially underestimate their children’s use of alcohol and other drugs, a new study has found. Researchers interviewed 591 adolescents ages 12 to 17 about their drug and alcohol use and then questioned at least one parent of each about what he or she thought the children were using. The analysis appears in the October issue of *Alcoholism: Clinical and Experimental Research*. Parents consistently said they believed that their children were using substances less frequently than the children reported. Alcohol use was most common, with 54.4 percent of the teenagers reporting having consumed at least one drink in their lifetimes, and 23.6 percent saying they had been intoxicated. But only 20.5 percent of parents believed that their children had ever had a drink, and only 8.1 percent said their children had ever been drunk. While 44 percent of the adolescents reported smoking cigarettes, only 27 percent of their parents knew they smoked.”

**Bakalar N. *Wall Street Journal*. October 2, 2006**

Noted by JFL, MD

**Intima-Media Thickness in Obese Children Before and After Weight Loss**  
Rainer Wunsch, Gideon de Sousa, André Michael Toschke and Thomas Reinehr  
*Pediatrics* 2006;118;2334-2340  
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