Is the association of continuous metabolic syndrome risk score with body mass index independent of physical activity? The CASPIAN-III study

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BACKGROUND/OBJECTIVES: Although the association of body mass index (BMI) with metabolic syndrome (MetS) is well documented, there is little knowledge on the independent and joint associations of BMI and physical activity with MetS risk based on a continuous scoring system. This study was designed to explore the effect of physical activity on interactions between excess body weight and continuous metabolic syndrome (cMetS) in a nationwide survey of Iranian children and adolescents.
SUBJECTS/METHODS: Data on 5,625 school students between 10 and 18 years of age were analyzed. BMI percentiles, screen time activity (STA), leisure time physical activity (LTPA) levels, and components of cMetS risk score were extracted. Standardized residuals (z-scores) were calculated for MetS components. Linear regression models were used to study the interactions between different combinations of cMetS, LTPA, and BMI percentiles.
RESULTS: Overall, 984 (17.5%) subjects were underweight, whereas 501 (8.9%) and 451 (8%) participants were overweight and obese, respectively. All standardized values for cMetS components, except fasting blood glucose level, were directly correlated with BMI percentiles in all models (P-trend < 0.001); these associations were independent of STA and LTPA levels. Linear associations were also observed among LTPA and standardized residuals for blood pressure, high-density lipoprotein, and waist circumference (P-trend < 0.01).
CONCLUSIONS: Our findings suggest that BMI percentiles are associated with cMetS risk score independent of LTPA and STA levels.

INTRODUCTION

Metabolic Syndrome (MetS) is a cluster of risk factors that confers increased risks for cardiovascular disease and type 2 diabetes compared to its individual components [1]. The prevalence of MetS has increased in the adult population worldwide [2]. The lack of a common definition for MetS in the pediatric age group may be the cause of controversial findings across epidemiologic studies as well as the low prevalence of MetS in some populations [3-5]. Therefore, the American

Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have suggested using continuous Metabolic Syndrome (cMetS) risk score for studies on associations between MetS and potential risk factors in children and adolescents [6].

Some studies suggest using cMetS risk score instead of the binary definition in epidemiologic studies [7,8]. Using a continuous system for scoring is proposed to have the following advantages: a) cardiovascular and diabetes risk is a progressive function of several other risk factors of metabolic syndrome;

this nullifies the need to configure dichotomous variables [9]; b) increasing statistical power; and c) compared to dichotomous approach, cMetS risk score is more sensitive and less error-prone [9-11]. Different statistical methods have been devised to determine a continuous score. Previous methods used to drive a comment's score include principal components [12], z-scores [13-15], and percentile rankings [16]. Few studies have examined the construct validity of cMetS value and its association with MetS in children and adolescence [17,18]. In a previous study, we assessed the validity of cMetS score in a nationally representative sample of Iranian children and identified the sex and age-specific optimal cutoff-points of cMetS associated with MetS.

Many studies have demonstrated that excess weight from early life as well as physical inactivity significantly contribute to the development of MetS during childhood and adolescence [19,20]. In adults, some evidence suggests that MetS is modified by physical activity. Although the association of body mass index (BMI) with MetS is well-documented, there is little knowledge on the independent and joint associations of BMI and physical activity with MetS risk based on a continuous scoring system [19]. Therefore, the aim of this study was to determine the associations of BMI percentiles and leisure time physical inactivity (LTPA) with cMetS risk score in a nationally representative sample of Iranian children and adolescents.

SUBJECTS AND METHODS

Sample

Data for this study were collected from the third survey of the school-based surveillance system entitled "Childhood and Adolescence Surveillance and Prevention of Adult Non-communicable Disease" (CASPIAN), which was conducted in 2009 and 2010. Descriptions of the method and operation of the survey have been described before [21]. The study was approved by the ethical committee and other relevant national regulatory organizations.

The present study was performed among 5,625 students aged 10-18 years. Data on some variables were missing in some students; therefore, students with available data were included in the statistical analysis. Students were selected via multistage random cluster sampling method from urban and rural areas of 27 provinces in Iran. Eligible schools in our study were stratified according to the information bank of the Ministry of Health and Medical Education, and they were selected randomly. In selected schools, students were also selected randomly. Sampling and examinations were begun after complete explanation of the study's objectives and protocols for students and their parents by obtaining written informed consent from parents and also oral consent from students. A team of trained health care professionals recorded information in a checklist and carried out examinations according to standard protocols using calibrated instruments.

Clinical and laboratory measurements

Height (Ht) and weight (Wt) were measured to the nearest 0.1 kg and 0.1 cm, respectively, without shoes and with light clothing. Body mass index [BMI = weight (kg) /height (m^2)] was

calculated, and waist circumference (WC) was measured midway between the lower border of the rib margin and the iliac crest at the end of normal expiration. WC and height were measured using a non-elastic tape.

Two measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were performed using a standardized mercury sphygmomanometer on the right arm after a 15-minute rest in a sitting position; the first and fifth Korotkoff sounds were recorded as systolic and diastolic BP, respectively. The mean of the two measurements was considered as the subject's blood pressure. Mean arterial pressure (MAP) was calculated using the following formula: MAP = [(SBP-DBP)/3] + DBP.

Venous blood samples were drawn after 12 to 14 hours of overnight fasting from all study participants and delivered to the laboratory on the same day. Fasting blood glucose (FBG), total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), and triglycerides (TG) were measured enzymatically by auto-analyzers. HDL-C was determined after dextran sulfate-magnesium chloride precipitation of non-HDL-C [22]. Since collection of the highest quality data was critical to the success of our multi-center project, the Data and Safety Monitoring Board (DSMB) of the project considered different levels of quality assurance and control.

Definition of terms

BMI categories

The BMI cutoffs were provided by the Centers of Disease Control and Prevention (CDC) [23]. Participants were divided into underweight (BMI < 5th percentile of the study population), normal (5-84th percentile), overweight (85-94th percentile), and obese (> 95th percentile) [24,25].

Screen time and physical activity

The screen time behavior of children was assessed by a questionnaire that asked the child to report the average number of hours per day spent watching TV/VCDs, personal computer (PC), and electronic games (EG). Screen time activity (STA) was categorized into two groups (less than 2 hours per day and equal or more than 2 hours) based on international screen time recommendations [26,27].

In this study, we collected the leisure time physical activity of participants in the prior week using a validated questionnaire [28]. Children reported their weekly frequency (None, 1-2 days, 3-6 days, everyday) of leisure time physical activity outside of school that lasted at least 30 minutes and caused heavy sweating or large increases in breathing or heart rate. For statistical analysis, each weekly frequency received a degree (0-2 days per week (Mild), 3-5 days per week (Moderate), and 6-7 days (Severe)) [20].

Continuous Mets (cMetS) score

We have previously published the methodology of the cMetS score calculation in detail [29]. In brief, the cMetS score was computed by standardizing the residuals (z-scores) of WC, MAP, HDL-C, TG, and FBG by regressing them according to age and sex to account for age and gender-related differences. HDL-C

Table 1. Basic anthropometric and demographic characteristics according to BMI levels in Iranian adolescents : the CASPIAN III study

Variables	BMI levels				P-value
	Underweight	Normal weight	Overweight	Obese	
N (%)	984 (17.5)	3689 (65.6)	451 (8.0)	501 (8.9)	
Age (yrs)	14.2 ± 2.3	14.9 ± 2.4	14.7 ± 2.3	14.4 ± 2.3	< 0.001[1]
Weight (kg)	34.1 ± 8.1	46.4 ± 12.1	58.9 ± 13.5	67.7 ± 16.7	< 0.001[2]
Height (cm)	149.8 ± 13.3	155.0 ± 13.9	156.3 ± 12.9	154.9 ± 14.6	< 0.001[3]
BMI (kg/m^2)	14.9 ± 1.3	19.0 ± 2.4	23.7 ± 2.1	27.8 ± 3.5	< 0.001[2]
Waist circumference (cm)	60.9 ± 24.5	67.7 ± 19.9	76.2 ± 10.7	84.6 ± 13.0	< 0.001[2]
Waist to height ratio	0.4 ± 0.2	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	< 0.001[2]
Sex (%)					
Male	498 (50.6)	1,775 (48.1)	265 (58.8)	286 (57.1)	< 0.001
Female	486 (49.4)	1,914 (51.9)	186 (41.2)	215 (42.9)	
Living Place (%)					
Urban	612 (63.3)	2448 (68.3)	347 (80.5)	378 (78.8)	< 0.001
Rural	355 (36.7)	1,136 (31.7)	84 (19.5)	102 (21.2)	
Family history of (%)					
Diabetes	229 (31.1)	992 (35.7)	148 (44.0)	179 (48.4)	< 0.001
Obesity	244 (33.3)	1,043 (39.0)	156 (48.4)	180 (54.5)	< 0.001
Hyperlipidemia	292 (39.1)	1,139 (40.6)	149 (44.3)	188 (50.3)	0.001
Hypertension	386 (50.4)	1,388 (48.2)	192 (54.1)	207 (53.4)	0.06
STA (%)					
< 2 h/day	542 (57.6)	1,930 (53.9)	217 (49.2)	257 (52.8)	0.03
≥ 2h/day	399 (42.4)	1,649 (46.1)	224 (50.8)	230 (47.2)	
Physical activity (%)					
Mild	273 (30.9)	1,104 (33.1)	161 (39.2)	157 (34.3)	0.03
Moderate	283 (32.0)	1,109 (33.3)	128 (31.1)	161 (35.2)	
severe	328 (37.1)	1,119 (33.6)	122 (29.7)	140 (30.6)	
Father's education (%)					
< 6 yrs	454 (47.5)	1,567 (43.6)	132 (30.8)	138 (29.2)	< 0.001
6-9 yrs	230 (24.1)	868 (24.1)	116 (27.1)	116 (24.5)	
> 9-12 yrs	198 (20.7)	838 (23.3)	127 (29.7)	148 (31.3)	
> 12 yrs	74 (7.7)	322 (9.0)	53 (12.4)	71 (15.0)	
Mother's education (%)					
< 6 yrs	561 (58.0)	2,072 (57.2)	196 (45.0)	175 (36.7)	< 0.001
6-9 yrs	216 (22.3)	701 (19.3)	96 (22.0)	115 (24.1)	
> 9-12 yrs	163 (16.8)	670 (18.5)	115 (26.4)	156 (32.7)	
> 12 yrs	28 (2.9)	181 (5.0)	29 (6.7)	31 (6.5)	
Father's occupation (%)					
Employed/office work	217 (22.8)	782 (22.1)	119 (28.1)	127 (27.1)	< 0.001
Agriculturist	107 (11.3)	478 (13.5)	33 (7.8)	24 (5.1)	
Workman/labor	255 (26.8)	778 (22.0)	78 (18.4)	79 (16.8)	
Self-employed	297 (31.3)	1,283 (36.3)	169 (40.0)	212 (45.2)	
Workless	74 (7.8)	217 (6.1)	24 (5.7)	27 (5.8)	
Mother's occupation (%)					
Employed/office work	33 (3.4)	213 (5.9)	31 (7.2)	41 (8.5)	0.006
Workwoman/labor	16 (1.7)	36 (1.0)	6 (1.4)	10 (2.1)	
Housewife	900 (93.5)	3,294 (91.0)	389 (89.8)	419 (87.1)	
Others	14 (1.4)	78 (2.1)	7 (1.6)	11 (2.3)	
Type of home (%)					
Personal home	745 (78.8)	2,876 (81.3)	328 (77.5)	363 (77.7)	0.06
Rented home	200 (21.2)	663 (18.7)	95 (22.5)	104 (22.3)	
Personal car (%)					
Yes	424 (44.4)	1,760 (48.9)	259 (59.7)	270 (57.2)	< 0.001
No	532 (55.6)	1,839 (51.1)	175 (40.3)	202 (42.8)	

n (%) or mean±SD

[1] According to Tukey post hoc test, the difference between underweight with normal and overweight is significant.
[2] According to Tukey post hoc test, all groups have significant differences with each other.
[3] According to Tukey post hoc test, all groups have significant differences with the underweight group.

was multiplied by -1, as it is inversely related to MetS risk. A higher cMetS score indicates a less favorable metabolic profile [30].

Statistical analysis

Data were analyzed by using SPSS software package (version 16.0; SPSS Inc., Chicago, IL, USA); P-values less than 0.05 were considered as statistically significant. All variables were checked for normality.

Findings on continuous variables were expressed as means ± standard deviation (SD), and categorical data were expressed as a percentage. The ANOVA test was applied to compare the mean differences of variables between BMI categories. Tukey's post hoc method was used for pair wise comparisons. Student's two-tailed *t* was used to compare the mean differences of cardiometabolic z-scores across the screen time activity categories. The association between categorical variables was assessed by the Chi square test.

Linear regression models were performed for each dependent variable (cMetS and its components). In model I, the crude association of BMI percentiles with cMetS and its components as well as the association of LTPA with cMetS and its components were analyzed. In models 2 and 3, the adjusted association of BMI percentiles with cMetS and its components as well as the association of leisure time physical activity with cMetS and its components were tested. In model 4, addition to variables of model 3, BMI percentile and LTPA were simultaneously in the model. In model 5, BMI percentile and LTPA interaction term were added to the previous model.

We assessed the association between cMetS and BMI percentiles across LTPA and STA categories by using linear regression models. The results of the linear regression model were reported as β coefficient.

RESULTS

Anthropometric and demographic characteristics

The study participants included 5,624 students (50.2% boys, mean age 14.7 ± 2.4 years). The numbers of students classified as underweight, normal weight, overweight, and obese were 984 (17.5%), 3,689 (65.6%), 501 (8.9%), and 451 (8%), respectively. The anthropometric and demographic characteristics of the subjects across BMI percentiles are shown in Table 1. All variables were statistically different between these BMI categories, except for family history of hypertension and type of home.

Table 2. Mean values of standardized components of cMetS in Iranian adolescents according to BMI, LTPA, and STA categories in Iranian adolescents: the CASPIAN-III study

Variables	BMI categories					LTPA categories				STA categories		
	Underweight	Normal weight	Overweight	Obese	P-trend	Mild	Moderate	Severe	P-trend	< 2 h/day	≥ 2 h/day	P-trend
Z_MAP	-0.28 ± 1.00	-0.02 ± 0.97	0.21 ± 0.95	0.51 ± 0.99	< 0.001	0.05 ± 0.98	-0.03 ± 1.01	-0.03 ± 1.00	0.03	-0.02 ± 1.00	0.01 ± 0.98	0.17
Z_TG	-0.22 ± 0.72	-0.07 ± 0.89	0.20 ± 1.10	0.76 ± 1.54	< 0.001	0.04 ± 1.06	-0.01 ± 0.97	-0.02 ± 0.97	0.08	-0.02 ± 0.97	0.03 ± 1.03	0.09
Z_FBG	-0.01 ± 0.91	-0.01 ± 0.98	0.05 ± 1.42	0.08 ± 0.87	0.08	-0.04 ± 1.10	0.06 ± 0.94	0.003 ± 0.99	0.3	0.02 ± 0.97	-0.01 ± 1.05	0.36
Z_WC	-0.34 ± 1.20	-0.07 ± 0.96	0.38 ± 0.46	0.82 ± 0.56	< 0.001	0.04 ± 1.01	-0.001 ± 1.08	-0.03 ± 1.00	0.03	-0.01 ± 1.11	0.02 ± 0.89	0.33
Z_HDL	0.09 ± 1.04	0.03 ± 1.02	-0.21 ± 0.82	-0.21 ± 0.81	< 0.001	-0.11 ± 1.01	0.07 ± 1.01	0.08 ± 1.01	< 0.001	0.05 ± 1.01	-0.05 ± 1.00	0.002
cMetS	-1.05 ± 1.98	-0.25 ± 2.23	1.06 ± 2.42	2.30 ± 2.54	< 0.001	0.11 ± 2.64	-0.08 ± 2.34	-0.19 ± 2.32	0.004	-0.11 ± 2.35	0.03 ± 2.52	0.08

BMI: Body mass index; LTPA: leisure time physical activity; STA: screen time activity; MAP: mean arterial pressure; TG: triglyceride; FBS: fasting blood glucose; WC: waist circumference; HDL: high-density lipoprotein; cMetS: continuous metabolic syndrome; Z, standardized components of cMetS

Table 3. Associations of BMI percentiles and LTPA with standardized components of cMetS in Iranian adolescents in linear regression model: the CASPIAN-III study

	Variables	Z_MAP	Z_TG	Z_FBG	Z_WC	Z_HDL-C	cMetS
Model I [1]	BMI percentiles	0.26*	0.32*	0.03	0.39*	-0.12*	1.13*
	LTPA	-0.04*	-0.03	0.02	-0.04*	0.10*	-0.15*
Model II [2]	BMI percentiles	0.26*	0.32*	0.03	0.39*	-0.12*	1.14*
	LTPA	-0.04*	-0.03	0.02	-0.04*	0.10*	-0.17*
Model III [3]	BMI percentiles	0.27*	0.32*	0.02	0.36*	-0.13*	1.11*
	LTPA	-0.05	-0.02	0.04	-0.02	0.10*	-0.12
Model IV [4]	BMI percentiles	0.26*	0.32*	0.01	0.36*	-0.13*	1.10*
	LTPA	-0.02	-0.02	0.05	-0.02	0.16*	-0.18
Model V [5]	BMI percentiles	0.29*	0.39*	< 0.001	0.45*	-0.20*	1.07*
	LTPA	0.001	0.05	0.04	0.06	0.10	-0.21
	BMI percentiles*LTPA	-0.01	-0.03	0.006	-0.04	0.03	0.02

[1] Without adjusted (crude models)
[2] Adjusted for age and sex
[3] Additionally adjusted for living place, family history of chronic disease, mother's education, father's education, socioeconomic status, STA
[4] In addition to Model III variables, BMI percentiles, and LTPA are simultaneously in the model
[5] In addition to Model III variables, BMI percentiles, and LTPA interaction is in model
BMI: Body mass index; LTPA: leisure time physical activity; BMI percentiles * LTPA: Interaction term between BMI and LTPA; MAP, mean arterial pressure; TG: triglyceride; FBS: fasting blood glucose; WC: waist circumference; HDL: high density lipoprotein; cMetS: continuous metabolic syndrome; Z, standardized components of cMetS
Values are Betas. * $P < 0.05$

Table 4. Associations of BMI percentiles with cMetS across LTPA and STA categories in Iranian adolescents: the CASPIAN-III study

Variables	LTPA			STA	
	Mild	Moderate	Sever	< 2 h/day	≥ 2 h/day
BMI percentiles					
Model I[1]	1.13*	1.04*	1.21*	1.17*	1.11*
Model R square	0.11	0.13	0.16	0.15	0.12
Model II[2]	1.14*	1.05*	1.22*	1.17*	1.11*
Model R square	0.11	0.13	0.16	0.16	0.12
Model III[3]	1.09*	1.04*	1.17*	1.14*	1.05*
Model R square	0.10	0.14	0.15	0.15	0.10

[1] Without adjusted (crude models)
[2] Adjusted for age and sex
[3] Additionally adjusted for living place, family history of chronic disease, mother's education, father's education, socioeconomic status
BMI: Body mass index; cMetS: continuous metabolic syndrome; LTPA: leisure time physical activity; STA: screen time activity
* $P < 0.05$

Components of cMetS according to BMIpercentiles

Mean and standard deviation values of various components of cMetS across BMI percentiles, leisure time physical activity (LTPA), and screen time activity (STA) levels are presented in Table 2. The mean of all cMetS components increased linearly with higher BMI percentiles (P-trend < 0.001), except for FBG standardized residuals (Z-FBG). The mean of all cMetS components was linearly associated with LTPA (P-trend < 0.01), except for standardized residuals of FBG and TG. The average of standardized residuals of HDL (Z-HDL) was significantly higher among students who had less than 2 h/day of STA compared with those who had more than 2 h/day of STA.

Association of BMIpercentiles and LTPA with standardized components of cMetS

Table 3 illustrates the β values of BMI percentiles and LTPA for standardized components of cMetS in different linear regression models. As shown in the table, Z_MAP, Z_TG, Z_WC, Z_HDL, and cMetS increased from 0.26 to 0.29, 0.32 to 0.39, 0.39 to 0.45, -0.12 to -0.20, and 1.07 to 1.14, respectively, with increasing BMI percentiles in all models; these associations were independent from LTPA effect according to model IV. The association of BMI percentiles with Z_FBG was not statistically significant in all models. In the multivariate models (model IV), LTPA showed a significant association with only Z_HDL (β: 0.16). According to model IV, the interaction term of BMI percentiles and LTPA with all components of cMetS was not statistically significant.

Association of BMI percentiles with cMetS across LTPA and STA categories

Associations of BMI percentiles with cMetS across LTPA and STA levels are shown in Table 4. The β values of BMI percentiles and cMetS associations in all LTPA and STA levels were approximately equal and statistically significant, which indicates that association of BMI percentiles with cMetS is independent from LTPA and STA levels.

DISCUSSION

The findings of this study demonstrate that BMI percentiles are associated with cMetS independent of leisure time physical activity (LTPA) and screen time activity (STA) levels. This finding contradicts previous studies in which high levels of LTPA were shown to be significantly associated with a lower MetS score at all BMI levels in children and adolescents [20,31]. On the other side, low levels of LTPA in overweight or obese subjects increases risk of developing metabolic syndrome or alteration of its components [20]. Although there are a number of studies analyzing the associations of LTPA and BMI with MetS risk [32-36], studies using cMetS risk score are scarce [20].

LTPA showed only a slight association with means of cMetS components (Table 3). Moreover, after adjustment for BMI percentile and other confounders such as STA, the relationship between activity and cMetS components was found to be weak or even non-existent.

Both increased body weight and inactivity have been shown to be predictors of cardiovascular disease, diabetes, and metabolic syndrome. This has led to some controversy over the relative contributions of each to cardiometabolic risk.

Physical activity has multiple beneficial effects that can improve insulin and glucose delivery to muscle. Epidemiological studies in children and adolescents have shown that aerobic exercise improves insulin dynamics in overweight or obese subjects [20]. However, physical activity may not totally stop the adverse effects of obesity [37,38]. In a large prospective cohort, the impact of obesity on risk of diabetes was shown to be greater than that of physical activity [39]. Another study showed that increasing physical activity in obese individuals is associated with reduced risk of diabetes [40]. Sullivan *et al.* also found that inactive normal weight subjects are at a lower risk of diabetes than obese and active subjects [41]. These findings are consistent with our study and suggest that obesity is more important than physical activity in cardiovascular disease.

It is well known that increased BMI is associated with inflammatory and lipid markers.

Visceral adipose tissue is metabolically active, promoting a thrombotic and inflammatory state, as well as an atherogenic lipoprotein state [42,43]. It is clear that physical activity is associated with inflammatory or lipid biomarkers [44]. Mora *et al.* showed that a high BMI is more strongly related to adverse cardiovascular biomarker levels than physical inactivity [45]. In our study, BMI was associated with cMetS in all models within physical activity categories.

In our study, STA was not associated with cMetS score risk. Indeed, previous studies revealed that STA is not associated with cardiometabolic risk factors in the abdominally obese [46,47]). We also observed that the association of BMI with cMetS is independent of STA. Therefore, BMI percentiles independently predict cardiometabolic risk in adolescents, whereas other factors such as LTPA and STA have no effect.

The main limitation of this study is its cross-sectional nature; therefore, temporal and causal associations cannot be inferred from these results, and prospective cohort studies are required to test for causal relationships. In addition, the method for assessment of LTPA pattern was simple and may not be a

sufficient representation of children's physical activity. We also were unable to include dietary factors in our study as confounding factors (dietary factors were not assessed in CASPIAN-III study), which may influence the cMetS score. The main strength of this study is the novelty in calculating cMetS.

To the best of our knowledge, this study is the first to evaluate the associations of cMetS with BMI percentile and LTPA in a large non-Western sample of children and adolescents.

The findings of this study demonstrate that BMI percentiles are associated with cMetS independent of LTPA and STA levels. Although an active lifestyle has many beneficial effects, activity per se cannot prevent risk factors of chronic diseases, and emphasis on controlling childhood overweight and obesity is crucial for primordial/primary prevention of non-communicable diseases.

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