Original Article

Weight and cardiometabolic risk among adolescents in Agano city, Japan: NICE EVIDENCE Study-Agano 1

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Background and Objectives: Pediatric obesity is associated with clustered cardiometabolic risk and the future incidence of cardiovascular disease. However, few studies have determined the effect of pediatric obesity in Asia, where obesity is less common than in Western countries. We aimed to clarify whether weight status including underweight and slightly overweight is associated with metabolic risk factors in Japanese adolescents. **Methods and Study Design:** We performed a cross-sectional analysis of 2241 adolescents aged 13–14 years. Participants were classified as underweight, normal weight, slightly overweight, overweight, or obese according to the International Obesity Task Force. The clustered cardiometabolic risk (Z-CMR) was estimated by summing standardized sex-specific Z scores of mean arterial pressure (MAP), non-high-density lipoprotein cholesterol (non-HDL-C), and HbA1c. **Results:** Linear regression analysis showed that MAP, non-HDL-C, and Z-CMR were higher in the slightly overweight, overweight, and obese groups than in the normal weight group after adjusting for confounders. Compared with the normal weight group, the slightly overweight, overweight, and obese groups had higher prevalence of high BP [odds ratios (ORs): 1.38 (95% CI, 1.03, 1.85); 2.63 (1.77, 3.91); and 2.39 (1.57, 3.64), respectively]. Compared with the normal weight group, underweight boys, but not girls, had a lower prevalence of high Z-CMR [OR=0.20 (0.05, 0.84)]. **Conclusions:** Adolescents classified as slightly overweight had higher levels of BP, serum lipids, and clustered cardiometabolic risk than those classified as normal weight. This observation showed significant associations between weight status and cardiometabolic risk factors during adolescence even in East Asians.

Key Words: overweight, underweight, blood pressure, lipids, glycated hemoglobin A1c

INTRODUCTION

The prevalence of pediatric obesity has dramatically increased ten-fold during the last four decades.[1] Evidence has shown that overweight or obese children are at high risk for metabolic abnormalities[2] and atherosclerosis[3] even in early life; moreover, an unfavorable metabolic profile tends to persist from youth to adulthood.[4] Therefore, screening of and interventions for high-risk children are essential for primary prevention of cardiovascular disease (CVD).

Recently, the American Academy of Pediatrics[5] recommended focusing on screening for associated individual risk factors (e.g., elevated blood pressure, decreased high-density lipoprotein, and hyperglycemia) and assessing cardiometabolic risk (CMR) clustering (defined as a continuous risk score computed from components of metabolic syndrome (MetS) or the presence of multiple risk factors) rather than using cutoff points based on MetS definitions. CMR clustering has a tendency to persist from childhood to adulthood;[4] moreover, recent studies revealed that the score for CMR clustering in youth is associated with long-term risk for type 2 diabetes[6] and CVD.[7]

Pediatric studies conducted in Western countries showed that an increasing degree of obesity (categorized by body mass index (BMI)) was associated with a high level of individual risk factors[8,9] and worse scores on CMR clustering.[10] However, in Asian pediatric popula-

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tions, few studies[11-14] have investigated the associations between overweight/obese and the prevalence of individual risk factors or clustering of CMR, and no study has comprehensively examined the relationship between overall weight status and both individual risk factors and clustering of CMR. Asian children have been reported to have a lower BMI at a given body fat percentage compared with Caucasians[15] and are considered to be more metabolically sensitive to adiposity.[16] In addition, thinness in Asian adolescents, especially girls, is more prevalent,[17] as is a lower mean BMI than in adolescents in Western countries.[18] Thus, in research it is necessary to separate boys and girls and to assess whether weight status including underweight and slightly overweight is associated with metabolic risk factors in Asian adolescents with different constitutional factors and BMI distributions from those of Caucasians.

The aim of this study is 1) to assess the relationships between all categories of weight status and CMR in Japanese adolescents and 2) to estimate the relationships between underweight, slightly overweight, and metabolic status in boys and girls.

METHODS

Study population

This cross-sectional study consisted of a total of 2416 children in Agano city, Japan, who were in the second grade of junior high school (aged 13-14 years) in 2010-2015 and were enrolled in a project to screen schoolchildren for poor cardiometabolic health.[19] Our analysis excluded individuals without health examination information (n=42) or without data on behavioral factors (n=117). We also excluded 28 adolescents who had low-density lipoprotein cholesterol (LDL-C) ≥140 mg/dL (3.62 mmol/L) because of the high possibility of familial hypercholesterolemia.[20] Finally, data on 2241 participants (1180 boys and 1061 girls) were analyzed.

This study was performed in accordance with the Declaration of Helsinki and the Japanese Government's Ethical Guidelines for Medical and Health Research Involving Human Subjects. The ethics committee of the Niigata University faculty of medicine approved this study. Informed consent was obtained from all participants and their parents or guardians by verbal between 2010-2014 and by using a form from 2015, respectively.

Anthropometric measurements and definition of weight status

Body height (cm) was measured to the nearest 0.1 cm with participants standing without shoes. Body weight (kg) with participants in light indoor clothes was measured to the nearest 0.1 kg. BMI was calculated by body weight (kg)/height^2 (m^2). According to both the universal and Asian BMI age and sex specific cutoffs of the International Obesity Task Force (IOTF)[21] equivalent to the adult BMI cutoffs, we defined the cutoff points for being underweight, slightly overweight, and overweight as adult BMIs of <18.5 kg/m^2 (universal cut-off points), ≥23 kg/m^2 (Asian cut-off points), and ≥25 kg/m^2 (universal cut-off points), respectively. Due to the low prevalence of obese and morbidly obese individuals with adult BMIs ≥30 kg/m^2 (universal cut-off points) and ≥35 kg/m^2 (universal cut-off points), respectively, in this study (obese, n=30 [1.3%]; morbidly obese, n=6 [0.3%]), we further reclassified overweight as adult BMIs of ≥25 kg/m^2 and obese as adult BMIs of ≥27 kg/m^2 (Asian cut-off points).

Assessment of metabolic risk factors

As previously described,[19] non-fasting blood samples were obtained according to standardized procedures. Non-HDL-cholesterol (non-HDL-C) was calculated as total cholesterol minus HDL-C. High non-HDL-C was defined as ≥120 mg/dL (3.10 mmol/L) according to the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.[22] High HbA1c was defined as HbA1c ≥5.7% (38 mmol/mol) according to the guidelines of the American Diabetes Association.[23]

A nurse measured blood pressure (BP) once using an automatic monitor with the adolescents seated. In those with either systolic blood pressure (SBP) ≥120 mm Hg or diastolic blood pressure (DBP) ≥70 mm Hg, measurements were repeated twice or more, and the lowest value was registered. Mean arterial pressure (MAP) was calculated as DBP + (SBP − DBP)/3. High BP was defined as being in the 90th percentile among Japanese junior high school students.[24]

Calculating clustering of cardiometabolic risk factors

Variables for CMRs (MAP, non-HDL-C, and HbA1c) were used to calculate the Z scores of CMRs (Z-CMR).[25] Z scores were computed for variables for all risk factors separately for sex and calculated as the sum of these three scores. In logistic regression, a high Z-CMR was defined as ≥1 standard deviation of Z-CMR. We also calculated the number of risk factors present as another index of clustering of CMR; this index was calculated by the sum of the presence of high BP, high non-HDL-C, and/or high HbA1c. We categorized participants as having clustering of CMR if ≥2 risk factors were present.

Statistical analysis

Analyses were performed for the overall population and stratified by sex. Sex differences in characteristics were compared using the Student's t-test for continuous variables and the χ^2 test for categorical variables. Linear regression models were used to examine the association of weight status with metabolic risk factors that were normalized by sex-specific Z scores and were reported as unstandardized *B* coefficients (95% confidence interval (CI)). Logistic regression models examined whether metabolic risks were associated with each weight status. All regression analyses were adjusted for sex, school district, and year data were collected (model 1) and additionally adjusted for long screen time (≥4 h of screen time per school day) and unhealthy breakfast habits (never eating breakfast or not always having breakfast within a 1-week period) (model 2). In sex-stratified analysis, the sex variable was excluded from model 1. The *p* values for a linear trend were computed by modeling weight status as a continuous variable. All tests were performed using IBM SPSS Statistics 24.0 software (IBM SPSS Inc., Chicago, IL, USA). Values of $p<0.05$ were considered statistically significant.

RESULTS

Characteristics of the participants (53% boys) are shown in Table 1. Mean BMI was higher in girls than in boys (p=0.011). Compared with boys, girls had a higher prevalence of underweight (6.2% vs 10.6%) and slightly overweight (13.1% vs 16.0%) and a lower prevalence of obesity (6.8% vs 3.8%). Mean value of non-HDL-C was higher in girls than in boys (p<0.001), but there were no significant differences in MAP and HbA1c between sexes (p=0.750 for MAP; p=0.071 for HbA1c). Girls had a greater prevalence of high BP (19.9% vs 24.5%), high non-HDL-C (13.7% vs 26.5%), and clustering of ≥2 risk factors (7.3% vs 13.0%) compared with boys.

Linear regression analysis (Table 2) showed that MAP (sex-specific Z score), non-HDL-C (sex-specific Z score), and Z-CMR were higher in the slightly overweight, overweight, and obese groups than in the normal weight group after adjusting for sex, school district, and year data were collected (model 1). No association was observed with weight status and the Z score for HbA1c. Adding adjustment for behavioral factors (model 2), the Z score for MAP was greater among the slightly overweight group and was lower among the underweight group than in the normal weight group. Compared with the normal weight group, the slightly overweight and underweight groups had no significant difference in Z scores for non-HDL-C. Lower Z-CMR was observed in the underweight group than in the normal weight group. In the sex-stratified analysis, a similar association was observed in boys, but there was no relationship in any risk factor between slightly overweight and normal weight boys (model 2). In girls, Z scores for MAP and Z-CMR were higher among slightly overweight, overweight, and obese groups compared with the normal weight group (model 2). Compared with the normal weight girls, a higher Z score for non-HDL-C was only observed in obese girls.

Compared with the normal weight group, the slightly overweight, overweight, and obese groups had significantly higher prevalence of high BP after multivariate adjustment [odds ratios (ORs)=1.38 (95% CI, 1.03, 1.85); OR=2.63 (95% CI, 1.77, 3.91); and OR=2.39 (95% CI, 1.57, 3.64), respectively] (model 2) (Table 3). Overweight and obese groups had higher prevalence of high non-HDL-C [OR 1.62 (95% CI, 1.07, 2.46); OR 3.07 (95% CI, 2.03, 4.63), respectively] than the normal weight group. Those overweight and obese groups had a significantly higher prevalence of high Z-CMR [OR 2.40 (95% CI, 1.59, 3.63); OR 2.93 (95% CI, 1.92, 4.47)] and a higher prevalence of clustering of ≥2 risk factors [overweight: OR 2.37 (95% CI, 1.46, 3.83); obese: OR 3.09

Table 1. Characteristics of study participants

	Total (n=2241)	Boys (n=1180)	Girls (n=1061)	$p^{\dagger}$
Height (cm)	158 (7)	161 (8)	156 (5)	<0.001
Weight (kg)	48.6 (8.9)	49.8 (9.7)	47.3 (7.8)	<0.001
BMI (kg/m^2)	19.3 (2.8)	19.2 (2.8)	19.5 (2.8)	0.011
Weight status (BMI range (kg/m^2))				
Underweight (Boys <16.11 /Girls <16.54)	185 (8.3%)	73 (6.2%)	112 (10.6%)	<0.001
Normal weight (16.11-20.30/16.55-20.90)	1479 (66.0%)	801 (67.9%)	678 (63.9%)	
Slightly overweight (20.31-22.23/20.91-22.89)	324 (14.5%)	154 (13.1%)	170 (16.0%)	
Overweight (22.24-24.21/22.90-24.91)	133 (5.9%)	72 (6.1%)	61 (5.7%)	
Obese (≥24.22/≥24.92)	120 (5.4%)	80 (6.8%)	40 (3.8%)	
Cardiometabolic risk factors				
SBP (mmHg)	112 (11)	114 (11)	110 (10)	<0.001
DBP (mmHg)	63 (8)	62 (8)	64 (8)	<0.001
MAP (mmHg)	79 (8)	80 (8)	79 (8)	0.750
High BP (boys ≥130/70 /Girls ≥125/70 mm Hg) (%)	495 (22.1%)	235 (19.9%)	260 (24.5%)	0.009
TC (mmol/L)	4.18 (0.62)	4.01 (0.58)	4.37 (0.60)	<0.001
HDL-C (mmol/L)	1.56 (0.29)	1.52 (0.29)	1.59 (0.28)	<0.001
Non-HDL-C (mmol/L)	2.63 (0.55)	2.49 (0.52)	2.78 (0.54)	<0.001
High non-HDL-C (≥120 mg/dL) (%)	443 (19.8%)	162 (13.7%)	281 (26.5%)	<0.001
HbA1c (%)	5.38 (0.25)	5.39 (0.25)	5.37 (0.25)	0.071
HbA1c (mmol/mol)	35 (2)	35 (2)	35 (2)	0.071
High HbA1c (≥5.7%) (%)	299 (13.3%)	170 (14.4%)	129 (12.2%)	0.118
Clustering of cardiometabolic risk factors				
High Z-CMR	346 (15.4%)	183 (15.5%)	163 (15.4%)	0.924
Number of clustering risk factors				
0	1250 (55.8%)	707 (59.9%)	543 (51.2%)	<0.001
1	767 (34.2%)	387 (32.8%)	380 (35.8%)	
2	202 (9.0%)	78 (6.6%)	124 (11.7%)	
3	22 (1.0%)	8 (0.7%)	14 (1.3%)	
Behavioral factors‡				
Long screen time	443 (19.8%)	242 (20.5%)	201 (18.9%)	0.353
Unhealthy breakfast habits	286 (12.8%)	150 (12.7%)	136 (12.8%)	0.940

BMI: body mass index; BP: blood pressure; CMR: cardiometabolic risk factors; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; MAP: mean arterial pressure; non-HDL-C: non-high-density lipoprotein cholesterol; SBP: systolic blood pressure; TC: total cholesterol.

Data are presented as mean (standard deviation) and n (%).

†Differences between boys and girls were examined by the Student's t test for continuous variables and by chi-squared test for categorical variables.

‡Behavioral factors were assessed using a standard questionnaire.

Table 2. Linear regression analysis of weight status explaining clustered cardiometabolic risk factors and its components

	Z score of MAP *B* (95% CI) †	*p*	Z score of non-HDL-C *B* (95% CI) †	*p*	Z score of HbA1c *B* (95% CI) †	*p*	Z-CMR (sum of Z score) *B* (95% CI) †	*p*
Total								
Model 1								
Underweight	-0.19 (-0.34, -0.04)	0.014	-0.07 (-0.22, 0.09)	0.394	-0.09 (-0.24, 0.07)	0.263	-0.11 (-0.20, -0.02)	0.014
Normal weight	0.00 (Reference)		0.00 (Reference)		0.00 (Reference)		0.00 (Reference)	
Slightly overweight	0.18 (0.06, 0.30)	0.003	0.13 (0.01, 0.24)	0.037	-0.05 (-0.17, 0.07)	0.410	0.09 (0.01, 0.16)	0.019
Overweight	0.47 (0.30, 0.65)	<0.001	0.35 (0.18, 0.53)	<0.001	0.05 (-0.13, 0.22)	0.613	0.29 (0.19, 0.40)	<0.001
Obese	0.51 (0.33, 0.69)	<0.001	0.64 (0.46, 0.82)	<0.001	0.09 (-0.10, 0.28)	0.349	0.41 (0.30, 0.52)	<0.001
p for trend‡		<0.001		<0.001		0.389		<0.001
Model 2								
Underweight	-0.18 (-0.33, -0.03)	0.019	-0.06 (-0.21, 0.10)	0.468	-0.10 (-0.26, 0.05)	0.193	-0.11 (-0.20, -0.02)	0.015
Normal weight	0.00 (Reference)		0.00 (Reference)		0.00 (Reference)		0.00 (Reference)	
Slightly overweight	0.17 (0.05, 0.29)	0.004	0.11 (-0.01, 0.23)	0.072	-0.04 (-0.16, 0.08)	0.531	0.08 (0.01, 0.15)	0.0270
Overweight	0.47 (0.29, 0.64)	<0.001	0.34 (0.16, 0.51)	<0.001	0.06 (-0.12, 0.23)	0.540	0.29 (0.18, 0.39)	<0.001
Obese	0.50 (0.31, 0.68)	<0.001	0.62 (0.44, 0.81)	<0.001	0.11 (-0.08, 0.29)	0.259	0.41 (0.30, 0.52)	<0.001
p for trend‡		<0.001		<0.001		0.285		<0.001
Boys								
Model 1								
Underweight	-0.45 (-0.69, -0.22)	<0.001	-0.02 (-0.25, 0.22)	0.872	-0.18 (-0.42, 0.07)	0.154	-0.22 (-0.36, -0.08)	0.003
Normal weight	0.00 (Reference)		0.00 (Reference)		0.00 (Reference)		0.00 (Reference)	
Slightly overweight	0.14 (-0.03, 0.31)	0.101	0.07 (-0.10, 0.24)	0.417	-0.05 (-0.22, 0.13)	0.609	0.06 (-0.05, 0.16)	0.283
Overweight	0.50 (0.26, 0.74)	<0.001	0.55 (0.31, 0.78)	<0.001	0.15 (-0.09, 0.39)	0.224	0.40 (0.26, 0.54)	<0.001
Obese	0.38 (0.15, 0.60)	0.001	0.72 (0.50, 0.95)	<0.001	0.10 (-0.13, 0.33)	0.412	0.40 (0.27, 0.53)	<0.001
p for trend‡		<0.001		<0.001		0.248		<0.001
Model 2								
Underweight	-0.43 (-0.67, -0.20)	<0.001	0.01 (-0.23, 0.24)	0.967	-0.20 (-0.44, 0.05)	0.111	-0.21 (-0.35, -0.07)	0.004
Normal weight	0.00 (Reference)		0.00 (Reference)		0.00 (Reference)		0.00 (Reference)	
Slightly overweight	0.13 (-0.04, 0.30)	0.124	0.06 (-0.11, 0.23)	0.493	-0.04 (-0.21, 0.14)	0.684	0.05 (-0.05, 0.15)	0.316
Overweight	0.49 (0.25, 0.72)	<0.001	0.52 (0.29, 0.76)	<0.001	0.17 (-0.07, 0.41)	0.173	0.39 (0.25, 0.53)	<0.001
Obese	0.38 (0.15, 0.60)	0.001	0.72 (0.50, 0.94)	<0.001	0.10 (-0.13, 0.33)	0.406	0.40 (0.27, 0.53)	<0.001
p for trend‡		<0.001		<0.001		0.195		<0.001

CMR: cardiometabolic risk factors; MAP: mean arterial pressure; non-HDL-C: non-high-density lipoprotein cholesterol; 95% CI: 95% confidence interval.
Model 1 was adjusted for sex, school district, and year data were collected. Model 2 was as model 1 but with additional adjustment for long screen time and unhealthy breakfast habits. In sex-stratified analysis, sex variable was excluded from model 1
†*B*-coefficient (95% CI) represents Z score changes in MAP, non-HDL-C, HbA1c, and Z-CMR (sum of Z score of MAP, non-HDL-C, and HbA1c), respectively, per weight status changes.
‡The *p* values for a linear trend were computed by modeling weight status as a continuous variable.

Table 2. Linear regression analysis of weight status explaining clustered cardiometabolic risk factors and its components (cont.)

	Z score of MAP *B* (95% CI) †	*p*	Z score of non-HDL-C *B* (95% CI) †	*p*	Z score of HbA1c *B* (95% CI) †	*p*	Z-CMR (sum of Z score) *B* (95% CI) †	*p*
Girls								
Model 1								
Underweight	0.00 (-0.20, 0.20)	0.999	-0.10 (-0.30, 0.10)	0.337	-0.03 (-0.23, 0.17)	0.788	-0.04 (-0.16, 0.08)	0.494
Normal weight	0.00 (Reference)		0.00 (Reference)		0.00 (Reference)		0.00 (Reference)	
Slightly overweight	0.23 (0.07, 0.39)	0.006	0.18 (0.02, 0.35)	0.031	-0.06 (-0.22, 0.11)	0.526	0.12 (0.02, 0.22)	0.020
Overweight	0.44 (0.19, 0.70)	0.001	0.12 (-0.14, 0.38)	0.375	-0.07 (-0.34, 0.19)	0.587	0.16 (0.01, 0.32)	0.042
Obese	0.75 (0.44, 1.06)	<0.001	0.51 (0.19, 0.82)	0.002	0.07 (-0.25, 0.40)	0.649	0.44 (0.25, 0.64)	<0.001
p for trend‡		<0.001		<0.001		0.904		<0.001
Model 2								
Underweight	0.00 (-0.20, 0.20)	0.997	-0.10 (-0.30, 0.10)	0.338	-0.04 (-0.24, 0.16)	0.704	-0.05 (-0.16, 0.07)	0.458
Normal weight	0.00 (Reference)		0.00 (Reference)		0.00 (Reference)		0.00 (Reference)	
Slightly overweight	0.22 (0.06, 0.39)	0.009	0.16 (-0.01, 0.33)	0.058	-0.04 (-0.21, 0.13)	0.617	0.11 (0.01, 0.21)	0.028
Overweight	0.44 (0.18, 0.69)	0.001	0.11 (-0.15, 0.37)	0.404	-0.07 (-0.33, 0.19)	0.593	0.16 (0.00, 0.32)	0.046
Obese	0.74 (0.43, 1.06)	<0.001	0.48 (0.16, 0.80)	0.003	0.13 (-0.20, 0.45)	0.441	0.45 (0.26, 0.64)	<0.001
p for trend‡		<0.001		<0.001		0.991		<0.001

CMR: cardiometabolic risk factors; MAP: mean arterial pressure; non-HDL-C: non-high-density lipoprotein cholesterol; 95%CI: 95% confidence interval.
Model 1 was adjusted for sex: school district: and year data were collected. Model 2 was as model 1 but with additional adjustment for long screen time and unhealthy breakfast habits. In sex-stratified analysis: sex variable was excluded from model 1.
†*B*-coefficient (95% CI) represents Z score changes in MAP, non-HDL-C, HbA1c, and Z-CMR (sum of Z score of MAP, non-HDL-C, and HbA1c), respectively, per weight status changes.
‡The *p* values for a linear trend were computed by modeling weight status as a continuous variable.

Table 3. Odds ratios (95% confidence interval) for cardiometabolic risk factors by weight status

Weight status	Underweight	Normal weight	Slightly overweight	Overweight	Obese	*p* for trend †
Total						
High BP						
Case/N	35/185	287/1479	82/324	49/133	42/120	
Model 1	0.94 (0.63, 1.40)	1.00 (Reference)	1.39 (1.04, 1.86)	2.65 (1.79, 3.93)	2.42 (1.59, 3.67)	<0.001
Model 2	0.94 (0.63, 1.41)	1.00 (Reference)	1.38 (1.03, 1.85)	2.63 (1.77, 3.91)	2.39 (1.57, 3.64)	<0.001
High non-HDL-C						
Case /N	24/185	269/1479	69/324	36/133	45/120	
Model 1	0.60 (0.38, 0.94)	1.00 (Reference)	1.17 (0.86, 1.58)	1.67 (1.10, 2.52)	3.19 (2.12, 4.79)	<0.001
Model 2	0.61 (0.39, 0.97)	1.00 (Reference)	1.12 (0.82, 1.51)	1.62 (1.07, 2.46)	3.07 (2.03, 4.63)	<0.001
High HbA1c						
Case /N	21/185	194/1479	46/324	19/133	19/120	
Model 1	0.93 (0.57, 1.52)	1.00 (Reference)	1.05 (0.74, 1.51)	1.04 (0.62, 1.75)	1.19 (0.70, 2.02)	0.465
Model 2	0.92 (0.56, 1.50)	1.00 (Reference)	1.07 (0.75, 1.53)	1.05 (0.62, 1.77)	1.21 (0.71, 2.05)	0.409
High Z-CMR						
Case /N	16/185	203/1479	51/324	38/133	38/120	
Model 1	0.62 (0.36, 1.06)	1.00 (Reference)	1.14 (0.81, 1.60)	2.43 (1.61, 3.67)	2.98 (1.96, 4.54)	<0.001
Model 2	0.63 (0.37, 1.08)	1.00 (Reference)	1.12 (0.80, 1.58)	2.40 (1.59, 3.63)	2.93 (1.92, 4.47)	<0.001
Clustering ≥2 risk factors						
Case /N	13/185	130/1479	30/324	25/133	26/120	
Model 1	0.73 (0.40, 1.32)	1.00 (Reference)	0.99 (0.65, 1.51)	2.41 (1.49, 3.89)	3.17 (1.96, 5.13)	<0.001
Model 2	0.74 (0.41, 1.35)	1.00 (Reference)	0.96 (0.63, 1.46)	2.37 (1.46, 3.83)	3.09 (1.90, 5.01)	<0.001
Boys						
High BP						
Case /N	7/73	143/801	32/154	29/72	24/80	
Model 1	0.49 (0.22, 1.11)	1.00 (Reference)	1.22 (0.79, 1.89)	3.53 (2.09, 5.98)	2.23 (1.32, 3.79)	<0.001
Model 2	0.51 (0.23, 1.15)	1.00 (Reference)	1.21 (0.78, 1.88)	3.45 (2.04, 5.85)	2.23 (1.31, 3.78)	<0.001
High non-HDL-C						
Case /N	6/73	96/801	15/154	19/72	26/80	
Model 1	0.67 (0.28, 1.59)	1.00 (Reference)	0.79 (0.44, 1.40)	2.66 (1.50, 4.71)	3.58 (2.14, 6.01)	<0.001
Model 2	0.74 (0.31, 1.77)	1.00 (Reference)	0.75 (0.42, 1.34)	2.53 (1.42, 4.52)	3.63 (2.14, 6.13)	<0.001
High HbA1c						
Case /N	8/73	113/801	24/154	12/72	13/80	
Model 1	0.84 (0.39, 1.84)	1.00 (Reference)	1.09 (0.67, 1.80)	1.16 (0.59, 2.27)	1.11 (0.58, 2.12)	0.501
Model 2	0.82 (0.37, 1.79)	1.00 (Reference)	1.11 (0.68, 1.83)	1.18 (0.60, 2.33)	1.12 (0.59, 2.14)	0.448

BP: blood pressure; CMR: cardiometabolic risk factors; non-HDL-C: non-high-density lipoprotein cholesterol.
Model 1 was adjusted for sex, school district, and year data were collected. Model 2 was as model 1 but with additional adjustment for long screen time and unhealthy breakfast habits. In sex-stratified analysis, sex variable was excluded from model 1.
†The *p* values for a linear trend were computed by modeling weight status as a continuous variable.

Table 3. Odds ratios (95% confidence interval) for cardiometabolic risk factors by weight status (cont.)

Weight status	Underweight	Normal weight	Slightly overweight	Overweight	Obese	*p* for trend †
High Z-CMR						
Case /N	2/73	108/801	25/154	25/72	23/80	
Model 1	0.19 (0.05, 0.79)	1.00 (Reference)	1.23 (0.76, 1.99)	3.57 (2.07, 6.18)	2.73 (1.59, 4.70)	<0.001
Model 2	0.20 (0.05, 0.84)	1.00 (Reference)	1.20 (0.74, 1.94)	3.48 (2.01, 6.04)	2.71 (1.57, 4.67)	<0.001
Clustering ≥2 risk factors						
Case /N	2/73	49/801	7/154	15/72	13/80	
Model 1	0.47 (0.11, 1.97)	1.00 (Reference)	0.70 (0.31, 1.58)	4.21 (2.19, 8.08)	2.94 (1.51, 5.74)	<0.001
Model 2	0.51 (0.12, 2.16)	1.00 (Reference)	0.66 (0.29, 1.50)	4.01 (2.08, 7.76)	2.93 (1.50, 5.74)	<0.001
Girls						
High BP						
Case /N	28/112	144/678	50/170	20/61	18/40	
Model 1	1.23 (0.76, 2.00)	1.00 (Reference)	1.55 (1.04, 2.31)	1.84 (1.01, 3.36)	2.59 (1.29, 5.20)	0.003
Model 2	1.23 (0.75, 1.99)	1.00 (Reference)	1.59 (1.06, 2.37)	1.86 (1.02, 3.40)	2.71 (1.34, 5.48)	0.002
High non-HDL-C						
Case /N	18/112	173/678	54/170	17/61	19/40	
Model 1	0.59 (0.34, 1.00)	1.00 (Reference)	1.41 (0.97, 2.05)	1.11 (0.61, 2.01)	2.67 (1.38, 5.16)	<0.001
Model 2	0.58 (0.34, 1.00)	1.00 (Reference)	1.35 (0.93, 1.97)	1.09 (0.60, 1.99)	2.62 (1.35, 5.10)	0.001
High HbA1c						
Case /N	13/112	81/678	22/170	7/61	6/40	
Model 1	0.99 (0.52, 1.89)	1.00 (Reference)	1.04 (0.62, 1.75)	0.94 (0.40, 2.20)	1.44 (0.57, 3.67)	0.639
Model 2	0.98 (0.52, 1.87)	1.00 (Reference)	1.06 (0.62, 1.78)	0.94 (0.40, 2.19)	1.49 (0.58, 3.81)	0.596
High Z-CMR						
Case /N	14/112	95/678	26/170	13/61	15/40	
Model 1	0.93 (0.51, 1.70)	1.00 (Reference)	1.09 (0.68, 1.76)	1.57 (0.81, 3.05)	3.91 (1.95, 7.85)	0.001
Model 2	0.91 (0.50, 1.68)	1.00 (Reference)	1.11 (0.69, 1.79)	1.57 (0.81, 3.05)	4.16 (2.05, 8.44)	<0.001
Clustering ≥2 risk factors						
Case /N	11/112	81/678	23/170	10/61	13/40	
Model 1	0.83 (0.43, 1.63)	1.00 (Reference)	1.14 (0.69, 1.88)	1.44 (0.70, 2.98)	3.36 (1.64, 6.87)	0.002
Model 2	0.83 (0.42, 1.61)	1.00 (Reference)	1.14 (0.69, 1.89)	1.44 (0.70, 2.98)	3.46 (1.68, 7.15)	0.002

BP: blood pressure; CMR: cardiometabolic risk factors; non-HDL-C: non-high-density lipoprotein cholesterol.
Model 1 was adjusted for sex, school district, and year data were collected. Model 2 was as model 1 but with additional adjustment for long screen time and unhealthy breakfast habits. In sex-stratified analysis, sex variable was excluded from model 1.
†The *p* values for a linear trend were computed by modeling weight status as a continuous variable

(95% CI, 1.90, 5.01)] than those with normal weight. In this analysis, no weight status was associated with high HbA1c. Among overweight and obese boys, the ORs of all risk factors, with the exception of high HbA1c, increased compared to those with normal weight. Compared with normal weight girls, slightly overweight, overweight, and obese girls had higher prevalence of high BP [OR 1.59 (95% CI, 1.06, 2.37); 1.86 (95% CI, 1.02, 3.40); 2.71 (95% CI, 1.34, 5.48), respectively]. Greater ORs for high Z-CMR and for clustering of ≥2 risk factors were only found in obese girls compared with normal weight girls [OR for high Z-CMR 4.16 (95% CI, 2.05, 8.44); OR for clustering of ≥2 risk factors 3.46 (95% CI, 1.68, 7.15)]. When compared with normal weight groups, underweight boys, but not girls, had a lower OR for high Z-CMR [OR 0.20 (95% CI, 0.05, 0.84)].

DISCUSSION

This study showed that MAP and Z-CMR increased linearly throughout the overall spectrum of weight status (underweight to obese) in Japanese adolescents. A similar association was found for non HDL-C (but not significant in underweight) and there was no relationship with HbA1c. In addition, girls classified as slightly overweight had a greater likelihood of high BP than those classified as normal weight. Our results suggested that significant associations between weight status and CMR could be seen during adolescence even in East Asians. Especially in early adolescent girls, a slightly elevated BMI might play an important role in the management of BP considering that in the present study, the mean BMI difference between normal weight and slightly overweight was 3 kg/m^2.

The use of the BMI to define weight status in children and adolescents is well established in clinical settings and research studies. At present, the IOTF cutoff values[21] have been one of the most widely used for these purposes; these BMI values were derived from data from six countries, including two Asian countries. The IOTF criteria provided age and sex-specific childhood BMI cutoff points for overweight and obese in Asian pediatric populations (equivalent to adult BMIs of 23 kg/m^2 and 27 kg/m^2, respectively) in addition to universal cutoff values. Friedemann et al[26] showed that obese children, as defined by universal IOTF cut-off values, had higher levels of BP, total cholesterol, triglycerides, and fasting insulin compared with normal and overweight children, but very few studies from Asia were included in this meta-analysis. Similar findings emerged from a study conducted in Korea;[11] the risk of having ≥2 co-morbidities significantly increased from the overweight to obese groups (aged 10-19 years; mean BMI: 24.7 kg/m^2 for overweight and 28.9 kg/m^2 for obesity). The effect of being slightly overweight is not well known especially in Asian pediatric populations. In Japanese girls aged 12-13 years old, when the <50th percentile BMI category was compared with the 75th to 84th percentile category the OR for high LDL-C was significantly higher for the latter category;[13] but the likelihood of high BP did not differ significantly between the 75th to 84th percentile BMI category and the <50th percentile BMI category.[14] Our findings are generally in line with previous studies; an unhealthier metabolic status, mainly for BP, reached statistical significance beginning at the categories of slightly overweight compared to normal weight. More importantly, overweight/obese boys (BMI ≥22.24 kg/m^2) and obese girls (BMI ≥24.92 kg/m^2), not slightly overweight individuals, had 2.7-4.0 times and 3.4-4.2 times higher likelihood of both definitions of the CMR clustering (i.e., high Z-CMR and clustering of ≥2 risk factors), respectively, compared with normal weight adolescents (boys: BMI 16.11-20.30 kg/m^2; girls: BMI 16.55-20.90 kg/m^2). Present results indicated that those with a higher weight status have a higher probability of having multiple clustered risk factors. In Asian children, assessing those slightly overweight may provide important information that may add to standard obesity classifications alone, and the definition of overweight/obese could be a useful screening tool for clusters of CMR.

Several studies suggested that the associations between increasing degrees of obesity and CMR were stronger in boys than in girls.[8,9,11] Intriguingly, we observed that girls had a higher prevalence of high BP and high non-HDL-C than boys. In addition, only in girls were Z-MAP and Z-CMR increased in slightly overweight, overweight, and obese groups when compared to the normal weight group. One explanation for the discrepancy in findings could be due to differences in categorization of weight status. We separated categories of normal weight (reference category) from underweight and slightly overweight, which would be a more detailed categorization than reference categories in previous studies (under/normal weight BMI <85th percentile;[9] normal weight, 5th percentile ≤ BMI <85th percentile[11]). Further studies in larger populations are needed to investigate the associations of underweight and slightly overweight with CMR. Further, previous studies used different age groups than our study. Some studies included preadolescents and adolescents[8,9,11] while our study included only adolescents (aged 13-14 years old). In addition, there might be ambiguity in the association between BMI and CMRs in boys because of the variability of the pubertal growth spurt that occurs at this age. Studies of other age groups and adjustments for pubertal status are needed.

Very few studies of pediatric populations have investigated CMR in relation to underweight. Although comparisons with our findings are difficult because of differences in socio-economic status and BMI distribution, a study of school children (aged 12.1-14.5 years) from Delhi, India[27] found that underweight children [18% of participants; defined as less than the cut off value of universal IOTF criteria for grade 2 thinness (extrapolation of BMI of <17 kg/m^2 at 18 years)] had a significantly lower probability of having any CMRs compared with children who were not underweight. A study of children in Spain[10] found that clustering of CMR (sum of Z scores) was the lowest in the underweight children [6% of participants; defined as less than the cut off value of universal IOTF criteria for grade 1 thinness (extrapolation of BMI of <18.5 kg/m^2 at 18 years)] after adjustment for age and sex. Our results showed that underweight boys (6.2% of participants; defined as less than the cut off value of universal IOTF criteria for grade 1 thinness) had lower mean values for clustering of CMR and MAP and decreased

probabilities of having high Z-CMR. However, thinness in youth has adverse effects on bone density in adulthood;[28] furthermore, low preconception BMI is an important risk factor for reduced fetal growth.[29] Thus, maintenance of a healthy weight during adolescence is a key factor in health promotion.

Current results showed that HbA1c was not associated with any BMI category. Previous research suggested that obese children tended to have a higher prevalence of impaired fasting glucose[8,9] and high levels of HbA1c.[8] However, a study in Korea[11] showed no relationship in the fasting plasma glucose level by weight status but that waist circumference was associated with fasting glucose in girls. This inconsistency among results could be explained by differences in indices of glucose metabolism. In obese adolescents,[30] a decreased early-phase insulin response was found even though insulin secretion was relatively maintained. Thus, HbA1c, reflecting chronic glycemic control, might fail to identify adolescents with relatively good glycemic control. More detailed information is needed to understand how pediatric obesity increases the risk for glycemic abnormality.

The emergence of the childhood obesity epidemic poses the challenge of understanding and assessing the presence of clustering of CMR in children. Although not pertaining to all risk factors, our results suggested that slightly overweight (high-normal BMI) Japanese adolescents had a worse metabolic status than those of normal weight. In addition, clustered metabolic risks were observed in those with an increased degree of obesity. Lifestyle intervention programs that included physical exercise, nutrition education, and behavior therapy have been shown to improve current weight and cardio-metabolic outcomes in pediatric obesity.[31,32] In addition, the resolution of MetS in youth by the time of adulthood showed risks for type 2 diabetes and high carotid artery intima-media thickness in adulthood similar to those that did not have MetS in youth and adult life.[33] These previous results as well as the present results showed that assessing pediatric metabolic risk using more detailed BMI classifications would be useful in identifying current unfavorable metabolic profiles and might be a potential strategy for preventing diabetes and CVD in adulthood. Encouraging self-assessment of weight status by adolescents may contribute to health education and raising public awareness of the health condition of adolescents.

Several limitations must be noted. First, the study population included in the present study may not have been representative of the overall Japanese population. However, the mean values of body height and body weight in this study were similar to those noted in the annual report of school health statistics in Japan.[34] Second, the single measurement of BP (except when the first BP measurement was above the reference value) and the use of non-fasting blood samples may decrease the data's accuracy. However, it was reported[35] that the decrement in BP with repeated measurements may not be large enough to affect BP classification. Similarly, that fasting might not be necessary before screening for lipid abnormalities[36] and impaired glucose tolerance was noted.[37] Third, our study population included such a small number of obese adolescents that the number was not sufficient to investigate the associations of increasing degrees of obesity and CMR in adolescents with more severe obesity (i.e., severe or morbid obese). Further studies of larger populations are needed to determine the relationship between the degree of the severity of obesity and CMR in Asian populations. Fourth, we could have falsely classified adolescents not at risk as being at risk or adolescents at risk as not being at risk because we used statistical cutoff points to define high levels of Z-CMR. However, when we performed linear and logistic regression analysis, we observed nearly the same results as when we used another definition for clustered CMR (i.e., number of clustering risk factors). Finally, residual confounding due to unmeasured risk factors (e.g. pubertal status, low physical activity, or under/over-nutrition) may have biased our observations; the effects of these factors in the relationship between weight status and CMR need to be further investigated.

In conclusion, our results showed that CMR became greater throughout groupings of slightly overweight to obese adolescents, especially with unfavorable BP and lipid parameters. Those with a higher weight status have a higher probability of unhealthier metabolic profiles than those without and it should be considered that they would maintain higher levels of clusters of CMR.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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