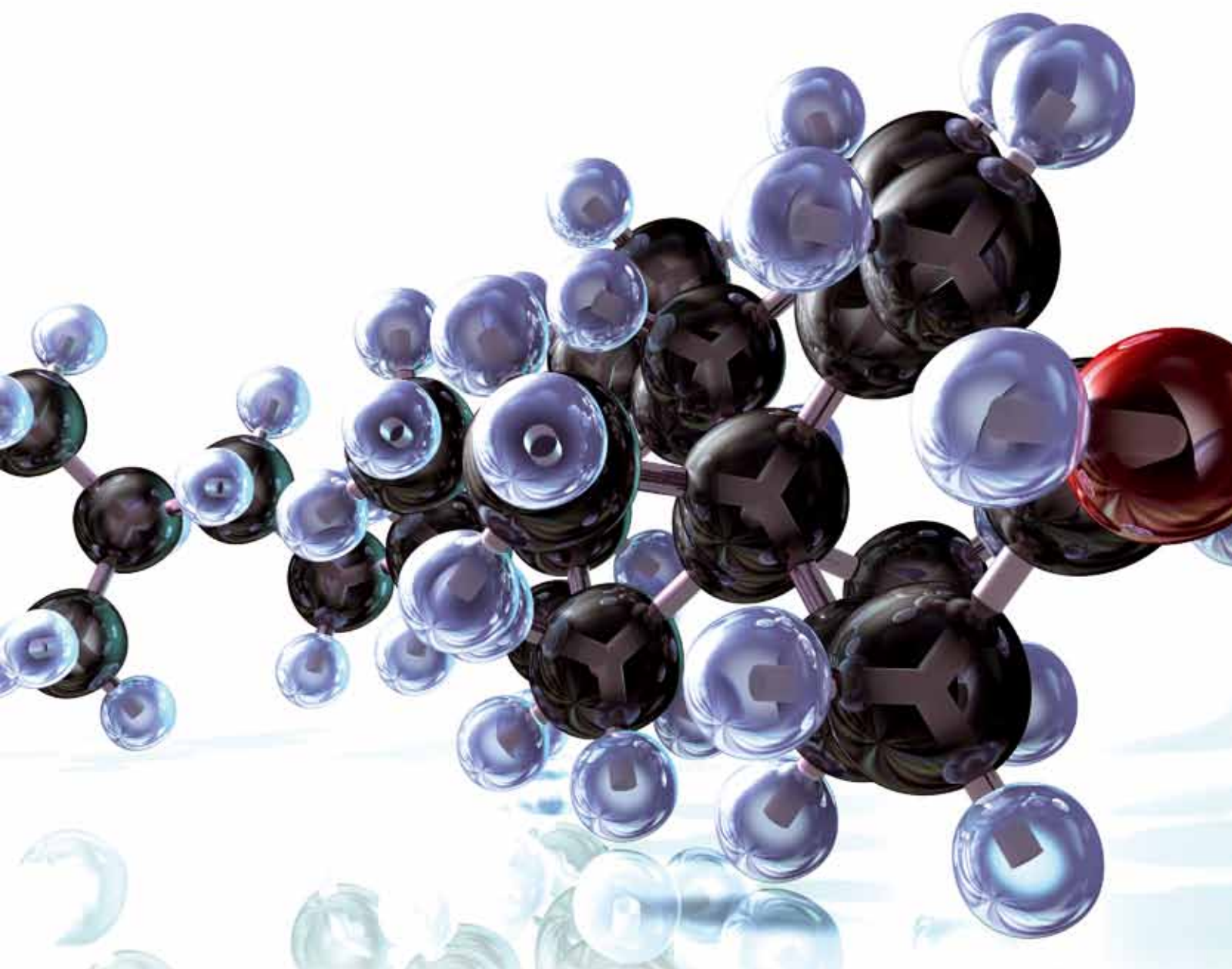


# Pediatric Metabolic Syndrome: From Prevention to Treatment

Guest Editors: Roya Kelishadi, Parinaz Poursafa, Sarah D. de Ferranti, Peter Schwandt, Khosrow Adeli, Altan Onat, and Samuel S. Gidding





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## Editorial

# Pediatric Metabolic Syndrome: From Prevention to Treatment

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Pediatric metabolic syndrome is becoming a substantial health problem at global level [1, 2]. It has a complex multifactorial etiology. Prevention and control of its modifiable risk factors from prenatal period can have long-term health effect on primordial prevention of chronic noncommunicable diseases. Given the increasing evidence on tracking of risk factors from childhood into adult life, the potential role of genetic, prenatal, environmental, biological, and behavioral determinants of pediatric metabolic syndrome should be underscored [3–5].

Pediatric metabolic syndrome is mainly related to “globesity,” a term used by the World Health Organization to focus on the escalating global epidemic of overweight and obesity [6]. Although most cases are secondary to obesity, actually a substantial number of normal-weight children and adolescents have at least some components of this syndrome [7]. The environmental factors, gene-gene, and gene-environment interactions should be considered in this context.

A growing body of evidence proposes that nonalcoholic fatty liver disease (NAFLD) and pediatric metabolic syndrome are interrelated and have common pathophysiological features [8–10]. The “two-hit hypothesis” is the most widely accepted model explaining the progression of NAFLD [11], and may also have a role in the development of the metabolic syndrome. Oxidative stress and proinflammatory cytokines are of the main factors initiating the second hit;

the association of environmental influences on these factors, even in the pediatric age group [12–14].

The other aspect of the influences of environmental factors on the development of pediatric metabolic syndrome can be the impact of these factors, as air pollutants, on intrauterine growth retardation, low birth weight, and prematurity [15, 16], and the impact of other factors as noise pollution and passive smoking on components of pediatric metabolic syndrome [17], which in turn can be associated with higher risk of chronic diseases in later life. Furthermore, currently many environmental obesogens are identified; they are classified as chemical simulators of metabolic hormones or brain neurotransmitters [18, 19]. All these mechanisms propose that the systemic responses to long-term exposure to environmental factors could potentially increase the risk for development of the pediatric metabolic syndrome.

Interventions including community involvement can be useful in improving health at individual and public health levels [20]. Prevention and control of modifiable risk factors as air and noise pollution, passive smoking, overweight, and unhealthy lifestyle, along with primordial prevention by good pregnancy care for prevention of low birth weight, encouraging breast feeding, and using healthy complementary foods during infancy can impact the overall health of children and adolescents as well as the prevention and control of pediatric metabolic syndrome and its treatment modalities.

This special issue is dedicated to increasing the depth of research across all areas of the pediatric metabolic syndrome, and highlights the preventive measures as well as management by nonpharmacological and pharmacological treatment.

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Parinaz Poursafa  
Sarah D. de Ferranti  
Peter Schwandt  
Khosrow Adeli  
Altan Onat  
Samuel S. Gidding

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## Research Article

# Determinants of Childhood Obesity in Representative Sample of Children in North East of Iran

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Childhood obesity has become, a global public health problem, and epidemiological studies are important to identify its determinants in different populations. This study aimed to investigate factors associated with obesity in a representative sample of children in Neishabour, Iran. This study was conducted among 1500 randomly selected 6–12-year-old students from urban areas of Neishabour, northeast of Iran. Then, through a case-control study, 114 obese ( $\text{BMI} \geq 95\text{th}$  percentile of Iranian reference) children were selected as the case group and were compared with 102 controls ( $15\text{th} \leq \text{BMI} < 85\text{th}$  percentile). Factors suggested to be associated with weight status were investigated, for example, parental obesity, child physical activity levels, socio-economic status (SES), and so forth. The analysis was conducted using univariate and multivariate logistic regression (MLR) in SPSS version 16. In univariate logistic regression model, birth weight, birth order, family extension, TV watching, sleep duration, physical activity, parents' job, parents' education, parental obesity history, and SES were significantly associated with children's obesity. After MLR analysis, physical activity and parental obesity history remained statistically significant in the model. Our findings showed that physical activity and parental obesity history are the most important determinants for childhood obesity in our population. This finding should be considered in implementation of preventive interventions.

## 1. Introduction

Obesity levels are increasing rapidly in children and youngsters of developed and developing countries [1, 2]. In 1998, the World Health Organization project monitoring of cardiovascular diseases (MONICA) showed that Iran is one of the seven countries with the highest prevalence of childhood obesity [3]. Overweight and obesity among Iranian children are becoming a major public health problem [4]. It is predicted that, by 2020, more than 60% of diseases and their related mortality and morbidity in the developing

countries will be due to noncommunicable diseases, for many of which obesity is a potential risk factor [5].

Obesity is a multifactorial consequence. In addition to genetic, metabolic, socioeconomic, and cultural factors, life style habits as unhealthy diet, low physical activity levels, weight and order of birth and other factors like history of breast feeding, as well as the age and type of complementary food are among factors affecting obesity [6]. Therefore, this study was designed to identify probable factors that might affect obesity in a group of Iranian children.

## 2. Materials and Methods

**2.1. Study Design.** In this study, 1500 6–12-year-old students were selected via two-stage sampling method from urban areas of Neishabour. Neishabour is a city in the Razavi Khorasan province in northeastern Iran and had a population of 205972 people. On the first stage, 60 primary schools, both public and private, were chosen, and, on the second stage, in each cluster, school children were selected randomly from the class attendance register. It was approved by the ethics committee of Tehran University of Medical Sciences (TUMS). Written informed consent was obtained from parents and oral assent from students.

Then, through a case-control study, 14 obese (body mass index (BMI)  $\geq$  95th percentile of Iranian reference) children were selected as the case group, and the first nonobese student ( $15^{\text{th}} \leq \text{BMI} < 85^{\text{th}}$  percentile) examined exactly after each obese student, and who was matched by age and sex, was selected as the control. Overall, 102 students were included in the control group.

**2.2. Anthropometric Profile.** We used the Iranian reference for BMI percentiles [7]. Physical examination was conducted by a trained team of health professionals using calibrated instruments. Height was measured by a stadiometer (Seca, Germany) in a standing position with bare feet (precision 0.5 cm), and body weight was determined with subjects wearing light clothes and no shoes or socks, using an electronic balance. BMI was calculated as weight (kg) divided by height squared ( $\text{m}^2$ ).

**2.3. Data Collection.** Data were collected by questionnaire via interview with mothers. Interviews were performed by trained health professionals. The questionnaire included mother-reported information about her child regarding the age, sex, birth weight, birth order, number of family household members, duration of breast feeding, age onset of complementary food, TV watching, playing electronic devices, sleep duration, father age, mother age, mother weight, economic status, and parental obesity history. The economic status of family was assessed by having some equipment such as color TV, refrigerators, washing machine, video, computer, video CD, and accessibility to car and private home. In data analysis, economic status was defined as low, moderate, and good based on an average score 3, 4–6, and more than 7, respectively. Physical activity score was evaluated using the modified Beacke et al. questionnaire that was asked from the pupils [8].

**2.4. Statistical Analysis.** Data were analyzed using the SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA). Quantitative variables are expressed as mean  $\pm$  standard deviation (SD) and categorical data as percentage. We computed the crude odds ratio (OR) by using logistic regression test to establish the degree of association between various risk factors and childhood obesity. Multiple logistic regression (MLR) model was fitted to data to adjust for the presence of confounding factors. All variables with  $P$  value  $< 0.1$  in

the univariate analysis were presented to the multiple model by using stepwise method. The results of logistic regression analysis are presented by OR and 95% confidence interval. A  $P$  value of less than 0.05 was considered as statistically significant.

## 3. Results

**3.1. Demographic Characteristics.** Overall, 216 children consisting of 114 obese and 102 nonobese students were assessed. The mean (SD) of age, weight, height, and BMI of the students were  $8.6 \pm 1.5$  years,  $33.4 \pm 9.9$  kg,  $132.3 \pm 9.5$  cm, and  $18.7 \pm 3.8$   $\text{kg}/\text{m}^2$ , respectively.

**3.2. Determinant Factors.** The crude ORs (univariate analysis) for birth weight, birth order, family extension, duration of breast feeding, age onset of complementary food, TV watching, playing electronic devices, sleep duration, physical activity score, father age, mother age, mother BMI as quantitative variables are shown in Table 1. The estimated crude ORs for birth weight, birth order, family extension, TV watching, playing electronic devices, sleep duration, physical activity score, father age, mother age, and mother BMI were statistically significant.

Associations between qualitative variables and obesity determined by univariate logistic regression model are shown in Table 2. The estimated crude ORs for father job, father education, mother job, mother education, economic status, and parental obesity history were statistically significant. After MLR analysis, at final step, physical activity and parental obesity history remained significant in the model (Table 3).

## 4. Discussion

This study has demonstrated that parental obesity history and physical activity were the strongest determinants of childhood obesity. These findings are in agreement with some investigations, showing that low physical activity and parental obesity to be the predictors of youngsters obesity [9–11].

The result of Veugelers and Fitzgerald's study showed that, as in other studies, normal-weight children were more physically active and engaged less in sedentary activities [12].

In our study, there was no significant association between mothers' BMI and children obesity, but Sekine and his colleagues found that mother's obesity was associated with children's BMI. In addition to genetic susceptibility, this may reflect environmental factors influencing children's body composition because children's food habits and preferences are usually shaped more by mothers than fathers [11].

The controversy between our result and other studies may be because of some factors related to family composition that we did not ask in our study and it may confound our conclusion. Our findings are also consistent with a previous study, which showed that a positive family history of being overweight is one of the most important indicators of the genetic risk for obesity and being overweight [13].

TABLE 1: Association between quantitative variables and obesity in univariate logistic regression model.

Variables	Cases ( <i>n</i> = 114) (mean $\pm$ SD)	Control ( <i>n</i> = 102) (mean $\pm$ SD)	Crude OR	95% CI
Birth weight (gr)	3900.90 $\pm$ 846.20	2837.10 $\pm$ 671.30	1.00	1.00–1.00
Birth order (n)	1.90 $\pm$ 1.20	5.09 $\pm$ 13.05	0.62	0.50–0.76
Family extension (n)	4.40 $\pm$ 0.97	5.10 $\pm$ 1.60	0.63	0.49–0.80
Duration of breast feeding (month)	22.02 $\pm$ 9.80	23.76 $\pm$ 14.33	0.99	0.97–1.11
Age-onset of complementary food (month)	8.77 $\pm$ 17.56	9.63 $\pm$ 15.63	1.00	0.98–1.01
TV watching, playing electronic devices (hour)	5.42 $\pm$ 1.99	2.77 $\pm$ 1.26	2.33	1.87–2.90
Sleep duration (hour)	10.40 $\pm$ 0.91	9.76 $\pm$ 0.89	2.24	1.60–3.15
Physical activity (score)	2.30 $\pm$ 0.37	3.02 $\pm$ 0.39	0.01	0.01–0.04
Father age (year)	39.57 $\pm$ 5.37	41.71 $\pm$ 6.27	0.94	0.90–0.99
Mother age (year)	35.51 $\pm$ 5.84	37.50 $\pm$ 6.88	0.95	0.91–0.99
Mother BMI (kg/m <sup>2</sup> )	26.98 $\pm$ 3.99	22.77 $\pm$ 3.81	1.40	1.25–1.55

TABLE 2: Association between qualitative variables and obesity in univariate logistic regression model.

Variables	Cases ( <i>n</i> = 114) <i>N</i> (%)	Control ( <i>n</i> = 102) <i>N</i> (%)	Crude OR	95% CI
Father job				
Jobless	1 (0.90)	4 (4.40)	Ref	
Worker	17 (15.00)	31 (31.60)	2.19	0.23–21.23
Employee	34 (30.10)	40 (40.80)	3.40	0.36–31.89
Other	61 (54.00)	23 (23.50)	10.60	1.13–99.96
Father education				
Illiterate and primary school	23 (20.40)	36 (36.70)	Ref	
Guidance school	16 (14.20)	29 (29.60)	0.86	0.39–1.92
Diploma	24 (21.20)	21 (21.40)	1.78	0.816–3.92
University degrees	50 (44.20)	12 (12.20)	6.52	2.87–14.79
Mother job				
Housewife	55 (48.20)	80 (78.40)	Ref	
Employee	59 (51.80)	22 (21.60)	3.90	2.14–7.09
Mother education				
Illiterate and primary school	35 (30.70)	49 (48.00)	Ref	
Guidance school	12 (10.50)	33 (32.40)	0.51	0.23–1.12
Diploma	12 (10.50)	14 (13.70)	1.20	0.50–2.90
University degrees	55 (48.20)	6 (5.90)	12.80	4.97–33.10
Economic status				
Weak	18 (15.80)	72 (63.20)	Ref	
Moderate	72 (63.20)	57 (55.90)	3.01	1.57–5.78
Good	24 (21.10)	2 (2.00)	28.66	6.12–134.20
Family history of obesity				
Without obesity history	7 (6.10)	76 (74.50)	Ref	
Father side obesity history	24 (21.10)	11 (10.80)	23.68	8.26–67.89
Mother side obesity history	5 (4.40)	13 (12.70)	4.17	1.15–15.16
Both of them	78 (68.40)	2 (2.00)	423.42	85.24–2010.00

We did not document any relationship between SES and obesity, but, in some other studies, investigators observed a gradient whereby children by low SES were more likely to be overweight or obese [12, 14]. This contradiction between our study and others may be related to the homogenous SES of families studied and also because differences in the SES

indicators were used. For instance, we asked some questions about having some equipment at home for assessing family income, but other researchers considered direct family income for evaluating economic status [15].

In present study, we did not find any association between the sleep duration and obesity. Some studies demonstrated

TABLE 3: Association between independent variables and obesity in multiple logistic regression model (last step).

Variables	Adjusted OR	*95% CI
Physical activity (score)	0.23	0.12-0.43
Family history of obesity		
Without obesity history	Ref	
Father side obesity history	47.41	9.87-227.60
Mother side obesity history	2.36	0.39-14.32
Both of them	547.58	45.26-6062.00

\*Adjusted for birth weight, birth order, family extension, TV watching, playing electronic devices, sleep duration, physical activity score, father age, mother age, mother BMI, father job, father education, mother job, mother education, economic status, and parental obesity history.

an inverse linear relationship between sleep duration and both mean BMI and obesity [16–18]. Researchers believe that there is association between the secretion of growth hormone and sleeping early at night. Going to sleep early at night increases the secretion of the growth hormone, which activates lipolysis in fat tissues, and obviously sleeping late increases the rate of obesity [19].

But, in our study, no significant association was observed between sleep duration at night and obesity. Maybe in current study, individuals of the case group went to bed later than the controls, and, in order to compensate for the lack of sleep, they slept more during the day instead of being more physically active or exercising.

Our study revealed no significant association between obesity and birth order. It may be related to increasing the knowledge of parents and paying more attention to the nutrition and health care of their children in both case and control groups.

In a meta-analysis carried out by Harder, the duration of breastfeeding was inversely and linearly associated with the risk of overweight. The risk of overweight was reduced by 4 percent for each month of breastfeeding [20]. Investigators think the protective effect of breast milk against obesity is attributed to its special components. Long-chain polyunsaturated fatty acid in breast milk may reduce the risk of obesity in the adulthood. High concentration of these fatty acids in the brain inhibits the production of cytokines and increases insulin receptors in several tissues which improves insulin, and other neurotransmitter functions. The dietary intake is regulated by complex interactions of some neurotransmitters, insulin and its receptors in the brain indicate the necessity of taking these fatty acids in the first year of life [20]. But, in our study, we find no association between obesity and duration of breast feeding and age of beginning complementary foods.

## 5. Limitation

This study had some limitations, which may have influenced the findings. First, the SES was measured indirectly by asking some relevant questions. Second, family composition was not assessed in this study, and it may be a confounder for

some parts of our results. Despite these limitations, this study provides some data on childhood obesity risk factors.

## 6. Conclusion

Finally, we suggested that a high priority has been given to research strategies to prevent the development of childhood obesity. Also, based on our findings, more physical education classes and providing healthy places for more extracurricular physical activity are strongly recommended, and family education for preventive public health actions should be targeted.

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## Research Article

# Trends of Components of the Metabolic Syndrome in German First Graders Throughout 10 Years: The PEP Family Heart Study

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Although childhood overweight and obesity are increasing worldwide, some countries report trends for stabilization. However, the trend for the potentially atherogenic components of the metabolic syndrome (MetS) in children and adolescents is not well understood. Therefore, the purpose of this study was to analyze the trend of the five components of over 10 years in 2228 first graders aged 6 years. Waist circumference (WC) remained mainly unchanged between 1994 and 2003 whereas the other four components continuously decreased. In boys and girls mean values of triglycerides (−25.9% and −28.6%, resp.), HDL cholesterol (−19.8% and −23.4%, resp.), fasting glucose (−7.3% and −9%, resp.), systolic (−3.8% and −4.1%, resp.), and diastolic (−10.2% and −9.7%, resp.) blood pressure significantly decreased. Whereas the prevalence of abdominal adiposity was stable at baseline and after 10 years (−1% in boys and +2% in girls), the prevalence of hypertension, hypertriglyceridemia, low HDL-C, and glucose was very low without any trend.

## 1. Introduction

Overweight, obesity, and the metabolic syndrome (MetS) are an emerging health problem in industrialized and developing countries [1, 2]. Ethnic disparities are reported regarding the prevalence of MetS, which was four times higher in Iranian than in German adolescents as well as regarding single components in terms of considerably higher prevalence of dyslipidemia in Brazilian and Iranian compared with German youths [3, 4].

Secular trends of childhood overweight and obesity in terms of increased body mass index (BMI) are heterogeneous in different countries with a large variation across countries [5–7]. However, BMI is not a component of the metabolic syndrome (MetS) according to the International Diabetes Federation (IDF) defining central obesity for children and adolescents as waist circumference (WC) at or above the 90th percentile [8]. Increasing prevalence of central adiposity indicates increasing cardiovascular risk [9, 10]. Furthermore, early elementary school years are a critical period for

increases in obesity prevalence sharply increasing from 10.4% to 19.6% below and above age six years [11]. Therefore, the purpose of this study was to assess the trend of the five single components over 10 years in a large sample of six-year-old first graders.

## 2. Material and Methods

We investigated 2228 German first graders (1116 boys and 1112 girls, median age 6.0 years) who participated in yearly cross-sectional surveys between 1994 and 2003. Continuously trained research assistants measured waist circumference (WC), systolic and diastolic blood pressure (BP), fasting triglycerides (TG), high-density cholesterol (HDL-C), and fasting plasma glucose (FPG) as previously described [12]. We used the IDF cut-offs for the five MetS components in terms of  $WC \geq 90$ th percentile,  $SBP \geq 130$  or  $DBP \geq 85$  mm Hg,  $TG \geq 1.7$  mmol/L,  $HDL-C \leq 1.03$  mmol/L and  $glucose \geq 5.6$  mmol/L [8].

TABLE 1: Characteristics and components of the metabolic syndrome in 2228 first graders between 1994 and 2003.

	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
	1,116 boys; mean (SD)									
Mean age (SD)	6.4 (0.5)	6.4 (0.5)	6.4 (0.5)	6.6 (0.5)	6.5 (0.5)	6.4 (0.5)	6.4 (0.5)	6.4 (0.5)	6.4 (0.5)	6.3 (0.5)
Median	6.0	6.0	6.0	7.0	6.0	6.0	6.0	6.0	6.0	6.0
BMI (kg/m <sup>2</sup> )	15.8 (2.4)	15.6 (1.7)	16.0 (1.8)	16.2 (2.4)	16.4 (2.3)	15.8 (1.7)	15.6 (1.7)	16.1 (1.8)	16.0 (2.1)	15.9 (2.4)
WC (cm)	56.9 (5.6)	56.0 (4.8)	58.0* (4.7)	58.6 (6.8)	58.7* (5.7)	57.4 (4.2)	56.8 (4.0)	56.3 (4.7)	56.6 (4.8)	56.3 (6.1)
SBP mmHg (SD)	105.1 (10.0)	104.2 (8.7)	104.7 (8.9)	106.2 (9.2)	104.5 (10.3)	104.0 (6.8)	103.9 (8.6)	101.8* (7.8)	102.6* (6.7)	101.1* (7.7)
DBP mmHg (SD)	70.7 (8.4)	67.1* (7.1)	70.9 (9.0)	71.1 (6.8)	71.8 (7.8)	66.2* (7.1)	67.4* (7.5)	62.1* (7.1)	63.8* (7.0)	63.5* (5.7)
Triglycerides (mmol/L) (SD)	0.85 (0.42)	0.65* (0.28)	0.64* (0.22)	0.67 (0.21)	0.63* (0.16)	0.76* (0.33)	0.67* (0.25)	0.61* (0.26)	0.62* (0.23)	0.63* (0.23)
HDL-cholesterol (mmol/L) (SD)	1.73 (0.35)	1.55* (0.40)	1.51* (0.28)	1.60 (0.34)	1.57* (0.26)	1.39* (0.31)	1.37* (0.24)	1.47* (0.28)	1.47* (0.36)	1.54* (0.26)
	1,112 girls; mean (SD)									
Mean age (SD)	6.4 (0.5)	6.4 (0.5)	6.3 (0.5)	6.6 (0.5)	6.4 (0.5)	6.4 (0.5)	6.4 (0.5)	6.3 (0.4)	6.3 (0.5)	6.3 (0.5)
Median	6.0	6.0	6.0	7.0	6.0	6.0	6.0	6.0	6.0	6.0
BMI (kg/m <sup>2</sup> )	15.6 (2.4)	15.7 (2.2)	15.7 (1.7)	16.2* (2.4)	15.8 (1.3)	15.9 (2.2)	16.2* (2.0)	15.8 (1.8)	16.3* (2.6)	15.9 (1.9)
WC (cm)	55.0 (5.4)	55.4 (5.5)	56.4* (4.4)	58.8* (5.9)	56.4 (3.9)	57.3* (6.1)	57.1* (5.8)	55.5 (4.7)	56.9* (5.5)	56.1 (4.8)
SBP mmHg (SD)	105.2 (10.0)	104.1 (9.0)	103.5 (9.2)	104.3 (9.4)	105.0 (9.6)	104.0 (10.2)	104.2 (8.2)	101.5* (7.6)	102.9 (6.9)	100.9* (7.6)
DBP mmHg (SD)	71.0 (8.5)	67.1* (6.9)	70.0 (8.4)	71.8 (9.7)	71.9 (7.6)	66.0* (8.6)	67.5* (7.5)	63.7* (7.0)	64.5* (6.7)	64.1* (7.0)
Triglycerides (mmol/L) (SD)	0.91 (0.41)	0.71* (0.26)	0.73* (0.30)	0.68* (0.07)	0.88 (0.42)	0.74* (0.21)	0.82 (0.22)	0.73* (0.30)	0.73* (0.29)	0.65* (0.21)
HDL-cholesterol (mg/dL)	1.71 (0.35)	1.38* (0.36)	1.49* (0.34)	1.50 (0.47)	1.38* (0.47)	1.41* (0.27)	1.41* (0.30)	1.28* (0.36)	1.40* (0.29)	1.31* (0.21)

*P* < 0.05 compared with baseline values.

TABLE 2: Prevalence (%) of the five components of MetS according to the IDF definition in 2228 German first graders between 1994 and 2003.

Year of enrollment of first graders	WC $\geq$ 90th percentile	TG $\geq$ 1.7 mmol/L	HDL-C $\leq$ 1.03 mmol/L	SBP $\geq$ 130 mmHg DBP $\geq$ 85 mmHg
boys				
1994	9.6	4.2	1.8	0
1995	5.3	2.9	7.8	0
1996	12.1	0	5.6	0
1997	10.7	0	0	3.6
1998	19.1	0	0	2.1
1999	7.6	3.3	10.0	0
2000	6.7	0	8.3	0
2001	6.5	0	0	0
2002	6.8	0	10.8	0
2003	9.1	0	5.9	0
girls				
1994	6.7	4.8	0.7	0
1995	5.5	0	14.0	0
1996	8.3	0	5.2	1
1997	18.8	0	20.0	6.3
1998	6.5	8.3	8.3	0
1999	12.7	0	4.8	0
2000	10.8	0	9.4	0
2001	9.5	0	26.3	1.6
2002	11.3	0	7.7	0
2003	11.4	0	18.9	0

WC indicates waist circumference, TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, SBP: systolic blood pressure, DBP: diastolic blood pressure.

For statistical analyses, we used SPSS 18.0 and the Kruskal-Wallis rank test for multisample ordinal comparisons, the Wilcoxon rank-sum test for pairwise comparisons and for linear trends across time ANOVA.  $P < 0.05$  was considered significant.

### 3. Results and Discussion

As presented in Table 1 mean values of waist circumference ( $-1\%$  in boys and  $+2\%$  in girls) and of body mass index ( $+0.6$  in boys  $+1.9\%$  in girls) remained stable between 1994 and 2003. This is consistent with the stabilization of BMI between 1999 and 2010 among children and adolescents in USA, UK, and Sweden [13–15]. In Stockholm, the prevalence of obesity differed in 10-year-old boys by  $+0.6\%$  and in girls by  $-1.6\%$  between 1999 and 2003 which is comparable with the urban area of Nuremberg [15]. “Mean WC greatly increased among US children between 1988–1994 and 1999–2004” [13]. However, among 2–5-year-old children the increase was  $+2.3\%$  in boys and  $+1.6\%$  in girls and among 6–11-year-old children WC increased by  $+4.2\%$  in boys and  $+4.9\%$  in girls. We found a slight decrease by  $-1\%$  in boys respectively, a slight increase by  $+2\%$  in girls from 1994 to 2003 among 6-year-old first graders. These small differences between the monocentric PEP Family Heart Study using the same staff, location, and equipment and the NHANES design, which includes different ethnicities, are remarkable

though different measuring points for WC were used (midway between lowest rib and iliac crest versus high point of the iliac crest). Furthermore, periods of assessment are different as well as age (6-year olds and ages 6–11 years). Among Australian children the mean WC z-score in 2–16-year-old children increased more in girls than in boys at a faster rate than BMI between 1985 and 2007 [9]. In Spanish adolescents and in British adolescents and children aged 2–5 years WC increased significantly in both genders from 1995 to 2000–2002, respectively, from 1977 to 1997 [16–18]. A recent review compares mean values of WC in 6-year-old children from 11 countries [19].

However, the mean values of the other four components of MetS significantly decreased (Table 1). The strongest decrease was observed for mean TG ( $-25.9\%$  in boys,  $-28.6\%$  in girls) and HDL-C ( $-19.8\%$  in boys,  $-23.4\%$  in girls). DBP ( $-10.2\%$  in boys,  $-9.7\%$  in girls) and SBP ( $-3.8\%$  in boys,  $-4.1\%$  in girls) decreased less, and fasting glucose ( $-7.3\%$  in boys,  $-9\%$  in girls) was available only for the last 4 years. Because all measurements were performed at entry in the PEP Family Heart Study before any lifestyle advice was implemented, we suggest that the decrease of the nonanthropometric risk variables might be due to secular changes.

We registered no clear trend of the prevalence of four MetS components between 1994 and 2003 among 6-year-old children except for glucose for the last four years of the study,



however unavailable values from the years before (Table 2). The prevalence of abdominal obesity decreased in boys ( $-0.5\%$  from  $9.6\%$  at baseline) but increased in girls ( $+4.7\%$  from  $6.7\%$  at baseline). In children with abdominal obesity the interrelationship with hypertension ( $\chi^2 = 29.3$ ,  $P < 0.001$ ) and hypertriglyceridemia ( $\chi^2 = 4.6$ ,  $P = 0.013$ ) was significant, and the interrelationship between hypertriglyceridemia and low HDL-C was ( $\chi^2 = 39.8$ ,  $P < 0.001$ ). In 1994 the prevalence of raised triglycerides ( $4.2\%$  in boys and  $4.8\%$  in girls) and of low HDL-C ( $1.8\%$  in boys and  $0.7\%$  in girls) was far less than  $21.5\%$ , respectively,  $18.7\%$  in 5–17.9-year-old obese children in European Union in 2006 [14]. The highest prevalence of hypertension in 6-year-old was  $3.6\%$  in boys and  $6.3\%$  in girls in 1997 and was considerably lower than in European Union in 2006. A very large European multicenter study in 26 008 overweight children reported that  $50\%$  had at least one cardiovascular risk factor related to the degree of overweight in terms of high BMI [20]. Since only  $5.9\%$  of the 12.6-year-old children were normal weight, the risk factor profiles cannot be compared with mainly normal-weight first graders of the current study, which however focused on WC as the major MetS component. Furthermore, studies from Germany reporting secular trends of BMI did not present nonanthropometric risk variables [21–24].

This is the first study documenting stable mean values of waist circumference and decreasing trends for the mean other four components of the metabolic syndrome over 10 years in first graders at the critical age of six years. However, it is unclear whether stable WC reflects a plateau between 1994 and 2003 and whether continuous decrease of MetS components mean values indicates leveling off in cardiovascular risk. Further strength of this monocentric study is constancy of staff, location, procedures, methods, and equipment and that all first graders lived in the same PEP families over ten years. A limitation of this study is the low prevalence of MetS components in this large cohort, which only allows a trend analysis of mean values regarding the four nonanthropometric variables. A further limitation is the relatively small sample size of 2228 first graders to detect a  $10\%$  difference between changes of prevalence [13]. Furthermore, the percentage of children with central obesity ( $\geq 90$ th percentile) was too small for categorizing the participants in prevalence groups of high WC ( $\geq 85$ th,  $\geq 95$ th,  $\geq 97$ th, and  $\geq 99$ th percentiles) as has been done for Californian adolescents. This very large study (8.3 million multiethnic adolescents) was powered to demonstrate declining prevalence of high BMI for some groups but not for Indian and black girls [25].

#### 4. Conclusions

This is the first study presenting ten years' trends of the mean values of the five components of the metabolic syndrome according to the definition of the International Diabetes Federation in first graders. Mean values of waist circumference as well as the prevalence of abdominal adiposity remained stable in 6-year-old children between 1994 and 2003. But the prevalence of hypertension, hypertriglyceridemia, low HDL-C, and hyperglycemia were low and inconsistent

though mean values of blood pressure, triglycerides, HDL-cholesterol, and glucose decreased continuously in both genders.

Longitudinal studies are needed to confirm these disparate trends.

#### Conflict of Interests

None of the authors has a conflict of interest.

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## Clinical Study

# Assessment of Metformin as an Additional Treatment to Therapeutic Lifestyle Changes in Pediatric Patients with Metabolic Syndrome

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**Objective.** To assess the effectiveness of metformin and therapeutic lifestyle changes (TLCs) in a clinical setting, compared to TLC alone in adolescents with metabolic syndrome (MS). **Methodology.** This study was a retrospective trial consisting of 60 patients, aged 8–18 years, who were treated for MS at an outpatient clinic. Two groups were formed: the metformin group (M group) and the control group (C group). The M group had been given metformin along with TLC, and the C group had been given TLC alone. Several outcome measures were obtained; the main outcome measure was measuring the change in percentile and z-score of weight and BMI. **Results.** There were no significant differences between the two groups at the conclusion of the study, except for height percentile ( $P = 0.02$ ) and z-score ( $P = 0.03$ ). Both groups showed promising significant intragroup decreases in weight z-score but BMI percentile and z-score were only significantly decreased in the M group. **Conclusion.** Metformin at an average dose of 1033 mg, when added to TLC, did not show any clinically important efficacy compared to TLC alone in a pediatric population with MS. However, both groups made significant changes in a positive direction, which may be solely due to TLC.

## 1. Introduction

During the last 30 years, childhood obesity rates have more than tripled in the United States [1]. The National Health and Nutrition Examination Survey (NHANES) from 2007–2008 estimated that 16.9% of children from ages of 2- to 19-years old were obese [1]. In 12–19 year olds the obesity rate has increased from 5.0% in the 1976–1980 NHANES survey to 18.1% in 2007–2008 [1]. Further, a strong correlation between childhood obesity and adult obesity has been found and an increasing need to intervene at a younger age may be important [2]. Despite available data in this field, no FDA approved medications that specifically target weight loss, are available for pediatric patients.

The most predictive factors for obesity, cardiovascular disease, and diabetes have been defined in the criteria for metabolic syndrome (MS) [3]. These risk factors include: hypertension, glucose intolerance, high triglycerides, low HDL-cholesterol concentrations, and elevated waist circumference

[3]. Outcome measures based on these criteria constitute a way to assess the effectiveness of a treatment plan. MS is possibly reversible and early intervention might prevent progression to a more serious illness.

One therapy of particular interest is the medication metformin, which is currently approved for use in type 2 diabetes mellitus. Metformin increases insulin sensitivity, and may assist with glycemic control, dyslipidemia, and diastolic blood pressure [4]. Further, metformin may decrease hyperinsulinemia, which in turn may reduce hunger [5]. Metformin has shown promising effects in several randomized pediatric controlled trials [6–10] but further research is needed to determine (1) if the benefits outweigh the side effects and (2) if metformin has a use in a clinical pediatric outpatient setting, outside of a tightly controlled clinical trial environment.

An observation of NHANES in 2007–2008 was the difference among ethnicities pertaining to increased obesity rate [1]. The increase in obesity over the last 30 years has

particularly affected Mexican-American and non-Hispanic Black boys and girls as compared to non-Hispanic White boys and girls [1]. After reviewing the studies performed with metformin in children, most of the studies had a non-Hispanic White majority of participants [6–10].

This study investigates the results of treatment with TLC alone, compared to TLC coupled with metformin, in pediatric patients with MS in a predominantly Hispanic population. Our specific aim was to determine in a free-living clinical outpatient setting if metformin plus TLC would give additional reduction in weight and BMI percentile or z-score in pediatric patients with MS as compared to TLC alone in a similar control population.

## 2. Methodology

The institutional review board of the University of Arizona approved this study. Study participants were retrospectively selected from the electronic medical record database for patients followed in our lipidology clinic between 2006 and 2011. Their selection was based on criteria for a diagnosis of MS and their age being between 8–18 years. No universally accepted criteria are available for diagnosis of pediatric MS. For the purpose of this study, diagnosis of MS was determined based on the presence of 3 or more of the following 5 factors: (1) blood pressure in the 90th percentile or above for age and gender [11], (2) triglycerides in the 90th percentile or above for age and gender [12], (3) HDL in the 10th percentile or below for age and gender [12], (4) a waist circumference in the 75th percentile or above for age and gender [13], and (5) evidence of impaired glucose tolerance or hyperinsulinemia. The latter criteria for our study required fasting glucose > 100 mg/dL, fasting insulin > upper limit of normal, or definite evidence of acanthosis nigricans. Patients treated with statins, niacin, fibric acids, bile acids sequestrants, ezetimibe, sulfonyleureas, or insulin were disqualified from the study. All patients with type I and type 2 diabetes were excluded. Patients who had a history of treatment with antihypertensive drugs were allowed to remain in the study as long as they still had 3 of the 5 requirements for MS. All patients were initially given detailed uniform instructions, both orally by the treating physician and in written material, regarding TLC for diet and exercise. Compliance with instructions was discussed and oral instructions were repeated during each subsequent visit by the physician as appropriate to the patient in the language of their choice (Spanish or English). Instructions included information regarding substituting an approximate 400 Kcal lunch brought from home instead of a much higher caloric school lunch, normal portion size, avoidance or marked limitation of caloric beverages, and inclusion of additional fruits and vegetables. Sweets and sugared cereals and other high sugar content foods were discouraged. Whole grain products were recommended. Fast food consumption was discouraged or better choices at fast food restaurants were recommended. Exercise was recommended for 30 minutes daily and brisk walking was emphasized. Ancillary personnel such as dietitians, exercise physiologists, pharmacists, and other personnel used in clinical trials were not included

in counseling patients. New patient visits with the treating physician were 45 minutes in duration, and follow-up visits were 30 minutes. A single physician treated all patients.

From the patients diagnosed with MS, two groups were formed. Group C, the control group, received only treatment with TLC. Group M patients received treatment with identical TLC and the addition of metformin therapy. Use of metformin for patients to assist with MS treatment was inspired by prior studies [8, 10]. Metformin in our patients was started for clinical indication only and without any plan for a future report. However, it was not used for all MS patients and we elected to use it only for alternating patients. Those in the M group were advised to take a multivitamin to provide vitamin B12. Metformin 500 mg twice a day was utilized and occasional patients were directed to take a higher dose. Potential adverse effects of metformin were explained and patients were directed to contact the physician if problems occurred. Initial data were collected from the time patients were first diagnosed with MS for the C group, or for the visit where they were first prescribed metformin for the M group. This initial data was compared to their last clinic visit. Thus not all patients who were recommended to take metformin were included in the final analysis and not all patients who were recommended TLC alone were included.

Each subject in the group that took metformin was matched, based on age, BMI z-score, and gender, with a TLC patient. The paired subjects at the start had to be within a year of age of each other, of the same gender and within 0.25 z-score for BMI. All participants that did not match to a member from the opposite group were eliminated from the study.

When they first started taking metformin for the M group, and compared to their last visit at the clinic. Information gathered from both groups included: age, gender, weight, height, presence of significant acanthosis, the percentage of body fat measured by caliper [14], waist circumference, fasting glucose, fasting insulin, blood pressure, HDL, LDL, triglycerides, and liver enzymes (AST, ALT). If a patient taking metformin was prescribed a secondary medication that could alter their results, data were collected from the time they first started taking metformin until the time before they first started taking their additional medication.

Results from the data collection for the 2 groups were compared using a paired *t*-test. Intragroup changes between the first visit and end visit were also compared using a paired *t*-test. Because of changes with growth and age, LDL, HDL, triglycerides, blood pressure, waist circumference, weight, height, and BMI were all converted to percentiles for age to standardize the values. Additionally, z-scores were analyzed for weight, height, and BMI [15].

## 3. Results

From a database of 241 possible subjects, 102 subjects met the requirements for MS and did not meet any of the exclusion criteria, and 46 of them took metformin. From the 46 participants in the M group and the 56 participants in the C group, only 30 from each group were comparable using the matching criteria described in the methodology section



TABLE 1: Participant characteristics.

	M group	C group	P value
Number of participants	30	30	
Average age (yr)	13.2	13.2	1.0
Gender			
Female %	46.7	46.7	
Male %	53.3	53.3	
Ethnicity			
Hispanic %	76.7	76.7	
Non-hispanic White %	23.3	20	
Non-hispanic Black %	0	3.3	
Treatment duration (days)	303	469	0.04
Avg. metformin dose (mg/daily)	1033.3	0	

(Table 1). The alternation of patients for metformin + TLC and TLC alone was imperfect since some patients in each group did not desire followup or come to further visits. Thus not all patients who were recommended to take metformin were included in the final analysis and not all patients who were recommended TLC alone were included. The ethnicity of both groups was 76.7% Hispanic. The M group had 23.3% non-Hispanic Caucasian participants and the C group had 20% non-Hispanic Caucasian and 3.3% non-Hispanic Black participants. The difference in duration between the groups was significant ( $P = 0.04$ ) (Table 1).

The M group took an average dose of 1033 mg/day of metformin with the median dose of 1000 mg/day. At this dosage, our M population did not report adverse effects when specifically asked. No residual pill counting was employed to test adherence to the medication. Patients affirmed at clinic visits that they were taking the medications. Their prescriptions were refilled at their local pharmacies. However, this did not absolutely guarantee compliance.

TLC were reviewed at each clinic visit and patients reported usually taking lunch from home to school 4 out of 5 days/week, markedly reducing the volume of caloric beverages, and decreasing portions sizes but usually not to the recommended size of the palm of their hand. Fast food frequency was also reported to be decreased and better choices were common. Exercise was reported to be substantially increased. Walking for a sustained 30 minutes was usually reported at 5 days/week but not the daily exercise as recommended.

Measures in both of the groups were compared at the beginning of the study and at the end of the study (Table 2). The only significant difference between measures at the start of the study for the M and C groups was duration of treatment ( $P = 0.04$ ), height measured in percentile ( $P = 0.046$ ) and z-score ( $P = 0.04$ ), and systolic blood pressure ( $P = 0.01$ ).

At the conclusion of the study, the only significant final value comparing the 2 groups was the difference of height between the two groups, which was measured using percentile ( $P = 0.02$ ) and z-score ( $P = 0.03$ ). Lipids (LDL,

TABLE 2:  $P$  values comparing the difference between the M group and the C group at the initial data collection and at the final data collection.

	Initial $P$ value	Final $P$ value
LDL (mg/dL)	0.86	0.62
LDL (percentile)	0.69	0.30
HDL (mg/dL)	0.68	0.46
HDL (percentile)	0.76	0.78
TG (mg/dL)	0.81	0.95
TG (percentile)	0.51	0.98
ALT (U/L)	0.31	0.16
AST (U/L)	0.26	0.14
Weight (kg)	0.16	0.63
Weight (percentile)	0.21	0.59
Weight (z-score)	0.08	0.22
Height (cm)	0.17	0.26
Height (percentile)	0.046*	0.02*
Height (z-score)	0.04*	0.03*
Insulin ( $\mu$ U/mL)	0.15	0.30
Glucose (mg/dL)	0.07	0.85
BP-systolic (mmHg)	0.01*	0.83
BP-diastolic (mmHg)	0.48	0.19
BP-systolic (percentile)	0.13	0.36
BP-diastolic (percentile)	0.08	0.40
Waist (in.)	0.14	0.24
Waist (percentile)	1.00	0.73
Body fat (%)	0.73	0.72
BMI ( $\text{kg}/\text{m}^2$ )	0.29	0.36
BMI (percentile)	0.80	0.51
BMI (z-score)	0.42	0.85

\* Reaches statistical significance ( $P$  value  $< 0.05$ ).

HDL, and triglycerides) showed no significant change when comparing the M and C groups. AST, ALT, fasting insulin, and fasting glucose were not significantly different. Weight, systolic blood pressure, diastolic blood pressure, waist circumference, the percentage of body fat, BMI percentile, and BMI z-score also showed no significant difference between the two groups at the end of the study (Table 2).

Intragroup changes from start to end of the study duration were evaluated similarly (Table 3). Despite the fact that there was little change when comparing the 2 groups at the end of the study, both of the groups showed significant intragroup changes in many of the parameters. The M group showed a significant decrease in LDL percentile ( $P = 0.01$ ), a decrease in weight z-score ( $P < 0.004$ ), an increase in height measured in centimeters ( $P < 0.004$ ), a decrease in height percentile ( $P < 0.004$ ), a decrease in height z-score ( $P < 0.004$ ), a decrease in glucose ( $P = 0.02$ ), a decrease in systolic blood pressure ( $P = 0.04$ ), a decrease in BMI percentile ( $P = 0.04$ ), and a decrease in BMI z-score ( $P < 0.004$ ).

The C group showed a significant decrease in AST ( $P = 0.03$ ), a decrease in weight in kilograms ( $P = 0.02$ ),

TABLE 3: Intragroup initial and final values, change and *P*-values.

	M group				C group			
	Initial	Final	Change	<i>P</i> value	Initial	Final	Change	<i>P</i> value
LDL (mg/dL)	111.87	108.23	−3.64	0.35	110.52	112.29	1.77	0.52
LDL (percentile)	73.67	65.77	−7.90	0.01*	71.72	41.79	−29.93	0.85
HDL (mg/dL)	38.73	40.04	1.31	0.18	39.69	152.89	113.20	0.49
HDL (percentile)	14.33	16.30	1.97	0.41	15.52	71.07	55.55	0.77
TG (mg/dL)	182.93	151.63	−31.30	0.053	187.69	17.32	−170.37	0.02*
TG (percentile)	91.00	86.48	−4.52	0.13	88.62	86.61	−2.01	0.15
ALT (U/L)	54.69	34.52	−20.17	0.17	38.53	23.32	−15.21	0.12
AST (U/L)	34.06	28.71	−5.35	0.43	27.60	21.91	−5.69	0.07
Weight (kg)	85.74	85.17	−0.57	0.68	78.63	82.74	4.11	0.02*
Weight (percentile)	97.87	96.67	−1.20	0.11	97.03	95.97	−1.06	0.10
Weight (z-score)	2.43	2.20	−0.23	<0.004*	2.21	2.03	−0.18	0.02*
Height (cm)	162.44	165.87	3.43	<0.004*	157.74	161.31	3.57	<0.004*
Height (percentile)	73.13	69.80	−3.33	<0.004*	58.60	53.13	−5.47	<0.004*
Height (z-score)	0.83	0.69	−0.14	<0.004*	0.28	0.12	−0.16	<0.004*
Insulin (μU/mL)	26.14	21.11	−5.03	0.22	19.63	17.26	−2.37	0.13
Glucose (mg/dL)	92.10	86.40	−5.70	0.02*	87.50	86.94	−0.56	0.70
BP-systolic (mmHg)	125.77	120.87	−4.90	0.04*	115.20	120.17	4.97	0.050*
BP-diastolic (mmHg)	71.07	69.70	−1.37	0.49	72.83	72.80	−0.03	0.99
BP-systolic (percentile)	74.40	70.57	−3.83	0.47	65.63	65.30	−0.33	0.95
BP-diastolic (percentile)	57.13	57.30	0.17	0.96	65.93	61.17	−4.76	0.32
Waist (in.)	42.10	41.30	−0.80	0.62	40.21	39.63	−0.58	0.37
Waist (percentile)	89.50	88.45	−1.05	0.29	89.50	88.00	−1.50	0.08
Body fat (%)	34.95	33.14	−1.81	0.26	34.41	32.48	−1.93	0.03*
BMI (kg/m <sup>2</sup> )	32.07	31.07	−1.00	0.44	30.78	33.64	2.86	<0.004*
BMI (percentile)	97.60	95.87	−1.73	0.04*	97.47	96.90	−0.57	0.26
BMI (z-score)	2.23	2.04	−0.19	<0.004*	2.17	2.06	−0.11	0.08

\* Reaches statistical significance (*P* value < 0.05).

a decrease in weight z-score ( $P = 0.02$ ), an increase in height in centimeters ( $P < 0.004$ ), a decrease in height percentile ( $P < 0.004$ ), a decrease in height z-score ( $P < 0.004$ ), an increase in systolic blood pressure ( $P = 0.050$ ), a decrease in the percentage of body fat ( $P = 0.02$ ), and an increase in BMI ( $P < 0.004$ ). All other values in both of the groups changed in an expected direction but not significantly.

#### 4. Discussion

The aim of this study was to determine the effectiveness of metformin plus TLC to treat MS as compared to TLC alone. Results show that at a median dose of 1000 mg/dL of metformin used in combination with TLC produced no significant improvement in outcome as compared to TLC alone for the primary endpoints of weight and BMI.

Previous research in this area has shown results varying from significant [8], modest [9], small [6], or no effect on overall weight loss [7] and BMI in adolescents taking metformin for MS symptoms. Since most of the other research in this field contains double blind clinical trials that were rigidly controlled [6–10], this study adds a new perspective on the

topic. Other studies required participants to meet monthly with a dietician [8], or attend a set amount of sessions with a trained health specialists [6] to make lifestyle modifications, both of which are expensive and would rarely occur in clinical practice. However, the clinical trials that found benefit from metformin, studied it at a higher dose that was almost double that used in this study [6, 8, 9]. A lower dose for our patients was selected to reduce adverse effects, mainly gastrointestinal effects, which probably allowed our patients to continue to take the medication. It is possible that metformin at a higher dose in the clinical setting could be more beneficial, but would have caused more adverse reaction and probably more medication discontinuance. Further research is needed to determine if an increased dosage and what level of dosage would be beneficial in a clinical situation.

Conducting a clinical study in a pediatric population undergoing a growth spurt, presents difficulties that are not inherent in an adult population. Specifically, in a growing population we must rely on percentile and z-scores to judge significance of change rather than absolute values as used in an adult study.

In both groups the average height increased which would be expected yet the z-score and percentile went down. This shows that although the absolute height increased, it did not increase at the same rate as before, perhaps as the result of (1) achieving, or nearly achieving, full stature or (2) slowing height increase as a result of decreasing excess calories.

The difference in the two groups at the beginning of the study was minimal. The only significant differences proved to be height and blood pressure. The difference in blood pressure could be attributed to the imbalance of patients that treated with blood pressure medications at the beginning of the study. Three patients from the C group were on anti-hypertensive therapy compared to zero patients in the M group. All patients still met the requirements stated in the methodology section despite their anti-hypertensive therapy and were therefore included in the study. Height percentile and z-score were also significantly different from the beginning of the study but they remained significant at the end as well.

Intragroup measures showed promising changes in the M group and C group. There were significant decreases in weight z-score in both groups, which may be attributable to TLC alone. BMI percentile and z-score significantly decreased in the M group whereas the C group measures did not reach significance.

The positive change in the C group, demonstrates the effectiveness of TLC in this population. The use of both oral and written instructions allowed patients to ask questions in the office and have a reminder of the information when they went home. Although all patients received the relatively same information, the approach was personalized and the session consisted of a problem identification interviewing technique rather than a disease-centered approach.

Limitations to this study include the population size of the study, the lack of ethnic diversity of the participants, the lower dose of metformin used, some incomplete laboratory values, and the fact that it was retrospective. The ethnicity was predominantly Hispanic, which decreases the applicability of this study to other ethnic groups. The median dose of metformin used was predominantly 1000 mg/day, with an average dose of 1033 mg/day. A higher dose may have produced different results but would probably have been more poorly tolerated. Since this study was retrospective, the visit frequency was not rigidly controlled and results could not be studied at defined intervals between start and end of the study.

Despite the limitations, this study demonstrates: (1) that metformin at a median dose of 1000 mg in this clinical setting did not produce a greater decrease in weight and BMI percentile and z-score than TLC alone, (2) that TLC demonstrated modest but significant intragroup weight z-score change in an outpatient pediatric MS population outside of a clinical trial.

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## Research Article

# Comparison of Serum Apolipoprotein Levels of Diabetic Children and Healthy Children with or without Diabetic Parents

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**Introduction.** The association of diabetes and atherosclerosis with disorders of lipids and lipoproteins, notably high apolipoprotein B (apoB) and low apolipoprotein A1 (apoA1) is well established. Because of the beginning of the atherosclerosis' process from early life, in this study, the plasma levels of apoA1 and apoB were compared in diabetic children with type I diabetes mellitus (DM), healthy children with diabetic parents (HDPs), and healthy children with nondiabetic parents (HNDPs). **Methods.** This case-control study was conducted among 90 children aged 9–18 years. Serum levels of apoA and apoB were compared among 30 diabetic children (DM), 30 healthy children with diabetic parents (HDPs), and 30 healthy children with nondiabetic parents (HNDP). **Results.** The mean serum apoA1 was higher in DM ( $153 \pm 69$  mg/dL) followed by HNDPs ( $138 \pm 58$  mg/dL) and HDPs ( $128 \pm 56$  mg/dl), but the difference was not statistically significant. The mean apoB value in HNDPs was significantly lower than DM and HDPs ( $90 \pm 21$  mg/dL versus  $127 \pm 47$  and  $128 \pm 38$  mg/dL,  $P < 0.05$ , respectively). The mean apoB levels in DM ( $127 \pm 47$  mg/dl) and HDP ( $128 \pm 38$  mg/dL) were not statistically significantly different ( $P > 0.05$ ). **Conclusions.** Diabetic children and healthy children with diabetic parent(s) are at higher risk of dyslipidemia and atherosclerosis. Thus for primordial and primary prevention of atherosclerosis, we suggest screening these children for low plasma apoA1 and high plasma apoB levels.

## 1. Introduction

Atherosclerosis is the most common cause of death in world [1]. Fatty streaks are the first atherosclerotic lesions and are developed since childhood. These lesions are also seen in a child of hyperlipidemic mothers. One of the risk factors of atherosclerotic cardiovascular disease is diabetes mellitus (DM) and is associated with worse prognosis in patients with diagnosed coronary artery disease. The risk of myocardial infarction (MI) in nondiabetic patients with and without previous history of MI is similar to diabetic patients without previous history of MI [2]. Then, treatment of risk factors in diabetic patients without previous history of MI should be the same with nondiabetic patients with previous history of MI [2].

The most important cause of atherosclerosis in diabetic patient's is diabetic dyslipidemia [2]. Diabetic dyslipidemia includes hypertriglyceridemia, increased LDL, decreased

HDL, high apoB and low apoA1 [3]. High apoB, and low apoA1 levels seen in type II DM are associated with increased risk of atherosclerotic cardiovascular diseases [3]. Increased plasma glycosylated lipoproteins are also seen in diabetic patients [4]. Diabetic dyslipidemia is associated with quantitative and qualitative changes in plasma lipids and lipoproteins [3]. In type I DM mild changes in shape and content of atherogenic apoB occur that predispose patients to increased risk of atherosclerosis [5]. In these patients, classic lipid profile may be normal but patient is at increased risk of atherosclerosis [5]. Measurement of apoA1 and apoB in diabetic patients may be helpful in diabetic patients at risk of cardiovascular diseases. Benefits of measurement of apoA1 and apoB in diabetic children or healthy children with diabetic parents are not determined. These patients are at increased risk of cardiovascular diseases. So, In this study, plasma levels of apoA1 and apoB were compared in diabetic children with type I diabetes mellitus (DM), healthy children



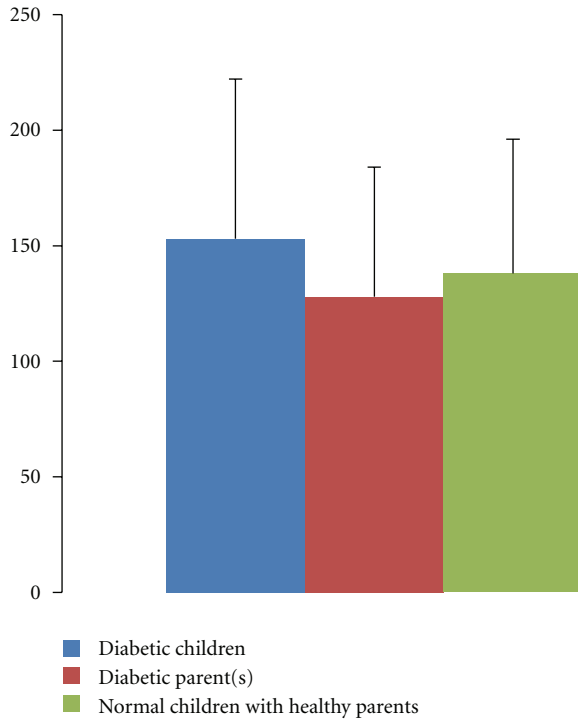


FIGURE 1: Comparison between serum apoA1 level in diabetic children, normal children with healthy parent(s), and healthy children with nondiabetic parents.

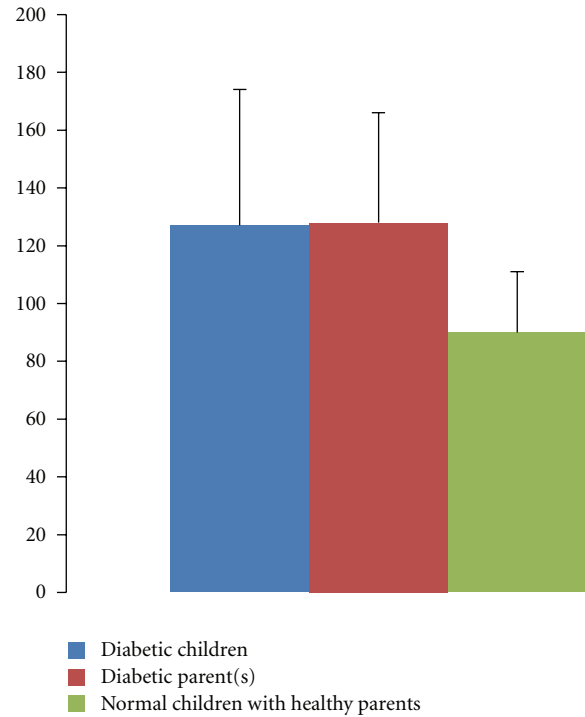


FIGURE 2: Comparison between serum apoB level in diabetic children, normal children with healthy parent(s), and healthy children with nondiabetic parents.

with nondiabetic parents (HNDPs), and healthy children with diabetic parents (HDPs).

## 2. Methods and Materials

In this case-control study, three groups of children (9–18 years old) were selected by simple random sampling: 30 healthy children (FBS < 110 mg/dL) without diabetic parents (HNDPs), 30 healthy children with diabetic parents (one or both) (HDPs), and 30 children with diagnosis of diabetes (DM) and under the treatment with Insulin for at least 2 year, both males and females. Exclusion criteria were poor control diabetes with HbA1C > 8.5%, history of lipodystrophy, glycogen storage disease, chronic kidney disease, nephritic syndrome, glomerulonephritis, chronic liver disease, physical inactivity, obesity, high-fat diet, alcohol consumption, hypothyroidism, treatment with corticosteroid, retinoid drugs, immune suppressive drugs, growth hormone, hydrochlorothiazide, beta-blockers, and steroid hormones. Serum levels of apoA (reference limit: 94–199 mg/dL) and apoB (reference limit: 60–133 mg/dL) were measured by Kits with 95% sensitivity (Parsazmon, Iran) using immunoturbidimetry method.

## 3. Results

The mean value of apoA1 in DM was  $138 \pm 58$  mg/dL lower than healthy children with mean values of  $153 \pm 69$  mg/dL, but this difference was not statistically significant

( $P > 0.05$ ). The mean value of apoA1 in healthy children with nondiabetic parent(s)  $128 \pm 56$  mg/dL was higher than healthy children with diabetic parent(s), but this difference was not statistically significant ( $P < 0.05$ ). The mean value of apoA1 in diabetic children was higher than healthy children with diabetic parent(s), but this difference was not statistically significant ( $P > 0.05$ ) (Table 1). Mean apoB value in healthy children with nondiabetic parent(s) was  $90 \pm 21$  mg/dL which was significantly lower than diabetic children with mean values of  $127 \pm 47$  mg/dL ( $P < 0.05$ ). The mean apoB levels in healthy children with nondiabetic parent(s) were  $90 \pm 21$  mg/dL which was significantly lower than children with diabetic parent(s) with the mean level of  $128 \pm 38$  mg/dL, but this difference was not statistically significant ( $P > 0.05$ ) (Table 2). The Mean levels values of apoA1 and apoB in healthy children with nondiabetic parents, healthy children with diabetic parents, and diabetic children are shown in Figures 1 and 2, respectively.

## 4. Discussion

The most common cause of death in diabetic is atherosclerotic cardiovascular disease [2]. Multiple cardiovascular risk factors like hypertension, obesity, and cigarette smoking are common in both type I and II DM, but diabetic dyslipidemia is the most important cause of increased risk of atherosclerosis in diabetic patients [2]. Increase of apoB in diabetic patients demonstrates increased plasma atherogenic lipids [3]. Decreased HLD is also associated

TABLE 1: Comparison of apoA1 levels in diabetic children, healthy children with diabetic parent(s), and healthy children with nondiabetic parent(s).

Groups studied	Apolipoprotein-in A1 (mg/dL) mean $\pm$ SD	P value		
		Diabetic children	Healthy children with diabetic parent	Healthy children with nondiabetic parent
Diabetic children	153 $\pm$ 69	—	0.27	0.62
Healthy children with diabetic parent	128 $\pm$ 56	0.27	—	0.80
Healthy children with nondiabetic parent	138 $\pm$ 58	0.62	0.80	—

TABLE 2: Comparison of apoB levels in diabetic children, healthy children with diabetic parent(s), and healthy children with nondiabetic parent(s).

Groups studied	Apolipoprotein-in B (mg/dL) mean $\pm$ SD	P value		
		Diabetic children	Healthy children with diabetic parent	Healthy children with nondiabetic parent
Diabetic children	127 $\pm$ 47	—	1.00	0.001
Healthy children with diabetic parent	128 $\pm$ 38	1.00	—	<0.0001
Healthy children with nondiabetic parent	90 $\pm$ 21	0.001	<0.0001	—

with decreased athero-protective apoA levels [3]. Fasting and postprandial apoB in diabetic patients is higher than healthy persons [6]. Improvement in control of type II DM was associated with decreased level of postprandial chylomicrons and lower transport of cholesterol to the apoB lipoproteins [7]. Plasma apoA1 and apoB levels are stronger predictors of premature atherosclerosis than other plasma lipoproteins [8]. Apoproteins are important risk factors for coronary artery disease in future for children with greater risk of atherosclerosis [9]. In one study on diabetic children, increased plasma apoB and dense LDL were associated with poor diabetic control [10].

In our study, in diabetic children apoB levels were higher than healthy children with and without diabetic parent(s). Plasma levels of apoA in diabetic patients were nonsignificantly higher than healthy children. In children with diabetic parent(s) plasma levels of apoA was nonsignificantly lower than healthy children with nondiabetic parent(s). In these children, plasma levels of apoB were nonsignificantly higher than healthy children with nondiabetic parent(s). Then, healthy children with diabetic parent(s) are at greater risk of atherosclerosis and screening for plasma apoA and apoB levels may be helpful in these children. Given the role of healthy lifestyle in prevention and control of non-communicable diseases [11], the barriers to healthy habits should be determined [12], and families should be encouraged for screening and preventive programs.

## 5. Conclusions

For primordial and primary prevention of atherosclerotic diseases, we suggest screening diabetic children and healthy children with diabetic parents for low plasma apoA1 and high plasma apoB.

## Conflict of Interests

Authors declare that they have no conflict of interests.

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## Research Article

# Are Dietary Cholesterol Intake and Serum Cholesterol Levels Related to Nonalcoholic Fatty Liver Disease in Obese Children?

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**Background.** Nonalcoholic fatty liver disease (NAFLD) in children has been recognized as a major health burden. Serum lipids as well as dietary cholesterol (DC) intake may positively relate to development of NAFLD. The purpose of this study was to investigate anthropometric, biochemical, and dietary intake parameters of obese Greek children with and without NAFLD. **Materials and Methods.** Eighty-five obese children aged 8–15 (45 boys/40 girls) participated in the study. NAFLD was diagnosed by ultrasonography (US) in all subjects. Liver indexes were measured in all children. A 3-day dietary was recorded for all subjects. **Results.** 38 out of 85 children (44.7%) were found to have fatty liver. Obese children with increased levels of TC (95% CI: 1.721–3.191), low density lipoprotein (LDL) (95% CI: 1.829–3.058), and increased dietary cholesterol intakes (95% CI: 1.511–2.719) were 2.541, 2.612, and 2.041 times more likely to develop NAFLD compared with the children without NAFLD. **Conclusion.** The present study showed that TC, LDL, and DC were the strongest risk factors of development of NAFLD. Reducing body weight and dietary cholesterol intakes as well as decreasing serum TC and LDL levels are urgently necessary in order to prevent NAFLD and possible other health implications later in life.

## 1. Introduction

Nonalcoholic fatty liver disease (NAFLD), which encompasses a broad spectrum of liver disorders ranging from simple hepatic steatosis to steatohepatitis (NASH) and cirrhosis, is currently the most common cause of chronic liver disease and abnormal liver function tests in Western countries [1]. The development of hepatic steatosis is considered to be associated with an excess intake of calories, visceral obesity, and insulin resistance, which result in an increased release of free fatty acids from adipocytes and increased rates of fatty acid synthesis in the liver [1]. Therefore, nutritional management and therapeutic exercise are fundamental steps to treat NAFLD.

The “two-hit theory” is increasingly being adopted to explain the pathogenesis of NAFLD and NASH [2]. In this theory, the first hit consists of the accumulation of

fatty acids/triglycerides in the liver, while the second hit involves oxidative stress, mitochondrial dysfunction, and inflammation, which ultimately cause liver damage.

Hepatic lipid homeostasis represents a balance between lipid uptake, synthesis, catabolism, and secretion. Therefore, steatosis, a typical characteristic of NAFLD, is expected to be caused by disordered lipid metabolism, particularly inhibition of fatty acid oxidation and enhanced lipogenesis. Many factors involved in hepatic lipid metabolism pathways have been identified, even though the precise cellular networks are not fully elucidated. In humans with NAFLD, cholesterol uptake in the form of LDL is limited by the intracellular accumulation of fatty acid and cholesterol, while fatty acid and cholesterol synthesis are upregulated in the NAFLD liver suggesting that the feedback system regulating and clearing up intracellular lipids levels is disrupted in NAFLD [3].

The prevalence of NAFLD in children remains unknown because of the lack of population-based studies and reliable screening tools. The available data suggests a prevalence range from 2.6% to 9.6% among children and adolescents in the United States and Asia which may reach to 12–80% in overweight and obese children [4]. Even though there is no consensus for the treatment for NAFLD in children, a recent review showed that many studies have been attempted to treat NAFLD using weight loss and exercise, antioxidants, and pharmacological agents [5].

Some studies have been suggesting that high-fat, high-fat plus low-protein, high-carbohydrate, and/or high-cholesterol diets are the main causes of NAFLD [6–8]. The reason for this is that cholesterol overload can upregulate gene expression and activate fatty acid synthesis by increasing oxysterol levels, metabolites of cholesterol that act as agonists for these genes indicating that excess cholesterol intake (i.e., cholesterol supply) itself can be a strong stimulant for the development of steatosis [9].

The purpose of this study was to investigate possible differences of certain parameters such as anthropometric, biochemical, and dietary of obese Greek children with and without NAFLD.

## 2. Materials and Methods

Eighty-five (85) obese children aged 8–15 y (45 boys/40 girls) were initially referred for obesity assessment to the outpatient 2nd Pediatric Department of Aristotle University of Thessaloniki, between January 2007 and January 2011. All children were screened for parameters of NAFLD. Written, informed consent was also obtained from each child's parents who participated in the study.

**2.1. Anthropometrics and Biochemical Indexes.** Anthropometrical indices such as height, weight, Tanner stage, and waist circumference were assessed in all children. Obesity was defined by International Obesity Task Force criteria for age and sex [10]. BMI was calculated by dividing weight (kg) by height squared ( $m^2$ ). Biochemical indices such as liver transaminases (ALT, AST), lipid profile, total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides (TG) were measured in all children. All children had normal serum levels of alanine aminotransferase (ALT)  $<40$  U/L and aspartate aminotransferase (AST)  $<37$  U/L. Participants were free of a history of clinical evidence of diabetes, cardiovascular, liver disease, hepatitis B or C, use of alcohol, drugs, or other disease (e.g., Wilson's disease, autoimmune hepatitis). NAFLD was diagnosed by ultrasonography (US) and was classified as having no or moderate hepatic steatosis (Grade II). The examination was performed by a radiologist with a convex probe (3.5–5 MHz) with Elegra-Siemens equipment. The echogenicity of the liver was estimated in a longitudinal US slice, showing the liver parenchyma and the neighboring right kidney [11].

Insulin resistance (IR) was calculated by means of the homeostasis model assessment (HOMA). IR was defined by  $HOMA >3.2 \mu U/mL$  [12].

**2.2. Dietary Intake.** A validated dietary intake [13] was used to collect information for a total of 3 days (2 weekdays and 1 weekend day). Study participants together with their parents were asked to describe the type and amount of food consumed after a detailed explanation and guidance provided by a registered dietician of our clinic. To improve the accuracy of food description, food models were used to describe the portion sizes. The dietary record was then analyzed using a software program (Sciencetech Diet 200A, Science Technologies, Athens, Greece, 2001) which consisted of more than 2500 Greek food items and recipes.

**2.3. Statistical Analysis.** Standard descriptive statistics were used for all patient characteristics. Data for continuous variables is expressed as mean values  $\pm$  standard deviation. *t*-test was used to compare characteristics of obese children with and without NAFLD. Partial correlation was estimated by using Spearman's correlation coefficient. Logistic regression analysis was used to estimate the relationship between ultrasound findings (normal or pathological) with HOMA, BMI, WC, HDL, LDL, dietary cholesterol, saturated fatty acid, sugar, and fiber consumed daily. *P* values  $< 0.05$  were considered statistically significant, while all confidence intervals (C.I.) represent 95% intervals.

## 3. Results

Based on ultrasonography, 38 out of 85 children (44.7%) were found to have fatty liver.

Anthropometric and biochemical characteristics of all subjects were presented in Table 1. Children with NAFLD were having higher BMI, WC TC, and LDL and lower HDL levels compared to children without NAFLD. In addition IR was significantly higher in obese children with NAFLD.

The dietary intakes of energy and major nutrients in the three categories are reported in Table 2. SFA, cholesterol, and sugar intakes were significantly higher in group with NAFLD compared with the group without NAFLD.

In Spearman's correlation model, BMI, WC, TC, LDL, and dietary cholesterol were found to be positively correlated with NAFLD, while HDL levels were negatively associated with NAFLD (Table 3).

In logistic regression analysis, obese children with increased levels of TC (95% CI: 1.721–3.191), low density lipoprotein (LDL) (95% CI: 1.829–3.058), and increased dietary cholesterol intakes (95% CI: 1.511–2.719) were 2.541, 2.612, and 2.041 times more likely to develop NAFLD compared with the obese children without NAFLD (Table 4).

## 4. Discussion

In the current study, we presented clinical data of 85 obese children with and without NAFLD proven by ultrasonography and its association with anthropometric and clinical



TABLE 1: Clinical characteristics of subjects based on fatty liver.

	Absent (n = 47)	Moderate (Grade II) (n = 38)	P value
Sex (M/F)	25/22	20/18	0.451
Age (y)	11 ± 2.1	11.5 ± 1.1	0.369
BMI (kg/m <sup>2</sup> )	25 ± 3.6	31 ± 2.9	<b>0.001</b>
WC (cm)	85.2 ± 11.2	97 ± 10.9	<b>0.001</b>
ALT (U/L)	22.7 ± 6.2	26 ± 4.1	0.942
AST (U/L)	21.1 ± 7.4	25.1 ± 3.2	0.212
TC (mg/dL)	168.7 ± 27.4	179 ± 19.8	<b>0.006</b>
HDL (mg/dL)	50.3 ± 13.1	40 ± 12.1	<b>0.002</b>
LDL (mg/dL)	103.7 ± 22.1	94 ± 9.6	<b>0.043</b>
TG (mg/dL)	110.2 ± 54.3	109.1 ± 60	0.294
CRP	2.2 ± 2.8	2.4 ± 2.6	0.591
HOMA-IR	4.3 ± 1.9	6.2 ± 2.1	<b>0.001</b>

Values are presented as means ± SD. Statistical significant difference ( $P < 0.05$ ). Abbreviations: BMI: body mass index, WC: waist circumference, ALT: alanine aminotransferase, AST: aspartate aminotransferase, TC: total cholesterol, LDL: low density lipoprotein, HDL: high density lipoprotein, TG: triglycerides, CRP: C-reactive protein, HOMA-IR: homeostasis model assessment of insulin resistance.

TABLE 2: Dietary intake of subjects based on fatty liver.

	Absent (n = 47)	Moderate (Grade II) (n = 38)	P value
Energy (kcal)	2444 ± 539	2605 ± 489	0.641
PRO (g)	103.1 ± 27.7	97 ± 23.3	0.323
CHO (g)	244.5 ± 67.5	276.1 ± 51.9	0.051
FAT (g)	139.7 ± 45.1	138 ± 41.9	0.079
SFA (g)	45.1 ± 12.6	61.9 ± 11.8	<b>0.032</b>
CHOL (mg)	321 ± 29.7	378 ± 28.7	<b>0.001</b>
Sugar (g)	10.8 ± 15.3	21 ± 12.9	<b>0.002</b>
Fiber (g)	20.0 ± 8.0	15 ± 9.1	0.081

Values are presented as means ± SD. Statistical significant difference ( $P < 0.05$ ). Abbreviations: PRO: protein, CHO: carbohydrates, SFA: saturated fatty acid, CHOL: dietary cholesterol.

parameters as well as with dietary intakes. The prevalence of our sample data was 38/85 (44.7%) which is between the prevalence (12–80%) found by other authors in a review study of different regions of the world such as Europe, America, and Asia [4].

It has been reported that the degree of steatosis in NAFLD is proportional to the degree of obesity [14]. BMI and WC were found in our study positively correlated with hepatic fat content. However, none of them were of the strongest risk factors of developing NAFLD in the logistic regression model analysis, suggesting that obesity and splanchnic fat distribution might also be effects of insulin resistance, rather than being directly involved in the etiology of fatty liver.

In our study the obese children with NAFLD were presented to have increased levels of insulin resistance, dyslipidemia, and WC. NAFLD is strongly associated with obesity, insulin resistance, hypertension, and dyslipidemia

and is now regarded as the liver manifestation of the metabolic syndrome (MetS) [15], a highly atherogenic condition.

Diets rich in fatty acids mainly saturated and trans-fatty acids, as well as carbohydrate-rich diets, favor an acute increase in IR independent of adiposity [16]. High SFA intake may also promote steatohepatitis directly by modulating hepatic triglyceride accumulation and oxidative activity as well as indirectly by affecting insulin sensitivity and postprandial triglyceride metabolism [17]. SFA consumption where found to be significantly higher in children with NAFLD compared with the children without NAFLD.

The consumption of sugar has been linked to risks for obesity, diabetes, metabolic syndrome, fatty liver, and heart disease, possibly by providing excess calories and large amounts of rapidly absorbable sugars [18, 19]. Our results showed that obese children with NAFLD had significantly higher intakes compared to children without NAFLD.

The most important finding of our study was that the children with NAFLD consumed significantly higher levels of dietary cholesterol compared to children without NAFLD. In addition, the total serum cholesterol levels of the same group were also found to be significantly higher, compared with the group without NAFLD.

Observational studies have been conflicting with regard to our findings. Some studies did not demonstrate different dietary intakes of cholesterol between NAFLD patients and controls [20, 21]. However, Musso et al. [17] did demonstrate a higher cholesterol consumption among normal weight NASH patients versus BMI matched controls. A recent study supported the role of dietary cholesterol in NAFLD. In this study, 12 normal weight NAFLD patients were compared to 44 obese NAFLD patients. A characteristic feature was that dietary cholesterol intake was significantly higher, while the intake of polyunsaturated fatty acids (PUFAs) was significantly lower, in the nonobese group. Similar differences were noted in comparison to 15 healthy nonobese controls. Therefore, this altered cholesterol and PUFA intake may be associated with the development of NAFLD in nonobese patients [9]. In addition, studies using nonobese animal models have confirmed that a diet high in cholesterol can induce NASH [22].

Obese children with NAFLD should be informed that a healthy diet has benefits beyond weight reduction. They should be advised to reduce saturated/trans-fat and increase polyunsaturated fat with special emphasize on omega-3 fatty acids. They should reduce added sugar to its minimum, and increase fiber intake. Physical activity should be integrated into behavioral therapy in NAFLD, as even small gains in PA and fitness may have significant health benefits. A combination of educational, behavioral, and motivational strategies is required to help patients achieve lifestyle change.

## 5. Conclusion

The present study showed that TC, LDL, and DC were the strongest risk factors of development of NAFLD. Reducing body weight and dietary cholesterol intakes as well as

TABLE 3: Parameters associating with NAFLD by Spearman's correlation coefficient.

Parameters	<i>r</i>	<i>P</i> value
BMI (kg/m <sup>2</sup> )	0.521	<b>0.001</b>
WC (cm)	0.296	<b>0.001</b>
HOMA-IR	0.175	0.501
TC (mg/dL)	0.533	<b>0.001</b>
HDL (mg/dL)	−0.281	<b>0.031</b>
LDL (mg/dL)	0.419	<b>0.021</b>
SFA (g)	0.081	0.092
CHOL (mg)	0.312	<b>0.009</b>
Sugar (g)	0.109	0.290

Statistical significant difference ( $P < 0.05$ ). Abbreviations: BMI: body mass index, WC: waist circumference, HDL: high density lipoprotein, HOMA-IR, homeostasis model assessment of insulin resistance, TC: total cholesterol, SFA: saturated fatty acids, CHOL: dietary cholesterol.

TABLE 4: Parameters associating with NAFLD by logistic regression analysis\*.

Parameters	Odds Ratio	95% CI	<i>P</i> value
BMI (kg/m <sup>2</sup> )	1.141	(0.871–1.645)	0.349
WC (cm)	1.192	(0.941–1.779)	0.452
HOMA-IR	1.488	(1.108–1.877)	0.229
TC (mg/dL)	<b>2.541</b>	(1.721–3.191)	<b>0.001</b>
HDL (mg/dL)	1.228	(0.877–1.524)	0.612
LDL (mg/dL)	<b>2.612</b>	(1.829–3.058)	<b>0.001</b>
SFA (g)	1.211	(0.544–1.612)	0.053
CHOL (mg)	<b>2.041</b>	(1.511–2.719)	<b>0.009</b>
Sugar (g)	0.448	(0.156–0.997)	0.319

Statistical significant difference ( $P < 0.05$ ). \*Adjusted for age, gender, and energy intake. Abbreviations: BMI: body mass index, WC: waist circumference, HDL: high density lipoprotein, HOMA-IR: homeostasis model assessment of insulin resistance, CHOL: dietary cholesterol, SFA: saturated fatty acids.

decreasing serum TC and LDL levels is urgently necessary in order to prevent NAFLD and possible other health implications later in life.

## 6. Limitations

Limitations of our study include the small size of the participants and the lack of liver biopsy. We also did not present activity level of patients as well as socioeconomic data.

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## Research Article

# The Triglyceride to HDL Ratio and Its Relationship to Insulin Resistance in Pre- and Postpubertal Children: Observation from the Wausau SCHOOL Project

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Insulin resistance (IR) is a risk factor for ischemic heart disease and diabetes and raises the triglyceride/high-density lipoprotein (TG/HDL) ratio in adults, but is not well defined in children. *Purpose.* To investigate the TG/HDL ratios in children as an IR marker. *Methods.* Wausau SCHOOL Project assessed 99 prepubertal and 118 postpubertal children. The TG/HDL ratio was correlated with numerous risk factors. *Results.* TG/HDL ratio was significantly correlated with QUICKI, HOMA-IR, zBMI, waist-to hip ratio, systolic and diastolic BP, LDL size and LDL number. A group of 32 IR children (HOMA-IR > 1 SD from the mean, i.e., >2.45) had significantly higher TG/HDL ( $3.11 \pm 1.77$ ) compared to non-IR children ( $1.86 \pm 0.75$ ). A TG/HDL ratio of  $\geq 2.0$  identified 32 of the 40 children deemed IR by HOMA-IR (>2.45) with a sensitivity of 0.80 and a specificity of 0.66. Children with TG/HDL ratio  $\geq 3$  were heavier and had higher BP, glucose, HOMA-IR, LDL number, and lower HDL level, QUICKI, and LDL size, regardless of pubertal status. *Conclusion.* The TG/HDL ratio is strongly associated with IR in children, and with higher BMI, waist hip ratio, BP, and more atherogenic lipid profile.

## 1. Introduction

Insulin resistance (IR) is a major risk factor for ischemic heart disease and diabetes [1–4]. IR significantly impacts lipoprotein metabolism and is associated with an increase in triglyceride (TG) levels, depressed high-density lipoprotein (HDL) levels, and an increase in the number of small dense LDL particles [4, 5]. The effect of IR on TG and HDL has made the TG/HDL ratio a useful marker of insulin resistance in adults [6, 7]. IR is increasingly identified in children [8]. Much less information is available regarding the impact of IR on lipid metabolism in children. The usefulness of the TG/HDL ratio in children as a marker of IR has not been adequately explored.

The Wausau SCHOOL Project is the result of a community-based effort to investigate the prevalence and magnitude of cardiovascular risk factors in school age children in the Wausau School District [9, 10]. The Wausau SCHOOL Project database includes anthropometric measurements,

fasting lipid profiles, and insulin and glucose levels from pre- and postpubertal children. The purpose of this investigation was to use this database to assess the impact of IR on lipid metabolism and determine the correlation of the TG/HDL ratio to IR and other markers of IR.

## 2. Methods

Details of the data collection for the Wausau SCHOOL Project have been described previously [9, 10]. Briefly, the investigation was reviewed and approved by the Aspirus Hospital Institutional Review Committee. A representative sample of Wausau School District students enrolled in grades 2, 5, 8, and 11 were recruited from all 17 schools. Approximately 480 students from each grade were invited to participate [9]. Consent was obtained from parent or guardian as well as assent from participating children. Weight and height measurements, waist and hip circumference, and blood pressure measurements were obtained for each

participant. Waist and hip circumference measurements were used to calculate the waist-to-hip ratio [9, 10]. A student was classified as having an elevated blood pressure if the systolic pressure was greater than 120 mm/Hg or the diastolic was greater than 80 mm/Hg on more than one occasion [9].

Twelve-hour fasting lipid levels were measured using nuclear magnetic resonance technology (LipoScience). This technique provides a standard lipid profile, as well as a measure of the size and number of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particles. From the fasting lipid profile, a TG/HDL ratio was calculated for each student.

The fasting blood sample was also used to obtain glucose and insulin levels. Insulin levels were measured by LipoScience using a commercial chemiluminescent immunometric assay (IMMULITE 2000). From the fasting insulin and glucose levels, the HOMA-IR [11] and the QUICKI [12] measurement of IR was calculated for each student. A student was considered IR if the HOMA-IR or QUICKI exceeded 1 standard deviation above the mean [10]. Because puberty affects IR [10, 13], calculations of HOMA-IR and QUICKI were analyzed separately for children in 2nd grade (prepubertal) and 11th grade (postpubertal) [10].

The BMI was corrected for age and sex based on revised growth charts developed by the Centers for Disease Control and Prevention (CDC) [14]. Using these data, a standardized body mass index (zBMI) was calculated as a measure of how much each student deviated from the CDC mean. For example, a zBMI of 1 indicates that the student exceeded the mean BMI for a child of that age and sex by 1 standard deviation (SD), while negative numbers indicate values below the mean. Students were considered overweight if they exceeded the 85th percentile in this distribution and obese if they exceeded the 95th percentile [15].

### 3. Statistical Methods

Means and SDs were calculated for the continuous variable data, and the groups were compared by independent group *t*-tests or analysis of variance tests (ANOVAs). Categorical comparisons were made using Chi-square analyses. From the calculations, the TG/HDL ratio was correlated with both the QUICKI and HOMA-IR method of determining insulin resistance, zBMI, and low-density lipoprotein (LDL) particle size and number. Data analyses were conducted using the Statistical Package for the Social Sciences, version 17.0, and  $P < 0.05$  was considered significant.

### 4. Results

Of the total 1920 students randomly recruited from grades 2, 5, 8, and 11, 715 were selected to participate in the SCHOOL Project. Of these, insulin, glucose, and lipid levels were obtained in 137 2nd graders and 126 11th graders. This study is based on 234 students who had complete data available, including HOMA-IR and lipid values. The mean HOMA-IR ( $1.22 \pm 1.07$ ) and QUICKI ( $0.39 \pm 0.050$ ) in 2nd graders was significantly different,  $t(167) = 3.71$ ,  $P < 0.001$ , and  $t(174) = 6.85$ ,  $P < 0.001$ , respectively, than 11th graders'

HOMA-IR ( $2.18 \pm 2.65$ ) and QUICKI ( $0.36 \pm 0.030$ ) and consistent with the postpubertal state being more IR. This higher degree of IR was also reflected in a higher TG/HDL ratio in 11th graders ( $2.59 \pm 1.81$ ) compared to 2nd graders ( $1.84 \pm 1.67$ ),  $t(231) = 3.28$ ,  $P = 0.001$ . When combining all students, the TG/HDL ratio was significantly correlated with both the HOMA:IR [ $r(232) = 0.319$ ,  $P < 0.001$ ] and the QUICKI [ $r(233) = -0.403$ ,  $P < 0.001$ ] method of assessing IR.

Table 1 summarizes correlations among TG/HDL and IR as measured by HOMA-IR and QUICKI, as well as to the lipid measurements, and anthropometric measurements. The TG/HDL ratio was significantly correlated with all of these parameters. Thus a higher TG/HDL ratio was associated with heavier students who were more likely to have smaller and more numerous LDL particles.

A TG/HDL of greater than 2.0 identified 32 of the 40 children deemed IR by HOMA-IR ( $>2.45$ ) with a sensitivity of 0.80 and a specificity of 0.66. A TG/HDL of  $\geq 3.0$  was especially specific for IR, with a specificity of 0.90 by the HOMA-IR method and .72 by the QUICKI method. Table 2 outlines the characteristic of the students whose TG/HDL level was  $\geq 3$  and compares them to the group as a whole. Note the striking differences and high prevalence of characteristics usually associated with IR. Although a TG/HDL  $\geq 3.0$  was highly specific for IR, the sensitivity for IR as measured by HOMA-IR was reduced to 0.42.

Just as a higher TG/HDL ratio predicted more IR, the converse was also true. The forty children considered IR by the HOMA-IR method had a TG/HDL of  $4.05 \pm 3.24$  compared to a ratio of  $1.86 \pm .94$  in non-IR children ( $t(40) = 4.25$ ),  $P < 0.001$ . This relationship was true regardless of puberty status.

### 5. Discussion

We have previously demonstrated that the HOMA-IR and the QUICKI method of assessing IR strongly correlated with zBMI, waist-hip ratios, and lipid abnormalities in pre- and postpubertal children in the Wausau School District [9, 10]. Although HOMA-IR and QUICKI are useful for research purposes, they are expensive and are not readily available to practicing clinician. In the present study, we found that the TG/HDL ratio in children, as in adults, correlates strongly with IR as measured by these two different methods. This relationship was already manifest as early as 2nd grade. Additionally, we found the TG/HDL ratio correlates strongly with other lipid abnormalities commonly found in the IR state: smaller and more numerous LDL particles. Not surprising, this ratio did not correlate as strongly with either total or LDL cholesterol. The poor correlation between IR and measurements of total and LDL cholesterol is well known [5]. Finally, a higher TG/HDL ratio was also strongly correlated with heavier students and a higher prevalence of elevated blood pressure. Thus the TG/HDL ratio in children could be useful in assessing relative IR and help direct resources appropriately to high risk children.

In an attempt to better define the meaning of any given TG/HDL ratio, we calculated the sensitivity and specificity of

TABLE 1: The correlation between TG/HDL ratio and other parameters of insulin resistance.

	TG	TC	LDL	HDL	LDL #	LDL Size	HOMA-IR	QUICKI	WH ratio	zBMI
TC	0.33***									
LDL	0.20**	0.94***								
HDL	-0.27***	0.28***	0.06							
LDL #	0.36***	0.82***	0.90***	-0.19**						
LDL Size	-0.36***	0.24***	-0.18**	-0.48***	-0.18**					
HOMA-IR	0.27***	-0.02	0.01	-0.28***	0.09	-0.24***				
QUICKI	-0.38***	-0.01	-0.04	0.37***	-0.13	0.29***	-0.73***			
WH ratio	0.16*	0.12	0.11	-0.08	0.13	0.02	0.09	0.03		
zBMI	0.24***	0.08	0.07	-0.17*	0.14*	-0.16*	0.25***	-0.34***	0.06	
TG/HDL	0.92***	0.18**	0.13*	-0.50***	0.36***	-0.54***	0.32***	-0.40**	0.17*	0.26***

TG: triglyceride, TC: total cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, LDL #: no. of LDL particles, LDL Size: Size of LDL particles, HOMA-IR: homeostasis model assessment of insulin resistance, QUICKI: quantitative insulin sensitivity check index, WH: waist hip, zBMI: age- and sex- corrected body mass index, TG/HDL: ratio of TG to HDL.

\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

TABLE 2: Clinical characteristics: TG/HDL ratio  $< 3$  compared to  $\geq 3$ .

Characteristic	TG/HDL ratio $< 3$	TG/HDL ratio $\geq 3$	<i>P</i> value
TC (mg/dl)	173.0 $\pm$ 28.6	180.2 $\pm$ 38.5	$P = 0.294$
LDL (mg/dl)	115.4 $\pm$ 25.6	120.0 $\pm$ 32.2	$P = 0.352$
HDL (mg/dl)	48.3 $\pm$ 9.2	36.7 $\pm$ 7.0	$P < 0.001$
LDL # (nmol/L)	1147.3 $\pm$ 238.0	1353.9 $\pm$ 388.2	$P = 0.004$
LDL Size (nm)	21.5 $\pm$ .36	20.9 $\pm$ .56	$P < 0.001$
HOMA-IR	1.46 $\pm$ 1.29	3.29 $\pm$ 4.3	$P = 0.017$
QUICKI	.38 $\pm$ .04	.34 $\pm$ .03	$P < 0.001$
WH ratio	.84 $\pm$ .10	.86 $\pm$ .09	$P = 0.269$
zBMI	.22 $\pm$ 1.39	1.03 $\pm$ 1.05	$P = 0.001$
BP-systolic (mmHg)	105.0 $\pm$ 14.9	117.2 $\pm$ 15.4	$P < 0.001$
BP-diastolic (mmHg)	65.9 $\pm$ 9.8	70.2 $\pm$ 8.2	$P = 0.014$
Glucose (mg/dl)	83.7 $\pm$ 6.2	86.0 $\pm$ 7.0	$P = 0.050$
% with elevated BP	34 (17%)	15 (43%)	$P = 0.001$

TG: triglyceride, TC: total cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, LDL #: no. of LDL particles, LDL Size: Size of LDL particles, HOMA-IR: homeostasis model assessment of insulin resistance, QUICKI: quantitative insulin sensitivity check index, WH: waist hip, zBMI: age- and sex- corrected body mass index, TG/HDL: ratio of TG to HDL, BP-systolic: systolic blood pressure, BP-diastolic: diastolic blood pressure.

\*All *P* values are based on independent *t*-tests, except the last, which is based on a Chi-square with 1 df. Elevated BP is defined as systolic  $> 120$  or diastolic  $> 80$ .

identifying IR students as based on HOMA:IR  $\geq 1$ SD above the mean [10] for a TG/HDL ratio  $\geq 2$  and  $\geq 3$ . Although a ratio  $\geq 2$  was quite sensitive for IR (80%), the relatively low specificity made this value less useful. However, a level  $\geq 3$  was especially specific for IR. Furthermore, such a level defined a cohort of students also possessing a high incidence of the features commonly associated with IR, including small dense LDL particles, increased BMI, and elevated blood pressure (Table 2). Thus a TG/HDL ratio  $\geq 3$  is especially concerning.

The correlation of the TG/HDL ratio in obese children (BMI averaging more than 2 SD above the mean) with IR has previously been made using the glucose clamp, HOMA-IR, and glucose tolerance testing by Giannini et al. [16]. These authors found that the TG/HDL ratio increased as IR increased. Our results confirm and extend upon these

findings by including obese and nonobese subjects as well as data on LDL particle size and number and pubertal state.

Bonito et al. [17] also found that the TG/HDL was correlated with IR in children as measured by the HOMA-IR method. Furthermore, they noted that as the TG/HDL ratio increased, so did the incidence of elevated systolic blood pressure and prevalence of increased left ventricular wall thickness on echocardiography suggesting the ratio was a marker of end organ damage. Our results confirm their observations as we also found the TG/HDL ratio to be associated with blood pressure. This was especially evident in those children with a TG/HDL ratio  $\geq 3$  (Table 2).

## 6. Limitation

Because we confined our measurements to pre- and post-pubertal states, the meaning of ratios in peripubertal states

remains undefined. Additionally, the extrapolation of our findings of students in the Wausau School District to children at large may not be appropriate. Additional investigations of other populations should be performed.

## 7. Conclusion

The results of this study indicate the TG/HDL ratio is strongly associated with IR in children as measured by HOMA-IR and the QUICKI method. An elevated ratio is characterized by a more atherogenic lipid profile, higher waist-hip ratio, and higher BMI. This pattern is already evident by 2nd grade, and the pattern becomes more prevalent in older children. A TG/HDL  $\geq 3$  is highly specific for IR and consequently, very concerning.

## Conflict of Interests

The authors report no conflict of interests.

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## Clinical Study

# Macronutrient Intake Influences the Effect of 25-Hydroxy-Vitamin D Status on Metabolic Syndrome Outcomes in African American Girls

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The objectives were to determine the effect of macronutrient modification on vitamin D status and if change in 25-hydroxy-vitamin D concentration influences components of metabolic syndrome in obese African American girls. *Methods.* Five-week intervention using reduced CHO (43% carbohydrate; 27% fat: SPEC) versus standard CHO (55% carbohydrate; 40% fat: STAN) eucaloric diet. Subjects were 28 obese African American females, aged 9–14 years. Dual energy X-ray absorptiometry and meal test were performed at baseline and five weeks. *Results.* Approximately 30% of girls had metabolic syndrome. Serum 25OHD increased in both groups at five weeks [STAN:  $20.3 \pm 1.1$  to  $22.4 \pm 1.1$  ( $P < 0.05$ ) versus SPEC:  $16.1 \pm 1.0$  to  $16.8 \pm 1.0$  ( $P = 0.05$ )]. The STAN group, increased 25OHD concentration over five weeks ( $P < 0.05$ ), which was positively related to triglycerides ( $P < 0.001$ ) and inversely associated with total cholesterol ( $P < 0.001$ ) and LDL ( $P < 0.001$ ). The SPEC group, had increase in 25OHD ( $P = 0.05$ ), which was positively related to fasting insulin ( $P < 0.001$ ) and insulin sensitivity while inversely associated with fasting glucose ( $P < 0.05$ ). The contribution of vitamin D status to metabolic syndrome parameters differs according to macronutrient intake. Improvement in 25OHD may improve fasting glucose, insulin sensitivity, and LDL; however, macronutrient intake warrants consideration.

## 1. Introduction

The steady rise in prevalence of pediatric obesity over the past three decades has been accompanied by accumulation of risk factors for metabolic syndrome (MetSyn) in childhood and adolescence. The occurrence of hypovitaminosis D (expressed as levels  $<20$  ng/mL of circulating 25-hydroxy vitamin D (25OHD)) has been increasingly documented in the same population [1, 2]. Moreover, children/adolescents with hypovitaminosis D have been reported to experience greater instances of hypertension, hypertriglyceridemia, hyperglycemia, and low high-density lipoprotein cholesterol (HDL) [1, 3, 4]. Further, it has been proposed that elevated parathyroid hormone (PTH), consequential to chronic low

vitamin D level, is mechanistically involved in the adverse perturbations of risk factors underlying MetSyn [5]. Given the emerging identification of vitamin D as an integral player in numerous metabolic pathways, it stands to reason that vitamin D status in the pediatric populace may play a role in the prevalence of metabolic disease risk factors [6, 7].

The relationship between 25OHD status and metabolic health is not equally distributed across groups. In particular, the relationship is more apparent among African American (AA) females, particularly those who are overweight/obese [8–11]. Although greater prevalence of hypovitaminosis D among obese AA may be in part attributed to skin pigmentation and sequestering of vitamin D in adipose tissue, differences in classical endocrine effects (e.g., PTH



and insulin response) likely also play a role [11]. Further, diet may modify the relationship between vitamin D bioavailability and underlying metabolic pathways. It is known that 25OHD level is dependent on intestinal absorption of dietary vitamin D, the extent to which vitamin D may exert effects on metabolic factors is at least in part dependent upon macronutrient profile of the diet. The metabolic response to dietary composition, specifically carbohydrate quantity of a meal, influences the postprandial cascade of events (increased glucose, insulin, lipogenesis, glycogenesis, etc.). Vitamin D has been independently associated with these processes, and the fact that vitamin D insufficiency stimulates secretion of PTH cannot be ignored. Data from this group has demonstrated that the physiological response to macronutrient concentration of the diet differs among racial groups [12]; however, to our knowledge there has been no investigation regarding the contribution of macronutrient profile to vitamin D involvement with metabolic components. Accordingly, the independent and interactive contribution of diet and vitamin D status (and consequent PTH level) on metabolic risk warrants investigation, particularly among obese adolescents.

Understanding the extent to which macronutrient composition influences vitamin D bioavailability may be particularly important during growth and development. Adolescence characterizes a time when risk factors for MetSyn can be identified, and modification of the dietary profile represents a strategy in which intervention may have the greatest directive impact. Therefore, the objective of this study was to determine the effect of macronutrient modifications on vitamin D status and if change in 25OHD concentration would influence components of MetSyn in obese AA girls. Further, as AA females are a population group that are at increased metabolic risk, this study seeks to evaluate the effect of macronutrient modification on associations of vitamin D concentrations and potential influence of PTH in AA adolescent females to parameters of MetSyn (fat distribution, insulin sensitivity, glucose tolerance, lipid concentrations, and blood pressure).

## 2. Methods

Participants included 28 overweight/obese AA girls aged 9–14 years. Obesity was defined as greater than 95th sex- and age-specific body mass index (BMI) percentile, and exclusion criteria were medical diagnosis and/or taking medications known to affect body composition, metabolism, and cardiac function. Participants were recruited through newspaper advertisements, flyers posted at various community partnerships, and by word-of-mouth. The nature, purpose, and possible risks of the study were carefully explained to each participant and guardian(s), and informed assent and consent, respectively were obtained. The protocol was approved by the Institutional Review Board for human subjects at the University of Alabama at Birmingham (UAB). All measurements were performed at the Participant and Clinical Interactions Resources (PCIRs) and the Department of Nutrition Sciences at UAB between 2008 and 2009.

**2.1. Protocol.** This study was part of a 16-week intervention comparing the effectiveness of a reduced CHO (43% carbohydrate: SPEC) versus a standard CHO (55% carbohydrate: STAN) diet on weight loss and metabolic health. Included data were derived from the initial five-week eucaloric phase, during which time the goal was for participants to maintain their baseline weight while consuming respective diets. Participants were block-randomized to one of the two diets which they remained on for the duration of the study. All food was provided, with the amount determined according to calculated individual needs determined by resting energy expenditure (REE; assessed via indirect calorimetry) multiplied by a 1.2 activity factor (averaging about 2000 kcal/d).

At baseline, participants attended two visits. The first visit entailed a physical examination by the study pediatrician, questionnaires on typical diet and regular physical activity, and a full-body dual energy X-ray absorptiometry (DXA) scan. At the second visit, participants reported to the PCIR in the morning in the fasted state for metabolic testing. After 30 minutes of rest, REE was assessed, and a liquid mixed-meal test (LMMT) was performed. To ensure weight stability, participants were weighed twice per week at food pickup to evaluate the caloric prescription throughout the five-week eucaloric phase. Weight changes exceeding two kilograms from baseline resulted in caloric modification in effort to maintain weight. Participants were asked to maintain their regular level of physical activity. At the duration of five weeks, the DXA scan, indirect calorimetry, and LMMT were repeated.

**2.2. Diets.** The SPEC diet comprised 42% of energy from CHO and 40% of energy from fat, whereas the STAN diet comprised 55% of energy from CHO and 27% of energy from fat. Both diets contained a similar content of protein (about 18%). Baseline energy levels for all diets were 1600 kcal with the addition of 100 to 400 kcal snack increments to participants who required more than 1600 kcal per day. All diets included culturally- and age-appropriate foods with no inclusion of supplements or formulas, and noncaloric fluid intake of  $\geq 64$  fluid ounces per day was recommended. All meals were prepared and packaged in the research kitchen at the UAB PCIR. A trained registered dietitian coded and entered data from each diet into the computerized Nutrition Data System for Research (NDSR).

**2.3. Anthropometrics.** The same registered dietitian obtained anthropometric measurements for all participants. Participants were weighed (Scale-Tronix 6702W; Scale-Tronix, Carol Stream, IL, USA) to the nearest 0.1 kg in minimal clothing without shoes. Height was also recorded without shoes using a digital stadiometer (Heightronic 235; Measurement Concepts, Snoqualmie, WA, USA). BMI percentile and obesity status ( $\geq 95$ th percentile) was calculated using sex- and age-specific CDC growth charts based on these measurements (<http://apps.nccd.cdc.gov/dnpabmi/>).

**2.4. Body Composition and Fat Mass Index.** Body composition was measured by DXA using GE Lunar Prodigy



densitometer (GE LUNAR Radiation Corp., Madison, WI, USA). Participants were scanned in light clothing, while lying flat on their backs with arms at their sides. Due to size limitations, participants not fitting within the scanning box were right-sided hemiscanned with the left side estimated as per instrument protocol. Fat mass index calculated as total body fat divided by height was used as a covariate [13].

**2.5. Liquid Mixed Meal Test/Insulin Sensitivity.** Insulin response to a standardized meal was determined from an index of insulin sensitivity and secretion through frequent blood sampling following ingestion of a LMMT (Carnation Instant Breakfast prepared with whole milk). To perform the LMMT, a flexible intravenous catheter was placed in the antecubital space of the left arm. The “dose” for the liquid meal test was obtained according to amount of lean body mass (LBM) of the participant (1.75 g CHO/kg LBM). Participants were required to consume the meal within five minutes. Blood was drawn at baseline (three samples over 15 minutes) prior to initiation of meal consumption at time “zero.” Subsequent blood samples were drawn every five minutes from time zero to 30 minutes, every 10 minutes from time 40 to 180 minutes, and at 210 and 240 minutes. Using the obtained measures, the insulin sensitivity index (SI) was calculated by oral glucose model [14].

**2.6. Assay of Metabolites.** Glucose was measured in 12  $\mu$ L sera with the glucose oxidase method using a SIRRUS analyzer (interassay CV 2.56%). Insulin was analyzed using a TOSOH 1800 Automated Immunoassay Analyzer. Assay sensitivity is 15.42 pmol/L, mean intraassay CV is 4.69%, and interassay CV is 6.0%. Triglycerides (TGs) were assessed with the glyceryl phosphate method. HDL was analyzed using a two-reagent system involving stabilization of low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol (VLDL), and chylomicrons using cyclodextrin and dextrin sulfate, and subsequent enzymatic-colorimetric detection of HDL. 25OHD and PTH concentration was obtained from fasting sera drawn and assayed in the UAB Core Laboratory with liquid chromatography/tandem mass spectrometry technique and a two-site radiometric assay, respectively.

**2.7. Statistical Analysis.** Differences at baseline in descriptive characteristics between girls in the two diet groups were examined using *t*-tests. The differences between diet groups regarding metabolic parameters were evaluated using ANOVA to allow for inclusion of covariates (pubertal stage, fat mass index, and baseline measures). Multivariate linear regression (Model A) was used to analyze the contribution of the change in 25OHD concentration over five weeks to individual components of metabolic syndrome. Due to the intricate relationship with PTH, for each component that was observed to be associated with 25OHD, a second regression model (Model B) was analyzed with inclusion of PTH as a covariate. To conform to the assumptions of linear regression, all statistical models were evaluated for residual normality and logarithmic transformations were performed

TABLE 1: Baseline descriptive characteristics.

	Total ( <i>n</i> = 28)	STAN ( <i>n</i> = 15)	SPEC ( <i>n</i> = 13)
Age (yrs)	12.4 $\pm$ 0.3	12.5 $\pm$ 0.4	12.4 $\pm$ 0.5
Tanner stage	4.4 $\pm$ 0.2	4.4 $\pm$ 0.3	4.4 $\pm$ 0.3
Height (cm)	159.5 $\pm$ 1.5	159.3 $\pm$ 2.0	160.3 $\pm$ 2.3
Weight (kg)	89.6 $\pm$ 4.6	93.8 $\pm$ 7.5	85.1 $\pm$ 4.8
BMI %	98.0 $\pm$ 0.3	98.1 $\pm$ 0.3	97.9 $\pm$ 0.5
BMI z-score	2.4	2.5	2.2
Trunk fat (%)	46.1 $\pm$ 1.4	48.1 $\pm$ 1.7	43.9 $\pm$ 2.3
Total fat (kg)	38.6 $\pm$ 2.4	41.1 $\pm$ 3.6	35.2 $\pm$ 2.7
Percent fat (%)	43.9 $\pm$ 1.0	45.8* $\pm$ 1.2	41.8* $\pm$ 1.5
Total lean (kg)	46.0 $\pm$ 2.2	47.4 $\pm$ 3.4	44.2 $\pm$ 2.3
Energy intake (kcal/d)	2105	2031	1991
MetSyn (%)	8 (29%)	4	4

\* Indicate significant difference between diet groups (*P* < 0.05).

STAN: standard diet (55% calories from carbohydrate).

SPEC: specialized diet (43% calories from carbohydrate).

TABLE 2: Circulating 25OHD levels at baseline and five weeks in the presence or absence of MetSyn.

	Baseline	SE	Five weeks	SE
MetSyn	17.6	1.59	17.7	1.49
No MetSyn	19.1*	0.93	21.3*	0.94

\* Indicates significant difference between baseline and five weeks (*P* < 0.05).

Abbreviations: standard error (SE).

when appropriate. All data were analyzed using SAS 9.2 software. Subsequently, models were evaluated by presence or absence of MetSyn. MetSyn was defined as meeting the IDF criteria for at least three of the components and was coded as zero for absence and one for presence. In addition, interaction terms were created (diet by change in 25OHD) and included in regression models to test the moderation by diet and change in 25OHD of relationships between metabolic outcomes.

### 3. Results

Descriptive characteristics and body composition at baseline in the total sample and by diet group are presented in Table 1. There were no differences between groups across variables, with the exception of percent body fat, which was significantly higher in the STAN diet group versus the SPEC diet group. At baseline, 29% of participants met the criteria for MetSyn, and individual components are illustrated at baseline and five weeks in Figure 1. Differences between diet groups were observed at baseline for circulating 25OHD and all lipid parameters [TG, LDL, HDL, and total cholesterol (tot chol)], and at five weeks for circulating 25OHD and TG.

Diet group evaluations related to MetSyn components are illustrated in Figure 2. Among those consuming the STAN diet, significant differences were observed from baseline to five weeks for circulating 25OHD (*P* < 0.05) and all lipid parameters (*P* < 0.001), except HDL. A significant

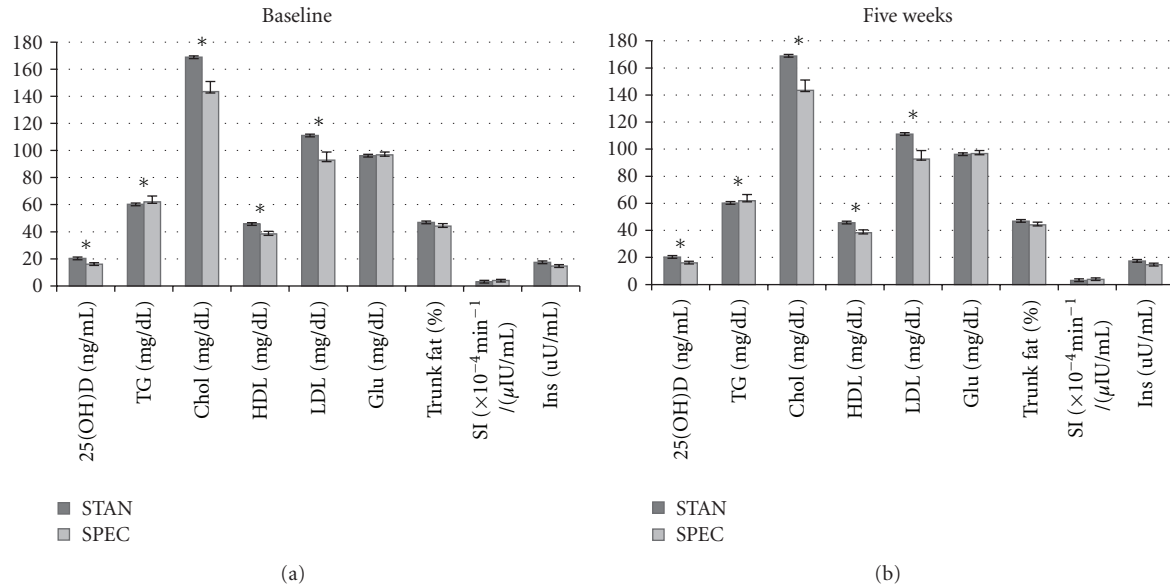


FIGURE 1: Components of metabolic syndrome at baseline and five weeks. \*Indicates significant difference between diet groups ( $P < 0.5$ ). Abbreviations: circulating vitamin D (25OHD), triglycerides (TGs), cholesterol (Chol), high-density lipoprotein (HDL), low-density lipoprotein (LDL), fasting glucose (Glu), insulin sensitivity (SI), and insulin (Ins).

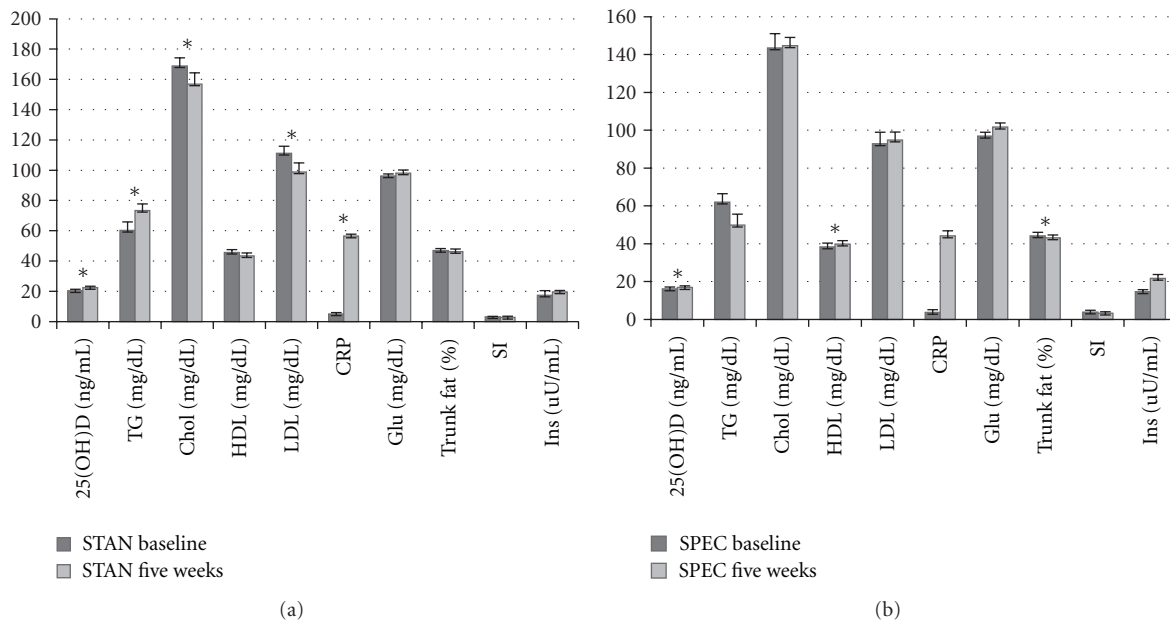


FIGURE 2: Diet group evaluations related to MetSyn components. \*Indicates significant differences between baseline and five weeks ( $P < 0.05$ ). Abbreviations: circulating vitamin D (25OHD), triglycerides (TGs), cholesterol (Chol), high-density lipoprotein (HDL), low-density lipoprotein (LDL), fasting glucose (Glu), insulin sensitivity (SI), and insulin (Ins).

increase was revealed for circulating 25OHD and TG with a decrease in total chol and LDL across the five-week period. Among those consuming the SPEC diet, a significant increase in circulating 25OHD and insulin ( $P = 0.05$  and  $P < 0.001$ , resp.) from baseline to five weeks was distinguished. Although an increase in circulating 25OHD was observed for both diet groups, circulating 25OHD levels were lower at baseline in participants presenting with MetSyn versus those with no MetSyn (Table 2). Similarly, greater

PTH concentrations were observed in those presenting with MetSyn than those without MetSyn at both baseline and five weeks ( $P < 0.001$ ). Further, individuals meeting criteria for MetSyn displayed no increase in circulating 25OHD across the five-week study period unlike participants without MetSyn.

The contribution of change in circulating 25OHD ( $\Delta\text{OHD}$ ) over the five weeks to MetSyn components is presented in Table 3. Two models were used to assess

TABLE 3: The contribution of  $\Delta$ OHD over the five weeks to MetSyn components represented by two models. Model A illustrates the independent contribution of  $\Delta$ OHD to metabolic parameters and Model B presents the inclusion of both  $\Delta$ OHD and PTH as independent variables.

STAN					SPEC			
REG Model A	ΔOHD <sup>a</sup>	<i>P</i> value			ΔOHD <sup>a</sup>	<i>P</i> value		
Glucose (mg/dL)	−0.06 ± 0.43	0.88			−2.33 ± 1.01*	0.04		
SI (×10 <sup>−4</sup> min <sup>−1</sup> /(μIU/mL))	−0.04 ± 0.06	0.49			0.66 ± 0.26*	0.02		
LDL (mg/dL)	−1.53 ± 0.60*	0.02			0.99 ± 2.54	0.70		
HDL (mg/dL)	−0.33 ± 0.38	0.39			−0.47 ± 0.89	0.60		
Triglycerides (mg/dL)	0.67 ± 0.44	0.14			4.71 ± 3.46	0.19		
Trunk fat (kg)	0.18 ± 0.12	0.15			0.35 ± 0.35	0.34		
REG Model B	ΔOHD <sup>a</sup>	<i>P</i> value	PTH <sup>a</sup>	<i>P</i> value	ΔOHD <sup>a</sup>	<i>P</i> value	PTH <sup>a</sup>	<i>P</i> value
Glucose (mg/dL)	0.68 ± 0.36	0.07	0.29 ± 0.07*	0.0007	−2.31 ± 1.04*	0.05	−0.14 ± 0.26	0.60
SI (×10 <sup>−4</sup> min <sup>−1</sup> /(μIU/mL))	−0.03 ± 0.07	0.69	0.00 ± 0.01	0.73	0.66 ± 0.22*	0.01	−0.11 ± 0.05*	0.04
LDL (mg/dL)	−1.84±0.70*	0.02	−0.13 ± 0.15	0.38	1.10 ± 2.62	0.68	0.31 ± 0.55	0.58
Triglycerides (mg/dL)	0.11 ± 0.37	0.75	−0.27 ± 0.07*	0.002	4.62 ± 3.62	0.23	−0.20 ± 0.85	0.81

\* Indicates significant difference ( $P < 0.05$ ).

<sup>a</sup>Values represent beta coefficient and standard error.

Abbreviations: insulin sensitivity (SI), low-density lipoprotein (LDL), high-density lipoprotein (HDL), parathyroid hormone (PTH), and change in 25OHD concentration ( $\Delta$ OHD).

the relationship. Model A illustrates the independent contribution of  $\Delta$ OHD to metabolic parameters, and Model B presents the inclusion of both  $\Delta$ OHD and PTH as independent variables. Among those consuming the STAN diet, an inverse relationship between  $\Delta$ OHD and LDL ( $P < 0.05$ ) was observed (Model A); in Model B, the association remained significant ( $P < 0.05$ ). However, in this model a marginal association between  $\Delta$ OHD and fasting glucose ( $P = 0.07$ ) was observed as well as an independent contribution of PTH to fasting glucose concentration ( $P < 0.001$ ). Additionally, a significant positive association between PTH and TG ( $P < 0.01$ ) was observed. Among those consuming the SPEC diet,  $\Delta$ OHD (Model A) was inversely associated with fasting glucose ( $P < 0.05$ ) and positively associated with SI ( $P < 0.05$ ); in Model B, these relationships remained, and an inverse relationship between PTH and SI was observed, whereas there was no relationship between PTH and fasting glucose.

At five weeks, 32% of participants met the criteria for MetSyn. There was no difference in those meeting criteria between diet groups; however, when the interaction term ( $\Delta$ OHD  $\times$  diet) was evaluated, those individuals who presented with MetSyn at five weeks displayed significantly positive associations between the interaction term and TG ( $P < 0.001$ ), HDL ( $P < 0.01$ ), LDL ( $P < 0.01$ ), and systolic blood pressure (SysBP;  $P < 0.01$ ). SI and insulin were inversely associated with the interaction term ( $P < 0.01$ ) in those individuals who did not present with MetSyn at five weeks. After five weeks, there was an increase in circulating 25OHD among those without MetSyn, yet no change was observed in those with MetSyn (Figure 3). Further, 25OHD concentration among those with MetSyn was at a level that would be deemed insufficient based on currently accepted criteria [15].

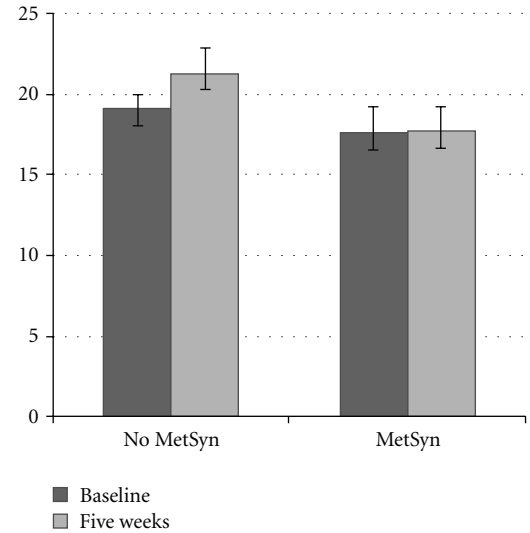


FIGURE 3: Circulating 25OHD levels at baseline and five weeks in the presence or absence of MetSyn.

#### 4. Discussion

Vitamin D's emerging role as an integral component of metabolism is accompanied by the occurrence of risk factors for metabolic disease early in life and displays a critical conduit to which dietary intervention may facilitate improved metabolic outcomes. The objective of this study was to determine the effect of macronutrient modifications in the absence of weight loss on vitamin D status and if  $\Delta$ OHD concentration would influence components of MetSyn in AA adolescent females. For those consuming a

reduced carbohydrate diet,  $\Delta$ OHD was inversely associated with fasting glucose and positively associated with SI. These relationships were maintained with inclusion of PTH. Clustering of metabolic parameters occurred such that glucose-related parameters in those without MetSyn, and lipid-related components in those with MetSyn were significantly associated with an interaction of diet and  $\Delta$ OHD. These results provide some evidence regarding the role that vitamin D may exert on alterations in the biological response to macronutrients lending itself to further exploration.

Numerous studies in children have suggested metabolic effects of 25OHD on several markers of glucose (e.g., fasting glucose, insulin concentrations, and HOMA score) [16–19] and lipid metabolism (e.g., TG, HDL, and LDL) [18, 19]. In this sample, the interaction term (diet and  $\Delta$ OHD) was positively associated with lipid profile among those meeting the criteria for MetSyn. Similarly, an independent effect of vitamin D on lipid profile was suggested by a weight-loss intervention study that found vitamin D supplementation resulted in improved lipid profile in the supplementation group despite similar weight-loss in nonsupplemented group [20]. Additionally, Al-Daghri and colleagues observed an association between total cholesterol and LDL and 25OHD which was apparent among adults with Type 2 Diabetes, but not in those without. Further, there was a reversal of MetSyn manifestations with vitamin D status correction [21]. From a physiologic standpoint, metabolic response to diet and potential relation with vitamin D status is an area in need of further exploration. The differential impact of the interaction between macronutrient composition and  $\Delta$ OHD is of particular interest in light of the lack of consensus regarding optimal 25OHD concentration as it relates to vitamin D recommendations.

It has been suggested that a reduction in carbohydrate intake requires increased insulin resistance to maintain glucose homeostasis, particularly during reproductive development [22]. Among the SPEC diet group, glucose concentration increased to a greater extent in those with a lesser increase in 25OHD, respectively insulin sensitivity decreased to a greater extent in those with a lesser increase in 25OHD. It is plausible that vitamin D mediates the effect of reduced carbohydrate intake through its direct action on pancreatic  $\beta$ -cell function [23]. Conversely, in the STAN diet group, in which carbohydrate intake reflected that which is more typical of the adolescent population [24], manifestations of altered 25OHD concentration were apparent in lipid parameters. LDL concentration increased to a greater extent in those with a lesser increase in 25OHD. Although cross-sectional analysis has consistently identified a favorable effect of 25OHD concentration on LDL, vitamin D's function in lipid metabolism remains uncertain. The confluence of macronutrient composition adds further complexity. The relationship observed in this study is clear, and our findings suggest that effect of dietary composition on 25OHD bioavailability warrant consideration.

Establishing the role of vitamin D in relation to MetSyn is complicated by its reciprocal association with PTH; in addition, several of the proposed predictors of MetSyn are also known to be associated with PTH. Not surprisingly, in those

meeting criteria, as opposed to those not meeting the criteria for MetSyn, PTH concentrations were significantly greater at both baseline and five weeks of this study. Many [25–27], but not all [28], studies report an inverse relationship between 25OHD and PTH. Moreover, AA generally present with lower 25OHD concentrations and higher PTH relative to European American counterparts [16, 26, 29, 30]. The relationship between vitamin D and PTH is influenced by various factors during growth and development, including dietary macronutrient composition, supported by findings reported herein. Independent of the positive association with vitamin D, an inverse relationship was found between PTH and SI, only apparent in those consuming the reduced carbohydrate, specialized diet. This may be translated into independent pathways of both PTH and vitamin D in linkage with MetSyn. It has been recently reported that PTH concentration, but not 25OHD, contributed to MetSyn in obese adults [5]. Support is provided for the postulation that influence by each of these factors diverges according to dietary composition.

This study had many strengths as well as evident limitations. Comprehensive phenotyping using robust measures of body composition is a major strength. The provision of food to each participant is an additional advantage because it ensured some degree of dietary control. Despite these strengths, it is important to evaluate certain shortcomings of this investigation. In noninstitutionalized subjects, dietary adherence is difficult to ascertain; beyond monitoring for weight change, the consumption of additional foods other than those provided cannot be certain. Also, the modest sample size and inclusion of only one racial group limits generalizability to other populations. Each participant was in the >99% BMI percentile, which may limit the ability to detect changes in outcome measures across body habitus. Finally, it is important to note that the short duration of the intervention may limit ability to identify the long-term effects of the diet on vitamin D.

## 5. Conclusions

Initiation and progression to MetSyn encompasses perturbations in glucose and lipid metabolism and is exacerbated by overweight/obesity, with AA females experiencing disproportionate incidence. Similar to what has been reported in other studies [7, 30–32], 29% of girls in this study presented with MetSyn and 25OHD was observed to be significantly lower and deemed insufficient in those presenting with MetSyn. Additionally, our results support the effect of macronutrient composition on the contribution of circulating 25OHD to parameters associated with MetSyn. Our findings also indicate that improvement in circulating 25OHD concentrations may normalize glucose parameters associated with initiation and progression to MetSyn. Additionally, though the mechanistic response of PTH to diet is unclear, its reciprocal relationship with vitamin D may mediate the effects of a reduced carbohydrate diet. This investigation builds upon previous findings which imply unique metabolic characteristics of peripubertal AA females.



In this context and considering the consistent reports of vitamin D insufficiency among this group, our findings may help inform recommendation efforts.

## Declaration of interest

The authors report no conflict of interest.

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## Research Article

# Metabolic Risk Factors, Leisure Time Physical Activity, and Nutrition in German Children and Adolescents

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**Purpose.** We assessed the five components of the metabolic syndrome (MetS) as defined by the International Diabetes Federation (IDF) in 6040 (3158 males) youths aged 6–16 years who participated in the Präventions-Erziehungs-Programm (PEP Family Heart Study) in Nuernberg between 2000 and 2007. The purpose of this cross-sectional study was to examine associations with lifestyle habits. **Results and Discussion.** The prevalence of MetS was low in children (1.6%) and adolescents (2.3%). High waist circumference (WC) and low HDL-C were slightly higher in females (9.5% and 7.5%, resp.) than in males (8.8% and 5.7%, resp.). Low leisure time physical activity (LTPA) was significantly associated with low HDL-C (odds ratio [OR] 2.4; 95% CI 1.2–5.0) and inversely associated with hypertension ( $r = -0.146$ ), hypertriglyceridemia ( $r = -0.141$ ), and central adiposity ( $r = -0.258$ ). The risk for low HDL-C ( $\leq 1.3$  mmol/L) was 1.7-fold (CI 1.0–2.6) higher in youth with high ( $\geq 33\%$ ) saturated fat consumption. A low polyunsaturated/saturated fat ratio (P/S ratio) was significantly associated with fasting hyperglycemia (OR 1.4; 95% CI 1.0–1.2).

## 1. Introduction

The metabolic syndrome (MetS) in youths is no more limited to industrialized countries, and ethnic disparities are well documented [1, 2]. Because MetS represents a serious risk of cardiovascular disease, tracking into young adulthood early intervention using healthy lifestyle is mandatory [3, 4]. Dietary intake has been linked to individual components of MetS suggesting that a western dietary pattern promotes the incidence of MetS [5]. Increase in moderate to vigorous physical activity was associated with better cardiometabolic risk factors in youths [6]. The purpose of this cross-sectional study was to examine associations between MetS components and lifestyle factors such as nutrition and physical activity in a large sample of healthy children and adolescents.

## 2. Material and Methods

We investigated 2393 children (1220 males) aged 6 to <10 years and 3647 adolescents (1938 males) aged 10 to <16

years participating in the community-based Präventions-Erziehungs-Programm (PEP) Family Heart Study between 2000 and 2007. Regularly trained research assistants measured height, weight, waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting triglycerides (TG), high-density cholesterol (HDL-C), and fasting plasma glucose (FPG) using standardized methods as described previously [7–9].

Parents and their children were trained to precisely document their daily intake of food and beverage on seven consecutive days including a weekend [9]. Each participating family was issued an accurately calibrated digital food scale (Soehnle Combi Plus, Nassau, Germany) to document their weighted protocols day by day. Completed dietary records were analyzed by trained dieticians using the computer program PRODI (version 4.5, Nutri-Science, Freiburg, Germany), which includes “Deutscher Lebensmittelschlüssel” supplemented with individual special items. The American Standard Code transferred the PRODI data for Information Interchange (ASCII) into SPSS (version 15.0) for documentation and calculation.

TABLE 1: Characteristics of 2393 children and of 3647 adolescents; \* $P < 0.05$  significant between genders.

(n)	Boys (1220)		Girls (1173)		Males (1938)		Females (1709)	
	mean	SD	mean	SD	mean	SD	mean	SD
Age (years)	8.7	1.7	8.7	1.7	14.3	1.9	14.3	1.9
Waist circumference (cm)	62.0*	7.5	60.7	7.5	74.0*	9.3	71.4	9.3
SBP (mm Hg)	104.7*	8.5	103.7	8.6	114.7*	11.5	109.5	9.3
DBP (mm Hg)	67.0*	7.6	66.1	7.7	71.5*	8.0	69.7	7.8
Total cholesterol (mmol/L)	4.7	0.8	4.8*	0.8	4.4	0.8	4.6*	0.8
LDL-C (mmol/L)	2.7	0.7	2.9*	0.7	2.5	0.7	2.6*	0.7
HDL-C (mmol/L)	1.7*	0.3	1.6	0.3	1.5	0.3	1.6*	0.3
Triglycerides (mmol/L)	0.7	0.3	0.8*	0.3	0.8	0.3	0.9*	0.4
Fasting plasma glucose (mmol/L)	5.2*	0.6	5.1	0.7	5.3*	0.6	5.1	0.6

Self-reported physical activity (PA) and sedentary behavior (SB) were assessed by assisted questionnaires as previously described [9]. SB was defined as typical behavior requiring low levels of energy expenditure to perform (1.0–1.5 METs). The participants were asked to register how often during the last seven days they performed leisure time sport activities (LTPAs) out of 39 listed items and sedentary activities (including computer use, playing video games, viewing television, videotapes, listening to music, reading, quiet sitting, sleeping, lying down, etc.) for at least 15 minutes. PA was calculated as the product of the duration and frequency of each activity (in hours per week). The time per week spent on each activity was multiplied by its typical energy expenditure in terms of metabolic equivalents of task (MET) and then summed over all activities to yield MET hours per week. We used special compendia for children and adolescents. LTPA was categorized into light, moderate (heart rate above rest and breathing somewhat harder than normal), and vigorous (heart rate considerably above rest and breathing much harder than normal) activities and MET levels presented for each effort level. As examples, leisurely, moderate-effort bicycling was assigned 6.2 METs, and moderate walking was considered as 3.6 METs [6, 10].

We used the IDF cut-offs for the five MetS components in terms of WC  $\geq$  90th percentile, SBP  $\geq$  130 or DBP  $\geq$  85 mm Hg, TG  $\geq$  1.7 mmol/L, HDL-C  $\leq$  1.03 mmol/L, and glucose  $\geq$  5.6 mmol/L [11].

For statistical analyses, we used SPSS 18.0 considering  $P < 0.05$  significant. Descriptive results are expressed as a mean for continuous variables and percentages for categorical variables. Differences between genders were tested by analysis of variance. Multiple linear regression models were calculated using all variables for LTPA. Multivariate logistic regression models were calculated using macronutrients as percentage of energy fat and consumption, respectively.

### 3. Results and Discussion

Mean values of WC, BP, HDL-C, and FPG were significantly higher in males than in females, whereas TG was significantly higher in females of both age groups (Table 1). As shown in Figure 1, the prevalence of the metabolic syndrome

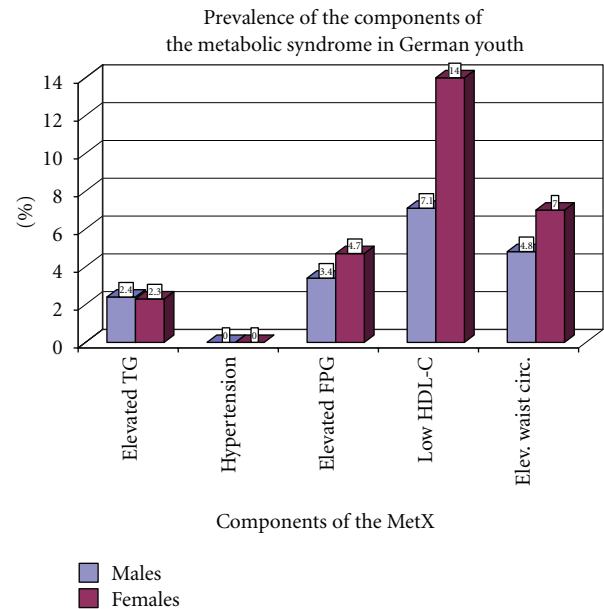


FIGURE 1

consisting of all five components was very low in children (1.4% in boys and 1.7% in girls) and adolescents (2.8% in males and 1.7% in females).

LTPA was higher in boys (26.3 METs) than in girls (15.5 METs) and higher in male (35.8 METs) than in female (21.2 METs) adolescents. We observed a significant ( $P < 0.001$ ) association between low HDL-C and sports less than 30 minute/day (OR 2.4; 95% CI 1.2–5.0). Low LTPA was significantly and inversely associated with elevated SBP ( $r = -0.446$ ) and elevated TG ( $r = -1.087$ ). We found the strongest associations of high WC with low sport activity ( $r = -0.749$ ) and with sedentary time ( $r = 0.307$ ), and sedentary time was significantly and inversely associated with high HDL-C ( $r = -0.903$ ). This is consistent with a recent meta-analysis of 14 studies with 20,871 youths showing significant and inverse associations between moderate to vigorous physical activity and HDL-C [6].

Mean absolute daily intake of energy (Kcal) and of fat was higher in male than in female adolescents but was

similar in terms of percentage of energy. Energy intake was inversely associated with HDL-C ( $r = -0.243$ ). The risk of low HDL-C ( $\leq 1.3$  mmol/L) was 1.7-fold (CI 1.0–2.6) higher in children and adolescents consuming much ( $\geq 33\%$ ) saturated fat compared with low SAFA intake. Significant associations have been observed between FPG  $> 5.6$  mmol/L and a low P/S ratio  $< 0.35$  (OR 1.4; CI 95% 1.0–2.1). The probability of high FPG was 10.3 (CI 2.9–36.2) times higher in youths consuming more than 35% fat than in youths consuming less fat. A comparison with the ARIC Study [4] is difficult because of different assessment of dietary intake (7-day weighed food versus dietary patterns).

A limitation is the cross-sectional design of the study, which should be confirmed by longitudinal data, which is not realistic for this setting. Vice versa, the strength of this study is to organize for more than 6,000 children and adolescents submitting weighed dietary protocols over 7 days and documenting simultaneously their physical leisure time activity as performed by the families participating in the PEP Family Heart Study.

#### 4. Conclusions

The prevalence of components of the metabolic syndrome as defined by the International Diabetes Federation definition is low in this sample of 6040 healthy children and adolescents. We found significant associations between MetS components and leisure time physical activity including sedentary behaviour and nutrition. This suggests that sustained lifestyle change in families participating in the PEP Family Heart Study might reduce even low cardiometabolic risk in their children. However, longitudinal studies should confirm this preventive approach.

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## Research Article

# Gender Differences Time Trends for Metabolic Syndrome and Its Components among Tehranian Children and Adolescents

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**Aims.** To investigate the trend of metabolic syndrome and its components in Tehran children and adolescents during a median followup of 6.6 years. **Methods.** Data from 1999–2001 (phase I), 2002–2005 (phase II), and 2006–2008 (phase III) of the Tehran, Lipid and Glucose Study were analyzed ( $n = 5439$ ; age 6–18 years) for the trend of metabolic syndrome (MetS) and its components. General estimation equation (GEE) models were used to analyze this correlated data. **Results.** The crude prevalence of MetS for boys at baseline was 13.2%, which increased to 16.4% in the third phase. In girls, the prevalence of MetS decreased from 11.8% at baseline to 6% during followup. The odd ratios (OR) of obesity over the whole study period were raised in both sexes. The OR of abdominal obesity increased significantly in boys, but no change was observed in girls. No significant OR was observed in boys, while OR for MetS was shown to have a decreasing trend in girls during the followup. In the three time points, the ORs of MetS decreased significantly in girls but no significant difference was observed in boys. **Conclusion.** In spite of increasing trend for obesity in both sexes, the trend of MetS decreased in girls and was relatively stable in boys, in Tehranian children, and adolescents.

## 1. Introduction

The metabolic syndrome (MetS) is defined as a clustering of metabolic risk factors including central obesity, hyperglycemia, dyslipidemia, and hypertension [1]. In recent decades, obesity and metabolic risk factors among children and adolescents have been much focused on several studies showing that increasing obesity and MetS in this population is associated with a number of adverse consequences in adulthood including type 2 diabetes mellitus and coronary heart disease, most likely due to overproduction of inflammatory mediators and insulin resistance [2–4].

While current estimates indicate a 2% to 9% prevalence for MetS in US adolescents [5], 14.1% of Iranian children have MetS based on ATP III criteria resulting from the increasing prevalence of overweight and abdominal obesity among Iranian children and adolescents [6, 7]. Previous

studies also demonstrated higher triglyceride and lower HDL-C levels in Iranian adolescents compared to their American counterparts [8, 9]. This increased prevalence would necessitate the need for identifying the time trend of MetS and its components in our population. Although the prevalence and associated risk factors of MetS have been widely studied in recent decades [10–12], much less is known in regard to changes in risk factor status over a longer period of time during childhood and adolescence, particularly in developing countries like Iran.

A few studies have evaluated the tracking of MetS and its components altogether [13–17] and most of them have provided data in support of a stability of MetS and its components in their populations [13, 14, 16]. Other studies have demonstrated an increasing trend in MetS [17] and its individual components [18–21]. In a recent study which used three independent sets of cross-sectional data with limited



sample size in Tehranian adolescents, aged 10–19 years, reported an increasing trend for obesity, abdominal obesity [22]. Given the above-mentioned limitations in this study, we aimed to examine the trend of MetS and its components from childhood to adolescence, due a mean of 6.6 years of followup for the first time in Middle East region using general estimation equation (GEE) analysis.

## 2. Materials and Methods

Subjects in this study were selected from among participants of the Tehran Lipid and Glucose Study (TLGS), a prospective study conducted to determine the risk factors and outcomes for noncommunicable diseases [23]. To summarize, 15,005 people, aged 3 years and over, residents of district-13 of Tehran underwent a baseline examination between February 1999 and August 2001. After this cross-sectional (phase I), subjects were categorized into the cohort and intervention groups, the latter to be educated for implementation of life-style modifications. We used metabolic and anthropometric data from phases I (1999–2001), II (2002–2005), and III (2006–2008) of the TLGS. For the current study, 5439 participants, 2643 boys and 2797 girls, aged 6–18 years who had participated at least in one of three phases, were enrolled. The study was approved by the institutional ethics committee of the Research Institute for Endocrine Sciences, affiliated to Shahid Beheshti University of Medical Sciences and was conducted in accordance with the principles of the Declaration of Helsinki.

Details of the TLGS protocol and all laboratory procedures have been published elsewhere [10]. Briefly, trained interviewers collected information, using a pretested questionnaire which included demographic data and anthropometric indices. Weight, height, and waist circumference (WC) were measured using standard protocols. Body mass index (BMI) was calculated as weight in kilograms, divided by height in meters squared. A qualified physician measured blood pressure twice with the subject in a seated position after one initial measurement for determining peak inflation level using a standard mercury sphygmomanometer; the mean of two measurements was considered to be the participant's blood pressure. Fasting blood samples for the measurement of glucose and lipid concentrations were drawn after the subjects had fasted overnight. Fasting blood glucose (FBG) was measured on the day of blood collection by the enzymatic colorimetric method using glucose oxidase. Triglyceride (TG) concentrations were measured by commercially available enzymatic reagents (Pars Azmoon, Tehran, Iran) adapted to a Selectra autoanalyzer. High-density lipoprotein cholesterol (HDL-C) was measured after precipitation of the apolipoprotein B-containing lipoproteins with phosphotungstic acid.

**2.1. Definitions.** We used the definition based on Cook et al. work for definition of the MetS in children and adolescents [24]. This definition is based on criteria analogous to that of the National Cholesterol Education Program Expert Panel

on Detection, Evaluation and Treatment of High Blood Cholesterol in Adult Treatment Panel III [1]; it defines MetS as three or more of the following: fasting TG  $\geq 110$  mg/dL; HDL cholesterol  $<40$  mg/dL; WC  $\geq 90$ th percentile for age and sex, according to national reference curves [25]; systolic blood pressure (SBP) and/or diastolic blood pressure (DBP)  $\geq 90$ th percentile for sex, age and height, from national reference cut-off points [26]; FBG  $\geq 100$  mg/dL. For the subjects who were aged over 18 years after the followup, we used the criteria for MetS in adults, specified by the Joint Interim Statement (JIS) [27]. Obesity was defined based on the standardized percentile curves of BMI suggested for Iranian children and adolescents as  $\geq 95$ th percentile of BMI for age and sex [6].

**2.2. Statistic Analysis.** All continuous data are expressed as mean  $\pm$  SD, and categorical variables are expressed as percentages. Independent *t*-test was used to compare difference between two sexes within in each phase. The general estimation equation (GEE) use the generalized linear model to estimate more efficient and unbiased analysis of demographic variables, anthropometric indices, and biochemical variables collected in longitudinal, nested, or repeated measures designs [28, 29]. This method relies on independence across subjects to consistently estimate the variance of the proposed estimators even when the assumed working correlation structure is incorrect. Logistic regression analysis was performed using GEE method for binominal variables. Variables were adjusted for age (years), time (phase) and intervention.

All analyses were performed using SPSS for Windows (version 16; SPSS Inc., Chicago, IL, USA), and significance was set at  $P < 0.05$ .

## 3. Results

For the current study, we had 3,854, 3,057, and 3,441 observations in phases I, II, and III, respectively. The GEE analysis was performed with 5,439 subjects (2643 boys), aged 6–18 years, who had at least one observation in whole period the study. At baseline, girls had higher mean values for WC ( $P = 0.04$ ), TG ( $P = 0.01$ ), LDL, and cholesterol ( $P < 0.001$ ) but lower SBP and FBS than boys ( $P < 0.001$ ). At the end of followup, all factors were higher in boys, while cholesterol and HDL values were higher in girls ( $P = 0.001$ , Table 1).

The crude prevalence of obesity increased in both sexes during a median follow-up of 6.6 years. Abdominal obesity increased from 12.3% to 33.1 in phase III in boys, but remained fairly stable in girls. The most frequent component of MetS was low HDL at baseline (39%) that increased up to 47% for boys and 43% for girls in the third phase. High TG was the next most prevalent component that decreased from 35% and 31% at baseline to 21% and 25% in girls and boys, respectively. The prevalence of MetS was 13.2% for boys at baseline that increased to 16.4% in the third phase. In girls, the prevalence of MetS decreased from 11.8% at baseline to 6% during followup (Figure 1).



TABLE 1: Anthropometric and metabolic characteristics of cohort participants by sex in 3 phases.

	Phase I		Phase II		Phase III	
	Boys N = 1858	Girls N = 1995	Boys N = 1415	Girls N = 1641	Boys N = 1592	Girls N = 1849
Age (year)	12.5 ± 3.5	12.6 ± 3.6	14.2 ± 4.53	14.7 ± 4.5	16.0 ± 5.6	16.6 ± 5.4
Weight (kg)	44.7 ± 19.2	42.7 ± 15.56*	53.1 ± 21.8	48.2 ± 16.0*	59.3 ± 23.6	51.4 ± 15.7*
BMI (kg/m <sup>2</sup> )	18.9 ± 4.4	19.0 ± 4.5	20.6 ± 5.0	20.6 ± 4.5	22.0 ± 6.3	21.4 ± 4.6*
Overweight (%)	19.7	17.5	28.3	23.7*	34.3	27.2*
Obesity (%)	8.3	6*	11.9	8.4*	13.8	8.9*
WC (cm)	65.0 ± 12.5	65.7 ± 10.8*	73.6 ± 14.6	69.0 ± 11.3*	77.8 ± 15.8	69.2 ± 11.0*
Abdominal obesity (%)	12.3	13.7	26.9	14.3*	33.1	13*
SBP (mmHg)	106.2 ± 12.2	103.6 ± 11.3*	104.0 ± 13.0	98.8 ± 11.3*	104.6 ± 13.2	98.3 ± 11.3*
DBP (mmHg)	71.1 ± 9.5	71.2 ± 9.4	67.2 ± 10.0	67.2 ± 9.4	67.5 ± 10.5	64.7 ± 9.6*
FBG (mg/dL)	88.9 ± 11.3	86.9 ± 8.3*	88.7 ± 11.6	86.2 ± 7.4*	86.9 ± 7.5	84.7 ± 7.0*
TG (mg/dL)	103.7 ± 60.7	107.9 ± 54.9*	101.6 ± 54.4	99.0 ± 47.7	105.2 ± 61.4	94.6 ± 45.9*
HDL-C (mg/dL)	44.0 ± 10.8	44.0 ± 10.5	40.8 ± 10.3	41.5 ± 10.1	42.8 ± 10.3	45.6 ± 10.4*

Data are presented as mean (SD) or percent.

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglycerides; HDL-C, high density lipoprotein cholesterol. Overweight defined as ≥85th to <95th percentile of BMI for age and sex; obesity defined as ≥95th percentile of BMI for age and sex; abdominal obesity defined as WC ≥ 90th percentile for age and sex.

\* $P < 0.001$  (between boys and girls in each phase).

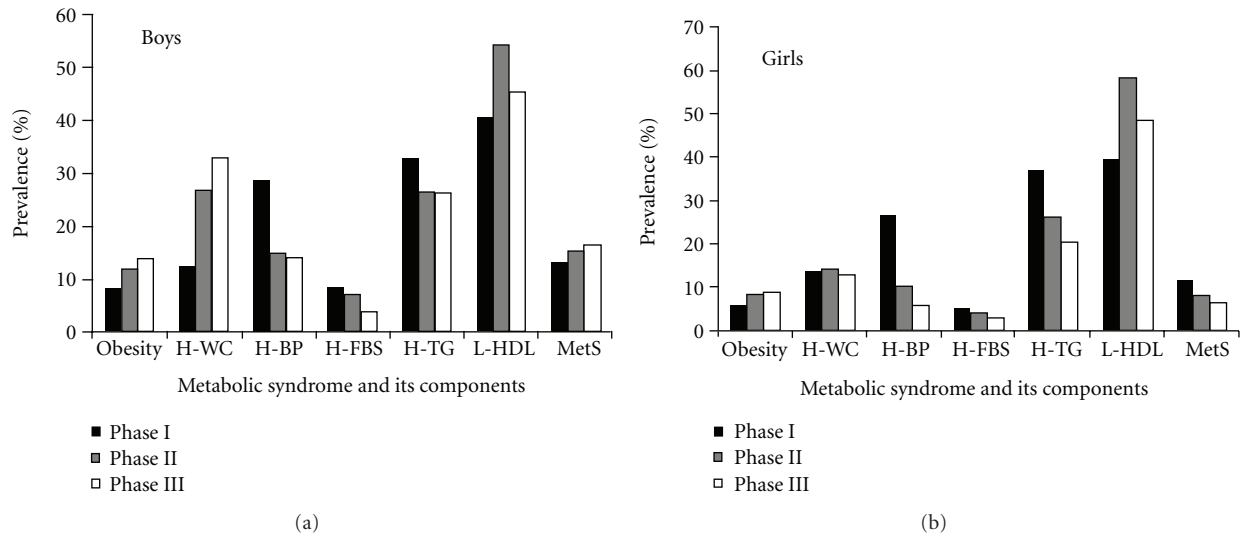


FIGURE 1: Prevalence of metabolic syndrome (MetS) and its components in boys ( $n = 2643$ ) and girls ( $n = 2797$ ). Obesity defined as ≥95th percentile of BMI for age and sex; high waist circumference (H-WC) ≥90th percentile for age and sex, according to national reference curves; high blood pressure (H-BP), SBP and/or DBP ≥90th percentile for sex, age and height, from national reference cut-off points; high fasting blood glucose (H-FBG), fasting glucose ≥100 mg/dL; high triglycerides (H-TG), fasting TG ≥ 110 mg/dL; low HDL cholesterol (L-HDL), HDL < 40 mg/dL.

The odds of obesity over the whole study period were raised in both sexes ( $P < 0.01$ ). While the odds of abdominal obesity increased significantly in boys ( $P < 0.001$ ), whereas no significant change was observed in girls ( $P = \text{NS}$ ). The odds for all other MetS component values declined towards the end of followup, except for HDL in girls. At three time points, the odds of MetS decreased significantly in girls (OR: 0.69 and 0.55  $P < 0.001$  in phases II and III, resp.) but no significant difference was observed in boys (OR: 1.1 and 0.94  $P = \text{NS}$  in phases II and III resp., Table 2).

#### 4. Discussion

Using GEE analysis, the results of present study conducted on 5,439 Tehranian children and adolescents, aged 6–18 years, suggest that during a median follow-up of 6.6 years, the trend of obesity increased in both sexes and for abdominal obesity increased almost three folds in boys. In spite of the increasing trend for the above factors, the trend for MetS decreased in girls and remained relatively stable in boys.

The high prevalence of obesity and MetS in childhood and adolescence has been shown to increase the prevalence

TABLE 2: Odd ratios<sup>a</sup> of the incident MetS parameters in phase I, II and III.

Characteristics	phase I	phase II	phase III
<b>Boys</b>			
obesity	1	1.40 (1.16–1.68)*	1.49 (1.19–1.87)*
Abdominal obesity	1	2.28 (1.95–2.67)*	2.61 (2.19–3.12)*
High FBG	1	0.90 (0.69–1.18)	0.47 (0.34–0.64)*
Low HDL-C	1	1.51 (1.32–1.73)*	0.84 (0.73–0.96)*
High TG	1	0.68 (0.58–0.78)*	0.63 (0.54–0.74)*
High BP	1	0.45 (0.37–0.53)*	0.42 (0.34–0.52)*
MetS	1	1.1 (0.90–1.33)	0.94 (0.73–1.22)
<b>Girls</b>			
obesity	1	1.42 (1.14–1.77)*	1.41 (1.07–1.84)*
Abdominal obesity	1	1.08 (0.912–1.28)	0.98 (0.79–1.21)
High FBG	1	0.78 (0.56–1.08)	0.59 (0.42–0.83)*
Low HDL-C	1	1.89 (1.66–2.14)*	1.07 (0.93–1.22)
High TG	1	0.65 (0.67–0.75)*	0.50 (0.43–0.58)*
High BP	1	0.50 (0.43–0.58)*	0.21 (0.16–0.27)*
MetS	1	0.21 (0.16–0.27)*	0.55 (0.41–0.75)*

Obesity, BMI  $\geq$  95th percentile for age and sex; abdominal obesity, WC  $\geq$  90th percentile for age and sex; high FBG, FBS  $\geq$  100 (mg/dL); Low HDL-C, HDL-C  $<$  40 (mg/dL); high TG, TG  $\geq$  110 (mg/dL); High BP, SBP, and/or DBP  $\geq$  90th percentile for sex, age, and height.

<sup>a</sup>(95% Confidence interval).

\*P value  $<$ 0.05 compare to phase I.

of cardiovascular events in adults [30]. Childhood and adolescent MetS have evolved into a worldwide epidemic, up to 14% in Australian [31] and 11% in Italian children [32]. Findings from previous studies in Iran have revealed a higher prevalence of MetS among Iranian children (9.8% [7]) compared with western (4.2% in US [24]) and Asian countries (1.4% in Japan [33] and 1.8% in Korea [15] 6.6% in China [34]). Several previous epidemiological studies demonstrated different trends for MetS and cardiometabolic risk factors among children and adolescents [13–17], which can be explained by variety in MetS definitions, length of followup, and also specific cultural and ethnical composition of studied population, lifestyle, and public health policies. In the Young Finns Study, a follow-up study of 1769 girls and 1688 boys, aged 3–18 years old, the prevalence of MetS increased with age in boys, and in 9–12 years old age girls [17]. The results from the Quebec family study indicated that indicators of MetS are moderately stable from childhood to adolescence [16]. Based on the Fels longitudinal study, authors concluded that 8 cardiometabolic risk factors associated with the MetS were relatively stable among children and adolescents [13]. On the other hand, results from the Korean NHANES Survey on 4164 subjects, aged 10–19 years, demonstrated a decline in prevalence of MetS, despite an increase in obesity in Korean adolescents [15]. In agreement with the Korean study, despite increasing trend of obesity, we found a decreasing trend of MetS in girls, but it relatively stable in boys mostly as a result of improvement in other MetS components. Similarly, an increasing prevalence of childhood obesity has been reported around the world [35–37]. Rapidly changing dietary practices and a sedentary lifestyle have led to increasing prevalence of childhood obesity (5–19 years) in developing countries recently [38] such

as Iran [22]. Moreover, recent systematic reviews and meta-analyses of available randomized trials reported nonsignificant effects of pharmacologic and behavioral treatments for reduction of overweight and obesity in children and adolescents [39, 40]. Regarding above mentioned studies, cardiometabolic risk factors were stable across time besides increasing trend of obesity in children and adolescents.

The decreasing prevalence of cardiometabolic risk factors can be explained by the positive effects of public health interventions in terms of lifestyle behaviors and increased physical activity on unfavorable risk factors. Accordingly, a systematic review has shown that higher physical activity levels were consistently associated with an improved metabolic profile and a reduced risk for MetS and/or insulin resistance in pediatric populations [41]. We speculate that recent changes in physical activity in addition to national health care initiatives in Tehran may have had a positive impact on the prevalence of MetS. We also found some notable differences between genders in the trend of MetS, for which however we do not have an adequate explanation; it could possibly be explained by more focus of public educational programs on girls compared to boys, leading to decreasing trend of MetS in girls.

The strength of our study was the considerable sample size of children and adolescents with a long followup period over which we measured MetS and its components enabling us to assess the time effect of these risk factors in our population using the GEE model for the first time.

However, our study had several limitations. First, our subjects were from a homogeneous population, potentially limiting the generalizability of our results. Second, we did not have data regarding puberty status which have helped us to assess the effects of puberty on MetS, and third, we

did not take into account some possible confounders such as physical activity, dietary habits, and socioeconomic status in our analysis.

## 5. Conclusion

In conclusion, inspite of the increasing trend for obesity in both sexes, the trend for MetS decreased in girls and remained relatively stable in boys in our population. Given the proven association between childhood and adolescence, obesity, and accuracy of cardiovascular events in adulthood, we are not sure that our observations, indicating persistency of excess weight along with reduction of cardiometabolic risk factors can be translated to decrease cardiovascular event rates in future adulthood. Further prospective studies with long-term followup are needed to answer this question.

## Conflict of Interests

All the authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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