IOSR Journal of Dental and Medical Sciences (JDMS)
ISSN: 2279-0853, ISBN: 2279-0861. Volume 1, Issue 3 (Sep-Oct. 2012), PP 40-46
www.iosrjournals.org

Association of metabolic biomarkers of cardiovascular disease in overweight and obese children in Emohua Local Government Area of Rivers State, Nigeria

Orluwene Chituru Godwill[1], Nnatuanya Isaac[2]
B.Med. Sci; MBBS; FMCPath AIMLS, MSC, Ph.D
[1]*Chemical Pathology Department, University of Port Harcourt Teaching Hospital Port Harcourt, Nigeria*
[2]*Chemical Pathology Department, Madonna University Teaching Hospital, Elele, Rivers State, Nigeria*

Abstract: *Obesity is associated with significant metabolic changes and subclinical inflammation. We looked at the clustering of cardio-metabolic markers in overweight and obese school children in a semi-urban local government area in Nigeria.*

In this population-based cross-sectional study among 400 school children aged 15years, we measured adiponectin, leptin, inflammatory markers, apolipoprotein (apo)A1 and B, and lipoprotein-associated phospholipase A_2 (Lp-PLA_2). Except for adiponectin, and apoA1 (10^{th} percentile) the 90^{th} percentile was used as cutoff point. Body weight was categorized in age-and sex-specific BMI percentiles and overweight and obesity according to international obesity task force definitions.

In linear regression models, all cardio-metabolic markers were significantly associated with overweight. In logistic regression models, compared with the reference category (25^{th}-75^{th} percentile BMI), overweight was associated with increased concentrations of leptin [odds ratio (OR) 62.78; 95%CI 18.21-201.15], C-reactive protein (8.15; 2.82-15.23), fibrinogen (3.02; 1.52-7.12), and low apoA1 (2.41; 1.46-4.99). Overweight was positively associated with interleukin-6, Lp-PLA2, and apo B concentrations and inversely with adiponectin concentrations. In obese children 40% showed one, 18% two, 13% three and 16% four or more abnormal cardio-metabolic biomarkers. The number of abnormal cardio-metabolic biomarkers increased in overweight (P_{trend} <0,001) and obese (P_{trend} < 0.001) children.

Overweight and obesity in children are associated with a cluster of metabolic changes and smoldering inflammatory response which might not only accelerate cardiovascular disease later on in life but may also be associated with early atherosclerosis.

Keywords: *Cardiovascular, Children, Metabolic-markers, Obese, Overweight, Nigeria.*

I. Introduction

Childhood overweight and obesity has been known to be associated with a range of health problems, which may last until adult life and cause premature morbidity and mortality [1]. In adults the relationship between metabolic syndrome (insulin resistance, dyslipidaemia, hypertension, obesity) and cardiovascular disease is well established [2]. There is increasing evidence that overweight and obesity are related to other cardiovascular risk factors even in childhood [3-5]. Moreover, the presence of cardiovascular risk factors in childhood has been shown to be associated with increased risk of cardiovascular disease in later life [6].

Current knowledge of white adipose tissue acting as an endocrine organ and playing major role in the regulation of insulin sensitivity and lipid metabolism has led to the discovery of various obesity-related biomarkers (the so-called adipocytokines) [7-9]. Biomarkers for low-grade inflammation, insulin sensitivity and lipid metabolism, particularly in adults, have been assessed in relation to cardiovascular disease [9,10]. Leptin correlates with body mass index (BMI) [6] by regulating food intake and basal metabolism and is linked to coronary artery disease [11]. Adiponectin is inversely related to BMI and plays a role in the regulation of insulin sensitivity and fatty acid metabolism [12]. In a prospective study, adiponectin predicted myocardial infarction in men [13]; however, more recent studies reveal mixed results [14, 15]. Inflammatory markers such as interleukin-6 (IL-6) [16] and in particular C-reactive protein (CRP) are considered risk factors for the metabolic syndrome [17] and cardiovascular disease [7]. Fibrinogen, an acute-phase reactant that also plays a central role in the coagulation cascade, has been linked to obesity in adults [18] and children [19].

As biomarkers of lipid metabolism, apolipoprotein (apo)A1 and apo B have been shown to be good predictors for cardiovascular disease [9]. In addition, lipoprotein-associated phospholipase A_2 (Lp-PLA_2), which is mainly produced by monocytes/macrophages and primarily bound to LDL cholesterol in the peripheral circulation, was found to be predictive for cardiovascular events in adults [8].

Childhood obesity tends to persist into adulthood and causes chronic conditions [1, 6]. Knowledge about pathomechanisms and early markers of disease may facilitate refined primary prevention strategies such as healthy diets and/or physical activity and thus represents an important public health issue [1].

The purposes of this study were to explore association between BMI and cardio-metabolic biomarkers and investigate their clustering among overweight and obese children in a representative large group of 15-year-old children in Rivers State, Nigeria.

II. Subjects and methods

Within the framework of a local government area children health surveillance programme, we carried out a cross-sectional study on bodyweight. The investigation was coordinated by the Local Government Council health office and was approved by the local ethics committee. In randomly selected schools in Emohua Local Government Area, 750 students were invited to participate in the study. After a written informed consent has been obtained from the parents, 600 children (all aged 15years) (48% boys and 52% girls) were recruited between September, 2000 and April 2001. Data from 400 children (53%) with complete set of anthropometric and laboratory parameters were available for analysis.

During physical examination, height was measured to the nearest 0.1cm and weight to the nearest 0.1kg in a standardized manner. BMI was calculated as weight (kg)/height $(m)^2$ and classified in BMI categories using established cut points [20]. We defined overweight and obesity using cutoff points as recommended by the international obesity task force (IOTF) according to Cole et al [20]. We calculated further BMI categories (0-10^{th}, 10^{th}-25^{th}, 75-90^{th}, and $\geq 90^{th}$ percentile) and compared them to the 25^{th}-75^{th} percentile range, which was defined as the reference category comprising about 50% of the study sample.

Random (non-fasting) EthyleneDiamine Tetracetic Acid (EDTA) blood was drawn from 400 children. After centrifugation, samples were separated and divided in aligots which were stored at -70^0C until analysis. All laboratory analysis were performed in a central laboratory at the Madonna University Teaching Hospital, Elele. We measured leptin (ng/L), adiponectin (mg/L), and IL-6 (ng/L) by use of ELIZA (R&D Systems) in EDTA plasma samples. The lower detection limits were approximately 7.8ng/L for leptin, 0.25mg/L for adiponectin and 0.11ng/L for IL-6. Interassay coefficient of variation (CV) or imprecision was 3.9% for leptin at 9530ng/L (n=7), 5.8% for adiponectin at 4.4mg/L (n-7) and 7.7% for IL-6 at 1.77ng/L (n=7). We also measured Lp-PLA_2 by use of ELIZA (PLAC test, diaDexus). The detection limit was 1.3µ/L, and the interassay CV was 8.8% at 204µg/L (n=7) and 4.0% at 376µg/L (n=7). We measured CRP, fibrinogen, apoA1 and apoB by use of immunonephelometry on a BNII auto-analyzer (Dade Behring). Detection limits were 0.16mg/L for CRP and 0.15g/L for fibrinogen. The interassay CVs were 4.7% for CRP at 1.25mg/L and 1.1% for fibrinogen at 2.2g/L. The interassay CV for apoA1 at 1.73g/L was 6.7% (n=6), and the corresponding CV for apoB at 0.92g/L was 4.6% (n=6).

For most of the analyzed biomarkers, no accepted external cutoff points were available to define increased concentrations in children. Therefore, we used values above the 90^{th} percentile of the biomarker distributions in our population, except for apoA1 and adiponectin for which the 10^{th} percentile was a biologically plausible cutoff point. We calculated sex-specific increased concentrations: CRP ($\geq$ 1.65mg/L for boys and $\geq$ 1.99 for girls), IL-6 ($\geq$ 2.82ng/L for boys and $\geq$ 3.14ng/L for girls), fibrinogen ($\geq$ 2.85g/L for boys and $\geq$ 2.93g/L for girls), apoB ($\geq$ 0.88g/L for boys and girls), Leptin ($\geq$ 13 918ng/L for boys and $\geq$ 20292ng/L for girls), and Lp-PLA_2 ($\geq$ 193ng/L for boys and $\geq$ 192ng/L for girls). For adiponectin ($\leq$ 4.63mg/L for boys and $\leq$ 5.17mg/L for girls) and apoA1 ($\leq$ 1.29g/L for boys and $\leq$ 1.26g/L for girls), abnormal results were defined as values below the 10^{th} percentile.

III. Statistical Analysis

We determined median and interquartile range (IQR, 25^{th}-75^{th} percentile) of the biomarkers in the 90^{th} BMI percentile and in overweight and obese children. Spearman rank correlation coefficient (ρ) was calculated between cardiometabolic markers. Statistical significance was determined on the basis of 2-sided P values of <0.05.

Linear regression models with continuous values of the explanatory variables (log-transformed if not normally distributed) were calculated using the 25^{th}-75^{th} BMI percentile as a reference group to examine the relationship with BMI by groups (0-10^{th}, 10^{th}-25^{th}, 75^{th}-90^{th}, and $\geq 90^{th}$ percentile). In addition, we calculated the associations of these BMI categories with concentrations of biomarkers compared with the reference BMI category using logistic regression models adjusted for age. Because sex-specific cut points were applied, no further adjustment for sex was performed. Clustering of abnormal biomarker concentration was determined by BMI categories and in overweight and obese children according to IOTF definitions. Because of the strong correlation between leptin concentrations and BMI ($P = 0.801$, $P < 0.001$), we did not include leptin concentrations in the clustering .Tests for trend across clusters were performed by including the ordered variable as continuous in the logistic regression model. All analysis were carried out with the statistical software package SAS release 9.1 (SAS institute).

IV. Result

Four hundred (400) school children (208 girls and 192 boys) mean age 15 years (standard deviation = 0.3) and mean BMI 19.3kg/m^2 (standard deviation = 2.2) were included in this analysis. Distribution of the plasma concentrations between obese children and children in the 25^{th} -75^{th} BMI percentile differed significantly in boys and girls for leptin ($P < 0.001$) and CRP ($P < 0.001$). For apoA1 and fibrinogen, significant associations were found only for boys ($P < 0.020$ and $P < 0.001$, respectively), and for IL-6, only for girls ($P = 0.030$).

Table 1 shows correlation coefficients of the cardiac metabolic markers. There were correlations between plasma leptin concentrations and CRP ($\rho = 0.41$), fibrinogen ($\rho = 0.24$), IL-6 ($\rho = 0.20$) and apoA1 ($\rho = -0.20$). The inflammatory markers were correlated: CRP with fibrinogen ($\rho = 0.47$), CRP with IL-6 ($\rho = 0.40$), and IL-6 with fibrinogen ($\rho = 0.28$).

Table 2 shows the linear associations of cardiac metabolic markers with BMI percentiles, overweight, and obesity. When compared with the reference category (25^{th}-75^{th} percentile of BMI), overweight children tended to have higher concentrations of leptin (β-coefficient 1.58; 95% CI 1.38 to 1.78), CRP (1.02; 0.80 to 1.24), fibrinogen (0.31; 0.21 to 0.45), IL-6 (0.34; 0.01 to 0.70), and Lp-PLA_2 (13.99; 6.98 to 24.01). In contrast, lower apoA1 (β-Coefficient -0.09; 95% CI -0.13 to -0.04) and adiponectin (-1.44; 95% CI -2.45 to -0.51) concentrations were found to be associated with overweight. There was no much change in ApoB concentrations (0.05; 0.01 to 0.06). The cardiac metabolic markers increased across the upper BMI categories and particularly in the range from overweight to obesity (Table 2).

Table 3 shows the odds ratios (ORs) for abnormal concentrations of various cardio-metabolic markers in children with different BMI categories, overweight and obesity using the 25^{th}-75^{th} percentile as a reference category. Plasma leptin concentrations showed the strongest associations with increased BMI categories and with overweight and obesity. Low adiponectin concentrations were associated with obesity whereas the association with overweight was not significant.

In contrast, high concentrations of the inflammatory markers CRP, IL-6 and fibrinogen were strongly related to obesity. The association of CRP and fibrinogen with overweight was also significant.

Apolipoprotein B and lipoprotein-associated phospholipase A_2 (Lp-PLA_2) concentrations (which are among the markers of lipid metabolism) did not show consistent association with obesity and overweight. Decreased apoA1 concentrations were associated with overweight and not obesity.

In obese children 40% showed one, 18% two, 13% three and 16% four or more abnormal markers. The number of abnormal cardiometabolic markers increased with increasing categories of BMI. Compared to the referenced category (25^{th}-75^{th} percentile), the number of abnormal cardio-metabolic markers increased in overweight ($P_{trrend} < 0.0001$) and obese ($P_{trend} < 0.0001$) children.

V. Discussion

In this study, cardiometabolic markers in general were associated with overweight and obesity in young children, with clustering particularly in obese children. There is a strong positive association between plasma leptin concentrations and increasing BMI. This finding is consistent with published reports [21]. Leptin may be linked to cardiovascular disease by enhanced platelets aggregation and promotion of a prothrombotic state, and by angiogenesis and impairment of vascular function in adolescents [11]. Our data for leptin, adiponectin, CRP, fibrinogen, IL-6, apoA1 and apoB are also consistent with literature [22-24]. There is no conclusive data on Lp-PLA_2 among children.

In line with the results of most previous studies, we found an inverse relationship between adiponectin concentrations and BMI [3, 12, 25]. In experimental studies, high adiponectin concentrations have been shown to exert antiatherogenic, anti-diabetic, and anti-inflammatory effects. Low plasma concentrations may indicate impaired insulin sensitivity and thus increased risk of type 2 diabetes, but the underlying biologic mechanism is not well known. There are controversial results from prospective studies regarding the association between low adiponectin and cardiovascular disease end points [14, 15].

We observed positive associations of plasma IL-6 and CRP concentrations with BMI and this is consistent with earlier reports [13, 26]. Studies have demonstrated that high CRP concentrations are associated with obesity in children [3, 17, 25] and in adults [13, 18]. Correlations between CRP concentrations and high blood pressure or dyslipidaemia were found in children and adolescent [27]. Other studies in vitro and in vivo have suggested a direct role of CRP in atherogenesis even if this issue has remained controversial [28].

In the children from our study, high concentrations of fibrinogen were associated with overweight and obesity. This is in keeping with reports from other studies [19, 29]. Fibrinogen plays a central role in coagulation [16] and correlates with inflammatory markers. Because IL-6 represents the main trigger for the hepatic production of CRP and fibrinogen, these inflammatory markers are interrelated. In our study, however, IL-6 was only moderately correlated with both CRP and fibrinogen, which is also consistent with the literature [16].

Overweight was found to be associated with low apoA1 concentrations, whereas no clear association was found with plasma apoB concentrations. This finding is in keeping with reports from other studies [29, 30].

In another cross-sectional study among 13-year-old children in Portugal, apoB concentrations were higher in obese than non-obese children [31]. In a similar study in Japan involving children aged 5-14years, no association between apoA1 concentrations and obesity was found but apoB concentrations were positively related to obesity [32]. In a recent case-control study on premature coronary artery disease among adolescent and children in India, higher apoB and lower apoA1 concentrations were found in cases compared to controls [33]. These different results may be due to differences in age range, ethnicity, or study design.

Oxidized Low-density lipoprotein (LDL) represents the substrate for Lp-PLA_2, which in turn generates proatherogenic compounds like lysophosphatidylcholine and oxidized fatty acids [10]. We found an association between increased Lp-PLA_2 concentrations and higher BMI percentiles, which is consistent with the correlation of plasma Lp-PLA_2 with apoB concentrations in our study. To date, a large number of prospective studies in initially healthy subjects and in patients with manifest atherosclerosis have documented that increased Lp-PLA_2 activity or mass is associated with increased cardiovascular risk, suggesting a proatherogenic activity [8, 10]. However, little is known about the effects of increased Lp-PLA_2 in children.

Our finding of a clustering of abnormal cardiometabolic biomarkers in obese children is in line with previous reports concerning traditional cardiovascular risk factors in relation to obesity [4, 5, 34]. Classic cardiovascular risk factors such as high blood pressure, hyperglycaemia, and dyslipidemia were investigated among children and adolescent in Finland (3-18years) [34], in Taiwan (12-16years old) [4], and in US (5-17 years old) [5]. Freedman et al [5] found that 26% of their study population had at least one risk factor and 4% had three or more. However, we observed at least one abnormal cardiometabolic marker in 87% of the obese children. Compared to overweight children, we observed a higher burden of abnormal cardiometabolic markers in obese children.

In our study, obesity was associated with abnormal plasma concentrations of inflammatory markers (CRP, fibrinogen, and IL-6) and adiponectin. However, some of the cardiometabolic markers, such as IL-6 and adiponectin could be more predictive for obesity. Leptin has been shown as a factor linked to the timing of puberty [35] which is associated with changes of body fat distribution and rapid growth. Our study sample was homogenous in age and this limited the study of the relevance of pubertal state as a modifying factor. Because cardiometabolic markers are biologically interrelated, correlations between these biomarkers and obesity may not be independent. In a cross-sectional study among adults, adiponectin concentrations were not significantly correlated with most immunological parameters, suggesting that adiponectin and inflammatory markers may act independently [36]. Except for apoA1, adiponectin was not correlated with other laboratory markers in this study.

The definition of overweight by means of BMI remains somewhat arbitrary in children, and its limitation regarding the distinction between fat and fat-free mass is well known [37]. Cole et al [22] suggested age and sex-specific BMI cutoff points for international comparisons of overweight and obesity in children, which are based on retrograde extrapolations in adults on childhood BMI. In linear and logistic regression models, markedly stronger associations with obesity than with overweight were found in our study sample for low plasma adiponectin and high IL-6, CRP, fibrinogen, Lp-PLA_2, and leptin concentrations. These associations suggest that unfavourable concentrations of cardiometabolic biomarkers may indicate the burden of metabolic changes caused by overweight and obesity. Particularly strong associations with obesity and overweight were seen for inflammatory markers.

So far, risk factors associated with BMI in early childhood are not clear, and risk-associated cutoff values for BMI have not been established for children. An increased BMI is currently defined by percentiles or standard deviation score (SDS) values obtained by reference values from a population. Several guidelines for diagnostic procedures and treatment are based on such cutoff values. Only few studies have tried to relate cardiovascular risk factors to BMI in children [4, 5, 34].

The present study adds information on the associations of the biochemical markers, leptin, CRP, IL-6, fibrinogen, apoA1, apoB and Lp-PLA_2 with overweight and obesity among 15-year-old children living in a semi-urban (Emohua) Local Government Area of Rivers State, Nigeria.

VI. Conclusion

Our study demonstrates that cardiometabolic risk factors cluster in higher BMI categories and in overweight and obese children. The strong association in children of cardiometabolic biomarker with overweight and obesity suggest an adverse effect on the vascular wall very early in life. The clustering of multiple unfavourable biomarkers in obese children in particular, strongly supports the need for early intervention. However, further research is required to understand the exact role of adiponectin in atherogenesis.

Our study sample was homogenous in age and this may have minimized the relevance of pubertal state as a modifying factor.

VII. Acknowledgments

We are grateful to Miss Vivian Chioma for her excellent technical assistance, Mr. Amobi Mini and Miss Favour C. Elechi for data management and analysis.

Finally, we remain thankful to all the study participants and the Emohua Local Government Council for sponsoring this study.

Table 1

Correlation coefficient (ρ) between cardiometabolic markers (Spearman) (n = 450)

	Adiponectin	IL-6	Leptin	ApoA1	APoB	CRP	Fibrinogen	Lp-PLA$_2$
Adiponectin	1.00	-0.02	-0.01	0.15	-0.01	-0.05	-0.02	-0.02
P value		0.50	0.72	0.001	0.70	0.25	0.48	0.65
IL-6	_	1.00	0.20	-0.10	-0.05	0.40	0.28	0.07
P value			<0.001	0.01	0.30	<0.0001	<0.001	0.08
Leptin	_	_	1.00	-0.02	0.11	0.41	0.24	0.12
P value				<0.0001	0.001	<0.001	<0.001	0.02
Apo A1	_	_	_	1.00	0.02	-0.22	-0.16	-0.03
P value					0.65	<0.001	0.0001	0.38
Apo B	_	_	_	_	1.00	0.10	0.07	0.25
P value						0.01	0.02	<0.001
CRP	_	_	_	_	_	1.00	0.47	0.20
P value							<0.001	0.0002
Fibrinogen	_	_	_	_	_	_	1.00	-0.01
P value								0.75
Lp-PLA$_2$	_	_	_	_	_	_	_	1.00

Note:

IL-6 = Interleukin-6
APOA1 = Apolipoprotein A1
APOB = Apolipoprotein B
CRP = C-reactive protein
Lp-PLA2 = Lipoprotein-associated Phospholipase A_2

Table 2

Association between cardio metabolic markers and BMI categories, overweight, and obesity in 15-year-old children

	BMI percentile						
	0 to <10th	10th to <25th	25th to <75th	75th to <90th	≥90th	Overweight	Obesity
n.	18	32	198	27	34	68	22
Adiponectin							
β-Coefficient*	0.36	-0.28	Reference	-1.01	-1.38	-1.44	-2.07
95% CI	-0.84 to 1.64	-1.36 to 0.72		-2.11 to 0.12	-2.51 to -0.35	-2.45 to 0.51	-4.0 to -0.20
Leptin**							
β-Coefficient*	-1.11	-0.67	Reference	1.03	1.62	1.58	2.22
95% CI	-1.41 to -0.92	-0.91 to 0.48		0.81 to 1.19	1.54 to -1.85	1.38 to 1.78	1.98 to 2.49
CRP**							
β-Coefficient*	0.01	-0.03	Reference	0.56	1.19	1.02	1.79
95% CI	-0.31 to 0.36	-0.30 to 0.22		0.31 to 0.87	0.93 to -1.48	0.80 to 1.24	1.38 to 2.29
Fibrinogen							
β-Coefficient*	0.04	-0.01	Reference	0.17	0.38	0.31	0.53
95% CI	-0.09 to 0.21	-0.13 to 0.10		0.04 to 0.30	0.23 to -0.51	0.21 to 0.45	0.25 to 0.65
IL-6							
β-Coefficient*	0.03	-0.16	Reference	-0.01	0.44	0.34	0.68
95% CI	-0.41 to 0.52	-0.48 to 0.20		-0.41 to 0.37	0.06 to 0.85	0.01 to 0.70	0.01 to 1.30
APO A1							
β-Coefficient*	-0.08	0.01	Reference	-0.05	-0.11	-0.09	-0.06
95% CI	0.02 to 0.12	-0.02 to 0.04		-0.10 to -0.02	-0.11 to -0.05	-0.13 to -0.04	-0.17 to -002
APO B							
β-Coefficient*	-0.02	-0.01	Reference	0.03	0.02	0.05	0.06
95% CI	-0.06 to 0.04	-0.05 to 0.02		0.01 to 0.07	-0.02 to 0.08	0.01 to 0.06	-0.01to -0.10
Lp-PLA$_2$							
β-Coefficient*	0.01	8.76	Reference	5.93	16.92	13.99	22.15
95% CI	-9.65 to 8.98	0.39 to 16.65		-1.29 to 15.81	8.40 to 23.85	6.98 to 24.01	5.90 to 37.01

Note:
* = Linear regression model adjusted for age
** = Log-transformed

Table: 3

Association of abnormal concentrations of adipokines, inflammatory parameters, and lipoproteins with BMI categories, overweight and obesity in 15-year-old children

	BMI Percentiles						
	0 to <10th	10th to <25th	25th to <75th	75th to <90th	≥90th	Overweight	Obesity
n	18	32	198	27	34	68	22
Adiponectin							
OR+	1.12	0.40	Reference	1.01	1.86	1.99	3.18
95% CI	(0.42 - 3.57)	(0.11 - 1.52)		(0.28 - 2.65)	(0.87 - 4.22)	(0.93 - 4.01)	(1.06 -9.88)
Leptin							
OR+	<0.001	0.78	Reference	7.11	68.52	62.78	>999.99
95% CI		(0.09 – 8.99)		(1.85 -32.55)	(22.90 - 309.14)	(18.21 - 201.15)	
CRP							
OR+	0.75	1.37	Reference	3.00	5.96	8.15	27.21
95% CI	(0.16 - 2.99)	(0.42 - 4.00)		(1.01 - 5.86)	(2.78 - 13.96)	(2.82 - 15.23)	(8.11 -67.92)
Fibrinogen							
OR+	1.65	0.70	Reference	2.13	3.11	3.02	4.23
95% CI	(0.48 - 5.01)	(0.15 - 2.42)		(0.78 - 5.14)	(1.38 - 6.95)	(1.52 - 7.12)	(1.18 -12.97)
IL-6							
OR+	1.13	0.33	Reference	1.02	1.99	1.85	2.96
95% CI	(0.41 - 3.41)	(0.1 - 0.37)		(0.34 - 2.48)	(0.92 - 4.35)	(0.89 - 3.84)	(0.99 -8.98)
APO A1							
OR+	<0.001	2.07	Reference	2.87	2.17	2.41	0.83
95% CI		(0.81 - 4.88)		(1.18 - 5.30)	(0.86 - 5.13)	(1.46 - 4.99)	(0.04 -5.06)
APO B							
OR+	0.32	0.23	Reference	1.22	1.24	1.71	1.49
95% CI	(0.08 - 1.45)	(0.07 - 1.25)		(0.47 - 2.97)	(0.45 - 2.85)	(0.76 - 2.69)	(0.37 -5.31)
Lp-PLA$_2$							
OR+	0.14	1.45	Reference	1.72	1.87	1.97	2.62
95% CI	(0.02 - 1.73)	(0.70 - 3.56)		(0.78 - 4.02)	(0.85 - 3.92)	(0.90 - 4.18)	(0.66 -7.80)

Note:
OR = Adds Ratio
\+ = Adjusted for age

References

[1]. D. Yach, D. Stuckler, K.D. Brownwell. Epidemiologic and economic consequences of the global epidemics of obesity and diabetes. *Nat Med 12*, 2006, 62-66.

[2]. S. M. Grundy. Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. *J AM Coll Cardiol 47*, 2006, 1093-1100.

[3]. R. Weiss, J. Dziura, T. S. Burgert, W. V. Tamborlane, S. E. Taksali, C. W. Yeckel, et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med 350*, 2004, 2362-2374.

[4]. N, F. Chu, E. B. Rimm, D. J. Wang, H. S. Liou, S. M. Shieh. Clustering of cardiovascular disease risk factors among obese school children: the Taipei Children Heart Study. *AM J Clin Nutr 67*, 1998, 1141-1146.

[5]. D. S. Freedman, Z. Mei, S. R. Srinivasan, G. S. Berenson, W. H. Dietz. Cardiovascular risk factors and excess adiposity among overweight children and adolescents: the Bogalusa Heart Study. *J Pediatr150*, 2007, 12-17.

[6]. S. Li, W. Chen, S. R. Srinivasan, M. G. Bond, R. Tang, E. M. Urbina, G. S. Berenson. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA 290*, 2003, 2271-2276.

[7]. P. M. Ridker, D. A. Morrow. C-reactive protein, inflammation and coronary risk. *Cardiol Clin 21*, 2003, 315-325.

[8]. W. Koenig, D. Twardella, H. Brenner, D. Rothenbacher. Lipoprotein-associated phospholipase A2 predicts future cardiovascular events in patients with coronary heart disease independently of traditional risk factors, markers of inflammation, renal function, and hemodynamic stress. *Arterioscler Thromb Vasc Biol 26*, 2006, 1586-1593.

[9]. A. Thompson, J. Danesh. Association between apolipoprotein B, apolipoprotein A1, the apolipoprotein B/A1 ratio and coronary heart disease: a literature-based metaanalysis of prospective studies. *J. intern Med 259*, 2006, 481-492.

[10]. N. Khuseyinova, W. Koenig, Lipoprotein-associated phospholipase A2 and other lipid-related biomarkers in cardiovascular disease, In D. A. Morrow (ed.), Cardiovascular Biomarkers: Pathophysiology and Disease Management, *(Totowa NJ: Humana press inc., 2006)*, 519-542.

[11]. A. Singhal, I. S. Farooqi, T. J. Cole, S. O'Rahilly, M. Fewtrell, M. Kattenhom, et al. Influence of leptin on arterial distensibility: a novel link between obesity and cardiovascular disease? *Circulation 106*, 2002, 1919-1924.

[12]. K. Asayama, H. Hayashibe, K. Dobashi, N. Uchida, T. Nakane, K. Kodera et al. Decrease in serum adiponectin level due to obesity and visceral fat accumulation in children. *Obes Res 11*, 2003, 1072-1079.

[13]. T. Pischon, C. J. Girman, G. S. Hotamisligil, N. Rifai, F. B. HU, E. B. Rimm. Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA 291*, 2004, 1730-1737.

[14]. W. Koenig, N. Khuseyinova, J. Baumert, C. Meisinger, H. Lowel. Serum concentrations of adiponectin and risk of type 2 diabetes mellitus and coronary heart disease in apparently healthy middle-aged men: results from the 18-year-follow-up of a large cohort from Southern Germany. *J AM Coll Cardiol 48*, 2006, 1369-1377.

[15]. N. Sattar, G. Wannamethee, N. Sarwa, J. Tchernova, L. Cherry, A.M. Wallace, et al. Adiponectin and coronary heart disease: a prospective study and metaanalysis. *Circulation 114*, 2006, 623-629.
[16]. C. Gabary, I. Kushner. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med 340*, 1999, 448-454.
[17]. S. D. de Ferranti, K. Gauvreau, D. S. Ludwig, J. W. Newburger, N. Rifai. Inflammation and changes in metabolic syndrome abnormalities in US adolescents: findings from the 1988-1994 and 1999-2000 National Health and Nutrition Examination Surveys. *Clin Chem 52*, 2006, 1325-1330.
[18]. M. Visser, L. M. Bouter, G. M. McQuillan, M. H. Wener, T. B. Harris. Increased C-reactive protein levels in overweight and obese adults. *JAMA 282*, 1999, 2131-2135.
[19]. M. Valle, F. Gascon, R. Martos, F. J. Ruz, F. Bermudo, R. Rios, R. Canete. Infantile obesity: a situation of atherothrombotic risk? *Metabolism 49*, 2000, 672-675.
[20]. T. J. Cole, M. C. Bellizi, K. M. Flegal, W. H. Dietz. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ 320*, 2000, 1240-1243.
[21]. J. Steinberger, L. Steffen, D. R. Jacobs Jr, A. Moran, C. P. Hong, A. R. Sinaiko. Relation of leptin to insulin resistance syndrome in children. *Obes Res 11*, 2003, 1125-1130.
[22]. J. M. Valle, R. M. Estepa, R. M. Camacho, R. C. Estrada, F. G. Luna, F. B. Guitarte. Endothelial dysfunction is related to insulin resistance and inflammation biomarker levels in obese prepubertal children. *Eur J Endocrinol 156*, 2007, 497-502.
[23] L. Gilardini, P. G. McTernan, A. Girola, N. F. da Silva, L. Alberti, S. Kumar, C. Invitti. Adiponectin is a candidate marker of metabolic syndrome in obese children and adolescents. *Atherosclerosis 189*, 2006, 401-407.
[24]. A. Dirisamer, A. Stadler, R. A. Bucek, K. Widbalm. APO B-100 and APO B/APOA-1 ratio in children and adolescents from families with very early myocardial infarction. *Acta paediatr 95*, 2006, 810-813.
[25]. N. F. Chu, M. H. Shen, D. M. WU, C. J. Lai. Relationship between plasma adiponectin levels and metabolic risk profiles in Taiwanese children. *Obes Res 13*, 2005, 2014-2020.
[26]. M. Valle, R. Martos, F. Gascon, R. Canete, M. A. Zafra, R. Morales. Low-grade systemic inflammation, hypoadiponectinemia and a high concentration of leptin are present in very young obese children, and correlate with metabolic syndrome. *Diabetes Metab 31*, 2005, 55-62.
[27]. M. Lambert,. E. E. Delvin, G. Paradis, J. O'Loughlin, J. A. Hanley, E. Levy. C-reactive protein and features of the metabolic syndrome in a population-based sample of children and adolescents. *Clin Chem 50*, 2004, 1762-1768.
[28]. P. Libby, P. M. Ridker, A. Maseri. Inflammation and atherosclerosis. *Circulation 105*, 2002, 1135-1143.
[29]. M. Halle, U. Korsen-Reck, B. Wolfarth A. Berg. Low-grade systemic inflammation in overweight children: impact of physical fitness. *Exerc Immunol Rev 10*, 2004, 66-74.
[30] Y. J. Choi, Y. E. Jo, Y. K. Kim, S. M. Ahn, S. H. Jung, H. J. Kim, et al. High plasma concentration of remnant lipoprotein cholesterol in obese children and adolescents. *Diabetes Care 29*, 2006, 2305-2310.
[31]. P. J. Teixeira, L. B. Sardinha, S. B. Going, T. G. Lohman. Total and regional fat and serum cardiovascular disease risk factors in lean and obese children and adolescents. *Obes Res 9*, 2001, 432-442.
[32]. K. Asayama, H. Hayashibe, K. Dobashi, N. Uchida, T. Nakane, K. Kodera, A. Shirahata. Increased serum cholesteryl ester transfer protein in obese children. *Obes Res 10*, 2002, 439-446.
[33]. B. Das, M. K. Daga, S. K. Gupta. Lipid pentad index: a novel bioindex for elevation of lipid risk factors for atherosclerosis in young adolescents and children of premature coronary artery disease patients in India. *Clin Biochem 40*, 2007, 18-24.
[34]. O. T. Raitakari, K. V. Porkka, J. S. Viikari, T. Ronnemaa, H. K. Akerblom. Clustering of risk factors for coronary heart disease in children and adolescents. The Cardiovascular Risk in Young Finns Study. *Acta Paediatr 83*, 1994, 935-940.
[35]. D. B. Dunger, M. L. Ahmed, K. K. Ong. Early and late weight gain and the timing of puberty. *Mol Cell Endocrinol 254-255*, 2006, 140-145.
36]. C. herder, H. Hauner, B. Haastert, K. Rohrig, W. Koenig, H. Kolb, et al. Hypoadiponectinemia and proinflammatory state: two sides of the same coin? Results from the Cooperative Health Research in the Region of Augsburg Survey 4 (KORA S4). *Diabetes Care 29*, 2006, 1626-1631.
[37] A. M. Prentice, S. A. Jebb. Beyond body mass index. Obes Rev 2, 2001, 141-147.