

# Reduced Arterial Compliance Associated with Metabolic Syndrome in Chinese Children and Adolescents<sup>1</sup>

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**Objective** To explore the metabolic syndrome and its association with arterial compliance in Chinese children and adolescents. **Methods** 337 participants aged 6 to 18 years with males accounted for 55.8% were grouped according to their traits of metabolic syndrome. Anthropometry, blood pressure, fasting plasma glucose, insulin and serum lipid profile were measured. Homeostasis model was assessed and insulin resistance (HOMA-IR) index was measured and calculated for estimating individual insulin resistance. Arterial compliance was also measured using digital pulse wave analyzing method (Micro medical, London), and stiffness index was calculated. **Results** The stiffness index in participants with metabolic syndrome was significant higher than that in participants with no risk of metabolic syndrome [(7.69±1.63) vs (6.25±0.86) m/s,  $P<0.01$ ] and stiffness index and HOMA-IR were progressively increased with the increase of traits of metabolic syndrome ( $P$  for linear trend  $<0.001$ ). After gender, age, and pubertal development were adjusted, both traits of metabolic syndrome and HOMA-IR were correlated positively with stiffness index (both  $P<0.05$ ). **Conclusion** The clustering of metabolic syndrome was closely associated with risk at increased arterial stiffness in Chinese children and adolescents. It was suggested that arterial compliance assessment of children and adolescents might be an important measure for prevention of cardiovascular diseases.

**Key words:** Metabolic syndrome; Arterial compliance; Children and adolescents

## INTRODUCTION

The metabolic syndrome (MS), i.e. the clustering of central obesity, dyslipidemia, hypertension, elevated fasting glucose levels, and insulin resistance, increases the risk of cardiovascular diseases (CVD) and type II diabetes mellitus<sup>[1-2]</sup>. Arterial compliance, which has relationship with the risk of cardiovascular disease, is an independent predictor for CVD and its mortality<sup>[3-4]</sup>. Recent studies look at pathological changes of blood vessels, especially the changes of blood vessel wall which is fundamental to the development of CVD. An adverse association between MS and arterial compliance was observed in adults<sup>[5-6]</sup>. However, the relevant researches in children and adolescents are lacking. At present, more and more young people are affected by CVD, which has become a trend worldwide. Therefore, it is particularly needed to conduct relevant studies to explore whether the presence of MS represents an increased risk at vascular disease in children and adolescents. Thus, as a sub-components of the

Beijing Child, and Adolescent Metabolic Syndrome Study, a cross-sectional survey was carried out in Chinese children and adolescents in 2004 in order to examine the negative impact of MS on arterial compliance. In this study, digital volume pulse (DVP), a recently developed simple and reliable automatic technique, was used for the measure of arterial compliance.

## MATERIALS AND METHODS

### Participants

337 participants aged 6 to 18 years with males accounted for 55.8% were recruited for the survey representing a sample of more than 20 000 Chinese children and adolescents aged 6 to 18 years in Beijing. The survey was conducted from April to October 2004. Body weight, height, waist circumference (WC), and blood pressure were measured. Fasting finger-stick capillary samples were collected and used to determine the concentration of blood glucose

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and lipid using ACCUTREND GCT (Roche y Diagnostics Shanghai Ltd., China). Then, the children

at high risk were identified by the screening criteria (Table 1).

TABLE 1

Screening Criteria for Children at High Risk of and The Definition of MS

Screening Criteria for Children at High Risk (Any One of the Followings)	Definition of MS (Three and above the Followings)
1. Obesity: BMI $\geq$ 85th percentile (in accordance with age and gender-specific BMI reference norm in China <sup>[8]</sup> ).	1. Central Obesity: Waist circumference $\geq$ 90th percentile (in accordance with the results from Child Metabolic Syndrome Study in Beijing, China)
2. Hypertension: SBP and/or DBP $\geq$ 90th percentile (in accordance with the results from a study conducted in 1987 in Beijing, China <sup>[9]</sup> ).	2. Hypertension: SBP and/or DBP $\geq$ 90th percentile (in accordance with the results from Child Metabolic Syndrome Study in Beijing, China)
3. Dyslipidemia: Fasting finger-stick capillary TC $\geq$ 5.2 mmol/L (190 mg/dL) or TG $\geq$ 1.7 mmol/L (150 mg/dL).	3. HDL-C $\leq$ 1.03 mmol/L (40 mg/dL)
4. Fasting finger-stick capillary glucose $\geq$ 5.6 mmol/L.	4. Hypertriglyceridemia: triglycerides $\geq$ 1.24 mmol/L (110 mg/dL)
	5. Fasting plasma glucose $\geq$ 5.6 mmol/L

Children at the high risk were divided into three groups (1 component, 2 components, 3 or more components of MS) and one control group in accordance with definition of MS<sup>[7]</sup> (Table 1). Participants and/or their parents or guardians were all informed and consent to the study, and the study was approved by the Ethics Committee of Capital Institute of Pediatrics.

#### Physical Examination

Body weight, height, and WC were measured twice and the average values were used. Blood pressure was measured on right arm in a relaxed, sitting position and, systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels were defined with the first and fourth Korotkoff sounds, respectively. The pubertal development was assessed by the Tanner 5-phase method. The development of penis of male participants and the breast of female participants were measured for phase definition of the pubertal development.

#### Blood Biochemistry

Participants were informed to fast for 12 hrs before taking part in the examination. Fasting blood samples were collected to measure levels of fasting plasma glucose (FPG), fasting plasma insulin (FIN), triglycerides (TG), serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). FPG levels were analyzed using a standard glucose oxidase method. FIN was measured using the enzyme linked immunosorbent assay<sup>[10]</sup>. Levels of serum TC, HDL-C, and TG were measured using standard enzymatic methods. LDL-C was calculated from the Friedewald formula. Glucose and lipid levels were determined by the Hitachi 7 170 Automatic Analyzer.

FIN levels were measured at the Peking Union Medical College Hospital. Insulin resistance (HOMA-IR) index was determined to estimate individual insulin resistance using the formula:  $HOMA-IR = [FIN (mU/L) \times FPG (mmol/L)] / 22.5$ .

#### Arterial Compliance Measurement

Arterial compliance was measured by digital pulse wave analyzing method, using a new non-invasive automatic device (Pulsetrace 2 000, Micro Medical, UK). Photophethysmographic digital volume was determined by using an infrared light-emitting diode (940 nm) and phototransistor applied to either side of the index finger of the right hand. The signal from the phethysmograph was digitized using a 12-bit analogue-to-digital converter with a sampling frequency of 100 Hz. Software developed in-house was used to provide an objective measurement of stiffness index (SI). The waveforms were recorded over a 10 s period and ensemble averaged to obtain a single waveform, whose  $\Delta T$  was determined as the time between the first systolic peak and the early diastolic peak/inflection point in the waveform. This point was defined as the point at which the first derivative of the waveform was closest to zero. SI was calculated from subject height and  $\Delta T$ :  $SI = h/\Delta T$  (Fig. 1). SI was correlated negatively with arterial compliance<sup>[11-13]</sup>. Each subject was examined for three times to get the mean value of SI.

#### Reproducibility

In order to explore repeatability and stability of the digital pulse wave analyzing method in Chinese people, arterial compliance of the participants was measured three times in a day with a 3 minutes

interval and one more time on another day with a 40 days interval. The measurement results ranged from 1.04 m/s to 0.02 m/s, with an intra-subject standard deviation of 0.35 m/s, which was 4.5% of the underlying mean across all participants. Bivariate correlation analysis demonstrated a correlation coefficient of 0.937 ( $P < 0.0001$ ) on data from 40-day-interval, indicating a satisfied repeatability of the measurement of DVP.

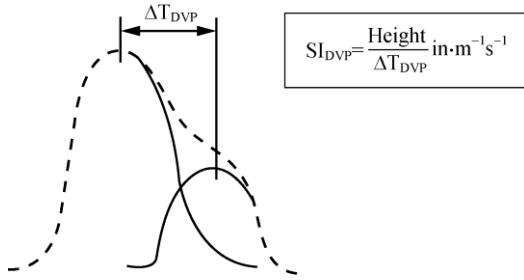


FIG. 1. Pulse wave and calculation of SI.

### Statistical Analysis

Data collected were processed and analysed using SPSS version 11.0 (SPSS, Inc., Chicago, IL, USA). Statistical normality of the data was checked using the Kolmogorov-Smirnov test. Continuous variables were presented as  $\bar{x} \pm s$ , with an exception of data on TG, FIN, and HOMA, which, because of their skewed distribution, were expressed as median and interquartile range, and were logtransformed before statistical analysis. Differences among groups were tested using Student's *t* test, and variance or covariance was analysed when age, gender, and pubertal development were adjusted. Pearson correlation analysis was applied to assess the degree of association between SI and HOMA-IR. Multiple linear regression was used to estimate the separate effects of HOMA-IR index and MS on SI after potential confounders were adjusted.  $P < 0.05$

was considered statistically significant.

## RESULTS

### Baseline Characteristics of the Study Groups

233 children at the high risk were studied and their fasting glucose and lipid were measured. 36 children from them were excluded in according with the MS definition shown in Table 1. Thus, the case number was reduced to 197 children. They were then divided into three case groups according to the traits of MS: group 1 (1 component,  $n=106$ ), group 2 (2 components,  $n=64$ ), and group 3 (3 or more components,  $n=27$ ). 140 children with no any MS component were selected into the control group. The 337 participants in total included 188 males and 149 females aged from 6 to 18 years (mean age:  $10.95 \pm 3.01$  years).

Of the MS clustering components in the case groups, central obesity was the most prevalent component (about 49.2%). In turn, the percentage of low HDL-C, hypertension, hypertriglyceridemia, and impaired fasting glucose accounted for 38.1%, 36.0%, 26.9%, and 14.2%, respectively.

### Clinical Characteristics of Case Groups

Table 2 showed the selected clinical characteristics of the participants by the number of components of MS. The WC, body mass index (BMI), SBP, DBP, pulse pressure (PP), FPG, TG, FIN, and HOMA-IR index in the case groups were significantly higher than those in the control group (all  $P < 0.05$ ). With the increase of the clustering of MS components, the WC, BMI, SBP, DBP, PP, FPG, TG, FIN, and HOMA-IR index increased progressively, while the HDL-C decreased progressively. However, there were no significant differences in age, TC and LDL-C among either case group and the control group.

TABLE 2

Clinical Characteristics of Control Group and Three Case Groups with the Clustering of Different MS Components ( $\bar{x} \pm s$ )

Variables	Control Group ( $n=140$ )	Case Groups			<i>P</i>
		Group 1 ( $n=106$ )	Group 2 ( $n=64$ )	Group 3 ( $n=27$ )	
Age (years)	$10.5 \pm 2.8$	$11.2 \pm 3.1$	$11.2 \pm 3.3$	$12.2 \pm 3.4$	$>0.05$
WC (cm)	$59.8 \pm 6.0$	$69.0 \pm 10.6$	$76.5 \pm 14.8$	$87.9 \pm 14.7$	$<0.01$
BMI ( $\text{kg}/\text{m}^2$ )	$16.7 \pm 2.1$	$20.3 \pm 3.8$	$23.4 \pm 4.9$	$27.8 \pm 5.1$	$<0.01$
SBP (mmHg)	$91.8 \pm 11.2$	$98.8 \pm 11.8$	$113.3 \pm 14.8$	$121.7 \pm 11.1$	$<0.01$
DBP (mmHg)	$57.0 \pm 8.5$	$61.9 \pm 9.1$	$69.7 \pm 11.1$	$73.4 \pm 9.3$	$<0.01$

(to be continued)

(continued)

Variables	Control Group (n=140)	Case Groups			P
		Group 1 (n=106)	Group 2 (n=64)	Group 3 (n=27)	
PP (mmHg)	34.8±7.7	37.0±8.1	43.6±11.4	48.3±10.4	<0.01
FPG (mmol/L)	4.8±0.4	5.2±0.6	5.0±0.5	5.3±0.7	<0.01
TC (mmol/L)	4.0±0.7	4.0±0.7	4.0±0.8	3.6±0.8	>0.05
TG (mmol/L)	0.7 (0.6-0.8)	0.9 (0.7-1.1)	1.1 (0.8-1.5)	1.4 (1.1-1.9)	<0.01
HDL-C (mmol/L)	1.6±0.3	1.5±0.3	1.3±0.3	1.0±0.2	<0.01
LDL-C (mmol/L)	2.4±0.6	2.3±0.5	2.5±0.6	2.3±0.7	>0.05
FIN (mU/L)	4.6 (2.8-8.5)	7.9 (4.9-12.2)	9.3 (6.8-14.6)	17.0 (10.2-24.6)	<0.01
HOMA-IR	1.0 (0.6-1.8)	1.9 (1.1-3.0)	2.1 (1.4-3.3)	4.0 (2.4-5.8)	<0.01

Note. Median and interquartile range when appropriate. WC: Waist circumference; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PP: pulse pressure; FPG: fasting plasma glucose; TC: serum total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol ; LDL-C: low-density lipoprotein cholesterol; FIN: fasting plasma insulin.

### Association of MS with Arterial Compliance

Participants with MS had significant higher SI [(7.69±1.63) vs (6.25±0.86) m/s,  $P<0.01$ ] as compared with those of no-risk of the syndrome. When the participants were divided into those with 0, 1, 2, 3 or more components of MS, SI increased progressively from the first to the last group (6.25±0.86 m/s, 6.51±1.11 m/s, 6.73±1.13 m/s, and 7.69±1.63 m/s respectively, and  $P$  for linear trend was  $<0.001$ ) after age, gender, and pubertal development were adjusted. The mean values of SI in the group 2 and the group 3 were both significantly higher than those in the control group (LSD- $t$  = 3.01,  $P<0.01$ , and LSD- $t$  = 4.46,  $P<0.001$ , respectively),

but there was no significant difference in that between the group 1 and the control group. Moreover, analysis of rank correlation suggested that SI be correlated positively with the number of MS components ( $r=0.313$ ,  $P<0.001$ ).

When the components of MS were considered separately, the hypertension group presented the highest SI (7.29±1.44 m/s), and SI values in central obesity group, hypertriglyceridemia group, low HDL cholesterol group, and high fasting glucose group were 6.97±1.38 m/s, 6.81±1.33 m/s, 6.80±1.33 m/s, and 6.62±1.12 m/s, respectively, which were significantly higher than those in the control group, except that in the high fasting glucose group (Fig. 2).

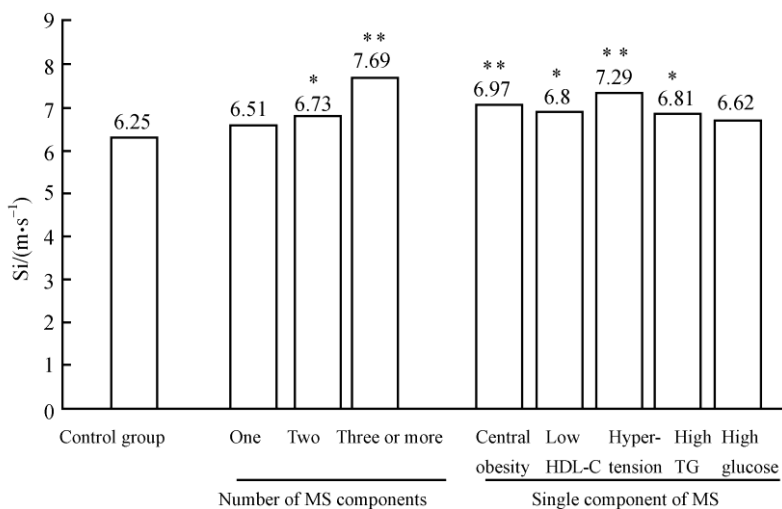


FIG. 2. Difference of SI values in groups according to the number of MS components and single component of MS compared with SI value in the control group. Data were adjusted for gender, age and pubertal development. \* $P<0.01$ , \*\* $P<0.001$ .

### Association of Insulin Resistance with Arterial Compliance

Pearson correlation analysis showed that SI was correlated positively with HOMA-IR ( $r=0.237$ ,  $P<0.001$ ). The partial correlation coefficient was 0.215 ( $P<0.001$ ) after age and gender were adjusted.

In order to determine the separate effects of HOMA-IR index and MS on arterial compliance in children and adolescents, multiple linear regression analysis was performed. After age, gender, and pubertal development were adjusted, the results showed that the clustering of MS components and HOMA-IR were both correlated positively with SI (the clustering of MS components:  $\beta=0.327$ ,  $P<0.001$ ; HOMA-IR:  $\beta=0.040$ ,  $P<0.05$ ).

### DISCUSSION

MS has become a major public health issue around the world. MS and its individual components are the risk factors of CVD. Arterial stiffness is also related to the development of CVD and has been a strong independent predictor of coronary events and cardiovascular mortality in several patient groups. However, the mechanism of how MS to increase the risk of CVD is incompletely understood, and many studies suggested that increased arterial stiffness might be relevant. Therefore, it is necessary to detect the early vascular pathological changes so as to control the prevalence of cardiovascular diseases<sup>[14-17]</sup>.

Arterial compliance represents the internal elastic function of blood vessels. Recent studies showed that the change of arterial stiffness in MS patients was emphasized. Association of MS and its components with arterial compliance was observed primarily in adults<sup>[18-24]</sup>. In a cohort of 180 nondiabetic, healthy, middle-aged women, van Popele *et al.*<sup>[22]</sup> found that carotid arterial dispensibility was associated with several variables of MS, even when the mean BP was adjusted. Moreover, clustered features of the MS were closely associated with the risk of decreased arterial compliance in middle-aged Japanese men<sup>[23]</sup>. Recently, a report showed an independent relationship of MS, defined according to NCEP-ATP 2001, with increased stiffness of the carotid artery in subjects participating in the Baltimore Longitudinal Study on Aging<sup>[24]</sup>.

To our knowledge, this was the first study on the influence of MS on arterial compliance in Chinese children and adolescents. The study demonstrated that the clustering of MS was closely associated with the risk of increased arterial stiffness in school-aged children, and the association remained even after

confounders such as age, gender and pubertal development were adjusted. Furthermore, this study showed that participants with MS had significantly severe insulin resistance as compared with those with no-risk at MS.

The findings from this study showed consistence with previous study in adults. The observed deleterious effects of the clustering of MS might be due to some of the pathophysiologic manifestations of the MS, such as stimulation of endothelial dysfunction (diminished nitric oxide response), inflammatory response (cytokines), sympathetic nervous activity, renin-angiotensin system and hyperdynamic circulation<sup>[25-29]</sup>. These interrelated abnormalities alter vascular tone and promote hyperplasia and hypertrophy of the smooth muscle cells and the attendant excess collagen synthesis, thereby influencing arterial compliance<sup>[30]</sup>.

Recently, the prevalence of MS has become higher in children and adolescents. In China, a rapid increase of obesity prevalence has been noticed in recent 20 years, especially in the developed metropolises<sup>[31]</sup>. Other studies also reported the similar trend of the prevalence of hypertension and type II diabetes mellitus in children and adolescents. Since MS was associated with decreased arterial compliance in children and adolescents as showed in this study, the latter can be considered as an independent risk predictor of CVD, which may play a important role in prevention for the disease. In addition, some researchers suggested that the early change in vascular wall could be reversible by taking proper physical exercise, balanced diet and proper drug therapy<sup>[32-34]</sup>. This characteristic of reversibility indicated that the early detection of arterial stiffness might be useful for the prevention of CVD.

In conclusion, our results showed an association between MS and decreased arterial compliance in Chinese children and adolescents, and this implicated that early detection of the arterial stiffness might be useful for the prevention and intervention of CVD<sup>[35]</sup>. Further studies, especially longitudinal studies, are needed to explore and confirm the present finding and determine whether the measurement of arterial compliance provides further information on risk of CVD in people with MS.

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