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Original Article

Hypertension and hypercholesterolemia aggregate in nondiabetic children and adolescents with higher fasting plasma glucose levels

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Objective: To investigate how hypertension and hypercholesterolemia aggregate at different fasting plasma glucose (FPG) levels in children aged 6–16 yr.

Research design and methods: In a nationwide survey conducted between 1992 and 2000, all schoolchildren aged 6–18 yr with abnormal results in repeated urine samples were included. In this study, we recruited 27 535 students aged 6- to 16-yr whose FPG levels were 90–125 mg/dL. Another 17 907 children were randomly selected as control from schoolchildren with FPG <90 mg/dL by stratification to reflect the age- and sex-specific proportion of the whole student population.

Results: The risk of having hypertension or hypercholesterolemia increased at FPG level above 90 mg/dL compared with children with FPG <90 mg/dL [6–10 yr, odd ratios (OR) = 1.51 and 1.82 for FPG 90–99 and 100–125 mg/dL for girls, OR = 1.35 and 2.03 for FPG 90–99 and 100–125 mg/dL for boys; 10–16 yr, OR = 1.24 and 1.66 for FPG 90–99 and 100–125 mg/dL for girls, OR = 1.17 and 1.41 for FPG 90–99 and 100–125 mg/dL for boys, all $p < 0.05$]. The risk of having both hypertension and hypercholesterolemia elevated at FPG 100–125 mg/dL (6–10 yr, OR = 2.76 for girls and 2.75 for boys; 10–16 yr, OR = 2.19 for girls and 1.74 for boys, all $p < 0.05$).

Conclusions: Aggregation of hypertension, hypercholesterolemia, and abnormal glycemia was found at FPG level above 100 mg/dL, which supported the definition of abnormal glycemia in metabolic syndrome by the International Diabetes Federation in 10- to 16-yr-old children. These findings also suggest that this FPG cutoff is reasonable for 6- to 10-yr-old children.

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Key words: abnormal glycemia – adolescent – children – cutoff – risk aggregation

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Atherosclerosis is a common disorder and is a major cause of death worldwide. In 1990, 10.6 million people were estimated to have died from atherosclerosis globally. By 2020, the number of deaths is expected to double, meaning that about 20 million people will die from atherosclerosis (1). Hyperglycemia is an important risk factors and adults with type 2 diabetes mellitus (T2DM) have been shown to have similar high risk for myocardial infarction compared with nondiabetic subjects with prior myocardial infarction (2). T2DM is therefore regarded as equivalent to cardiovascular disease (CVD). Moreover, hyperglycemia is an important risk factor and adults with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) are associated with elevated risk of CVDs (3). Aside from hyperglycemia *per se*, another reason for their elevated cardiovascular risk is that cardiovascular risk factors tend to aggregate in prediabetic stages. Indeed, metabolic syndrome (MS), defined by a clustering of abnormal glycemia and other cardiovascular risk factors, has been shown to be a predictor of future CVD (4).

The current worldwide epidemic of obesity has led to a dramatic increase in the incidence of T2DM in children (5). In Taiwan, through a nationwide screening program, we have found that T2DM has replaced type 1 diabetes mellitus (DM) as the leading cause of incident diabetes in children (6). Children with glycohemoglobin A1C >8% have been shown to have a higher prevalence of atherosclerosis in their coronary arteries (7), indicating that even DM in children leads to atherosclerosis. Furthermore, children with T2DM tend to have other cardiovascular risk-factors, such as obesity and hypertension, putting them at higher risk for CVD (8). Indeed, obesity, hypertension, and elevated total or non-high-density lipoprotein (HDL) cholesterol have been shown to be associated with elevated risk of atherosclerosis in children's aorta and coronary arteries (7, 9). In keeping with the idea of risk-factor aggregation, the International Diabetes Federation (IDF) announced a new definition of MS in children in 2007 (10). In 10- to 16-yr-old children, MS is diagnosed by abdominal obesity and the presence of two risk factors including elevated triglyceride, low HDL-cholesterol, high-blood pressure, and increased fasting plasma glucose (FPG). In 6- to 10-yr-old children, the IDF suggests that MS should not be diagnosed, but the measurement of blood pressure (BP), glucose, and lipid profile should be made in high-risk children.

According to the IDF definition of MS for children, the cutoff for abnormal glycemia is a FPG level above 100 mg/dL. However, the reason for choosing this cutoff is not described. As children are at relatively low risk for DM and CVD compared with adults, the predictability of DM or CVD by different cutoffs of FPG levels can only be answered by prospective studies followed over a long period of time. For example, the incidence of DM in Children in Taiwan is about 1 per 10 000 (6), which means that if we follow a cohort of 10 000 children for 10 yr, only 10 children will develop DM. To the best of our knowledge, there is no such prospective study in children and adolescents has been done. Instead, a study on the aggregation of cardiovascular risk factors can help to suggest cutoffs for abnormal glycemia and is easier to perform. In this study, we investigated the tendency of aggregation of cardiovascular risk factors in different FPG ranges in children and adolescents 6- to 16-yr-old.

Research methods and procedures

Study population and procedure

From 1992 to 2000, the Chinese Foundation of Health conducted an annual, nationwide survey for DM, and renal disease in Taiwan (6, 11). All students (~3 000 000 per semester) in Taiwan Province school system grades 1 through 12, aged 6–18 yr, were given a letter for their parents, which explained the program and invited them to participate in the survey. Each student brought instructions and a specimen container home to collect a first morning, midstream urine sample before breakfast. Providing a urine specimen was taken as consent from the parents and the student to participate. The program achieved a 97% participation rate. Those with abnormal results, including glucosuria, proteinuria, or microscopic hematuria, in two sequential urine samples were invited for a physical examination and blood tests after fasting 8 h. Those who completed the examination were included. Body height (to the nearest 0.5 cm) and body weight (to the nearest 0.1 kg) were measured by attending nurses. Body mass index (BMI) was calculated by dividing body weight (kg) by the square of body height (in meters). BP was measured by mercury sphygmomanometers after seating with leg uncrossed and refraining from talking for 10 min. Plasma glucose and total cholesterol were measured with an automatic analyzer (Technician RA 2000 Autoanalyzer, Bayer Diagnostic, Michawaka, IN, USA).

During the period (1992–2000), 190 664 students were found to have abnormal results in two sequential urine samples. A total of 123 712 students agreed to receive physical examination and blood tests. A total of 27 535 children aged 6- to 16-yr , whose FPG levels were 90–125 mg/dL, were recruited in this study. For comparison, another 17 907 children, aged 11.6 ± 2.4 yr including 8937 boys and 8970 girls, were randomly selected as control from schoolchildren with FPG <90 mg/dL by stratification to reflect the age- and sex-specific proportion of the whole student population.

Definitions

FPG was classified into three categories, <90, 90–99, and 100–125 mg/dL. Obesity was defined according to age- and sex-specific 95th percentile BMI, derived from a general survey in Taiwan (12). Hypertension was diagnosed if systolic or diastolic BP was equal to or above the age- and sex-specific 95th percentile cutoffs for children in Taiwan (13). Hypercholesterolemia was defined by age- and sex-specific 95th percentile by American Academy of Pediatrics in 2008 (14). Parental education levels (≦6, 7–12, and ≧13 yr of education) were used as the indicator of socioeconomic status (SES) in this study.

Statistical analyses

Data were presented as means and standard deviations for continuous variables, and as percentage for categorical variables. P-values for linear trend by one-way analysis of variance (ANOVA) and linear regression were derived from the comparisons of selected variables by FPG category. Odd ratios (OR) and the 95% confidence intervals (CI) for hypertension and/or hypercholesterolemia by FPG category were derived from multivariate logistic regression models, using those with an FPG <90 mg/dL as the reference group (OR = 1). Age, sex, BMI, and height (for hypertension) were considered as potential confounders. In Figs 1–3, only ORs with BMI adjustment were shown because the results were similar between models with and without BMI adjustment. Collinearity was confirmed by Hosmer–Lemeshow tests. A P-value below 0.05 was considered significant. The statistical analyses were performed with SPSS 12.0 (SPSS Inc., Chicago, IL, USA).

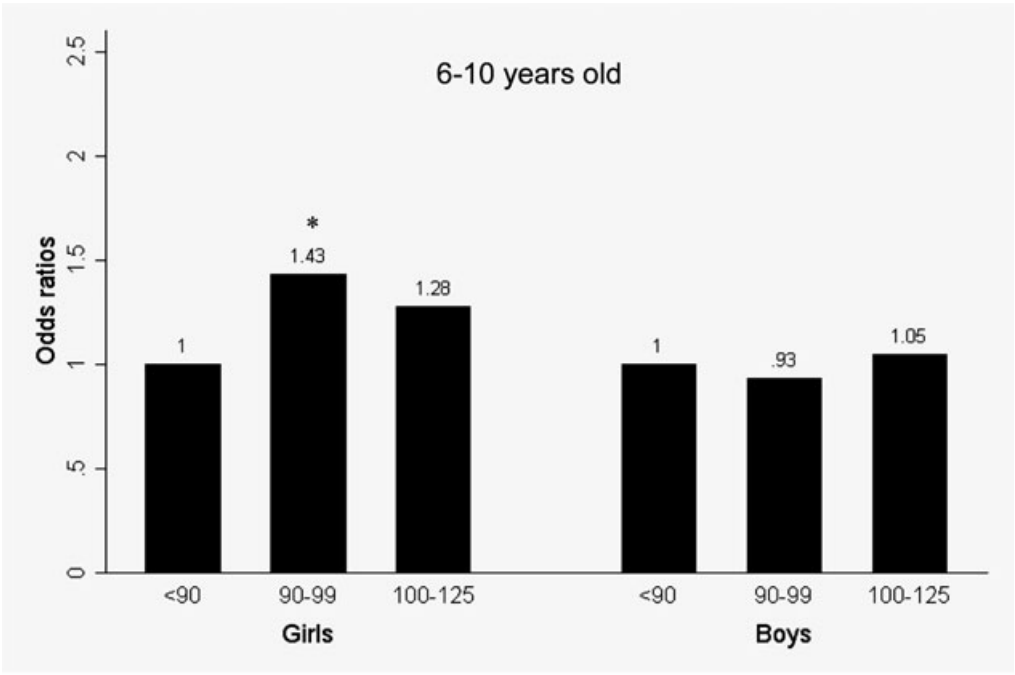
Results

In 6- to 10-yr-old children (Table 1), there were 2510, 667, and 1058 girls whose FPG levels were <90, 90–99, and 100–125 mg/dL, respectively. The mean FPG was 87 ± 14 mg/dL. There were 2398, 780, and 640 boys whose FPG levels were <90, 90–99, and 100–125 mg/dL, respectively. Children in the higher FPG category were older, had greater BMI, higher systolic and diastolic BP, plasma total cholesterol, and rate of hypercholesterolemia. In girls (Fig. 1, upper panel), the ORs for hypertension were significantly higher in FPG category 90–99 mg/dL (OR = 1.43, 95% CI = 1.01–2.03) but not in FPG category 100–125 mg/dL (OR = 1.28, 95% CI = 0.93–1.77), adjusted for age, height, and BMI. In boys, the ORs for hypertension were similar among the three FPG categories. In Fig. 2 (upper panel), girls and boys in the higher FPG category showed a greater risk for hypercholesterolemia, adjusted for age and BMI (for girls: OR = 1.44, 95% CI = 1.15–1.79 for FPG 90–99 mg/dL and OR = 1.96, 95% CI = 1.67–2.35 for FPG 100–125 mg/dL; for boys: OR = 1.43, 95%CI = 1.20–1.71 for FPG 90–99 mg/dL and OR = 2.20, 95% CI = 1.83–2.64 for FPG 100–125 mg/dL).

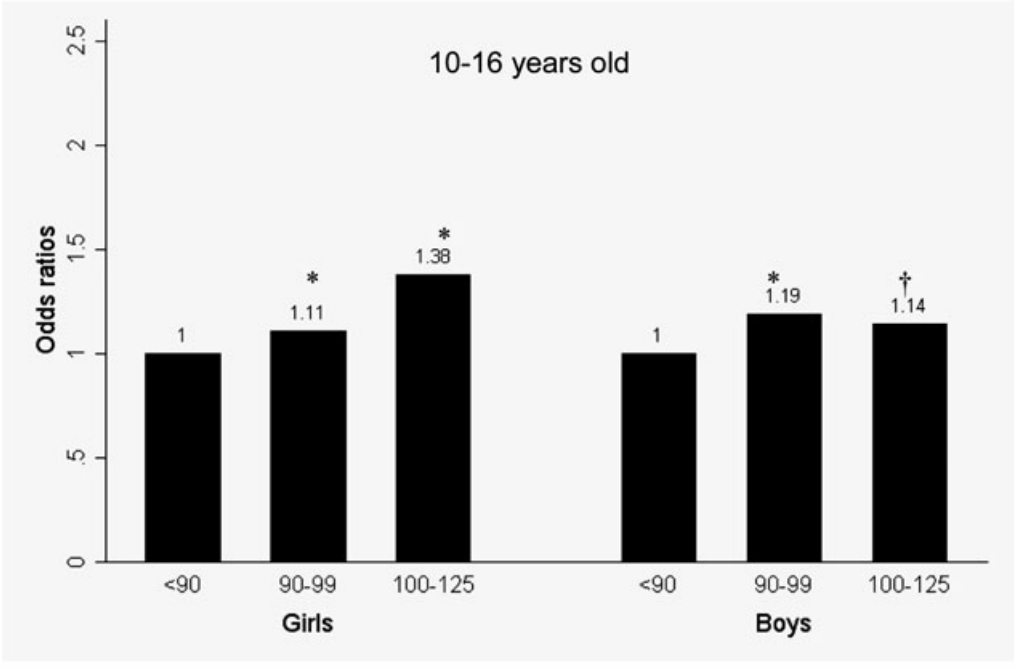
To study the aggregation of the cardiovascular risk factors among different glycemia categories, we explored the ORs of having hypertension or hypercholesterolemia or both. In 6- to 10-yr-old children, the ORs of having hypertension or hypercholesterolemia were significantly higher in FPG category 90–99 and 100–125 mg/dL, adjusted for age and BMI (for girls: OR = 1.51, 95% CI = 1.24–1.85 for FPG 90–99 mg/dL and OR = 1.82, 95% CI = 1.54–2.16 for FPG 100–125 mg/dL; for boys: OR = 1.35, 95% CI = 1.14–1.61 for FPG 90–99 mg/dL, OR = 2.03, 95% CI = 1.69–2.43 for FPG 100–125 mg/dL). In Fig. 3, only children with FPG 100–125 mg/dL showed higher ORs of having both hypertension and hypercholesterolemia, adjusted for age and BMI (OR = 2.76, 95% CI = 1.57–4.85 for girls; OR = 2.75, 95% CI = 1.53–4.97 for boys).

In 10- to 16-yr-old children (Table 1), there were 6460, 9509, and 5102 girls whose FPG levels were <90, 90–99, and 100–125 mg/dL, respectively. The mean FPG was 92 ± 12 mg/dL. There were 6539, 6124, and 3655 boys whose FPG levels were <90, 90–99, and 100–125 mg/dL, respectively. Children in higher FPG categories showed higher systolic and diastolic BP, rate of hypertension, plasma total cholesterol, and rate of hypercholesterolemia. Boys with higher FPG were older and had higher BMI. In girls (Fig. 1, lower panel), the ORs for hypertension were significantly higher in FPG category 90–99 (OR = 1.11, 95% CI = 1.00–1.24) and 100–125 mg/dL (OR = 1.38, 95% CI = 1.22–1.55), adjusted for age, height, and BMI. Similarly, in boys, the ORs for hypertension were higher in FPG category 90–99 (OR = 1.19, 95%CI = 1.05–1.34) and 100–125 mg/dL (OR = 1.14, 95% CI = 0.99–1.31, p = 0.06), adjusted for age, height, and BMI. In Fig. 2 (lower panel), girls in the higher FPG category had greater risk of hypercholesterolemia (FPG 90–99 mg/dL, OR = 1.33, 95% CI = 1.18–1.49; FPG 100–125 mg/dL, OR = 1.86, 95% CI = 1.65–2.11), whereas boys with FPG 100–125 mg/dL (OR = 1.66, 95% CI = 1.45–1.90), but not 90–99 mg/dL, showed increased risk of hypercholesterolemia.

The tendency of cardiovascular risk aggregation in 10- to 16-yr-old children was also explored. The ORs of having hypertension or hypercholesterolemia were significantly higher in FPG category 90–99 and 100–125 mg/dL adjusted for age and BMI (for girls: OR = 1.24, 95% CI = 1.14–1.35 for FPG 90–99 mg/dL and OR = 1.66, 95% CI = 1.51–1.82



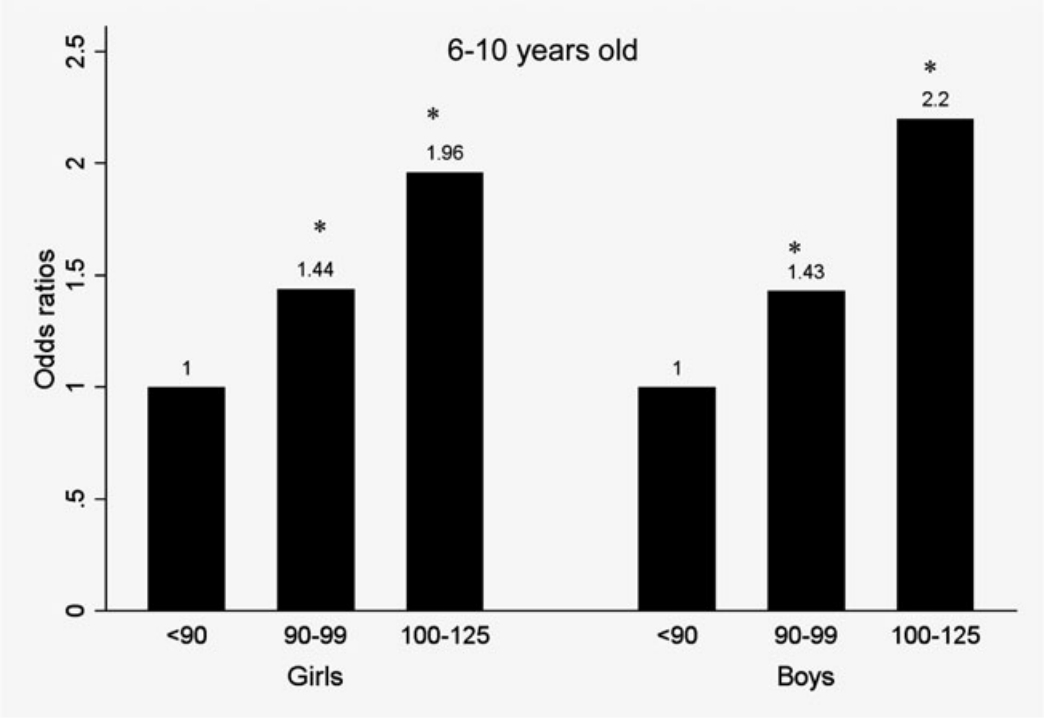
Case	131	48	63	122	37	33
Control	2371	619	995	2276	743	607



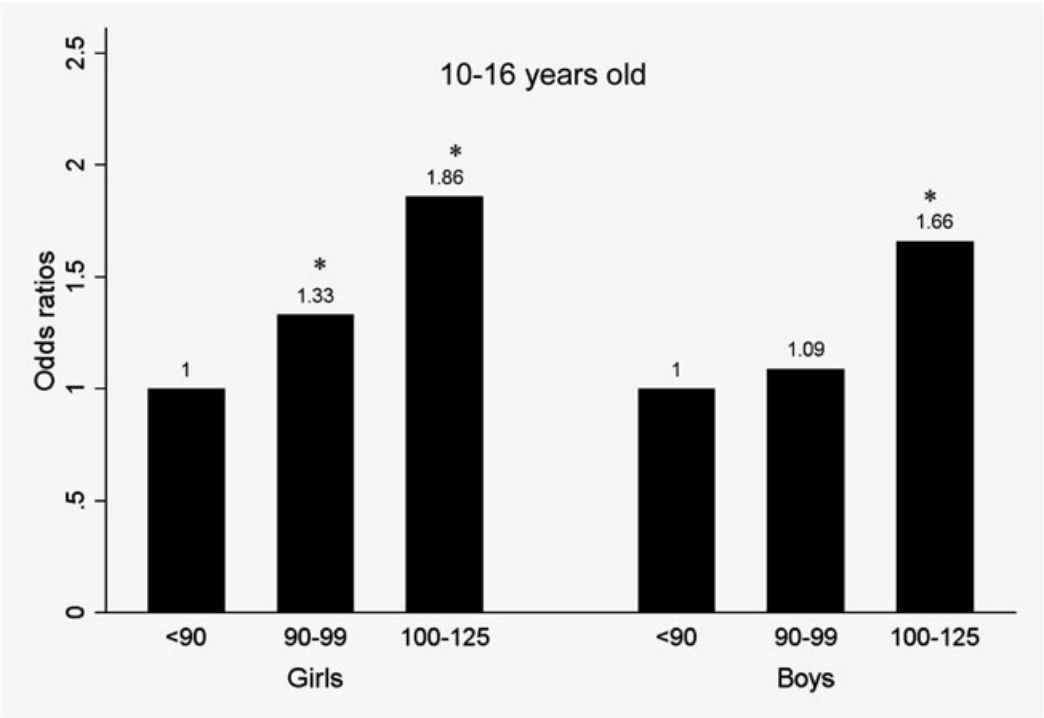
Case	628	1003	659	599	672	401
Control	5832	8506	4443	5940	5452	3254

Fig. 1. Odd ratios (OR) for hypertension in children aged 6–10 yr (upper panel) or 10–16 yr (lower panel) by fasting plasma glucose category and gender, adjusted for age, height, and body mass index (BMI). *$p < 0.05$, †$p = 0.06$.

for FPG 100–125 mg/dL; for boys: OR = 1.17, 95% CI = 1.07–1.29 for FPG 90–99 mg/dL and OR = 1.41, 95% CI = 1.27–1.56 for FPG 100–125 mg/dL). In Fig. 3, only those with FPG 100–125 mg/dL demonstrated higher ORs of having both hypertension and hypercholesterolemia, adjusted for age and BMI (for girls, OR = 2.19, 95% CI = 1.56–3.07; OR = 1.74, 95% CI = 1.22–2.49 for boys).

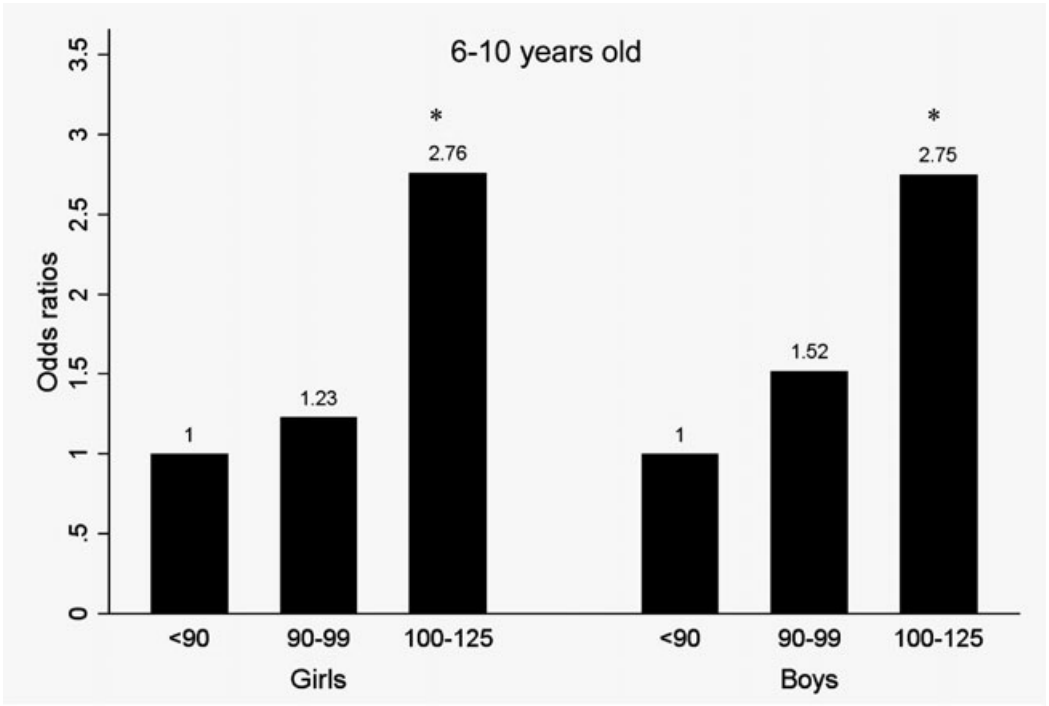


Case	384	136	271	586	246	265
Control	2126	513	787	1812	534	375

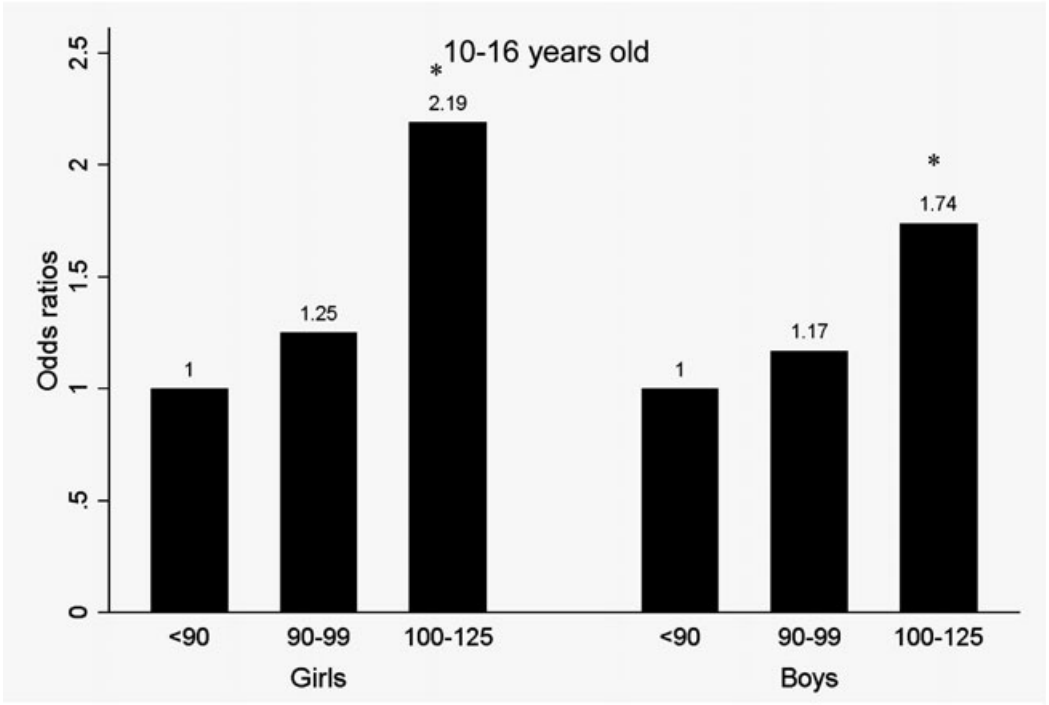


Case	480	914	663	528	509	453
Control	5980	8595	4439	6011	5615	3202

Fig. 2. Odd ratios (OR) for hypercholesterolemia in children aged 6–10 yr (upper panel) or 10–16 yr (lower panel) by fasting plasma glucose category and gender, adjusted for age and body mass index (BMI). *$p < 0.05$.



Case	30	8	24	33	15	19
Control	2017	491	748	1723	512	361



Case	58	100	89	65	73	68
Control	5410	7692	3869	5477	5016	2869

Fig. 3. Odd ratios (OR) for hypertension and hypercholesterolemia in children aged 6–10 yr (upper panel) or 10–16 yr (lower panel) by fasting plasma glucose category and gender, adjusted for age and body mass index (BMI). *$p < 0.05$.

Table 1. Comparisons of selected demographic and biochemical characteristics by fasting plasma glucose category

	6–10 yr old						10–16 yr old					
	Girls			Boys			Girls			Boys		
FPG (mg/dL) category	<90	90–99	100–125	<90	90–99	100–125	<90	90–99	100–125	<90	90–99	100–125
Variable												
N	2510	667	1058	2398	780	640	6460	9509	5102	6539	6124	3655
Age (yr)	7.5 ± 1.1	7.7 ± 1.1	8.0 ± 1.0*	7.5 ± 1.1	7.6 ± 1.1	7.9 ± 1.0*	12.5 ± 1.7	12.3 ± 1.5	12.2 ± 1.5*	12.5 ± 1.7	12.8 ± 1.4	12.8 ± 1.4*
FPG mg/dL	78 ± 8	94 ± 3	106 ± 6*	78 ± 8	94 ± 3	106 ± 6*	79 ± 7	94 ± 3	106 ± 6*	79 ± 7	94 ± 3	106 ± 6*
(mmol/L)	(4.3 ± 0.4)	(5.2 ± 0.2)	(5.9 ± 0.3)	(4.3 ± 0.4)	(5.2 ± 0.2)	(5.9 ± 0.3)	79 ± 7	94 ± 3	106 ± 6*	79 ± 7	94 ± 3	106 ± 6*
BMI (kg/m^2)	16.3 ± 2.6	16.5 ± 2.7	16.8 ± 3.1*	17.0 ± 3.4	17.2 ± 3.6	17.4 ± 3.4*	19.3 ± 3.5	19.2 ± 3.3	19.3 ± 3.5	19.1 ± 3.5	19.3 ± 3.4	19.6 ± 3.6*
Obesity rate (%)	8.0	7.3	8.6	9.3	8.6	9.7	6.3	5.7	6.8	5.5	5.4	6.4
Systolic BP (mmHg)	97 ± 12	98 ± 12	100 ± 13*	99 ± 13	100 ± 12	101 ± 13*	107 ± 13	108 ± 13	109 ± 13*	111 ± 14	113 ± 14	113 ± 14*
Diastolic BP (mmHg)	61 ± 10	62 ± 10	63 ± 11*	62 ± 10	62 ± 10	63 ± 10*	68 ± 10	68 ± 10	69 ± 10*	69 ± 10	70 ± 10	70 ± 10*
Hypertension (%)	5.5	7.2	6.0	5.1	4.7	5.2	9.7	10.5	12.9*	9.2	11.0	11.0*
Total cholesterol mg/dL	169 ± 37	175 ± 32	173 ± 36*	171 ± 49	177 ± 47	186 ± 54*	161 ± 32	167 ± 31	171 ± 32*	157 ± 41	158 ± 33	164 ± 37*
(mmol/L)	(4.37 ± 0.96)	(4.53 ± 0.83)	(4.47 ± 0.93)	(4.42 ± 1.27)	(4.58 ± 1.22)	(4.81 ± 1.40)	(4.16 ± 0.83)	(4.32 ± 0.8)	(4.42 ± 0.83)	(4.06 ± 1.06)	(4.08 ± 0.85)	164 ± 37*
Hyperchol-esterolemia (%)	15.3	20.4	25.6*	24.4	31.5	41.4*	7.4	9.6	13.0*	8.1	8.3	12.4*
Family history of DM (%)	2.8	3.6	4.4	4.1	3.2	2.7	5.1	4.7	4.6	4.1	3.8	3.8
SES (%)												
Low	44.3	48.4	46.7	45.4	46.4	48.1	52.6	56.4	56.0	53.1	57.2	58.4
Middle	41.8	40.4	39.8	40.8	41.6	39.9	34.7	32.1	33.3	34.2	31.8	31.9
High	13.9	11.1	13.5	13.8	12.0	12.0	12.7	11.5	10.7	12.7	11.0	9.7

Data are means ± SD unless specified.
FPG, fasting plasma glucose; BMI, body mass index (kg/m^2); BP, blood pressure; DM, diabetes mellitus; SES, socioeconomic status.
*$p < 0.05$ for trend by ANOVA or linear regression.

Discussion

In this study, we demonstrated that nondiabetic children and adolescents with a FPG level over 90 mg/dL were associated with increased individual risk of hypertension and hypercholesterolemia in both 6–10 and 10–16 age groups. However, the tendency of having cardiovascular risk aggregation occurs at a higher FPG category of 100–125 mg/dL. Our data suggest that in the younger age group, i.e., 6- to 10-yr-old children, there is also an obvious clustering of hypertension and hypercholesterolemia in subjects with IFG with FPG level at 100–125 mg/dL.

The definitions of MS in children used in most studies were based on the definitions established by the World Health Organization (WHO) (15), National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) (16), and the American Diabetes Association (ADA) (17). According to the WHO criteria, impaired glucose tolerance by an oral glucose tolerance test and/or insulin resistance by hyperinsulinemic eugylcemic clamp were used to define abnormal glycemia. However, two or more blood tests are required in the criteria, raising problem of feasibility in children. In 2001, NCEP-ATP III defined abnormal glycemia in MS by FPG $\geqq$110 mg/dL in adults, which was in agreement with the definition by ADA in 1997. In 2003, the ADA modified the cutoff of FPG to 100 mg/dL for the following reasons (17). In adults, a cutoff of FPG around 100 mg/dL can predict DM with optimal sensitivity and specificity in several ethnic groups. In Pima Indians, the risk of DM increased sharply at FPG level above around 100 mg/dL. In 2007, the IDF has proposed the definition of MS in children (10). In 10- to 16-yr-old children, FPG $\geqq$ 100 mg/dL was defined as abnormal glycemia. To the best of our knowledge, there is no study investigating how different FPG levels predict future DM or CVD in children. Data from this study showed that the clustering of hypertension, hypercholesterolemia, and abnormal glycemia was significant if abnormal glycemia was defined as FPG $\geqq$ 100 mg/dL. Our findings supported the definition of abnormal glycemia by the IDF in 10- to 16-yr-old children. Moreover, the risk-factor clustering was also observed in 6- to 10-yr-old children, indicating that the aggregation of MS characteristics also developed even in a younger age group.

In this study, the risk of hypertension was increased in the higher FPG category in 10- to 16-yr-old children (puberty) but not in 6- to 10-yr-old children (prepuberty) (Fig. 1). Decreased insulin sensitivity has been demonstrated in puberty, compared with prepubertal stage (18), which may result in elevated FPG. Insulin resistance may also increase the risk of hypertension through activation of sympathetic nervous system (19) and salt retention (20). Elevated growth hormone and insulin-like growth factor 1 are thought to be one of the causes of pubertal insulin resistance, which supports our different findings in the two age groups. However, we cannot provide an appropriate explanation as to why the risk of hypertension was elevated in FPG category 90–99 mg/dL in 6- to 10-yr-old girls.

The strength of this study is its large sample size, which makes analyses in different FPG subgroups feasible and reliable. Moreover, the control group (children with FPG <90 mg/dL) was representative to the whole student population by sampling from age- and sex-specific strata in proportion to the whole student population. On the contrary, this study is limited in the lack of the information about Tanner's stage, which is practically difficult to assess in such a nationwide study. Although, this does not confound the clustering of abnormal glycemia, hypertension, and hypercholesterolemia observed in this study, the lack of information of Tanner's stage prevented us from carrying out further analyses about the detailed effect of puberty on cardiovascular risk aggregation.

In conclusion, the aggregation of hypertension or hypercholesterolemia was found at FPG $\geqq$ 90 mg/dL in 6- to 16-yr-old children and adolescents. The aggregation of hypertension, hypercholesterolemia, and abnormal glycemia was observed at FPG $\geqq$ 100 mg/dL. Our findings supported the definition of abnormal glycemia by the IDF in 10- to 16-yr-old adolescents. These findings also suggest that this FPG cutoff is reasonable for 6- to 10-yr-old children to have cardiovascular risk aggregation.

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