SUPPLEMENTARY DATA

## The study on adolescent CV risk factors in Brazil

*Study sample*

This study was conducted in 18 public high schools in Campina Grande, Northeastern Brazil from September 2012 to June 2013[1]. We included 441 adolescents aged 15-17 years (White: 19.7%, Black: 9.8%, Asian: 11.1%, Brown: 56.5%, Other, 3.0%) with complete data on anthropometric variables, blood biochemical parameters, and cIMT measurements.

*Clinical measurements*

BP was measured using an oscillometric device (OMRON-HEM 742, Osaka, Japan) by trained examiners with an appropriately sized cuff for each participant in sitting position. OMRON-HEM 742 device has been clinically validated in adolescents aged 10-16 years[2]. The mean values of three consecutive BP readings were used for data analyses. High density lipoprotein-cholesterol (HDL-C), triglycerides (TG), and fasting blood glucose (FBG) were measured using Hitachi 911 automatic analyzer (Roche, Basel, Switzerland).

*Carotid artery ultrasound measurements*

B-mode ultrasound examination of the common carotid artery was performed using a portable ultrasound machine with a high-definition linear transducer of 7–12 MHz (model MySonoU5®; Samsung/Medison, Seoul, South Korea). Three manual measurements in each of the left and right sides on the far wall of common carotid artery were performed at about 1 cm from the bifurcation. The measurements were performed by a single qualified professional who was blinded to risk factor data. Another sonographer re-evaluated cIMT in 10% of the sample and the interobserver correlation coefficient was found to be 0.80 (CI 95% 0.65–0.89).

## The Shandong Children Cardiovascular Health Cohort

*Study sample*

Baseline data for the Shandong Children Cardiovascular Health Cohort (SCCHC) study were obtained from one primary school in Huantai county of Zibo city, China, from November 2017 to January 2018. The SCCHC study was designed to examine the impact of CV influencing factors in childhood on the risk of CVD in adulthood, with follow up visits taking place every 2 years. We included 1416 children aged 6-11 years (all were Asians) at baseline with complete data on anthropometric variables, blood biochemical parameters, and cIMT measurements.

*Clinical measurements*

BP was measured using an oscillometric device (OMRON-HEM 7012, Osaka, Japan) by trained examiners with an appropriately sized cuff for each participant in sitting position. The OMRON-HEM 7012 device has been clinically validated in Chinese children and adolescents aged 2-17 years[3]. The mean values of three consecutive BP readings were used for data analyses. HDL-cholesterol, TG, and FBG were measured using a Beckman Coulter AU480 automatic analyzer (Mishima, Shizuoka, Japan).

*Carotid artery ultrasound measurements*

Color Doppler ultrasound examination of the carotid artery was performed using a portable ultrasound machine with a L12-4 linear transducer of 4–12 MHz (CX30, Philips Corp., USA). Four manual measurements of cIMT in both left and right sides on the far wall of the common carotid artery were performed at about 1 cm proximal to the carotid bulb. The measurements for all participants were performed by a single qualified professional who was blinded to the data obtained.

## The study on youth CV risk factors in Greece

*Study sample*

This study was conducted in five schools of the Karlovassi province (semi-rural region in the island of Samos, Greece) from September 2008 to May 2010[4]. We included 439 children and adolescents aged 8-17 years (all were Whites) with complete data on anthropometric variables, blood biochemical parameters, and cIMT measurements.

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*Clinical measurements*

BP was measured using an oscillometric upper-arm cuff device (OMRON-705IT, Osaka, Japan) by trained examiners with an appropriately sized cuff for each participant in sitting position. The OMRON-705IT device has been clinically validated in children and adolescents aged 6-16 years[5]. The mean values of three consecutive BP readings were used for data analyses. HDL-C, TG, and FBG were measured using with automatic analyzer Menarini BT3000 PLUS (Biotechnica, Italy).

*Carotid artery ultrasound measurements*

Ultrasound examination of the carotid artery was performed using a Sonosite MicroMaxx ultrasound device (Sonosite Inc., Bothell, WA) paired with a 10 MHz multifrequency high-resolution linear transducer. 3-4 measurements in each of the left and right sides were made using electronic calipers at the point of maximum thickness on the far wall of the common carotid artery along a 1 cm section of the artery proximal to the carotid bulb. All measurements of cIMT were performed by a single observer who was blinded to the participants' cardiovascular risk factors status. The intraobserver coefficient of variation was 6.8% (n=15).

**The study on child CV risk factors in Italy**

*Study sample*

This study was conducted in 8 primary schools of Reggio Calabria in Italy from November 2007 to October 2008[6]. We included 570 children aged 10-13 years (all were Whites) with complete data on anthropometric variables, blood biochemical parameters, and cIMT measurements.

*Clinical measurements*

BP was measured using a calibrated mercury sphygmomanometer by trained examiners with an appropriately sized cuff for each participant in sitting position. The mean values of three consecutive BP readings were used for data analyses. HDL-C, TG, and FBG were measured in dry chemistry on a Vitros 950 automatic analyzer (Ortho Clinical Diagnostics, Raritan, New Jersey).

*Carotid artery ultrasound measurements*

Carotid artery ultrasonography was performed using a 10-MHz linear transducer on the MyLab 25 scanner (Esaote). Three measurements of the common carotid artery in each of left and right sides on the far wall were taken at points 0.5 cm, 1 cm, and 2 cm proximal to the bifurcation. All cIMT measurements were carried out by a single sonographer who was blind to the participants' identities and characteristics. Repeated measurements were conducted by this sonographer who was blinded to pervious results, in the same 90 subjects and the intra-observer coefficient of variation was 3.3%.

**The study on child CV risk factors in Spain**

*Study sample*

This study was conducted in primary care settings in Alt Empordà [7] and Girona, regions in northern Spain from November 2007 to December 2014[8]. We included 631 healthy children aged 6-13 years (all were Whites) with complete data on anthropometric variables, blood biochemical parameters, and cIMT measurements.

*Clinical measurements*

BP was measured using an electronic sphygmomanometer (Dinamap Pro 100, GE Healthcare, Chalfont St. Giles, United Kingdom) by trained examiners with an appropriately sized cuff for each participant in sitting position. We used the mean values of two consecutive BP readings. FBG was measured by the hexokinase method. TG was measured by glycerol-phosphate oxidase method and HDL-C by homogenous method of selective detergent with accelerator (ARCHITECT, Abbott Laboratories, Abbott Park, IL).

*Carotid artery ultrasound measurements*

Carotid artery ultrasonography was performed using high-resolution ultrasonography (MyLabTM25, Esaote, Firenze, Italy) with a linear 7.5-12 MHz transducer. Measurements were performed three times, at the level of the right distal on the far wall of the common carotid artery, 1 cm proximal to the bifurcation. All cIMT

measurements were performed by a well-trained operator. For all sites, the within-operator variability was less than 6%.

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SUPPLEMENTARY DATA

**Supplementary Table S1. Sensitivity analyses of the association between combinations of weight and metabolic status and risk of high cIMT(defined based on the 75th, 80th and 95th percentile values for sex, age and study population, and the 90th percentile values for sex and age from 1051 European children and adolescents published in *Hypertension*)**

| | Normal weight | | Overweight | | Obese | |
|---|---|---|---|---|---|---|
| | Metabolically healthy | Metabolically unhealthy | Metabolically healthy | Metabolically unhealthy | Metabolically healthy | Metabolically unhealthy |
| **cIMT 75th percentile** | | | | | | |
| NCEP criteria † | 1.00 (ref) | 1.23 (1.00-1.54) | 2.37 (1.84-3.05) | 2.62 (2.05-3.33) | 3.13 (2.19-4.47) | 4.81 (3.73-6.19) |
| IDF criteria ‡ | 1.00 (ref) | 1.38 (1.06-1.80) | 2.16 (1.61-2.91) | 2.74 (2.20-3.41) | 3.99 (3.04-5.23) | 4.61 (3.44-6.19) |
| **cIMT 80th percentile** | | | | | | |
| NCEP criteria † | 1.00 (ref) | 1.40 (1.10-1.78) | 2.55 (1.94-3.34) | 2.81 (2.17-3.64) | 3.55 (2.45-5.14) | 5.44 (4.18-7.09) |
| IDF criteria ‡ | 1.00 (ref) | 1.41 (1.06-1.89) | 2.16 (1.57-2.98) | 2.86 (2.27-3.61) | 4.41 (3.32-5.84) | 4.99 (3.68-6.75) |
| **cIMT 95th percentile** | | | | | | |
| NCEP criteria † | 1.00 (ref) | 1.24 (0.76-2.03) | 2.45 (1.47-4.07) | 3.77 (2.41-5.88) | 5.40 (3.03-9.61) | 8.29 (5.45-12.61) |
| IDF criteria ‡ | 1.00 (ref) | 1.67 (0.96-2.89) | 3.24 (2.09-5.01) | 3.76 (2.21-6.40) | 7.34 (4.67-11.52) | 8.55 (5.37-13.62) |
| **cIMT 90th percentile published in Hypertension** | | | | | | |
| NCEP criteria † | 1.00 (ref) | 1.49 (1.21-1.84) | 2.20 (1.70-2.83) | 2.75 (2.12-3.55) | 2.48 (1.72-3.56) | 3.42 (2.62-4.47) |
| IDF criteria ‡ | 1.00 (ref) | 0.73 (0.55-1.01) | 1.97 (1.58-2.45) | 2.08 (1.51-2.86) | 2.38 (1.81-3.14) | 2.96 (2.16-4.07) |

Adjusted for sex, age, race/ethnicity and study center.

† Based on the National Cholesterol Education Program (NCEP) criteria, metabolic status (metabolically healthy, no risk factors, and metabolically unhealthy, one or more risk factors) was defined as the presence/absence of the following four traditional CV risk factors : elevated BP, elevated TG, reduced HDL-C and elevated fasting glucose

‡ Based on the International Diabetes Federation (IDF) criteria, metabolic status (metabolically healthy, no risk factors, and metabolically unhealthy, one or more risk factors) was defined as the presence/absence of the following four traditional CV risk factors : elevated BP, elevated TG, reduced HDL-C and elevated fasting glucose

SUPPLEMENTARY DATA

**Supplementary Table S2. Odds ratios and 95% confidence intervals of high cIMT across waist-to-height ratio and metabolic status categories**

| | Normal WHtR | | Central obese | |
|---|---|---|---|---|
| | Metabolically healthy | Metabolically unhealthy | Metabolically healthy | Metabolically unhealthy |
| NCEP criteria † | | | | |
| Total | 1.00 (ref) | 1.72 (1.25-2.36) | 3.17 (2.27-4.42) | 5.42 (4.08-7.20) |
| Boys | 1.00 (ref) | 2.63 (1.55-4.46) | 4.47 (2.65-7.54) | 9.06 (5.73-14.33) |
| Girls | 1.00 (ref) | 1.36 (0.91-2.04) | 2.62 (1.67-4.11) | 3.67 (2.49-5.41) |
| IDF criteria ‡ | | | | |
| Total | 1.00 (ref) | 1.88 (1.30-2.71) | 3.95 (3.00-5.21) | 4.89 (3.58-6.69) |
| Boys | 1.00 (ref) | 2.83 (1.61-4.99) | 5.43 (3.55-8.29) | 8.04 (5.07-12.74) |
| Girls | 1.00 (ref) | 1.38 (0.85-2.26) | 3.18 (2.18-4.65) | 3.09 (1.96-4.85) |

Adjusted for sex, age, race/ethnicity and study center.

† Based on the National Cholesterol Education Program (NCEP) criteria, metabolic status (metabolically healthy, no risk factors, and metabolically unhealthy, one or more risk factors) was defined as the presence/absence of the following four traditional CV risk factors: elevated BP, elevated TG, reduced HDL-C and elevated fasting glucose

‡ Based on the International Diabetes Federation (IDF) criteria, metabolic status (metabolically healthy, no risk factors, and metabolically unhealthy, one or more risk factors) was defined as the presence/absence of the following four traditional CV risk factors : elevated BP, elevated TG, reduced HDL-C and elevated fasting glucose

SUPPLEMENTARY DATA

**Supplementary Table S3. Sensitivity analyses of the association between combinations of weight and metabolic status and risk of high cIMT after exclusion of children aged <10 when using IDF criteria**

| | Normal weight | | Overweight | | Obese | |
|---|---|---|---|---|---|---|
| | Metabolically healthy | Metabolically unhealthy | Metabolically healthy | Metabolically unhealthy | Metabolically healthy | Metabolically unhealthy |
| Total | 1.00 (ref) | 1.48 (0.94-2.32) | 1.98 (1.23-3.16) | 2.30 (1.55-3.41) | 3.93 (2.37-6.50) | 3.84 (2.38-6.19) |
| Boys | 1.00 (ref) | 2.13 (1.05-4.32) | 2.73 (1.49-4.99) | 2.95 (1.51-5.74) | 4.26 (2.05-8.86) | 4.52 (2.29-8.91) |
| Girls | 1.00 (ref) | 1.13 (0.62-2.03) | 1.30 (0.64-2.65) | 2.10 (1.22-3.59) | 4.00 (1.95-8.20) | 3.57 (1.77-7.19) |

Adjusted for sex, age, race/ethnicity and study center.

Based on the International Diabetes Federation (IDF) criteria, metabolic status (metabolically healthy, no risk factors, and metabolically unhealthy, one or more risk factors) was defined as the presence/absence of the following four traditional CV risk factors : elevated BP, elevated TG, reduced HDL-C and elevated fasting glucose

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