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ORIGINAL ARTICLE
Epidemiology

An Alternative Approach to Determining Metabolic Syndrome Component Cutoffs in Children and Adolescents Using Segmental Regression Analysis

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Background: The prevalence of metabolic syndrome is increasing in children and adolescents. Although some diagnostic criteria for metabolic syndrome exist, further research is needed to determine appropriate age-, sex-, and race-specific cutoffs for each component.

Methods and Results: Health examinations were conducted in 1,679 children aged 6–15 years in 9 regions of Japan. Participants were divided into 3 age groups for each sex: 6–8, 9–11, and 12–15 years. For metabolic syndrome components in each group, inverse cumulative percentile graphs were drawn and approximated by 3 regression lines using segmented regression analysis. The intersection of each regression line was defined as the breakpoint, and the measured value corresponding to the breakpoint percentile as the breakpoint value. Breakpoint values for waist circumference were age dependent at approximately 60, 70, and 80 cm for ages 6–8, 9–11, and 12–15 years, respectively. Breakpoint values for blood pressure were age- and/or sex dependent, while those for triglycerides, high-density lipoprotein cholesterol, and fasting blood glucose were neither age nor sex dependent. Based on these results, we proposed new cutoffs for diagnosing metabolic syndrome in Japanese children and adolescents.

Conclusions: Breakpoint values obtained by segmented regression analysis on inverse cumulative percentile graphs can be useful for determining metabolic syndrome component cutoffs in children and adolescents.

Key Words: Cardiovascular disease; Children; Metabolic syndrome; Obesity; Prevention

The prevalence of obesity in children and adolescents has increased worldwide in recent decades. Although mean body mass index (BMI) values in many countries had plateaued since the early 2000s, during the coronavirus disease 2019 (COVID-19) pandemic, average BMIs began to rise again,[1–3] a trend also observed in Japan.[4] Even in children and adolescents, abdominal obesity is associated with metabolic syndrome, which leads to increased cardiovascular disease risk in the future. Therefore, establishing methods for the early detection of metabolic syndrome, which enables early intervention, is an urgent issue.[5]

The current diagnostic criteria for metabolic syndrome in children and adolescents were provided by Cook et al in 2003 and by the International Diabetes Federation (IDF) in 2005;[6,7] diagnostic criteria were developed specifically for Japan in 2007.[8,9] Many criteria use percentile values or the values that are linked to those for adults as cutoffs because it is difficult to determine evidence-based cutoffs using morbidity as an endpoint in children and adoles-

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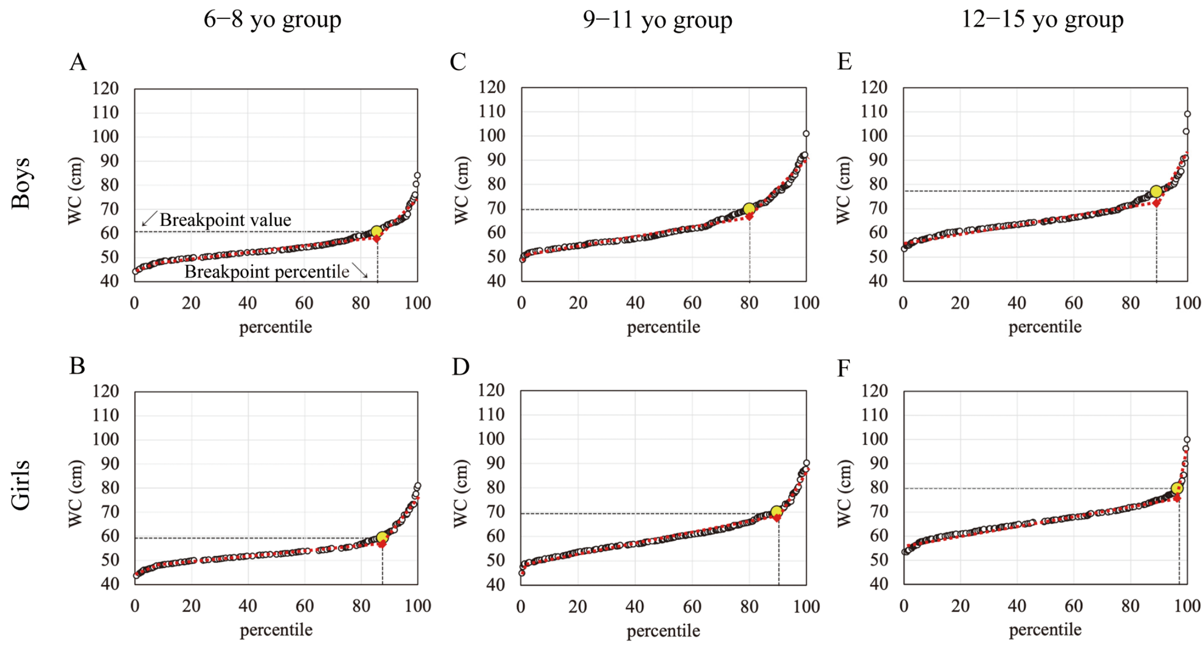

Figure 1. Inverse cumulative percentile graphs for waist circumference (WC). Left column (**A**,**B**), 6–8 yo group; Middle column (**C**,**D**), 9–11 yo group; Right column (**E**,**F**), 12–15 yo group; Top row (**A**,**C**,**E**), boys; Bottom row (**B**,**D**,**F**), girls. Red dotted line, regression line; red diamond, breakpoint; yellow circle, inflection point.

cents.[6–10] Therefore, further research is needed to validate and identify optimum cutoffs for metabolic syndrome componets.[7,10]

Cumulative percentile graphs of normally distributed data have an S-shaped curve with a straight central line and upper and lower tails.[11] Segmented (i.e., broken-line) regression analysis is a method of analyzing non-linear relationships by identifying breakpoints at the intersections of regression lines.[12] This approach has been used to assess mortality, environmental pollution, and predicting COVID-19 transmission trends.[13–17]

The aim of the present study was to determine age- and sex-specific cutoffs for metabolic syndrome components. In a novel approach, we applied segmented regression analysis to cumulative percentile graphs to obtain breakpoints as potential metabolic syndrome component cutoffs using the data of healthy, school-age volunteers throughout Japan.

Methods

Participants

The participants were 1,843 (907 boys and 936 girls) healthy volunteers, under junior high school age, who participated in a project to obtain normal values for health parameters in Japanese children and adolescents between July 2012 and January 2014. Health examinations were conducted in 9 prefectures of Japan: Kagoshima, Fukuoka, Okayama, Hyogo, Aichi, Toyama, Kanagawa, Chiba, and Hokkaido. Participants were recruited through school officials, the regional education board, or the websites of the authors' affiliated hospitals. Written consent was obtained from the guardians of participants. From the original sample, 174 participants were excluded: 164 participants aged under 5 years were excluded because they were not school age, and 10 participants were excluded because of difficulties with blood sampling. Therefore, data from 1,679 participants aged from 6 to 15 years were analyzed in the study. The participants were divided into 3 groups according to age and analyzed separately for boys and girls: 529 (263 boys and 266 girls) participants aged 6–8 years were in the 6–8 yo group, 591 (282 boys and 309 girls) participants aged 9–11 years were in the 9–11 yo group, and 559 (276 boys and 283 girls) participants aged 12–15 years were in the 12–15 yo group. This study was approved by the Ethics Committee of the National Hospital Organization Kagoshima Medical Center (No. 24-5).

Measurement of Metabolic Syndrome Components

Height was measured to the nearest 0.1 cm and weight was measured to the nearest 0.1 kg. Waist circumference (WC) was measured at the umbilical level to the nearest 0.1 cm. BMI was calculated as: weight (kg)/height (m^2). Obesity was defined as ≥20% overweight, which is the consensus recommendation as the definition for childhood obesity in Japan.[18] Percent overweight is calculated from a reference as: [(individual body weight)/(age-, sex-, and height-specific reference body weight) − 1]×100.[19] Blood pressure (BP) was measured 3 times after 10 min of rest using the same automated oscillatory system (TM-2571; A&D Co. Ltd, Tokyo, Japan) in each Japanese region, and the average of the second and third measurements was used. Fasting blood samples were collected to measure triglycerides (TGs), high-density lipoprotein cholesterol (HDLC), and fasting blood glucose (FBG) concentrations. The TG and HDLC levels were determined using enzymatic and direct

Table 1. Participant Characteristics

	6–8 yo	9–11 yo	12–15 yo	Trend P‡	Tukey§
Number					
Boys	263	282	276		
Girls	266	309	283		
Age (years)					
Boys	7.5 (0.9)	10.5 (0.9)	13.7 (1.0)		
Girls	7.5 (0.9)	10.4 (0.9)	13.6 (1.0)		
Height (cm)					
Boys	123.3 (7.1)	139.5 (7.8)	159.9 (9.5)	<0.001	a,b,c
Girls	122.2 (7.0)	140.0 (8.9)	154.9 (5.6)†	<0.001	a,b,c
Weight (kg)					
Boys	24.2 (5.5)	34.9 (8.5)	48.0 (10.5)	<0.001	a,b,c
Girls	23.6 (5.1)	34.0 (8.6)	45.7 (7.3)†	<0.001	a,b,c
BMI (kg/m^2)					
Boys	15.8 (2.2)	17.8 (3.2)	18.6 (2.7)	<0.001	a,b,c
Girls	15.7 (2.2)	17.1 (2.9)†	19.0 (2.5)	<0.001	a,b,c
WC (cm)					
Boys	54.6 (6.4)	62.7 (9.7)	66.6 (7.9)	<0.001	a,b,c
Girls	54.0 (6.3)	60.4 (8.2)†	66.9 (6.9)	<0.001	a,b,c
SBP (mmHg)					
Boys	94 (9)	98 (9)	104 (11)	<0.001	a,b,c
Girls	93 (9)	97 (9)	101 (9)†	<0.001	a,b,c
DBP (mmHg)					
Boys	53 (8)	55 (8)	56 (9)	<0.001	c
Girls	53 (7)	55 (8)	56 (7)	<0.001	a,c
TGs (mmol/L)*					
Boys	0.60 [0.42/0.76]	0.63 [0.43/0.89]	0.59 [0.41/0.84]	0.16	
Girls	0.59 [0.42/0.76]	0.72 [0.51/0.98]†	0.70 [0.50/0.97]†	<0.001	a,c
HDLC (mmol/L)					
Boys	1.65 (0.34)	1.66 (0.34)	1.62 (0.34)	0.24	
Girls	1.64 (0.31)	1.60 (0.31)†	1.60 (0.28)	0.26	
FBG (mmol/L)					
Boys	4.76 (0.33)	4.84 (0.33)	4.81 (0.39)	0.03	a
Girls	4.60 (0.33)†	4.71 (0.33)†	4.77 (0.28)	<0.001	a,c

Data are expressed as mean (standard deviation). *Skewed data are expressed as the median [25th/75th percentiles]. †P<0.05, boys vs. girls using Student's t-test. ‡Statistical analysis for trend P was performed using one-way analysis of variance. §Differences in the mean values between groups were analyzed using Tukey's post hoc tests. [a]P<0.05, 6–8 yo group vs. 9–11 yo group. [b]P<0.05, 9–11 yo group vs. 12–15 yo group. [c]P<0.05, 6–8 yo group vs. 12–15 yo group. BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDLC, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TGs, triglycerides; WC, waist circumference; yo, years old.

quantitative assays, respectively, with an automated analyzer (JCA-BM8060; JEOL Ltd, Tokyo, Japan). The FBG levels were determined using the hexokinase method with an automated analyzer (JCA-BM9000 series, JEOL Ltd). All assays were performed by SRL, Inc. (Tokyo, Japan).

Published Data for Japanese Children and Adolescents

Published data for Japanese elementary and junior high school students in 2013 were obtained from the School Health Survey of the Ministry of Education, Culture, Sports, Science and Technology.[4]

Statistical Analysis

T-tests were used for comparisons between boys and girls in each group. One-way analyses of variance followed by Tukey's post hoc tests were used for comparisons between age groups. The present data were compared with published data using t-tests and Chi-squared tests. For all analysis, P<0.05 was considered statistically significant.

Segmented regression analysis, an application of the least squares method, was applied to an inverse cumulative percentile graph for each metabolic syndrome component in the study (**Figure 1A**). An inverted S-shaped curve with a linear center was drawn with the x-axis as the percentile and the y-axis as the measured value. The curve was divided into 3 parts: a relatively linear central part, and steep lower and upper parts. A regression line was then drawn on each part. After calculating the sum of the residual squares between the inverted S-curve and the 3 regression lines, the Solver function of Microsoft Excel (Microsoft Japan, Ltd., Tokyo, Japan) was used to adjust the regression equations so that the sum of the residual squares was minimized. The Solver function uses an iterative least squares fitting routine to produce optimal goodness of fit between data and function.[20] The intersection of each adjusted regression line was defined as the break-

Table 2. Difference in the Prevalence of Obesity Between the Present Study and Published Data From the Ministry of Education, Culture, Sports, Science and Technology

	6–8 yo			9–11 yo			12–15 yo		
	Present study	Published data	P value	Present study	Published data	P value	Present study	Published data	P value
Boys	6.8%	5.6%	0.32	14.0%	9.9%	0.02	6.9%	9.6%	0.12
Girls	6.0%	5.2%	0.55	10.7%	8.1%	0.09	3.5%	7.9%	0.006

Data from the present study were compared with published data from the 2013 School Health Survey conducted by the Ministry of Education, Culture, Sports, Science and Technology, which covered approximately 500,000 students nationwide (5% of all students in Japan).[4] Data were compared using the Chi-squared test. yo, years old.

Table 3. Breakpoint Percentiles, Breakpoint Values, and 90th Percentile Values for Each Metabolic Syndrome Component

Metabolic syndrome component	Breakpoint value [Breakpoint percentile]			90th percentile value		
	6–8 yo	9–11 yo	12–15 yo	6–8 yo	9–11 yo	12–15 yo
WC (cm)						
Boys	61 [86]	70 [80]	77 [90]	64	78	78
Girls	59 [87]	70 [89]	80 [96]	62	71	75
SBP (mmHg)						
Boys	107 [92]	108 [87]	118 [90]	106	111	118
Girls	108 [96]	108 [87]	112 [89]	104	110	113
DBP (mmHg)						
Boys	62 [85]	68 [93]	69 [93]	64	65	67
Girls	62 [89]	66 [93]	65 [90]	63	64	65
TGs (mmol/L)						
Boys	1.25 [97]	1.44 [94]	1.20 [92]	1.01	1.29	1.14
Girls	1.15 [89]	1.27 [89]	1.30 [92]	1.17	1.30	1.24
HDLC (mmol/L)						
Boys	1.22 [10]	1.17 [6]	1.14 [3]	1.22*	1.24*	1.24*
Girls	1.17 [4]	1.14 [7]	1.14 [3]	1.24*	1.22*	1.24*
FBG (mmol/L)						
Boys	5.22 [92]	5.38 [95]	5.33 [94]	5.22	5.27	5.27
Girls	5.16 [94]	5.16 [91]	5.33 [97]	5.05	5.11	5.11

*HDLC values are expressed as 10th percentile values instead of 90th percentile values because low HDLC concentrations are diagnostic for metabolic syndrome. Abbreviations as in Table 1.

point. The x-axis value of the breakpoint was taken as the breakpoint percentile, and the corresponding point on the curve was designated the inflection point. The breakpoint value was defined as the y-axis value corresponding to the inflection point. Statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM Japan, Ltd., Tokyo, Japan) and Microsoft Excel.

Results

Characteristics of the participants are shown in **Table 1**. Boys had significantly higher heights and weights than girls in the 12–15 yo group, and a significantly higher BMI than girls in the 9–11 yo group. Metabolic syndrome components also showed age- and/or sex-dependent differences. In both boys and girls, WC, systolic BP (SBP), and diastolic BP (DBP) were significantly different across age groups (all $P<0.001$), showing a positive association with age. Sex-specific age-related differences were found in other components: TG levels were only significantly ($P<0.001$) different across age groups for girls, while FBG trends showed different degrees of significance for boys ($P=0.03$) and girls ($P<0.001$). Sex-dependent differences were as follows: boys had significantly higher values than girls for WC in the 9–11 yo group, SBP in the 12–15 yo group, HDLC in the 9–11 yo group, and FBG in the 6–8 yo and 9–11 yo groups, while girls had significantly higher values than boys for TGs in the 9–11 yo and 12–15 yo groups (all $P<0.05$).

Data on the prevalence of obesity in the present study were compared with data published by the Ministry of Education, Culture, Sports, Science and Technology (**Table 2**). The prevalence of obesity in the present study was significantly ($P=0.02$) higher than in the published data in the 9–11 yo boys' group. Conversely, the prevalence of obesity was significantly ($P=0.006$) lower than in the published data in the 12–15 yo girls' group.

Breakpoint percentiles, breakpoint values, and 90th percentile values for each metabolic syndrome component grouped by age and sex are shown in **Table 3**. Breakpoint percentiles for WC were the lowest (80th percentile) in the 9–11 yo boys' group, and highest (96th percentile) in the 12–15 yo girls' group (**Table 3**, **Figure 1**), probably because prevalence of obesity was the highest (14.0%) and the lowest (3.5%) in these groups, respectively (**Table 2**). However, breakpoint values showed few sex differences, and for both

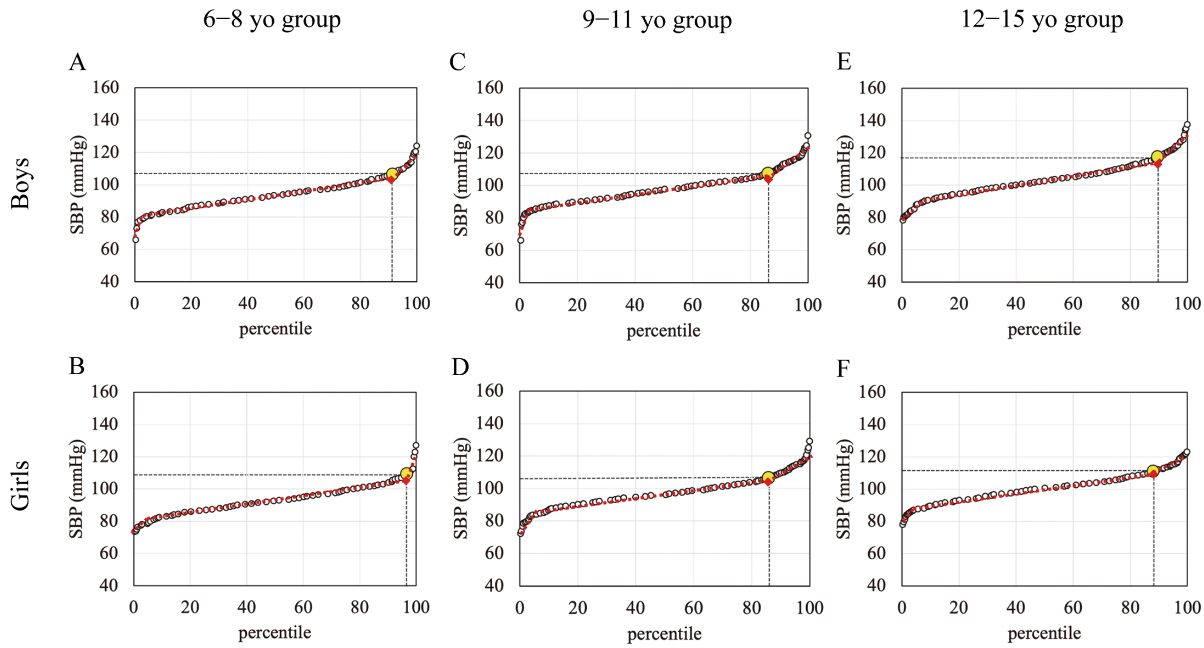

Figure 2. Inverse cumulative percentile graphs for systolic blood pressure (SBP). Left column (**A**,**B**), 6–8 yo group; Middle column (**C**,**D**), 9–11 yo group; Right column (**E**,**F**), 12–15 yo group; Top row (**A**,**C**,**E**), boys; Bottom row (**B**,**D**,**F**), girls. Red dotted line, regression line; red diamond, breakpoint; yellow circle, inflection point.

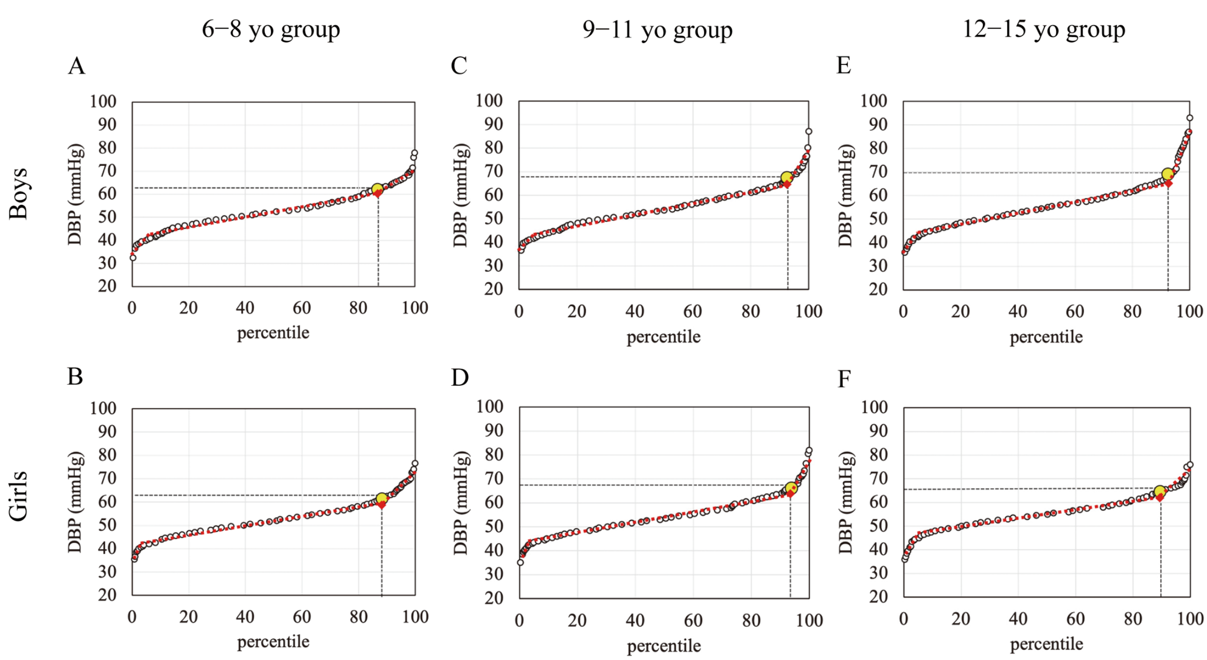

Figure 3. Inverse cumulative percentile graphs for diastolic blood pressure (DBP). Left column (**A**,**B**), 6–8 yo group; Middle column (**C**,**D**), 9–11 yo group; Right column (**E**,**F**), 12–15 yo group; Top row (**A**,**C**,**E**), boys; bottom row (**B**,**D**,**F**), girls. Red dotted line, regression line; red diamond, break point; yellow circle, inflection point.

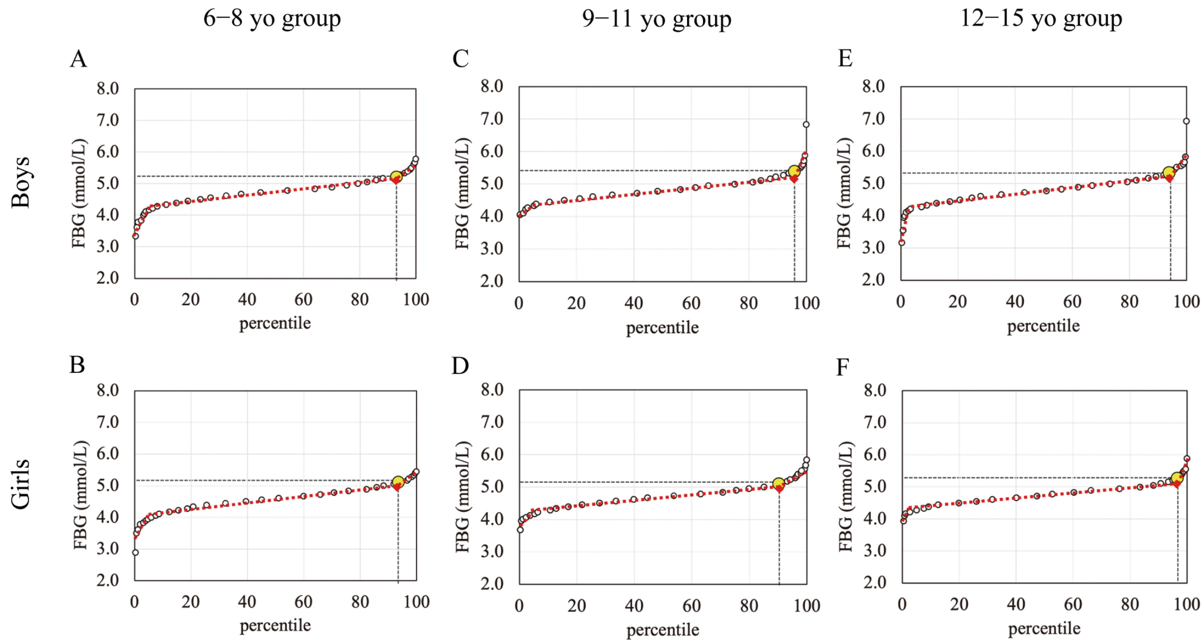

Figure 4. Inverse cumulative percentile graphs for fasting blood glucose (FBG). Left column (**A**,**B**), 6–8 yo group; Middle column (**C**,**D**), 9–11 yo group; Right column (**E**,**F**), 12–15 yo group; Top row (**A**,**C**,**E**), boys; Bottom row (**B**,**D**,**F**), girls. Red dotted line, regression line; red diamond, breakpoint; yellow circle, inflection point.

sexes increased in a step-wise manner as approximately 60, 70, and 80 cm for the 6–8, 9–11, and 12–15 yo groups, respectively.

Breakpoint percentiles for SBP were located around the 90th percentile in all groups except for the 6–8 yo girls' group, where it was located at the 96th percentile (**Table 3**, **Figure 2**). Breakpoint values were almost the same in the 6–8 yo and 9–11 yo groups (107 or 108 mmHg) for both sexes, and higher in the 12–15 yo group (118 mmHg in boys and 112 mmHg in girls). Breakpoint values for DBP tended to increase with age (**Table 3**, **Figure 3**).

Breakpoint percentiles for TGs were above the 90th percentile except for the 6–8 yo and 9–11 yo girls, resulting in breakpoint values of 1.15–1.44 mmol/L, which were higher than the 90th percentile values of 1.01–1.30 mmol/L (**Supplementary Figure 1**). TG values are often not normally distributed, and therefore are log-transformed for analysis. We performed analysis on both measured and log-transformed TG values for comparison and confirmed the results were the same. HDLC was evaluated using the lower breakpoint of the 3 regression lines because low HDLC values are diagnostic for metabolic syndrome. Breakpoint percentiles were below the 10th percentile in all groups, resulting in breakpoint values of 1.14–1.22 mmol/L (**Supplementary Figure 2**). Breakpoint percentiles for FBG were also above the 90th percentile in all groups, resulting in breakpoint values of 5.16–5.38 mmol/L (**Figure 4**).

Discussion

In the present study, breakpoint values obtained using segmented regression analysis revealed that cutoffs for some metabolic syndrome components were age and sex specific. Breakpoint values for WC and DBP varied across age groups, but were consistent across sexes; those for SBP varied by both age and sex, and those for TGs, HDLC, and FBG were neither age nor sex dependent. Based on these results, we proposed new cutoffs for metabolic syndrome components in Japanese children and adolescents.

Potential for Cutoffs Using Breakpoint Values in Children and Adolescents

In children and adolescents, many diagnostic cutoffs use 90th or 95th percentile values of childhood data or adult cutoffs because of the paucity of evidence for morbidity and mortality in children. The 90th percentile of BP is defined as prehypertensive and the 95th percentile as hypertensive,[21] while the 95th percentile of lipid levels is defined as abnormally high.[22] Previously reported cutoffs for metabolic syndrome in children and adolescents also used the 90th percentile values for WC and BP, and adult cutoffs for FBG.[6,7] Jolliffe and Janssen developed adolescent metabolic syndrome cutoffs linked to the Adult Treatment Panel III and IDF adult criteria using Lambda Mu Sigma growth curve modeling.[10] However, further research is needed to reach a consensus on appropriate values.[7,10]

We sought an alternative statistical method to determine cutoffs for children and adolescents, using cumulative percentile graphs and segmented regression analysis. Reimann et al reported that, for geochemical data, graphical inspection of exploratory data analyses is better suited than outlier removal methods for estimating the range of background variation and determining thresholds.[11] In addition, they concluded that the cumulative probability plot, which is synonymous with the cumulative percentile graph, is one of the best graphical displays of geochemical data distribu-

Table 4. Criteria for Metabolic Syndrome Component Cutoffs in Previous Studies and in the Present Study

Variable	IDF[7]	Cook et al[6]	Ohzeki et al (Japanese criteria)[8]	Our proposed criteria
Applicable age	10–16 yo	12–19 yo	6–15 yo	6–15 yo
Defining criteria	Central obesity (A) plus at least 2 of 4 other criteria (B, Ca, Cb, D)	≥3 criteria (A, B, Ca, Cb, D)	Central obesity (A) plus at least 2 of 3 other criteria (B, C, D)	Same as Ohzeki et al
A. Central obesity				
WC	≥90th percentile or adult cutoff if lower	≥90th percentile	Elementary school: ≥75 cm Junior high school: ≥80 cm or waist-to-height ratio ≥0.5	6–8 yo: ≥60 cm 9–11 yo: ≥70 cm 12–15 yo: ≥80 cm
B. Hypertension				
a. SBP	≥130 mmHg	≥90th percentile	≥125 mmHg	6–11 yo: ≥110 mmHg 12–15 yo (girls): ≥115 mmHg 12–15 yo (boys): ≥120 mmHg
b. DBP	≥85 mmHg	≥90th percentile	≥70 mmHg	6–8 yo: ≥65 mmHg 9–15 yo: ≥70 mmHg
C. Dyslipidemia				
a. TGs	≥1.7 mmol/L (≥150 mg/dL)	≥1.2 mmol/L (≥110 mg/dL)	≥1.36 mmol/L (≥120 mg/dL)	≥1.36 mmol/L (≥120 mg/dL)
b. HDLC	<1.03 mmol/L (<40 mg/dL)	≤1.03 mmol/L (≤40 mg/dL)	<1.03 mmol/L (<40 mg/dL)	<1.17 mmol/L (<45 mg/dL)
D. Impaired glucose tolerance				
FBG	≥5.6 mmol/L (≥100 mg/dL)	≥6.1 mmol/L (≥110 mg/dL)	≥5.6 mmol/L (≥100 mg/dL)	≥5.27 mmol/L (≥95 mg/dL)

IDF, International Diabetes Federation. Other abbreviations as in Table 1.

tions.[11] In addition, segmented regression (i.e., broken-line) analysis has been previously used to analyze non-linear relationships and to identify breakpoints.[12,15–17] Eriksson et al analyzed the relationship between exacerbation of chronic obstructive pulmonary disease and changes in lung function to determine the threshold of rapid exacerbation,[15] while Jauk et al attempted to use segmented regression analysis to determine the threshold between intelligence and creativity.[16] Recently, Santamaria and Hortal used the analyses to identify shifts in the effective reproduction number reported for Spanish administrative regions.[17]

We introduced breakpoint values using segmented regression analysis on inverse cumulative percentile graphs as an alternative approach to determine cutoffs in the present study. The results suggest that breakpoint percentiles/values offer a number of benefits in determining cutoffs for metabolic syndrome components. First, breakpoint percentiles/values identify turning points from healthy to undesirable conditions specific to each component: breakpoint percentiles for BP tended to be located around the 90th percentile levels, whereas those for FBG were located around the 95th percentile. Second, breakpoint percentiles/values correct sample bias. If there is a high prevalence of obesity in a population, the 90th percentile value for WC will be higher than in other populations. For example, in the present study, the 9–11 yo boys' group had a higher prevalence (14.0%) of obesity than the same age group in the published data (9.9%); therefore, in our population, the 90th percentile value of WC was 78 cm, as high as that for the 12–15 yo boys' group. However, breakpoint values, 70 cm for the 9–11 yo boys' group and 77 cm for the 12–15 yo boys' group, showed age group-appropriate differences, suggesting that breakpoint percentiles/values corrected for this sample bias. On the basis of our results, we propose new cutoffs for metabolic syndrome components in Japanese children and adolescents. **Table 4** compares worldwide diagnostic criteria with existing Japanese criteria and our proposed cutoffs.

Cutoffs for WC

WC varies by age, sex, and race.[23] WC cutoffs proposed by Cook et al and the IDF therefore adopted 90th percentile values according to age, sex, and race. The Japanese cutoff of 80 cm was determined based on visceral fat data from 290 boys and girls with obesity of various ages ranging from 6 to 15 years by Asayama et al.[24] Our cutoffs were set at 60, 70, and 80 cm for 6–8, 9–11, and 12–15 yo groups, respectively, according to each of the breakpoint values in the present study. In Japan, Fujiwara and Inoue reported data on the WC of approximately 20,000 children (**Supplementary Table A**).[25] Comparing their data with ours, the mean values of height, weight, and WC in their first and second grade (7–8 yo), fourth and fifth grade (10–11 yo), and seventh and eighth grade (13–14 yo) groups were close to those in our 6–8, 9–11, and 12–15 yo groups. In addition, their optimal cutoffs for screening children with percentage overweight of ≥20% in those grades also approximated to our breakpoint values.

Cutoffs for BP

BP values also vary by age, sex, and height, as shown in the data of the American Academy of Pediatrics.[21] Cutoffs were set at the 90th percentile in the criteria by Cook et al, while a single numerical value was used in the IDF and Japanese criteria. We propose age- and sex-specific cutoffs for SBP because age- and sex-specific differences were observed in breakpoint values in the present study; for DBP, only age-specific cutoffs are proposed because sex-specific differences were small compared with those for SBP. In Japan, Kikuchi et al reported mean and percentile values according to age and sex in approximately 12,000 children (**Supplementary Table B**).[26,27] The mean age, height and weight in second, fifth, and eighth graders were close to those in our 6–8, 9–11, and 12–15 yo groups, respectively. Although mean SBP levels in their second and fifth graders were almost the same as those in our 6–8 and 9–11 yo groups, respectively, the mean SBP levels in their eighth graders were higher than those in our 12–15 yo groups for both sexes. In contrast, the mean DBP levels in their second and fifth graders were lower than those in our 6–8 yo and 9–11 yo groups, respectively, and those in their eighth graders were almost the same as those in our 12–15 yo groups for both sexes. One reason for these differences might be that the mean levels of both SBP and DBP increased relatively sharply between their sixth and seventh graders compared with a gradual increase between their first and sixth graders. Another reason might be due to the measurement instruments used in the 2 studies: as Wattigney et al reported, the early automatic oscillatory system used by Kikuchi et al resulted in significantly lower DBP levels than those produced using mercury sphygmomanometers.[28]

Cutoffs for TGs

TG levels are highly variable and easily influenced by diet. As a result, TG cutoffs proposed in the diagnostic criteria in **Table 4** vary widely, ranging from 1.24 to 1.70 mmol/L (110–150 mg/dL). The 90th percentile values of TGs in Japan determined by Okada et al from approximately 40,000 subjects between 1993 and 1999 ranged from 1.25 to 1.54 mmol/L (111–136 mg/dL) (**Supplementary Table C**).[29] Consequently, the Japanese cutoff was determined as 1.36 mmol/L (120 mg/dL)[8,9] based on their 90th percentile values. Breakpoint values in the present study ranged from 1.15 to 1.44 mmol/L (102–127 mg/dL), meaning our cutoff was also set as 1.36 mmol/L (120 mg/dL), similar to the borderline high concentration included in the National Heart Lung and Blood Institute guidelines.[22]

Cutoffs for HDLC

In most diagnostic criteria, the cutoff for HDLC is 1.03 mmol/L (40 mg/dL), including the Japanese criteria (**Table 4**), which is lower than our cutoff of 1.17 mmol/L (45 mg/dL). The cutoff of 1.03 mmol/L (40 mg/dL) in Japanese diagnostic criteria was determined based on the 5th percentile value by Okada et al because values in their report ranged from 1.01 to 1.17 mmol/L (39–45 mg/dL) (**Supplementary Table C**).[29] More recent data by Abe et al from approximately 440,000 subjects recruited between 2006 and 2011 had 5th percentile values for HDLC that ranged from 1.11 to 1.24 mmol/L (43–48 mg/dL) (**Supplementary Table D**).[30] The data of Abe et al, and the present data, suggest that a cutoff of 1.17 mmol/L (45 mg/dL) is a more appropriate value than 1.07 mmol/L (40 mg/dL) for Japanese children and adolescents. The value of 1.17 mmol/L (45 mg/dL) is also consistent with the borderline low concentration included in the National Heart Lung and Blood Institute guidelines.[22]

Cutoffs for FBG

There are limited data on FBG levels in children. Therefore, the IDF and Japanese criteria set the cutoff for FBG as 5.55 mmol/L (100 mg/dL), the same as the adult prediabetes diagnostic cutoff.[1,31] The FBG breakpoint values ranged from 5.16 to 5.33 mmol/L (93–96 mg/dL) in the present study; therefore, our proposed cutoff is 5.27 mmol/L (95 mg/dL), which is lower than the conventional cutoff. Nguyen et al reported that childhood FBG concentrations above their median value of 4.77 mmol/L (86 mg/dL) were associated with an increased risk of future prediabetes or diabetes,[32] suggesting a lower cutoff might be more appropriate for children and adolescents.

Study Limitations

There are some limitations in the present study. First, the prevalence of obesity in our participants was higher than published data, which suggests sampling bias; however, the use of breakpoint percentiles/values corrected this bias. Second, our proposed cutoffs are tentative and might be a little complex; evidence from further longitudinal studies is required to determine whether these are superior to previously reported cutoffs for the early prediction of future cardiovascular diseases. Last, the data in this study were from Japanese children; to account for regional and ethnic differences, each country should establish specific cutoffs.

Conclusions

In the present study, segmented regression analysis for metabolic syndrome components revealed that some breakpoint values varied by age and sex. Breakpoint values for WC were age dependent, for BP were age and/or sex dependent, and for TGs, HDLC, and FBG were neither age nor sex dependent. Our proposed cutoffs for metabolic syndrome components based on these breakpoint values might identify specific turning points associated with adverse health outcomes in Japanese children and adolescents. However, further studies are needed to confirm their usefulness in diagnosing metabolic syndrome and predicting future disease.

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Disclosures

The authors have no relevant conflicts of interest to disclose.

IRB Information

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References

1. Jebeile H, Kelly AS, O'Malley G, Baur LA. Obesity in children and adolescents: Epidemiology, causes, assessment, and management. *Lancet Diabetes Endocrinol* 2022; **10:** 351–365, doi:10.1016/S2213-8587(22)00047-X.
2. World Obesity Federation. Global obesity observatory. 2021. https://data.worldobesity.org/maps/?area=trends (accessed September 16, 2023).
3. Woolford SJ, Sidell M, Li X, Else V, Young DR, Resnicow K, et al. Changes in body mass index among children and adolescents during the COVID-19 pandemic. *JAMA* 2021; **326:** 1434–1436, doi:10.1001/jama.2021.15036.
4. Ministry of Education, Culture, Sports, Science and Technology of Japan. The School Health Statistics Survey (2006–2021) [in Japanese]. https://www.mext.go.jp/b_menu/toukei/chousa05/hoken/1268826.htm (accessed September 16, 2023).
5. Magge SN, Goodman E, Armstrong SC. The metabolic syndrome in children and adolescents: Shifting the focus to cardiometabolic risk factor clustering. *Pediatrics* 2017; **140:** e20171603,

doi:10.1542/peds.2017-1603.
6. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: Findings from the third National Health and Nutrition Examination Survey, 1988–1994. *Arch Pediatr Adolesc Med* 2003; **157:** 821–827, doi:10.1001/archpedi.157.8.821.
7. Zimmet P, Alberti G, Kaufman F, Tajima N, Silink M, Arslanian S, et al. The metabolic syndrome in children and adolescents. *Lancet* 2007; **369:** 2059–2061, doi:10.1016/S0140-6736(07)60958-1.
8. Ohzeki T. Diagnostic criteria for obesity-disease and metabolic syndrome in Japanese children. *Nihon Rinsho* 2010; **68:** 679–683 [in Japanese].
9. Ohzeki T. Diagnostic criteria for metabolic syndrome in Japanese children. *In*: Igarashi T, editor. Metabolic syndrome in children, 1st edn. Tokyo: Nakayama Shoten, 2009; 20–21 [in Japanese].
10. Jolliffe CJ, Janssen I. Development of age-specific adolescent metabolic syndrome criteria that are linked to the Adult Treatment Panel III and International Diabetes Federation criteria. *J Am Coll Cardiol* 2007; **49:** 891–898, doi:10.1016/j.jacc.2006.08.065.
11. Reimanna C, Filzmoserb P, Garrett RG. Background and threshold: Critical comparison of methods of determination. *Sci Total Environ* 2005; **346:** 1–16, doi:10.1016/j.scitotenv.2004.11.023.
12. Muggeo VMR. Estimating regression models with unknown break points. *Statist Med* 2003; **22:** 3055–3071, doi:10.1002/sim.1545.
13. Kunst AE, Looman CWN, Mackenbach JP. Outdoor air temperature and mortality in the netherlands: A time-series analysis. *Am J Epidemiol* 1993; **137:** 331–341, doi:10.1093/oxfordjournals.aje.a116680.
14. Hites RA. Break point analyses of human or environmental temporal trends of POPs. *Sci Total Environ* 2019; **664:** 518–521, doi:10.1016/j.scitotenv.2019.01.353.
15. Eriksson G, Jarenbäck L, Peterson S, AnKerst J, Bjermer L, Tufvesson E. A new approach to assess COPD by identifying lung function break-points. *Int J COPD* 2015; **10:** 2193–2202, doi:10.2147/COPD.S86059.
16. Jauk E, Benedek M, Dunst B, Neubauer AC. The relationship between intelligence and creativity: New support for the threshold hypothesis by means of empirical breakpoint detection. *Intelligence* 2013; **41:** 212–222, doi:10.1016/j.intell.2013.03.003.
17. Santamaría L, Hortal J. COVID-19 effective reproduction number dropped during Spain's nationwide dropdown, then spiked at lower-incidence regions. *Sci Total Environ* 2021; **751:** 142257, doi:10.1016/j.scitotenv.2020.142257.
18. Mitsui T, Barajima T, Kanachi M, Shimaoka K. The significant drop in physical activity among children on holidays in a small town in the Tohoku district. *J Physiol Anthropol* 2010; **29:** 59–64, doi:10.2114/jpa2.29.59.
19. Ikiuo K, Hashimoto R, Murata M. Discussion on the New Physical Fitness Definition in School Health Program. *J Child Health* 2010; **69:** 6–13 [in Japanese].
20. Brown AM. A step-by-step guide to non-linear regression analysis of experimental data using a Microsoft Excel spreadsheet. *Comput Methods Programs Biomed* 2001; **65:** 191–200, doi:10.1016/s0169-2607(00)00124-3.
21. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics* 2017; **140:** e20171904, doi:10.1542/peds.2017-1904.
22. National Heart Lung and Blood Institute. Lipids and lipoproteins. *In*: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; Summary Report. NIH Publication 2012; No. 12-7486A; 38–58.
23. Fernandez JR, Redden DT, Pietrobelli A, Allison DB. Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. *J Pediatr* 2004; **145:** 439–444, doi:10.1016/j.jpeds.2004.06.044.
24. Asayama K, Hayashibe H, Endo A, Okada T, Hara M, Masuda H, et al. Threshold value of visceral fat and waist girth in Japanese obese children. *Pediatr Int* 2005; **47:** 498–504, doi:10.1111/j.1442-200x.2005.02117.x.
25. Fujiwara H, Inoue F. The examination about the change by the age of abdominal circumference. *Journal of Japan Society for the Study of Obesity* 2009; **15:** 45–52 [in Japanese].
26. Kikuchi T. Pediatric hypertension based on Japanese Society of Hypertension guidelines (JSH 2019) with actual school blood pressure screening data in Japan. *Clin Exp Pediatr* 2022; **65:** 283–290, doi:10.3345/cep.2021.00920.
27. Kikuchi T, Nagasaki K, Ogawa Y, Abe Y, Hiura M, Tanaka Y, et al. Blood pressure reference values by sex and grade in Japanese children, Mitsuke Study. *Jpn J Pediatr Hypertens* 2011; **8:** 21–25 [in Japanese].
28. Wattigney WA, Webber LS, Lawrence MD, Berenson GS. Utility of an automatic instrument for blood pressure measurement in children: The Bogalusa Heart Study. *Am J Hypertens* 1996; **9:** 256–262, doi:10.1016/0895-7061(95)00334-7.
29. Okada T, Murata M, Yamauchi K, Harada K. New criteria of normal serum lipid levels in Japanese children: The nationwide study. *Pediatr Int* 2002; **44:** 596–601, doi:10.1046/j.1442-200x.2002.01634.x.
30. Abe Y, Okada T, Sugiura R, Yamauchi K, Murata M. Reference ranges for the non-high-density lipoprotein cholesterol levels in Japanese children and adolescents. *J Atheroscler Thromb* 2015; **22:** 669–675, doi:10.5551/jat.28100.
31. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 2. Classification and diagnosis of diabetes: *Standards of Care in Diabetes—2023. Diabetes Care* 2023; **46**(Suppl 1)**:** S19–S40, doi:10.2337/dc23-S002.
32. Nguyen QM, Srinivasan SR, Xu JH, Chen W, Berenson GS. Fasting plasma glucose levels within the normoglycemic range in childhood as a predictor of prediabetes and type 2 diabetes in adulthood: The Bogalusa Heart Study. *Arch Pediatr Adolesc Med* 2010; **164:** 124–128, doi:10.1001/archpediatrics.2009.268.

Supplementary Files

Please find supplementary file(s);
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