



Performance of gender- and age-specific cut-points *versus* NCEP pediatric cutpoints in dyslipidemia screening among Chinese children



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HIGHLIGHTS

- The trajectories of lipid levels according to age are different between genders.
- The proposed cutpoints have a better capability to predict obesity and hypertension than NCEP pediatric cutpoints.
- The distribution of lipids among Chinese children are proposed to be compared with other countries.
- The new cutpoints should improve the accuracy of abnormal lipids classification in China.

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ABSTRACT

Background and aims: Considerable attention is given nowadays to the presence of cardiovascular diseases risk factors in children. The current blood lipid classification system for Chinese children was based on the United States National Cholesterol Education Program (NCEP) cutpoints, which did not take the age, gender and race differences into consideration. This study aimed to develop gender- and age-specific lipid cutpoints for dyslipidemia screening in Chinese children and compare the ability of new cutpoints and NCEP pediatric cutpoints to predict obesity and unfavorable blood pressure (BP) levels.

Methods: Data were obtained from a nationwide multicenter cross-sectional study: The China Child and Adolescent Cardiovascular Health Study, comprising 12,875 Chinese children aged 6–18 years. We calculated cutpoints for abnormal levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) that were linked to Chinese adult abnormal lipid thresholds using the General Additive Model for Location Scale and Shape method.

Results: Borderline-high and high cutpoints (TC, LDL-C and TG) as well as low cutpoints (HDL-C) were developed to classify the abnormal blood lipid levels in Chinese children. Better performance for prediction of obesity, elevated BP, and hypertension were found with the proposed cutpoints in comparison with the NCEP pediatric cutpoints (AUC for obesity: 0.612 vs. 0.597, $p = 0.017$; AUC for elevated BP: 0.529 vs. 0.521, $p = 0.017$; AUC for hypertension: 0.536 vs. 0.527, $p = 0.016$).

Conclusions: The gender- and age-specific cutpoints should improve the accuracy of dyslipidemia screening in China and be more reasonable in practice.

1. Introduction

Dyslipidemia, characterized by abnormal levels of blood lipid (e.g. triglycerides and/or cholesterol), is one of the major causes of

atherosclerotic cardiovascular disease (ASCVD) [1–3]. Abnormal blood lipid levels in childhood track into adulthood and are associated with preclinical atherosclerosis in later life [4–8]. Therefore, early identification and treatment of children with lipid disorders may improve long-

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term cardiovascular health [9–11]. In adults, dyslipidemia is defined based on associations between lipid levels and cardiovascular outcomes [12]; however, lipid thresholds for defining dyslipidemia in children are usually determined based on the population distributions of lipid levels [3]. The US National Cholesterol Education Program (NCEP) [13] proposed a single set of cutpoints for lipid concentrations to define dyslipidemia aged 2–19 years, however, it did not take lipid variations during normal growth and development into account. To overcome this shortage, gender- and age-specific cutpoints of TC, LDL-C, HDL-C, and TG for adolescents aged 12–19 years were derived from lipid growth curves that were linked to adult abnormal lipid thresholds using data from National Health and Nutrition Examination Surveys (NHANES) [14].

The lipid concentrations may vary among different races because of genetic factors as well [15]. Several gender- and age-specific lipid references of children from different populations have been established [16–18]. To date, there are no gender- and age-specific lipid references to define dyslipidemia among Chinese children and the NCEP pediatric cutpoints are mainly used for the dyslipidemia diagnosis in Chinese children. Moreover, the NCEP pediatric cutpoints have been published over two decades and it has been shown the distribution of these lipids changed over time [19–22]. Therefore, leveraging data from a large-scale nationwide cross-sectional study, we aimed to establish gender- and age-specific cutpoints of blood lipid for dyslipidemia screening in Chinese children and compare the ability of these cutpoints and NCEP cutpoints to predict obesity and unfavorable blood pressure levels.

2. Materials and methods

2.1. Study population

The China Child and Adolescent Cardiovascular Health (CCACH) Study was a nationwide cross-sectional study conducted from 2013 to 2015, which was designed to examine cardiovascular health of school-age children in China. Multistage sampling method was used to select a representative sample of children aged 6–18 years in China. We stratified China into North and South regions by Qinling-Huaihe Line (longitude 104°15'E – 120°21'E and latitude 32°18'N – 34°05'N) according to the characteristics of climate, economic development status and life habits. Then several representative cities (Supplemental Fig. 1) from each region were selected using a nonrandom sampling method. Next, several schools were randomly selected from each city. All the students from selected schools were invited to participate in questionnaire survey, anthropometric measurements and blood sample collection. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by Ethical Review Committee of Capital Institute of Pediatrics (approval number: 2012062). Written informed consent forms for children were obtained from all participants or their legal guardians.

Exclusion criteria included: (1) any condition, or use of any drug known to affect cardiovascular health; (2) non-removable objects (e.g., deformity, fracture or prostheses); (3) body weight greater than 204 kg or height greater than 197.5 cm; (4) pregnancy; (5) absence from school and (6) the inability to give informed consent. A total of 13,395 eligible participants agreed to collect blood samples. After excluding individuals with invalid lipid measurement and diseases (e.g. congenital heart disease, kidney disease and thyroid disease) that may influence the level of lipid concentrations, 13,219 participants were obtained. Of these children, 344 children who were out of study age, with missing or extreme values (Z -score ≥ 3 or ≤ -3) of body mass index (BMI) were excluded. A final study population of 12 875 children were used for establishing the lipid references (Supplemental Fig. 2).

2.2. Physical examination

Measurements were performed wearing light indoor clothes and without shoes. Height was measured to the nearest 0.1 cm by a

stadiometer. Weight was measured to the nearest 0.1 kg in fasting status with an electronic scale. Weight and height were measured twice and the mean values were used for analysis. BMI was calculated as weight (kg) divided by the square of height (m²). Blood pressure (BP) was measured three times with 1–2 min intervals on the right arm using the Omron HEM-7012 electronic sphygmomanometer (Omron Co., Kyoto, Japan) and suitable cuff size was used according to the arm circumference (small, medium and large size cuff were chosen for the 13–22, 22–32 and 32–42 cm, respectively), then the mean value of the last two readings was used for analysis. Waist circumference was measured midway between the lowest rib and the superior border of the iliac crest with an inelastic measuring tape at the end of normal expiration to the nearest 0.1 cm.

2.3. Lipid measurements

After an overnight fast of at least 12 h, blood samples were collected from the antecubital vein in the morning and then were transfused into vacuum tubes containing ethylene diamine tetra acetic acid. Blood specimens were centrifuged at 2000g for 10 min within 1 h of collection at room temperature, and then aliquoted and frozen at -80°C . Plasma specimens collected in each center were shipped on dry ice by air to the central clinical laboratory of Capital Institute of Pediatrics in Beijing, where the specimens were stored at -80°C until laboratory assays were performed. The enzymatic method (Sekisui Medical Inc., Tokyo, Japan) was allowed to assess on the spot values for total cholesterol (TC) and triglycerides (TG) while high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were directly measured using the Hitachi 7080 automated analyzer (Hitachi Inc., Tokyo, Japan).

2.4. Data quality control

A set of strategies was implemented for data quality control. All instruments from the same manufacture were used, and were calibrated every day during the survey. The central laboratory was certificated by the National Center for Clinical Laboratories. Field investigators of each study center participated in central training and organized local training sessions thereafter. The coordinating center implemented site visits to each study location during field surveys to check the adherence of field investigators to the standard operating procedures. Data was double entered with automatic plausibility checks and questionable records identified by checks were returned to the original study center for rectifying.

2.5. Definitions

Weight status was classified as underweight, normal, overweight and obesity according to gender- and age-specific BMI cutoff values recommended by the International Obesity Task Force (IOTF) [23,24]. Abdominal obesity was defined by the waist circumference ≥ 90 th gender- and age-specific percentile, which derived from a Chinese national representative sample [25]. Blood pressure (BP) was classified into three stages by the American Academy Pediatrics (AAP) 2017 guideline: normal BP (< 90 th percentile for < 13 years of age; $< 120/ < 80$ mmHg for ≥ 13 years of age), elevated BP (≥ 90 th percentile to < 95 th percentile or $120/80$ mmHg to < 95 th percentile for < 13 years of age; $120/ < 80$ to $129/ < 80$ mmHg for ≥ 13 years of age) and hypertension (≥ 95 th percentile or $\geq 130/ \geq 80$ mmHg for < 13 years of age; $\geq 130/ \geq 80$ mmHg for ≥ 13 years of age) [26].

Dyslipidemia was defined by the cutpoints (borderline-high for TC, LDL-C, and TG, or low for HDL-C) proposed by current study and NCEP (TC ≥ 5.18 mmol/L; LDL-C ≥ 3.37 mmol/L; HDL-C ≤ 0.91 mmol/L; TG ≥ 1.13 mmol/L for 2–9 years of age or ≥ 1.47 mmol/L for 10–19 years of age), respectively.

2.6. Establishment of blood lipid cutpoints

Smoothed centile curves for blood lipid levels according to the covariate age by gender were constructed using the General Additive Model for Location Scale and Shape (GAMLSS) as an extension of the least mean squares method. GAMLSS is a general framework for fitting regression type models where the distribution of response variable does not have to belong to the exponential family and includes high skewness and kurtosis [27]. Most of these distributions have four parameters including μ , σ , ν and τ which represent location (median), scale (approximate coefficient of variation), skewness (power transformation to symmetry), and kurtosis (degrees of freedom or power exponential parameter), respectively.

Distribution of Normal, Box-Cox Cole and Green (BCCG), Box-Cox Power Exponential (BCPE), and Box-Cox-t (BCT) were tried to fit the observed distributions of blood lipid. The additive functions, that is, linear, cubic splines, penalized splines, loess and fractional polynomials were used to model the influence of age on parameters of the considered distribution. The final models were chosen by the Bayesian Information Criterion. Then the gender- and age-specific cutpoints that

were linked to the Chinese adult abnormal blood lipid thresholds (Supplemental Table 1) [28] at 18 years of age were calculated based on the chosen model.

To assess the effect of obese children in study population on the cutpoints, sensitivity analyses were conducted by recalculating cutpoints using sample without obese individuals.

2.7. Statistical analysis

Mean (SDs) or median (IQRs) were used to describe the levels of lipids, body mass index, waist circumference and BP, while frequency (%) were used for age, weight status, study center group, abdominal obesity and BP stages. The Mann-Whitney *U* test was applied to compare the difference of TG between genders due to skewness. The Student's *t*-test or χ^2 test was chosen to examine differences in other characteristics according to gender. Wald asymptotic method was carried out to estimate the confidence interval of prevalence. Area under the receiver operating characteristic curves (AUCs) were obtained to assess the ability of dyslipidemia define by the proposed cutpoints and NCEP pediatric cutpoints to predict obesity, abdominal obesity, ele-

Table 1
Characteristics of the study population by gender.

Characteristics	Gender		p value
	Boys (N = 6625)	Girls (N = 6250)	
Age, No. (%), y			< 0.001
6	364 (5.5)	354 (5.7)	
7	576 (8.7)	512 (8.2)	
8	586 (8.8)	481 (7.7)	
9	486 (7.3)	514 (8.2)	
10	513 (7.7)	453 (7.3)	
11	515 (7.8)	451 (7.2)	
12	540 (8.2)	451 (7.2)	
13	534 (8.1)	431 (6.9)	
14	469 (7.1)	381 (6.1)	
15	575 (8.7)	553 (8.8)	
16	671 (10.1)	738 (11.8)	
17	518 (7.8)	608 (9.7)	
18	278 (4.2)	323 (5.2)	
BMI, mean (SD), kg/m ²	20.2 (4.4)	19.2 (3.6)	< 0.001
Weight status, ^a No. (%)			< 0.001
underweight	95 (1.4)	144 (2.3)	
normal	4424 (66.8)	4959 (79.3)	
overweight	1337 (20.2)	899 (14.4)	
obesity	769 (11.6)	251 (4.0)	
Study center, No. (%)			< 0.001
Beijing	972 (14.7)	777 (12.4)	
Changchun	1764 (26.6)	1528 (24.4)	
Chengdu	658 (9.9)	680 (10.9)	
Chongqing	845 (12.8)	880 (14.1)	
Jinan	816 (12.3)	720 (11.5)	
Shanghai	807 (12.2)	818 (13.1)	
Yinchuan	763 (11.5)	847 (13.6)	
Waist circumference, mean (SD), cm	69.0 (12.8)	64.2 (9.8)	< 0.001
Abdominal obesity, No. (%)	1611 (24.3)	1156 (18.5)	< 0.001
Systolic BP, mean (SD), mmHg	114.8 (13.6)	109.2 (11.2)	< 0.001
Diastolic BP, mean (SD), mmHg	66.8 (8.6)	66.7 (8.4)	0.610
BP stages, ^b No. (%)			< 0.001
normal	3498 (54.3)	4302 (71.5)	
elevated BP	1195 (18.6)	715 (11.9)	
hypertension	1742 (27.1)	998 (16.6)	
TC, mean (SD), mmol/L	3.79 (0.73)	3.86 (0.74)	< 0.001
LDL-C, mean (SD), mmol/L	2.11 (0.60)	2.15 (0.61)	< 0.001
HDL-C, mean (SD), mmol/L	1.39 (0.29)	1.43 (0.28)	< 0.001
TG, median (IQR), mmol/L	0.69 (0.48–0.98)	0.71 (0.52–0.99)	< 0.001

BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; BP, blood pressure.

SI conversion factors: to convert TC, LDL-C, and HDL-C to mg/dL, multiply values by 38.67. To convert TG to mg/dL, multiply values by 88.5.

^a Classified by BMI cutpoints according to the International Obesity Task Force criteria.

^b Defined by the American Academy Pediatrics (AAP) 2017 pediatric hypertension guideline.

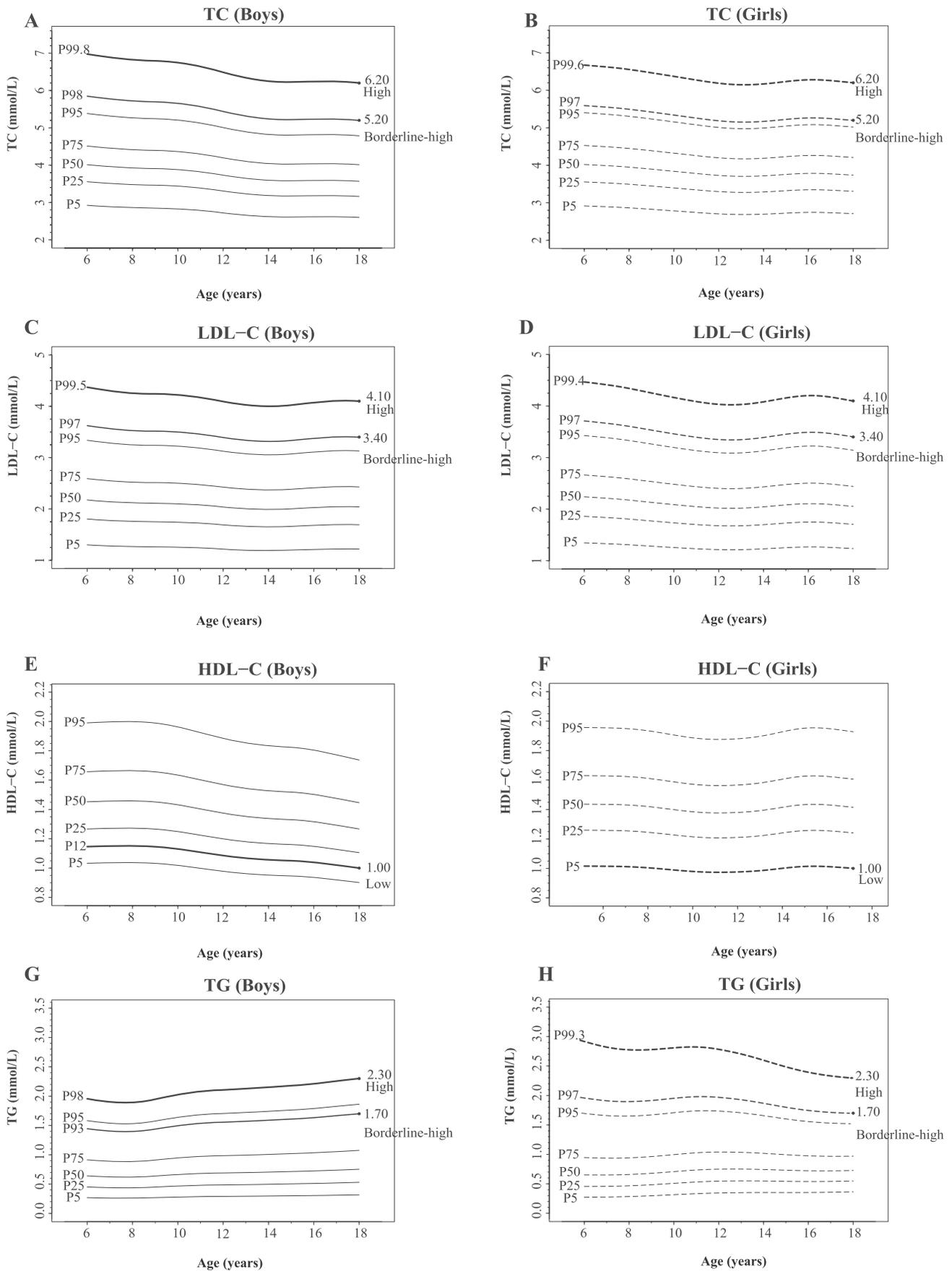


Fig. 1. Age-specific reference curves of blood lipid for Chinese children aged 6–18 years. (A) TC, (C) LDL-C, (E) HDL-C, and (G) TG curves in boys. (B) TC, (D) LDL-C, (F) HDL-C, and (H) TG curves in girls. Bold lines are going through the Chinese adult abnormal blood lipids thresholds at 18 years of age.

Table 2
Gender- and age-specific abnormal lipid cutpoints and corresponding centiles.

Age, y	TC, mmol/L				LDL-C, mmol/L				HDL-C, mmol/L		TG, mmol/L			
	Borderline-High		High		Borderline-High		High		Low	Borderline-High		High		
	Boys (98.0th)	Girls (96.6th)	Boys (99.8th)	Girls (99.6th)	Boys (97.4th)	Girls (97.3rd)	Boys (99.5th)	Girls (99.4th)	Boys (12.4th)	Girls (4.7th)	Boys (93.2nd)	Girls (96.9th)	Boys (97.7th)	Girls (99.3rd)
6	5.85	5.59	6.98	6.67	3.62	3.71	4.37	4.47	1.15	1.02	1.44	1.97	1.96	2.94
7	5.78	5.55	6.89	6.62	3.56	3.67	4.30	4.41	1.15	1.01	1.40	1.92	1.90	2.83
8	5.72	5.49	6.82	6.56	3.53	3.61	4.25	4.34	1.15	1.01	1.40	1.90	1.89	2.78
9	5.70	5.42	6.79	6.47	3.52	3.53	4.24	4.25	1.15	1.00	1.44	1.91	1.95	2.77
10	5.66	5.34	6.75	6.37	3.50	3.46	4.22	4.17	1.13	0.99	1.50	1.95	2.02	2.80
11	5.57	5.26	6.64	6.27	3.46	3.40	4.17	4.09	1.11	0.98	1.54	1.98	2.08	2.82
12	5.44	5.19	6.49	6.19	3.39	3.35	4.09	4.03	1.09	0.97	1.56	1.97	2.11	2.79
13	5.32	5.15	6.34	6.15	3.34	3.35	4.03	4.03	1.07	0.98	1.57	1.94	2.13	2.72
14	5.24	5.17	6.25	6.17	3.32	3.39	4.00	4.08	1.06	0.99	1.59	1.88	2.15	2.62
15	5.22	5.22	6.23	6.23	3.33	3.45	4.02	4.16	1.05	1.00	1.61	1.81	2.18	2.51
16	5.23	5.26	6.24	6.28	3.37	3.49	4.07	4.20	1.04	1.01	1.63	1.75	2.21	2.41
17	5.23	5.25	6.24	6.26	3.40	3.47	4.11	4.17	1.02	1.01	1.67	1.72	2.26	2.34
18	5.20	5.20	6.20	6.20	3.40	3.40	4.10	4.10	1.00	1.00	1.70	1.70	2.30	2.30

SI conversion factors: to convert TC, LDL-C, and HDL-C to mg/dL, multiply values by 38.67. To convert TG to mg/dL, multiply values by 88.5.

ated BP, and hypertension. Differences between the AUCs were compared by using a DeLong test.

All *p* values were 2-tailed with significance accepted at *p* value less than 0.05 and not adjusted for multiple testing. All statistical analyses were carried out using R software (version 3.4.0, www.cran.r-project.org).

3. Results

A total of 12,875 children (51.5% boys) aged 6–18 years were included to establish blood lipid cutpoints (Table 1). Significant differences were observed in lipid concentrations between genders (all *p* < 0.05): the levels of TC, LDL-C, HDL-C, and TG were all higher in girls than in boys.

3.1. Centile curves and cutpoints

The smoothed 5th, 25th, 50th, 75th, and 95th centile curves of lipid profiles in each gender are presented in Fig. 1 (see corresponding cutpoints in Supplemental Table 2; model fitting information can be found in Supplemental Table 3). The borderline-high and high (low for HDL-C) centile curves that linked to Chinese adult thresholds are also shown in this figure. Additionally, the gender- and age-specific cutpoints (in 1-year increments) to classify abnormal blood lipid levels are listed in Table 2.

The centile curves of TC concentrations followed a similar trajectory for boys (Fig. 1A) and girls (Fig. 1B): TC concentrations declined from 6 to about 14 years of age and then approached adult levels. Slightly different trajectories of LDL-C concentrations were observed between genders: LDL-C concentrations in boys were increasing from 16 to 18 years of age, whereas those in girls decreased to adult levels (Fig. 1C and D). For HDL-C concentrations, a slightly declined trend was found in boys (Fig. 1E) while small age-related changes were shown in girls (Fig. 1F). The boys (Fig. 1G) and girls (Fig. 1H) centile curves for TG did not follow similar trajectories, while the boys ones increased with age throughout adolescence, the girls ones declined before approaching adult concentrations.

3.2. Comparison of proposed cutpoints versus NCEP pediatric cutpoints

The prevalence of dyslipidemia among the study population was 15.9% (95% CI: 15.2%–16.5%) for the proposed cutpoints or 16.0% (95% CI: 15.3%–16.6%) for NCEP pediatric cutpoints, respectively. The prevalence of abnormal HDL-C and TG for boys was significantly higher

than girls in both the overweight and obesity subgroups when classifying by the proposed cutpoints (all *p* < 0.05), while no significant difference was found between genders in these two subgroups for NCEP cutpoints (Fig. 2).

Table 3 presents the performance of dyslipidemia defined by two different sets of cutpoints in predicting obesity, abdominal obesity, elevated BP, and hypertension. For any of the outcomes, the proposed cutpoints had higher sensitivity, specificity, positivity predictive value, and negative predictive value than the NCEP pediatric cutpoints. Significant larger AUCs for prediction of obesity, elevated BP, and hypertension were found with proposed cutpoints in comparison with the NCEP pediatric cutpoints.

3.3. Sensitivity analyses

To test whether the exclusion of obese individuals (*n* = 1020; 7.9% of total population) significantly changes the references, we recalculated the cutpoints by limiting the sample to non-obese individuals. The results revealed that the cutpoints of high TG in girls were slightly lower (range: 0.00–0.18 mmol/L) when excluding obese children. The differences of other cutpoints were within 0.10 mmol/L and centiles curves that linked to the adult thresholds were almost same (Supplemental Fig. 3 and Supplemental Fig. 4).

4. Discussion

In the present study, we established gender- and age-specific cutpoints for borderline-high and high TC, LDL-C, TG, as well as low HDL-C for Chinese children aged 6–18 years. In addition, dyslipidemia defined by these cutpoints was associated better with obesity and unfavorable BP levels than that defined by NCEP fixed cutpoints. Therefore, these cutpoints should be more reasonable in screening dyslipidemia among Chinese youths.

It is well known that lipid disorders in children and adolescents are associated with increased risk of cardiovascular disease in adults [3–5,10]. Early screening of dyslipidemia in children and adolescents can improve the cardiovascular health during adulthood. However, differing from adult abnormal lipid cutpoints defined based on the associations between lipid levels and CVD outcomes, the cutpoints for children are mainly derived from the distribution of lipid levels [29]. In 1992, the NCEP [13] proposed a single set of cutpoints for borderline-abnormal and abnormal lipid concentrations, which represented the 75th and 95th centiles (25th and 5th for HDL-C) of the lipids distribution among North Americans. However, changes of concentrations

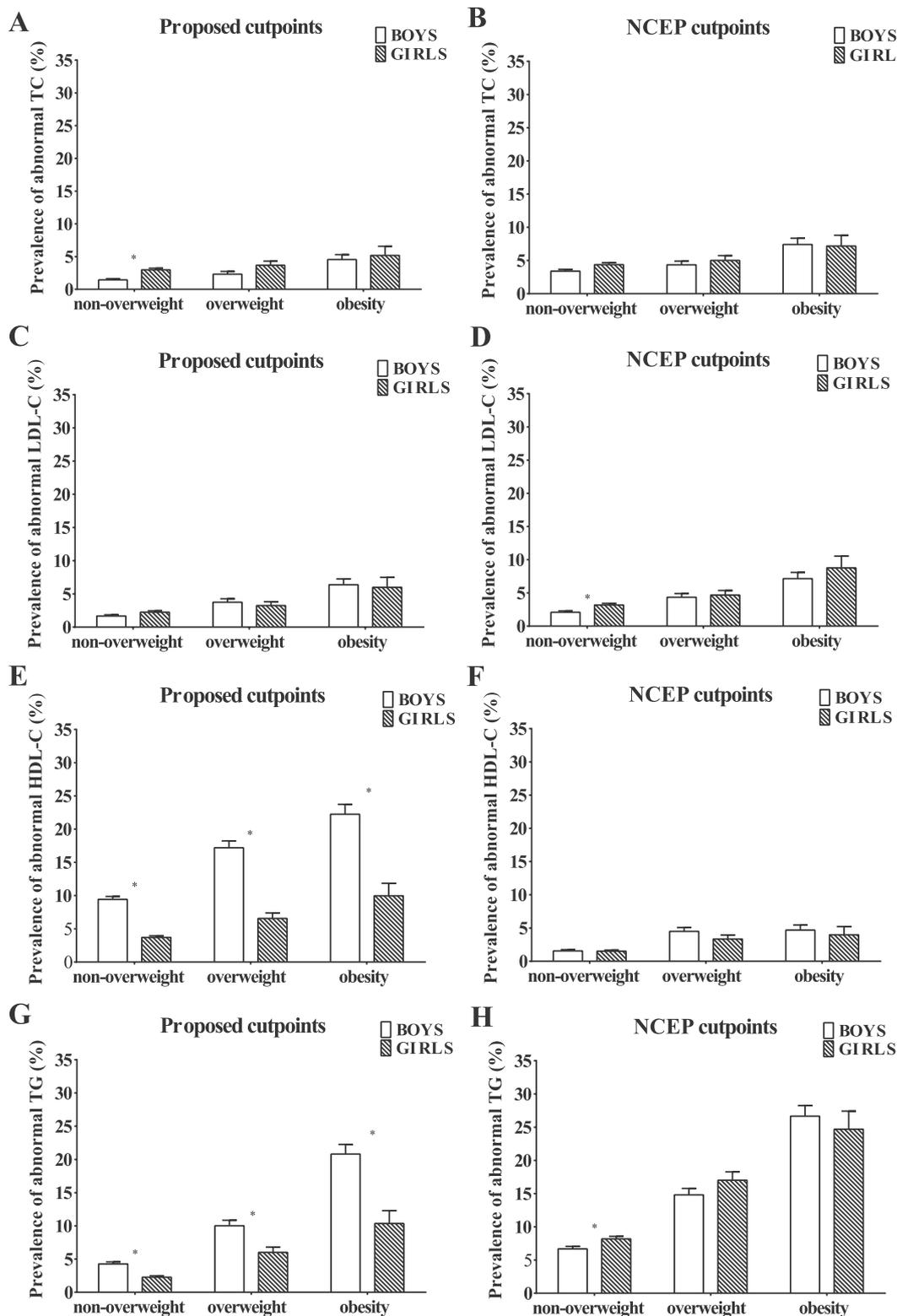


Fig. 2. Prevalence of abnormal lipids according to different groups of gender and weight status. (A) TC, (C) LDL-C, (E) HDL-C, and (G) TG defined by proposed cutpoints. Prevalence of abnormal (B) TC, (D) LDL-C, (F) HDL-C, and (H) TG defined by NCEP pediatric cutpoints. Error bars stand for standard error. * $p < 0.05$ between genders.

of lipid profiles during sexual maturation and growth were not considered by these cutpoints [30,31]. Our data showed that girls had significantly higher lipid levels than boys and different lipids trajectories were found between genders during adolescence, especially for HDL-C and TG. Studies [32,33] have shown that higher testosterone

was inversely associated with HDL-C in adolescent boys, and higher estrogens, which played important roles in the prevention of lipid disorder, was positively associated with TG but negatively associated with HDL-C in adolescent girls, indicating that the difference in hormone level during maturation may partly account for sex difference in lipid

Table 3
Performance of 2 definitions of dyslipidemia in predicting obesity, abdominal obesity, elevated BP, and hypertension.

Outcomes	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC (95% CI)	<i>p</i> value for AUC difference
Obesity						0.017
NCEP pediatric cutpoints	33.9	85.6	16.8	93.8	0.597 (0.583–0.612)	
Proposed cutpoints	36.6	85.9	18.3	94.0	0.612 (0.597–0.628)	
Abdominal obesity						0.588
NCEP pediatric cutpoints	31.6	84.8	21.8	90.2	0.586 (0.574–0.599)	
Proposed cutpoints	31.9	85.9	23.5	90.3	0.589 (0.577–0.602)	
Elevated BP						0.017
NCEP pediatric cutpoints	19.0	85.3	43.5	63.8	0.521 (0.515–0.528)	
Proposed cutpoints	19.7	86.0	45.7	64.3	0.529 (0.522–0.536)	
Hypertension						0.016
NCEP pediatric cutpoints	20.5	84.9	27.8	79.1	0.527 (0.519–0.536)	
Proposed cutpoints	21.8	85.5	29.8	79.5	0.536 (0.528–0.545)	

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; AUC, area under curve; BP, blood pressure.

levels. Therefore, Jolliffe et al. [14] utilized the LMS method to develop gender- and age-specific cutpoints for US adolescents aged 12–19 years using data from NHANES.

Both NCEP and NHANES cutpoints have been published over ten years and it has been suggested that the distribution of blood lipids had changed over time [34]. During the past decade, the levels of TC, LDL-C and TG increased significantly among Chinese adults, although the levels were still lower than the American ones [20,35]. Previous studies have demonstrated the racial differences in lipid levels. The Bogalusa Heart Study [36] reported that mean levels of TC, LDL-C, and HDL-C were higher in black children than in white children. The NHANES III data confirmed that non-Hispanic black children and adolescents had higher TC, LDL-C, and HDL-C compared with non-Hispanic white and Mexican Americans [37]. While blood lipid levels in Chinese adults were lower than US adults [12,28,38], the same dyslipidemia definition was used for the two different populations. Therefore, most centiles of abnormal blood lipid cutpoints for Chinese children which passed through adults' cutpoints at 18 years of age were over 95th percentile. Taking this into account, we recommend the borderline-high cutpoints for dyslipidemia screening among Chinese children.

Low HDL-C was the most prevalent lipid abnormality in the current population, which was consistent with results from Chinese adults [20]. Our findings further showed that the prevalence of abnormal HDL-C and TG in overweight/obesity group was significantly higher than that in non-overweight group, which was in agreement with results from NHANES [19] that the excess weight was positively associated with TG and inversely associated with HDL-C. Additionally, we found that boys had higher prevalence of abnormal HDL-C and TG than girls in the overweight and obesity group when defining by proposed cutpoints. This sex disparity could be partly explained by the fact that boys have more abdominal and visceral fat masses, which have shown to be associated with greater metabolic risk compared with subcutaneous and peripheral fat [39]. The receiver operating characteristic curve analysis showed that the proposed cutpoints had a better capability to predict obesity and unfavorable BP levels than NCEP cutpoints, suggesting that the new definitions perform well for abnormal lipids classification in Chinese children. When establishing the cutpoints, we included obese children in the reference population, which might have an effect on the cutpoints. However, the sensitivity analysis showed that their exclusion did not significantly change the cutpoints.

Our study has several strengths. First, our participants were from a nationwide multicenter school-based study, which was more representative than hospital-based sample. Second, we established the growth curves of lipid levels using GAMLSS method. The GAMLSS has been widely accepted as a standard technique for establishing references for biological parameters [40,41]. Compared with LMS method, which summarizes the distribution of the dependent variable by its median (M), coefficient of variation (S) and a measure of skewness based on the Box-Cox power (L) required to transform the data to

normality, GAMLSS takes not only dispersion and skewness but also the kurtosis of distributions into consideration. Third, the proposed cutpoints take the gender-, age-, and race-related variations into consideration, which should provide a more accurate diagnosis of high-risk lipid levels than fixed cutpoints. Fourth, these cutpoints are linked to the adult adverse lipoprotein thresholds at 18 years of age, which are established on increased risk of CVD. The relevancy between elevated levels of blood lipids during childhood and dyslipidemia in adult life has been reported in previous studies [42,43]. Therefore, our new classification system is less arbitrary and has an indirect connection with abnormal outcomes in adults.

There are several limitations to be considered. First, the proposed classification system is limited to children and adolescents 6–18 years of age. The data of 2–5 years age are lacking and further studies are needed. Second, the reference curves were established based on population distributions of lipid concentrations rather than cardiovascular outcomes. Although less arbitrary and potentially more acceptable than other alternatives, these cutpoints need to be validated in longitudinal studies followed from childhood.

The different trajectories of lipid levels indicate that it is necessary to take age and gender into consideration when defining dyslipidemia among children. The new classification system could improve the accuracy of abnormal lipids classification in Chinese children that associated with further cardiovascular health risks, and should be recommended for screening dyslipidemia in China.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

JM had full access to all of the data in the study and took responsibility for the integrity of the data, conceptualized and designed the study, reviewed and revised the manuscript. PX conducted all analyses, interpreted the results, drafted and revised the manuscript. TH and YKY critically reviewed and revised the manuscript. XYZ and HBL were involved in data acquisition.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.atherosclerosis.2018.11.018>.

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