ORIGINAL ARTICLES

Proatherogenic Lipid Profile in Early Childhood: Association with Weight Status at 4 Years and Parental Obesity

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Objectives To determine lipid profiles in early childhood and evaluate their association with weight status at 4 years of age. Additionally, we evaluated whether the risk of overweight or having an altered lipid profile was associated with parental weight status.

Study design Five hundred eighty two mothers and their 4-year-old children from 2 Spanish population-based cohorts were studied. Weight status in children at 4 years of age was classified as overweight or obese using the International Obesity Task Force criteria. Plasma total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were determined in children and lipid ratios were calculated. A proatherogenic lipid profile was defined as having the 3 lipid ratios in the third tertile.

Results A total of 12.9% of children were overweight and 6.4% were obese. Weight status at 4 years of age was related to maternal prepregnancy body mass index, paternal body mass index, gestational diabetes, and birth weight, but not with other sociodemographic characteristics of the mother. We found no association with gestational age, sex of the child, or breastfeeding. The risk of overweight/obesity was increased 4.17-fold if mothers were overweight/obese (95% CI 1.76-9.88) and 5.1-fold (95% CI 2.50-10.40) if both parents were overweight/obese. There were 133 children (22.8%) with a proatherogenic lipid profile. The risk of a proatherogenic lipid profile was increased 2.44-fold (95% CI 1.54-3.86) if they were overweight/obese at 4 years of age and 2-fold if the father was overweight/obese (95% CI 1.22-3.35).

Conclusions Four-year-old overweight/obese children have higher lipid risk profiles. Offspring of overweight/obese parents have an increased risk for obesity and a proatherogenic lipid profile. *(J Pediatr 2017;187:153-7).*

The prevalence of overweight and obesity in children is a well-recognized public health problem in Europe,[1] as well as in other developed countries.[2] Obesity persists from childhood to adolescence and into adulthood, and is a leading cause of health problems.[3]

Identification of children at risk for early atherosclerosis is essential because predisposing cardiovascular disease (CVD) risk factors cluster in childhood and persist into adulthood.[4-6] Even though atherogenesis is a multifactorial process, abnormalities in lipoprotein metabolism represented approximately 50% of the population-attributable risk of developing CVD.[7] The best predictor of lipid or lipoprotein levels in adulthood is the level observed in childhood,[6] although the cutoff for defining dyslipidemia in children remains controversial.[8] Several lipoprotein ratios or "atherogenic indices" have been defined in an attempt to optimize the predictive capacity of the lipid profile.[9] The total/high-density lipoprotein (HDL) cholesterol ratio and the low-density lipoprotein/HDL cholesterol ratio are 2 important indicators of vascular risk, with a predictive value greater than the single variables.[10] Furthermore, the association between triglycerides (TG) and HDL cholesterol in late adolescence predicts a proatherogenic lipid profile in adulthood, independent of obesity and weight gain.[11] Associations with insulin resistance have been found in obese children.[12] A high TG/HDL ratio is associated with an unfavorable cardiometabolic profile in a population aged 6 to 16 years.[13] To date, the clinical value of lipid ratios has not been evaluated in younger children.

This study aimed to determine lipid profiles in early childhood and to evaluate their association with weight status at 4 years of age. We also evaluated whether the risk of being overweight/obese or having an altered lipid profile at the age of 4 years was associated with maternal and/or paternal overweight/obesity.

BMI	Body mass index
CVD	Cardiovascular disease
GWG	Gestational weight gain
HDL	High-density lipoprotein
TG	Triglycerides
WHO	World Health Organization

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Methods

This population-based birth cohort study (Infancia y Medio Ambiente [Environment and Childhood Project]) recruited pregnant women during the first trimester of pregnancy from 7 Spanish areas between 2003 and 2008, and followed a common protocol.[14] Inclusion criteria were as follows: age >16 years, singleton pregnancy, no assisted conception, intention to deliver at the reference hospital, and no communication handicap. The population considered in the present study consisted of mothers who agreed to participate in the Infancia y Medio Ambiente cohorts of Asturias and Sabadell, and their children who had lipid data available. A total of 1151 eligible women (494 from Asturias and 657 from Sabadell) agreed to participate. A total of 1044 children (453 from Asturias and 591 from Sabadell) of these women were followed up to 4 years of age. Finally, 582 children (266 from Asturias and 316 from Sabadell) had lipid data available and were included in this study.

The study was approved by the local ethics committee, and all participants signed the informed consent.

Maternal height was measured and prepregnancy weight reported by the mother at the first trimester visit. These values were used to calculate prepregnancy body mass index (BMI) (in kg/m^2). Reported prepregnancy weight was highly correlated with measured weight at 12 weeks of pregnancy ($r^2 = 0.96$; $P < .0001$).[15] Paternal weight and height were reported by the mother at the first trimester visit and used to calculate paternal BMI. Maternal and paternal BMI were grouped according to the World Health Organization (WHO) categories for underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30 kg/m^2).

Height and weight of children were measured by staff trained in anthropometry. Height was measured twice to the nearest 0.1 cm using a wall-mounted stadiometer after the participant removed their shoes. Weight was measured twice to the nearest 0.1 kg using a digital scale with the participant wearing only light clothes. Overweight/obesity in children were defined using the International Obesity Task Force criteria that enable global comparison of prevalence.[16]

Nonfasting blood samples were collected from children in both cohorts. Serum total cholesterol, TG, and HDL levels were determined using a Roche analyzer (Modular Analytics Serum Work Area, Mannheim, Germany) in Asturias. Plasma total cholesterol, TG, and HDL levels were determined using the ABX-Pentra 400 (HORIBA ABX SAS, Madrid, Spain) in samples from Sabadell. Low-density lipoprotein levels were calculated using the Friedewald formula.[17] Concentrations of all these cardiometabolic biomarkers were homogeneous across cohorts.

Lipid ratios (TG/HDL cholesterol, low-density lipoprotein cholesterol /HDL, and total/HDL cholesterol) were calculated. The variable TG/HDL ratio was not normally distributed and thus underwent a natural logarithmic (ln) transformation. They were also stratified into tertiles to further evaluate their relationship with other variables. A proatherogenic profile was defined as having the 3 lipid ratios in the third tertile of our population.

Questionnaires were administered during the first and third trimesters of pregnancy. We obtained information on maternal and paternal age and education, maternal and paternal occupations, maternal country of birth, maternal smoking during pregnancy, and parity. Social class was defined according to occupation during pregnancy of the mother or the father using a widely used Spanish adaptation of the International Standard Classification of Occupations coding system.[18] Gestational weight gain (GWG) was calculated as the difference between the first prepregnant weight and the last weight measurement before delivery. GWG was classified as low, recommended, and high based on the US Institute of Medicine guidelines.[19] Information on gestational diabetes and on children's birth weight, gestational age, and sex was obtained from clinical records. Data on breastfeeding duration were collected when infants were approximately 6 and 14 months. All questionnaires were conducted face to face by trained interviewers.

Statistical Analyses

Differences between BMI categories were examined by the χ^2 test for categorical variables, and the Student *t* test or ANOVA for continuous variables.

For multivariable analysis, we used logistic regression models to evaluate the risk of the proatherogenic profile on being overweight/obese, initially adjusting for education, mother's BMI, father's BMI, birth weight, weeks of gestation, sex, and predominant breastfeeding. We then used a stepwise procedure under the forward method and variables with a significance of $P < .1$ were maintained in the model according to the likelihood ratio test. We further analyzed the risk of either overweight/obesity and the proatherogenic profile by having overweight/obese parents using the same procedure. Sensitivity analyses using the WHO classification for overweight and obesity in children were performed to assess the robustness of our results. Statistical analyses were conducted using SPSS for Windows, Version 15.0 (SPSS Inc, Chicago, Illinois).

Results

Overall, 12.9% of the 4-year-old children were classified as overweight and 6.4% as obese according to the International Obesity Task Force. The highest prevalence of overweight and obesity was observed in children from Asturias (14.3% and 9.4%, respectively), whereas this prevalence in children from Sabadell was lower (11.7% and 3.8%, respectively). Using the WHO classification, the overall prevalence of overweight was 13.8% and obesity was 14.2%.

Table I (available at www.jpeds.com) shows anthropometric variables, sociodemographic characteristics, and other factors related to gestation and breastfeeding from the 582 mothers in relation to the weight status of their offspring, as well as data of the father's BMI. A total of 20.9% of mothers were overweight and 9.6% were obese, whereas 45.5% of fathers were overweight and 13.9% were obese. A total of 39% of women gained more than the recommended weight during pregnancy (32%, normal weight; 60%, overweight; 44%, obese).

Table II. Risk of overweight or obesity in 4-year-old children according with the parental weight status

	Child's BMI at 4 years of age										
	Normal weight		Overweight/obesity								
Parents' BMIs	n	%	n	%	P (χ^2)	OR (crude)	95% CI		OR (adjusted)*	95% CI	
Both normal weight	164	35.7	12	11.1	**<.001**	1.00					
Father overweight or obese	169	36.8	47	43.5		**3.80**	**1.95**	**7.42**	**3.73**	**1.90**	**7.34**
Mother overweight or obese	41	8.9	13	12.0		**4.33**	**1.84**	**10.20**	**4.17**	**1.76**	**9.88**
Both overweight or obese	85	18.5	36	33.3		**5.79**	**2.86**	**11.70**	**5.10**	**2.50**	**10.40**

Bold values indicate statistically significant results.
*Adjusted by birth weight and cohort.

Predominant breastfeeding lasted a mean of 12 weeks in these children and 25% received artificial feeding from the first week of life. Less than 11% of the total had predominant breastfeeding for longer than 24 weeks.

The risk of overweight/obesity at 4 years of age according to parental weight status is shown in **Table II**. The risk of overweight/obesity in 4-year-old children was increased 4.17-fold if their mothers were overweight/obese (95% CI 1.76-9.88) and 5.1-fold (95% CI 2.50-10.40) if both parents were overweight/obese. Sensitivity analysis using the WHO classification showed that results were similar and statistically significant, albeit to a lesser degree (data not shown).

Descriptive data of the lipid profile, as well as lipid ratios, are shown in **Table III** (available at www.jpeds.com). The **Figure** (available at www.jpeds.com) shows a positive correlation between the lipid profile and weight status at 4 years of age, with an unfavorable lipid profile in children who are overweight/obese. We found a positive relationship between increased lipid ratios and increased BMI. These lipid ratios distributed by tertiles were also positively associated with BMI category in children (**Table IV**). Obese 4-year-old children had a mean ln(TG-to-HDL) ratio of 0.53. A total of 133 4-year-old children (22.8%) had the 3 calculated lipid ratios in the third tertile of our population.

The risk of having a proatherogenic profile in 4-year-old children is shown in **Table V** according to their own and their parent's weight status. There were 19.7% of normal weight children vs 36% of overweight/obese 4-year-old children who had a proatherogenic profile at 4 years of age. The risk of having a proatherogenic profile in 4-year-old children was increased 2.44-fold (95% CI 1.54-3.86) if they were overweight/obese. This risk is increased 2.01-fold (95% CI 1.14-3.55) if both parents were overweight/obese.

Discussion

The prevalence of overweight/obesity in 4-year-old children in our cohort is high for this age compared with European children.[1] Estimates based on International Obesity Task Force definitions are substantially lower than those based on WHO definitions.[20] Based on tracking in body weight from childhood to adults and their health sequelae, this represents a public health concern.[3,4] Similar to other studies on children in primary school,[1] we did not find differences by sex of the child.

No association with social class was found in our study. The impact of social position on the risk of obesity in developed countries has been clearly demonstrated in adults[21]; data for children are less consistent, but nonetheless suggestive.[22]

Our study showed that the prevalence of overweight/obesity was high in mothers, and even higher in fathers. Nevertheless, only 10% of women in our cohort were obese, which is a lower prevalence than that in the US and the UK.[2,5]

Our results are consistent with previous studies,[23,24] which reported that maternal BMI was associated positively with weight status of the offspring. The burden of prepregnancy overweight/obesity and GWG is not understood completely. Excessive GWG is associated with an increased risk of overweight/obesity in offspring at 12 months of age.[25] Nevertheless, Xie et al[24] have found childhood growth trajectories of infants born large for gestational age to differ by etiologic subgroup. The subgroup with co-occurrence of maternal overweight/obesity and diabetes

Table IV. Lipid ratios distributed by tertiles according to weight status at 4-year-old children*

			Child's BMI at 4 years of age		
		Total	Normal weight	Overweight/obese	P value (χ^2)
ln(TG-to-HDL ratio)					
<−0.04	n	133	113	20	**.012**
	%	22.85	23.99	18.02	
≥−0.04 and <0.42	n	212	180	32	
	%	36.43	38.22	28.83	
≥0.42	n	237	178	59	
	%	40.72	37.79	53.15	
LDL-to-HDL ratio					
<1.44	n	144	126	18	**.011**
	%	24.74	26.75	16.22	
≥1.44 and <2.00	n	230	189	41	
	%	39.52	40.13	36.94	
≥2.00	n	208	156	52	
	%	35.74	33.12	46.85	
Total-to-HDL ratio					
<2.80	n	181	157	24	**.008**
	%	31.10	33.33	21.62	
≥2.80 and <3.30	n	193	159	34	
	%	33.16	33.76	30.63	
≥3.30	n	208	155	53	
	%	35.74	32.91	47.75	

LDL-to-HDL ratio, low-density lipoprotein/HDL cholesterol ratio; *ln(TG-to-HDL) ratio*, logarithmic TG/HDL cholesterol ratio; *Total-to-HDL ratio*, total/HDL cholesterol ratio.
Bold values indicate statistically significant results.
*Total n = 582; 471 normal weight and 111 overweight/obese.

Table V. Risk of proatherogenic lipid profile in 4-year-old children according to their own and their parents' weight status

	Child's lipid profile at 4 years of age										
	Normal		Atherogenic								
	n	%	n	%	*P*-value (χ^2)	OR crude	95% CI		OR adj*	95% CI	
Child BMI											
Normal weight	378	80.25	93	19.75	<.001	1.00					
Overweight or obese	71	63.96	40	36.04		**2.29**	**1.46**	**3.59**	**2.44**	**1.54**	**3.86**
Parents' BMI											
Both normal weight	147	83.52	29	16.48	.065	1.00					
Father overweight/obese	158	73.15	58	26.85		**1.86**	**1.13**	**3.07**	**2.02**	**1.22**	**3.35**
Mother overweight/obese	42	77.78	12	22.22		1.45	0.68	3.08	1.42	0.68	3.03
Both overweight/obese	88	72.73	33	27.27		**1.90**	**1.08**	**3.34**	**2.01**	**1.14**	**3.55**

Proatherogenic lipid profile was considered when having the 3 lipid ratios in the third tertile of our population.
Bold values indicate statistically significant results.
*Adjusted by cohort.

had the highest BMIs at 4 years of age, whereas the subgroup free of maternal overweight/obesity, diabetes, or excessive GWG were tall but lean ("a healthy phenotype"). de Zegher et al[26] confirmed that long, heavy newborns with increased fat mass from mothers without diabetes mellitus and without excessive GWG tend to become tall and lean toddlers. That finding means that it is necessary to examine all of these factors to better predict childhood growth and obesity risk.

In our cohort, the risk of overweight/obesity at 4 years of age was increased 4.17-fold if children's mothers were overweight/obese, higher than that reported by Whitaker.[27] In our children, that risk was increased even more if both parents were overweight/obese. We assumed that the mother and father contribute to the shared lifestyle between parents and offspring to a comparable extent. However, the role of both parents in contributing to the child's diet, feeding habits, or level of exercise may require further evaluation. Furthermore, epigenetic mechanisms could be involved, which could explain the greater effect of mothers.

Overall, we found a proatherogenic lipid profile in 4-year-old children that was related to weight status. Few prospective studies have analyzed abnormalities of the lipid profile from childhood to adulthood. We used a combined lipid ratio because it may best reflect the overall interaction between lipid/lipoprotein fractions and therefore associations with insulin resistance.[12] In adults, lipoproteins ratios are recognized as being more useful than isolated lipid values for CVD risk assessment because they better reflect the interactions between lipid fractions.[28] The TG-to-HDL ratio could be a useful index in identifying children at risk for dyslipidemia, hypertension, and the metabolic syndrome.[12] Bailey et al[29] support the use of the TG/HDL ratio to identify children with cardiometabolic risk factors who may be at risk of developing cardiometabolic disease. Furthermore, Di Bonito et al[13] found that a high TG-to-HDL ratio was associated with an unfavorable cardiometabolic profile in a population aged 6 to 16 years.

Our obese 4-year-old children had a mean ln(TG-to-HDL) ratio of 0.53. An atherogenic plasma index of less than 0.5 has been proposed as the cutoff point in adults indicating atherogenic risk.[30] Musso et al[31] demonstrated that this lipid ratio was positively correlated with BMI and waist circumference in high school adolescents. Urbina et al[32] found stiffer vessels in youths (aged 10-26 years) with a higher cardiovascular risk factor-adjusted TG-to-HDL, especially in obese subjects. They consider that TG-to-HDL ratio is an independent determinant of arterial stiffness in children, adolescents, and young adults. A high TG/HDL ratio may be useful in clinical practice to detect children with an unfavorable cardiometabolic profile who need early intervention to promote healthier lifestyles and to prevent CVD in adulthood.

Similar to Urbina et al,[32] we stratified the lipid ratios by tertiles, and we defined a proatherogenic profile when having the 3 lipid ratios in the third tertile of our population. In our overweight/obese children, the risk of a proatherogenic profile after adjusting for the cohort was increased by 2.44-fold. This finding suggests that these children will have abnormal lipid levels earlier and may have associated atherosclerotic changes at a younger age. It is increasingly recognized that atherosclerosis begins early in life in association with dyslipidemia and obesity and both cluster in childhood and track into adulthood.[5-8] Weiss et al[11] showed that adolescents with an elevated TG/HDL ratio are prone to express a proatherogenic lipid profile in adulthood in a longitudinal study of adolescents 16 to 17 years of age who were reevaluated 13 years later. The most appropriate cutoffs and methods should be established to improve the quality and comparability of studies.

This study has some limitations. First, BMI is not the ideal measure of adiposity because it is not an indicator of fat mass and fat-free mass. Nevertheless, BMI is highly correlated with other measures of adiposity, and it is a robust measure that is used widely in population-based studies. BMI facilitates assessment of temporal trends and allows for comparisons with other studies on a population level. Another limitation is that blood samples were not collected after 12 hours of fasting. Calculating lipid ratios can minimize this concern.[32] Recent studies have shown that lipid profiles only minimally change in response to normal food intake in individuals in the general population. Furthermore, nonfasting lipid profiles predict an increased risk of cardiovascular events.[33]

Our findings highlight the urgent need for strategies for preventing obesity in women of childbearing age and to assess the offspring of obese parents for their cardiovascular risk. Preconceptionally, overweight women should receive individual counseling to improve diet quality, increase physical activity, and normalize weight. During pregnancy, all women should be encouraged to gain weight as recommended. Identifying children at risk for obesity provides pediatricians with an opportunity for earlier individualized intervention with the goal of limiting progression of the proatherogenic lipid profile, which results in development of obesity-related morbidity. ■

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Table I. Sociodemographic characteristics, parents' anthropometric variables, and other factors related to gestation and breastfeeding according to the weight status of the offspring at 4 years of age

	Child's BMI at 4 years of age						
	Total		Normal weight		Overweight/obese		
	n	%	n	%	n	%	*P* value*
Country of origin							
Spain	536	92.73	435	93.15	101	90.91	.184
Latin America	29	5.02	22	4.71	7	6.36	
Other European countries	12	2.08	10	2.14	2	1.82	
Other	1	0.17	0	0.00	1	0.91	
Mother age (y)							
Mean (SD)	581	31.19 (4.34)	469	31.14 (4.34)	112	31.00 (4.00)	.764
Parity							
Primiparous	328	56.55	260	55.56	68	61.26	.266
Multiparous	252	43.45	208	44.44	44	38.74	
Education							
Primary	123	21.24	92	19.70	31	27.03	.207
Secondary	257	44.39	214	45.82	43	38.74	
University	199	34.37	161	34.48	38	34.23	
Social class							
I + II	131	22.55	109	23.24	22	19.82	.746
III	151	25.99	121	25.80	30	27.03	
IV + V	299	51.46	239	50.96	60	53.15	
Smoked in pregnancy							
No	488	85.76	399	86.55	89	82.24	.247
Yes	81	14.24	62	13.45	19	17.76	
Mother height (cm), mean (SD)	582	162.18 (5.71)	470	162.09 (5.56)	112	162.00 (6.00)	.514
Mother BMI, mean (SD)	582	23.96 (4.50)	470	23.46 (4.10)	112	26.08 (5.42)	**<.001**
Mother BMI (kg/m^2)							
<18.5	26	4.47	26	5.53	0	0.00	**<.001**
18.5-25	378	64.95	315	67.02	63	55.86	
25-30	122	20.96	98	20.85	24	21.62	
>30	56	9.62	31	6.60	25	22.52	
Total weight gain (kg), mean (SD)	567	13.73 (5.09)	458	13.72 (4.77)	109	13.74 (6.27)	.970
Total weight gain (kg), IOM							
Recommended	220	38.80	183	39.96	37	33.94	.082
Low	124	21.87	105	22.93	19	17.43	
High	223	39.33	170	37.12	53	48.62	
Father BMI, mean (SD)	567	26.30 (3.62)	458	26.01 (3.40)	109	27.52 (4.26)	**<.001**
Father BMI (kg/m^2)							
<18.5	3	0.53	2	0.44	1	0.93	**<.001**
18.5-25	227	40.04	203	44.32	24	22.22	
25-30	258	45.50	199	43.45	59	53.70	
>30	79	13.93	54	11.79	25	23.15	
Sex of the child							
Female	284	48.80	230	48.94	54	48.65	.972
Male	298	51.20	240	51.06	58	51.35	
Gestational diabetes							
None or low risk	498	96.89	406	98.07	92	92.00	**.005**
Mellitus diabetes	15	2.92	8	1.93	7	7.00	
Before pregnancy	1	0.19	0	0.00	1	1.00	
Week of gestation at delivery, mean (SD)	573	39.63 (1.49)	462	39.68 (1.48)	111	39.47 (1.49)	.201
Birthweight (g), mean (SD)	577	3271.3 (441.1)	465	3244.7 (442.6)	112	3383.5 (420.3)	**.003**
Predominant breastfeeding (wk), mean (SD)	549	12.23 (9.73)	447	12.18 (9.74)	102	12.44 (9.77)	.810
Predominant breastfeeding (wk)							
0	136	24.77	113	25.28	23	22.55	.817
>0-16	156	28.42	124	27.74	32	31.37	
>16-24	199	36.25	164	36.69	35	34.31	
>24	58	10.56	46	10.29	12	11.76	

IOM, Institute of Medicine.
Bold values indicate statistically significant results.
*χ^2 or *t*-test.

Table III. Lipid profile and lipid ratios descriptives in the 4-year-old children

	n	%	Mean	SD	Mínimum	P25	Median	P75	Máximum
Total cholesterol (mg/dL)	582	100.0	165.24	26.70	87.00	147.00	164.00	180.00	318.00
HDL (mg/dL)	582	100.0	53.78	11.81	15.50	46.00	53.50	61.00	102.00
LDL (mg/dL)	582	100.0	95.18	23.05	37.00	79.50	94.15	107.90	261.00
TG (mg/dL)	582	100.0	81.49	41.93	23.00	55.00	72.00	95.00	396.00
ln(TG-to-HDL ratio)	582	100.0	0.34	0.54	-1.15	-0.01	0.32	0.63	2.48
LDL-to-HDL ratio	582	100.0	1.86	0.62	0.61	1.44	1.82	2.16	6.69
Total-to-HDL ratio	582	100.0	3.19	0.75	1.75	2.70	3.10	3.53	8.26

LDL, low-density lipoprotein cholesterol; *LDL-to-HDL ratio*, low-density lipoprotein/HDL cholesterol ratio; *ln(TG-to-HDL) ratio*, logarithmic TG/HDL cholesterol ratio; *P25*, 25th percentile; *P75*, 75th percentile; *Total-to-HDL ratio*, total/HDL cholesterol ratio.

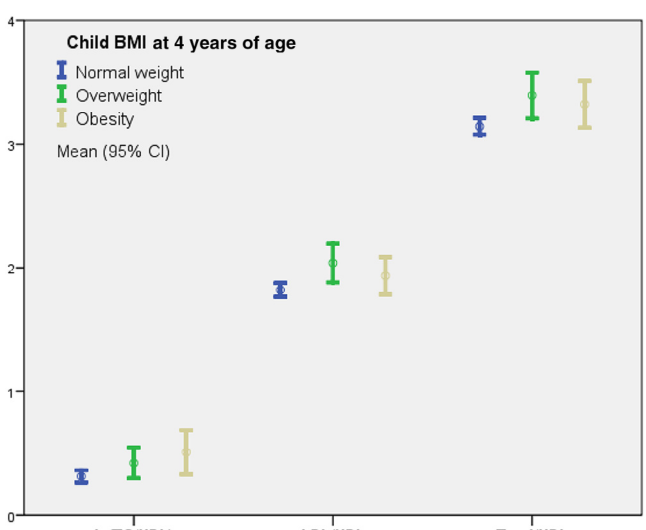

Figure. Lipid ratios according to the weight status at 4 years of age. *ln(TG/HDL)*, natural logarithm of TG/HDL cholesterol ratio; *LDL/HDL*, low-density lipoprotein/HDL cholesterol ratio; *Total/HDL*, the total/HDL cholesterol ratio.