Trajectories of cardiovascular risk factors during childhood as predictors of subclinical atherosclerosis in young adults

Tien-Jyun Chang[1,2], Chung-Yen Chen[3,4,5], Fung-Chang Sung[6], Ta-Chen Su[4,5,7,8]*

[1]Department of Internal Medicine, Division of Endocrinology and Metabolism, National Taiwan University Hospital, Taipei, Taiwan
[2]National Taiwan University College of Medicine, Taipei, Taiwan
[3]Department of Environmental and Occupational Medicine, National Taiwan University Hospital Yunlin Branch, Yunlin, Taiwan
[4]Institute of Environmental and Occupational Health Sciences, National Taiwan University College of Public Health, Taipei, Taiwan
[5]Department of Environmental and Occupational Medicine, National Taiwan University Hospital, Taipei, Taiwan
[6]Department of Health Services Administration and Management Office for Health Data, China Medical University, Taichung, Taiwan
[7]Department of Internal Medicine, Division of Cardiology, National Taiwan University Hospital, Taipei, Taiwan
[8]The Experimental Forest, National Taiwan University, Nantou, Taiwan

***Corresponding author:**
Professor and Director
Ta-Chen Su MD, PhD
Department of Environmental and Occupational Medicine
National Taiwan University Hospital
National Taiwan University College of Medicine
7 Chung-Shan South Road
Taipei, Taiwan 10002
Phone: +886-223123456 ext 267467
Fax: +886-223712361
E-mail: tachensu@gmail.com

Submitted: 10 September 2024; **Accepted:** 5 December 2024
Online publication: 28 February 2025

Arch Med Sci
DOI: https://doi.org/10.5114/aoms/196908

Abstract

Introduction: Studies on cardiovascular risk factors in childhood/adolescence and subclinical cardiovascular disease in young Asian adults remain limited. The aim of this study was to investigate the effects of childhood cardiovascular risk factors as predictors of subclinical atherosclerosis in young adults.

Material and methods: From a sample of children of school-going age enrolled in the Young Taiwanese Cohort (YOTA) Study conducted in Taipei, Taiwan, who completed the mass urine screening program between 1992 and 2000, we included 303 subjects with hypertension and 486 subjects with a normal blood pressure during childhood (2006–2008). In total, 789 young adults (mean age: 21.32 years) underwent carotid duplex to measure carotid intima-media thickness (CIMT).

Results: The major cardiovascular risk factors during childhood significantly predicted CIMT in adulthood. After adjusting for covariates, multivariate linear regression analysis showed that childhood cardiovascular risk factors such as male sex, increased body mass index (BMI), elevated diastolic blood pressure (DBP), raised fasting glucose, and abnormal cholesterol profiles predict subclinical atherosclerosis (CIMT ≥ 75th percentile) in young adulthood after a mean follow-up period of 8.5 years. Multivariate-adjusted odds ratios (95% confidence interval) for risk factors in childhood (the upper quartile vs. lower three quartiles) significantly predicting thickened CIMT (≥ 75th percentile) were 2.32 (1.46–3.70) for BMI, 6.88 (4.63–10.21) for DBP, and 4.10 (2.79–6.04) for childhood with hypertension.

Conclusions: This study highlights the importance of prevention and management of cardiovascular risk factors during childhood for the primary prevention of cardiovascular disease in adulthood.

Key words: carotid intima-media thickness, subclinical atherosclerosis, childhood, cardiovascular risk factors.

Introduction

Cardiovascular disease (CVD) is a major contributor to the global health burden and the leading cause of morbidity and mortality in many Asian countries [1–3]. Atherosclerosis generally occurs in middle-aged and older adults; however, it is thought to begin in childhood and to develop silently for decades before clinical events such as stroke, myocardial infarction, and peripheral vascular disease occur [4]. Autopsy studies in children and adolescents have confirmed that the presence of preclinical atherosclerotic lesions is associated with antemortem cardiovascular risks [5–7]. Preclinical atherosclerosis refers to the early stages of atherosclerotic disease where structural and functional changes in the arterial walls, including arterial wall thickening, coronary calcium deposits, and increased arterial wall rigidity, alter the elastic function and the reactivity of arteries and abnormal thrombogenicity occurs without causing any symptoms. This is a crucial phase for early detection and intervention to prevent the progression to symptomatic cardiovascular disease [8]. Therefore, it is important to ensure early detection of preclinical atherosclerosis and associated risk factors as the major predictors of CVD and stroke in later life.

Common carotid artery intima-media thickness (CIMT) assessed by ultrasonography is a well-known marker of subclinical atherosclerosis [9–11]. The Bogalusa Heart Study showed that low-density lipoprotein cholesterol (LDL-C) levels and body mass index (BMI) measured during childhood could predict CIMT in young adults [12]. The Cardiovascular Risk in Young Finns Study also identified LDL-C, systolic blood pressure (SBP), BMI and smoking in adolescents aged 12–18 years as predictors of CIMT in young adults aged 33–39 years [4]. Addressing the above-mentioned modifiable risk factors evident in childhood and adolescence could therefore help prevent atherosclerosis in adulthood.

Childhood overweight/obesity and metabolic syndrome have been associated with cardiovascular risk and a further increase in risk of the development of CVD in later life [13, 14]. In addition to the Bogalusa Heart Study [12] and the Cardiovascular Risk in Young Finns Study [4], several other studies have also reported the link between childhood obesity and premature mortality from CVD [15–18]. However, few studies have investigated these association in the Asian population. Evidence concerning the associations between overweight/obesity during childhood/adolescence and subclinical atherosclerosis in young adults of ethnic Chinese descent is also limited. The YOung TAiwanese Cohort (YOTA) Study was conducted between 2006 and 2008 to investigate the effect of childhood hypertension on cardiovascular risk later in life [19]. We found that childhood BMI tracked well from childhood to adulthood, with an adjusted R^2 of 0.551. Childhood hypertension and overweight/obesity were significant predictors of preclinical atherosclerosis and elevated cardiovascular risk in young adulthood. The YOTA cohort also showed that childhood overweight and obesity predicted the adulthood subclinical atherosclerosis (CIMT ≥ 75th percentile) with relative risks of 2.99 (95% confidence interval (CI): 1.37–6.52) in association with overweight and 3.33 (95% CI: 1.65–6.74) with obesity, respectively, after a mean follow-up of 8.5 years. However, investigation on the association between childhood/adolescent cardiovascular risk factors and preclinical atherosclerosis in young adults is scarce in the Asian population. Information concerning the determinants and aggravating factors of subclinical CVD and endocrine/metabolic disorders in young adults remains lacking in Taiwan, particularly when considering long-term follow-up data.

We therefore conducted this prospective cohort study aimed at evaluating the role of childhood/adolescent cardiovascular risk factors and CIMT associated with subsequent subclinical atherosclerosis in young adulthood.

Material and methods

Participants

This is a longitudinal observational cohort study. From 1992 to 2000, a nationwide mass urine screening on renal health was conducted among school children aged 6 to 18 years in Taiwan (N = 2,862,083) [14, 20, 21]. Anthropometric characteristics and blood pressure were also measured for students who tested positive for proteinuria or glucosuria (N = 103,756). Among them, 9,227 students were hypertensive. Students who had participated in the urine screening program were contacted for participation in the YOTA Study. Detailed information about research procedures is available in our previous study [19, 20]. The diagram (Figure 1) shows the flow chart of the present study from the urinary screening program to the recruitment of participants. Among the 9,227 subjects with hypertension in their childhood (6–12 years old [y/o]) or adolescence (13–18 y/o), 707 subjects who lived in Taipei were contacted via telephone and mail during 2006–2008. Overall, 303 subjects with hypertension reported in their childhood or adolescence completed the follow-up health examinations (response rate, 42.9%; 303/707). From 94,529 students with normal BP during childhood or adolescence, 6,390 living in Taipei were randomly contacted by mail during 2006–2008. Among them, 486 students

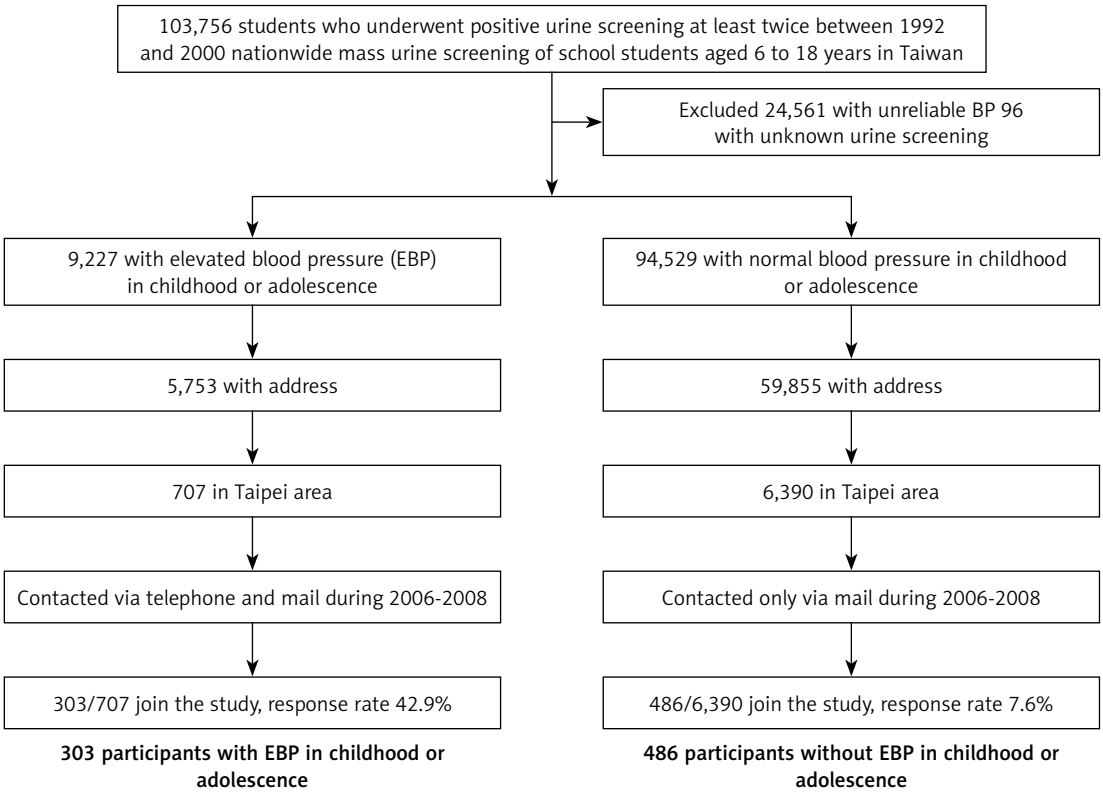

Figure 1. Flowchart of participants' recruitment with and without childhood elevated blood pressure (EBP) in the Young Taiwanese Cohort (YOTA) study during 2006-2008

completed the follow-up health examinations (response rate, 7.6%; 486/6,390). The mean follow-up period is 8.5 years.

Participants who had provided blood and urine specimens were subjected to subclinical atherosclerotic measures, including CIMT and brachial-ankle aortic pulse wave velocity [20]. One subject with normal BP during childhood without available childhood measurements was excluded. All participants provided written informed consent.

Assessments of vascular risk factors and clinical information

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) defined hypertension as BP values higher than 140/90 mm Hg or participants being treated with anti-hypertensive agents. Among the 6–18 y/o participants, hypertension was defined as systolic blood pressure, diastolic blood pressure, or both greater than or equal to the sex-, age-, and height-percentile-specific 95th percentile blood pressure values [22]. BP was measured with a mercury sphygmomanometer in a standardized fashion, and the cuff size adjusted to the circumference of the arm. BP was recorded using the mean of two measurements taken after 5 min of seated rest. Data on body weight and height were also obtained. BMI was calculated as the body weight in kilograms divided by the height in meters squared. Overweight in children and adolescents was defined according to age and sex-specific criteria for BMI ≥ 85th percentile for 2–18 years old stipulated by the Taiwanese Department of Health (http://www.ctaso.org.tw/news5.htm). Adults (≥ 18 years old) with a BMI 24–26.99 kg/m^2 were defined as overweight, and a BMI of 27 kg/m^2 or over was defined as obesity. Prevalent diabetes mellitus (DM) was defined as fasting glucose > 6.99 mmol/l and/or a history of taking hypoglycemic agents. Lifestyle information, including smoking, drinking and exercise data, was obtained from a structured and self-administered questionnaire. Dietary habits were evaluated using a modified frequency scale of a dietary questionnaire for hyperlipidemia available in Taiwanese. Information on family history of CVD, hyperlipidemia, DM, and hypertension was also documented.

Serum markers

All subjects with a fasting period for 10–14 h were asked to provide a venous blood sample of 20 ml from an antecubital vein for serum and plasma analysis as well as DNA extraction. Blood glucose, and serum total cholesterol, triglyceride, LDL-C, and high-density lipoprotein cholesterol (HDL-C) levels were measured by an auto-analyz-

er (Hitachi 7250 Special; Hitachi, Tokyo, Japan) in a central laboratory at the National Taiwan University Hospital. High-sensitivity C reactive protein (hs-CRP) levels were measured in plasma using a commercially available high-sensitivity mechanism (Immulite®, Siemens, USA). For the assays, blood samples were first centrifuged at 3000 rpm for 15 min within 30 min of collection, and then stored at –70°C until the time of assessment.

Assessment of intima-media thickness of carotid arteries

The protocol for the carotid atherosclerosis measurements, including CIMT and carotid atherosclerotic plaque burden, is well documented [20, 23, 24]. An experienced technician measured CIMT at the extra-cranial carotid artery using a high-resolution B-mode ultrasonography device (GE Vivid ultrasound system, Horten, Norway) equipped with a 3.5–10 MHz real-time B-mode scanner. A quantification package was applied to conduct offline automatic calculation for vascular ultrasound. The maximum and mean intima-media thickness values were calculated for the bilateral common carotid artery (CCA) proximal to the carotid bifurcation, bulb, and internal carotid artery. CCA1 and CCA2 on the CCA distal were measured at 0–1 cm and 1–2 cm, respectively, from the carotid bifurcation. The measurement of CIMT at the posterior wall of the distal CCA was made from the leading edge of the first echogenic line (interface between lumen and vascular intima) to the leading edge of the second line (interface between vascular media and adventitia) [23]. The measurement of CIMT included RCCA1 (right CCA 1cm), RCCA2 (right CCA 2 cm), LCCA1 (left CCA 1 cm), LCCA2 (left CCA 2cm), right bulb, left bulb, ICA Rt (right internal carotid artery), and ICA Lt (left internal carotid artery). A digitalized memory system in the DICOM format recorded all measurements. We acquired a clipped moving image for the carotid bulb and CCA for 5 s. A computer program was used to analyze the digitized M-mode and to measure the CIMT between two successive R waves. This method was able to obtain a mean value of 150 CCA measurements on a 10-mm segment. The technician was required to conduct the reliability test by repeating measurements for 30 subjects over 2 weeks. The intra-observer coefficients of correlation reliability of CIMT measurement were 98.8% for the right side CCA and 98.5% for the left side CCA [25].

Statistical analysis

Statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC, USA). We first presented distributions of cardiovascular risk markers by the quartile of CIMT in adulthood, including BMI, fasting glucose, SBP and DBP, cholesterol, HDL-C, LDL-C, triglyceride, DM, hypertension, smoking, drinking, hs-CRP, albumin, creatinine and household income. Sex-specific mean levels of BMI, cholesterol, fasting glucose, SBP and DBP measured in childhood and adulthood were presented by the quartile of CIMT. Significance levels were estimated by ANOVA among means, quartile trends and Q4 to Q1 values.

We then used simple correlation analysis to measure the relationships between CIMT and BMI, SBP, DBP, fasting glucose and total cholesterol measured in childhood and adulthood separately. We arbitrarily defined a CIMT ≥ 75th percentile as thickened CIMT (a surrogate marker of subclinical atherosclerosis) according to our previous YOTA cohort [19]. We used multivariate logistic regression analyses to measure the strength of childhood and adulthood cardiovascular risk factors associated with adulthood subclinical atherosclerosis (CIMT ≥ 75th percentile). We estimated sex specific odds ratios (ORs) and 95% confidence intervals (CIs) of CIMT ≥ 75th percentile associated with childhood and adulthood risk factors, including BMI, SBP, DBP, hypertension, cholesterol and fasting glucose. The Q_4 level to $Q_{1\text{-}3}$ level OR of CIMT was measured for each risk factor after controlling for other factors. Furthermore, we also conducted subgroup analysis to compare sex-specific mean values of the above five cardiovascular risk factors measured in childhood (6–11 y/o) and adolescence (12–18 y/o) at baseline (Period I: 1992–2000) or measured in adolescence (12–18 y/o) and adulthood (19–30 y/o) at follow-up (Period II: 2006–2008) by quartile CIMT of adolescents (12–18 y/o) and adults (19–30 y/o) at follow-up (Period II: 2006–2008) separately.

Results

Characteristics of five cardiovascular risk factors in adulthood by quartile CIMT and association with subclinical atherosclerosis in adulthood

Most of the major cardiovascular risk markers in adulthood, including age, male sex, waist circumference, BMI, SBP and DBP, fasting glucose, lipid profile, hs-CRP level, hypertension, and alcohol intake, were significantly associated with CIMT across quartile distributions (Table I). However, DM, smoking habits, and household income were not significantly associated with CIMT. On the other hand, HDL-C and albumin levels were significantly inversely associated with CIMT.

Features of five cardiovascular risk variables in childhood and adulthood by quartile CIMT and correlation with gender-specific subclinical atherosclerosis in adulthood

A stratified CIMT analysis showed that all five cardiovascular risk factors, except for glucose levels and childhood cholesterol levels in male participants, were significantly associated with CIMT independent of childhood, adulthood, and cumulative factors (Table II). Pearson correlation analysis showed that all childhood, adulthood, and cumulated cardiovascular risk factors were significantly associated with adulthood subclinical atherosclerosis, CIMT (Supplementary Table SI). BMI, SBP, DBP, fasting glucose and total cholesterol levels in childhood were all significantly correlated with respective factors in adulthood (Supplementary Figure S1).

Cardiovascular risk factors in childhood and adulthood as determinants of CIMT in adulthood

Multiple linear regression analysis showed that childhood cardiovascular risk factors predicted adulthood CIMT independent of age. On the other hand, male sex, cholesterol levels, fasting plasma glucose levels, DBP, and BMI of adulthood risk factors were significantly associated with CIMT in adulthood. However, age and SBP in adulthood were not significantly associated with CIMT (Table III).

Upper quartile to the lower three quartiles odds ratio of cardiovascular risk factors in childhood and adulthood predicted thickened CIMT (≥ 75th percentile) in young adults

After adjusting for covariates of childhood, the multivariate logistic regression analysis in Table IV shows that childhood BMI, DBP, and hypertension status were significant determinants of adulthood thickened CIMT (≥ 75th percentile), with the Q_4 to $Q_{1\text{-}3}$ adjusted ORs of 2.32 (95% CI: 1.46–3.70) associated with BMI, 6.88 (95% CI: 4.63–10.21) associated with DBP, and 4.10 (95% CI: 2.79–6.04) associated with hypertension. The corresponding ORs associated with these adulthood risk factors were all reduced in both model 1 and model 2 (Table IV).

Table I. Basic average levels of cardiovascular risk factors in adulthood by quartile and carotid intima-media thickness

Characteristics	Carotid intima-media thickness, mean [mm]				*P*1	*P*2	*P*3
	Quartile 1 < 0.40	Quartile 2 0.40–0.43	Quartile 3 0.43–0.46	Quartile 4 ≥ 0.46			
	N = 197	*N* = 200	*N* = 195	*N* = 197			
Age [years]	20.8 ±3.4	21.2 ±3.2	21.7 ±3.0	21.6 ±3.6	0.033	0.014	0.004
Male, %	28.9	35.5	44.0	50.8	< 0.001	< 0.001	< 0.001
Waist [cm]	66.9 ±8.6	67.9 ±8.3	71.4 ±10.7	76.4 ±15.3	< 0.001	< 0.001	< 0.001
BMI [kg/m^2]	21.0 ±3.4	20.9 ±3.1	22.0 ±3.7	23.7 ±5.28	< 0.001	< 0.001	< 0.001
SBP [mm Hg]	104.8 ±12.4	104.4 ±12.55	108.29 ±13.6	113.0 ±17.6	< 0.001	< 0.001	< 0.001
DBP [mm Hg]	65.0 ±9.8	64.7 ±8.6	65.8 ±9.7	72.2 ±14.0	< 0.001	< 0.001	< 0.001
Hypertension, %	3.6	7	8.8	21.3	< 0.001	< 0.001	< 0.001
Glucose [mmol/l]	4.73 ±0.51	4.7 ±0.75	4.76 ±0.56	5.18 ±2.0	< 0.001	< 0.001	< 0.001
Diabetes mellitus, %	0.5	1	1.0	2.5	0.303	0.138	0.086
Cholesterol [mmol/l]	4.48 ±0.93	4.42 ±0.88	4.48 ±0.75	4.74 ±1.01	0.002	0.005	0.002
LDL-C [mmol/l]	2.53 ±0.76	2.48 ±0.76	2.62 ±0.72	2.89 ±0.92	< 0.001	< 0.001	< 0.001
HDL-C [mmol/l]	1.34 ±0.26	1.31 ±0.26	1.30 ±0.27	1.25 ±0.24	0.01	0.001	0.001
Triglyceride [mmol/l]	0.91 ±0.51	0.94 ±1.05	0.92 ±0.46	1.11 ±1.20	0.074	0.022	0.031
Smoking habit, %	11.7	11	14.5	15.7	0.451	0.243	0.146
Alcohol habit, %	6.6	7.5	7.8	13.7	0.053	0.022	0.017
hs-CRP [µg/l]	70 ±120	80 ±160	100 ±170	120 ±270	0.031	0.008	0.006
Albumin [g/l]	49 ±3	49 ±2	49 ±2	49 ±3	0.018	0.012	0.006
Creatinine [µmol/l]	85.77 ±40.67	82.23 ±13.26	84.88 ±15.92	92.84 ±70.74	0.078	0.084	0.045
Household income ≥ USD 1,600/mon	64.0	60.5	59.1	58.4	0.677	0.256	0.244

BMI – body mass index, SBP and DBP – systolic and diastolic blood pressure, LDL-C and HDL-C – low-density and high-density cholesterol, hs-CRP – high-sensitivity C-reactive protein. P1-value is test for ANOVA or χ^2. P2-value is for CIMT quartile 4 compared with CIMT quartile 1. P3-value is test for trend.

Table II. Averages of 5 cardiovascular risk factors in childhood and adulthood measured by quartile of adulthood carotid intima-media thickness

Characteristics	Carotid intima-media thickness [mm]				*P*-value		
	Quartile 1 < 0.40 *N* = 197	Quartile 2 0.40–0.43 *N* = 200	Quartile 3 0.43–0.46 *N* = 195	Quartile 4 ≥ 0.46 *N* = 197	ANOVA	Trend	Q4 vs. Q1
Male							
Body mass index [kg/m^2]							
Childhood	18.8 ±3.0	18.3 ±3.0	19.5 ±3.5	21.7 ±5.2	< 0.001	< 0.001	< 0.001
Adulthood	21.8 ±3.4	21.4 ±3.2	23.0 ±4.1	25.1 ±5.6	< 0.001	< 0.001	< 0.001
Cumulative risk	20.4 ±2.8	19.7 ±2.9	21.1 ±3.4	23.2 ±5.2	< 0.001	< 0.001	< 0.001
Glucose [mmol/l]							
Childhood	4.6 ±0.6	4.8 ±0.9	4.7 ±0.7	4.7 ±0.8	0.756	0.955	0.805
Adulthood	4.7 ±0.4	4.9 ±1.2	4.7 ±0.3	5.0 ±1.0	0.142	0.119	0.055
Cumulative risk	4.7 ±0.4	4.8 ±1.0	4.7 ±0.4	4.8 ±0.7	0.451	0.311	0.176
Cholesterol [mmol/l]							
Childhood	3.9 ±0.9	4.1 ±0.9	4.0 ±0.8	4.2 ±0.9	0.324	0.172	0.101
Adulthood	4.3 ±1.2	4.4 ±0.8	4.4 ±0.9	4.8 ±1.0	0.026	0.015	0.012
Cumulative risk	4.1 ±1.0	4.2 ±0.8	4.2±0.7	4.5 ±0.9	0.059	0.033	0.019
Systolic BP [mm Hg]							
Childhood	109.6 ±17.6	110.9 ±16.2	115.5 ±19.5	120.3 ±16.8	< 0.001	< 0.001	< 0.001
Adulthood	114.0 ±13.2	112.1 ±12.3	114.62±12.7	119.4 ±17.7	0.008	0.015	0.027
Cumulative risk	112.0 ±11.4	111.0 ±11.5	114.8 ±12.9	119.0 ±13.4	< 0.001	< 0.001	0.001
Diastolic BP [mm Hg]							
Childhood	67.4 ±11.5	67.9 ±10.1	70.7 ±11.3	80.9 ±15.1	< 0.001	< 0.001	< 0.001
Adulthood	70.6 ±10.4	68.6 ±8.3	69.7 ±9.5	76.1 ±14.2	< 0.001	0.003	0.003
Cumulative risk	69.1 ±8.5	68.1 ±7.2	70.03 ±8.2	78.0 ±11.8	< 0.001	< 0.001	< 0.001
Female							
Body mass index [kg/m^2]							
Childhood	18.1 ±3.2	18.6 ±2.9	18.8 ±3.0	20.9 ±5.1	< 0.001	< 0.001	< 0.001
Adulthood	20.6 ±3.3	20.5 ±2.9	21.4 ±3.4	22.3 ±4.5	< 0.001	< 0.001	< 0.001
Cumulative risk	19.6 ±2.8	19.7 ±2.6	20.1 ±2.8	21.6 ±4.4	< 0.001	< 0.001	< 0.001
Glucose [mmol/l]							
Childhood	4.6 ±0.6	4.9 ±1.2	4.7 ±0.7	5.2 ±2.3	< 0.001	< 0.001	< 0.001
Adulthood	4.7 ±0.6	4.7 ±0.7	4.7 ±0.4	5.4 ±2.7	0.002	0.003	< 0.001
Cumulative risk	4.7 ±0.4	4.8 ±0.9	4.7 ±0.5	5.3 ±2.4	< 0.001	< 0.001	< 0.001
Cholesterol [mmol/l]							
Childhood	4.3 ±1.0	4.2 ±0.9	4.3 ±0.8	4.6 ±1.2	0.010	0.013	0.015
Adulthood	4.5 ±0.8	4.5 ±0.9	4.5 ±0.6	4.8 ±1.0	0.031	0.045	0.033
Cumulative risk	4.4 ±0.8	4.3 ±0.8	4.4 ±0.6	4.7 ±1.0	0.003	0.011	0.009
Systolic BP [mm Hg]							
Childhood	103.7 ±13.4	107.3 ±16.1	108.1 ±16.1	118.9 ±18.7	< 0.001	< 0.001	< 0.001
Adulthood	101.5 ±9.7	99.4 ±10.6	104.2 ±11.7	106.0 ±14.9	< 0.001	< 0.001	0.003
Cumulative risk	103.3 ±8.4	103.7 ±11.3	106.1 ±11.4	112.4 ±13.4	< 0.001	< 0.001	< 0.001
Diastolic BP [mm Hg]							
Childhood	66.5 ±11.8	69.4 ±12.3	70.7 ±12.9	81.9 ±15.0	< 0.001	< 0.001	< 0.001
Adulthood	62.7 ±8.7	62.2 ±8.3	63.6 ±8.4	67.9 ±13.0	< 0.001	< 0.001	< 0.001
Cumulative risk	65.0 ±7.7	66.0 ±8.6	67.1 ±8.5	74.9 ±10.6	< 0.001	< 0.001	< 0.001

Table III. Multiple linear regressions for cardiovascular risk factors in childhood and adulthood as determinants of carotid intima-media thickness in adulthood

Characteristics	Childhood			Adulthood		
	B	SE	*P*-value	β	SE	*P*-value
Age [years]	0.000356	0.000633	0.574	0.000437	0.000502	0.385
Male, yes	0.016510	0.003270	< 0.001	0.007740	0.003740	0.039
Cholesterol [mmol/l]	0.269739	0.063855	< 0.001	0.260064	0.071982	< 0.001
Fasting glucose [mmol/l]	0.003168	0.001404	0.024	0.005274	0.001476	< 0.001
Systolic BP [mm Hg]	–0.000263	0.000129	0.042	–0.000211	0.000187	0.261
Diastolic BP [mm Hg]	0.001410	0.000153	< 0.001	0.000937	0.000236	< 0.001
BMI [kg/m^2]	0.002630	0.000476	< 0.001	0.002300	0.000455	< 0.001
Adjusted R^2	0.2747			0.1644		

Subgroup analysis among children (6–11 y/o), adolescents (12–18 y/o) and adults (19-30 y/o)

The average ages (mean ± SD) at screening (Period I: 1992–2000) during childhood (6–11 y/o) and adolescence (12–18 y/o) were 9.36 ±1.42 y/o and 14.09 ±1.66 y/o, respectively. The corresponding ages at follow-up (Period II: 2006–2008) during adolescence (12–18 y/o) and adulthood (19–30 y/o) were 16.74 ±1.40 y/o and 22.59 ±2.47 y/o, respectively. As shown in Supplementary Table SII, the stratified CIMT analysis showed that none of the male cardiovascular risk factors in childhood during Period I (1992–2000) and followed up in adolescence during Period II (2006–2008) was associated with CIMT in the adolescence period. For females, only SBP and DBP in childhood were significantly associated with CIMT for adolescence. In contrast, most of the cardiovascular risk factors measured in the adolescence period and in adulthood were significantly associated with CIMT in adulthood during Period II (2006–2008).

Multiple linear regression showed that only DBP in childhood during Period I (1992–2000) predicted CIMT in adolescence during period II (2006–2008) (Supplementary Table SIII). In contrast, almost all the cardiovascular risk factors in both adolescence during Period I (1992–2000) and adulthood during Period II (2006-2008) except SBP in adulthood during Period II (2006–2008) predicted adulthood CIMT during Period II (2006–2008) independent of age (Supplementary Table SIII).

Discussion

This study traced the cardiovascular risk from childhood to adulthood. We found that childhood cardiovascular risk factors could predict adulthood subclinical atherosclerosis. The most important predictors were childhood BMI, DBP and hypertension. Childhood levels of cholesterol and fasting glucose, SBP, and male sex were also positively associated with CIMT during adulthood. This study confirmed that childhood cardiovascular risk factors play an important role in the initiation and progression of subclinical atherosclerosis during adulthood.

Post-mortem studies have demonstrated that cardiovascular risk factors in children/adolescents are associated with the early stages of coronary atherosclerosis [26, 27]. Importantly, the extent of lesions increases remarkably with multiple cardiovascular risk factors [7]. The cross-sectional Bogalusa Heart Study found a deleterious trend towards increased CIMT as the number of cardiovascular risk factors in asymptomatic healthy young adults increased [28]. The study also reported that SBP, race, age, LDL-C, and HDL-C were significantly associated with CIMT, and accounted for 16.7% of variance in CIMT in a multivariate analysis [28]. The Young Finns Study also showed that CIMT was associated with cardiovascular risk factors during early adulthood (age 33–39 years), including LDL-C level, total cholesterol level, LDL-C/HDL-C, SBP, DBP, BMI and smoking in men. In women, LDL-C/HDL-C ratio, triglyceride level, SBP, DBP, BMI and smoking were associated with CIMT [4]. In our study, cardiovascular risk determinants during young adulthood, including age, male sex, waist circumferences, BMI, SBP, DBP, the presence of hypertension, fasting plasma glucose levels, lipid profile, hs-CRP levels, and alcohol intake, but not smoking habits, differed significantly among CIMT quartiles during adulthood. Most of the cardiovascular risk factors in young adulthood associated with CIMT in our study were similar to previous studies found in Western populations [4, 28]. However, unlike those studies [4, 28], smoking was not associated with CIMT in the present study. In the Young Finns Study, 54.2% of men and 43.2% of women were current or former smokers [4]. In contrast, the prevalence of smoking was 21.01% in men and 6.5% in women in this study [19]. A lower prevalence of smoking and younger

Table IV. Upper quartile to the lower three quartiles odds ratio of cardiovascular risk factors in childhood and adulthood predicted thickened CIMT (≥ 75th percentile) in young adults

Variable		BMI Q_4 vs. Q_{1-3}	SBP Q_4 vs. Q_{1-3}	DBP Q_4 vs. Q_{1-3}	Hypertension	Cholesterol Q_4 vs. Q_{1-3}	Fasting Glucose Q_4 vs. Q_{1-3}
Childhood							
All		2.32 (1.46, 3.70)‡	0.89 (0.57, 1.41)	6.88 (4.63, 10.21)‡	4.10 (2.79, 6.04)‡	1.53 (1.00, 2.34)	1.03 (0.67, 1.57)
	Male	2.72 (1.33, 5.54)†	0.64 (0.34, 1.21)	5.82 (3.17, 10.68)‡	2.40 (1.36, 4.24)†	1.84 (0.92, 3.69)	0.73 (0.38, 1.40)
	Female	2.01 (1.07, 3.79)*	1.24 (0.65, 2.36)	7.73 (4.58, 13.08)‡	6.4 (3.71, 11.05)‡	1.36 (0.78, 2.37)	1.24 (0.70, 2.19)
Adulthood							
Model 1							
All		1.97 (1.32, 2.93)‡	1.17 (0.74, 1.84)	2.17 (1.36, 3.46)‡	1.81 (0.90, 3.66)	1.36 (0.92, 2.00)	1.08 (0.73, 1.60)
	Male	2.64 (1.53, 4.56)‡	1.08 (0.63, 1.88)	1.57 (0.87, 2.83)	1.48 (0.63, 3.48)	1.14 (0.63, 2.06)	0.93 (0.53, 1.65)
	Female	1.41 (0.76, 2.60)	1.39 (0.59, 3.25)	3.97 (1.80, 8.78)‡	3.01 (0.81, 11.23)	1.51 (0.89, 2.55)	1.28 (0.74, 2.18)
Model 2							
All		1.97 (1.28, 3.03)‡	1.17 (0.73, 1.89)	2.13 (1.31, 3.44)‡	1.87 (0.90, 3.86)	1.36 (0.91, 2.02)	1.11 (0.74, 1.65)
	Male	2.90 (1.55, 5.41)‡	1.02 (0.57, 1.83)	1.51 (0.80, 2.82)	1.45 (0.58, 3.63)	1.12 (0.60, 2.09)	0.90 (0.50, 1.62)
	Female	1.33 (0.68, 2.58)	1.38 (0.56, 3.39)	3.79 (1.61, 8.93)‡	3.12 (0.8, 12.24)	1.55 (0.90, 2.69)	1.35 (0.76, 2.42)

*P-value for these parameters: *< 0.05, †< 0.01, ‡ < 0.005. BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure.*
Multivariate adjustment:
Childhood:
Body mass index: adjusted for age, sex, SBP, DBP, fasting glucose, and cholesterol levels
SBP, DBP, and hypertension: adjusted for age, sex, BMI, fasting glucose, and cholesterol levels
Cholesterol: adjusted for age, sex, BMI, fasting glucose, SBP and DBP
Glucose AC: adjusted for age, sex, BMI, cholesterol levels, SBP and DBP
Adulthood:
Model 1: Risk factors same as childhood
Model 2:
Body mass index: adjusted for age, gender, fasting glucose, SBP, DBP, current smoking and drinking history, LDL-C, HDL-C, high sugar diet, high fat diet, household income, father education, creatinine levels
SBP, DBP, and hypertension: adjusted for age, gender, BMI, fasting glucose, smoking and drinking history, LDL-C, HDL-C, high sugar diet, high fat diet, household income, father education, creatinine levels
Cholesterol: adjusted for age, gender, BMI, fasting glucose, SBP, DBP, current smoking and drinking history, high sugar diet, high fat diet, household income, father education, creatinine levels
Glucose AC: adjusted for age, gender, BMI, SBP, DBP, current smoking and drinking history, LDL-C, HDL-C, high sugar diet, high fat diet, household income, father education, creatinine levels

age in adulthood in this study may explain why smoking was not significantly associated with CIMT during young adulthood.

In this study, the five cardiovascular risk factors, except glucose levels in male participants, tracking from childhood to adulthood are associated with CIMT measured 8.5 years later. It is inferred that the cardiovascular risk factors in childhood and adolescence were significantly associated with subclinical atherosclerosis during young adulthood, which was compatible with findings in previous longitudinal studies [4, 28]. Childhood cholesterol was the only factor significantly different among the four quartile-stratified groups in women, but not in men. There was a lower cholesterol level in boys than in girls during childhood (Table II: childhood cholesterol, boys: 3.9–4.2 mmol/l, girls: 4.3–4.6 mmol/l). Similarly, glucose levels in males from childhood to adulthood were not significantly different among the four quartile-stratified groups, which may be due to the lower fasting plasma glucose levels in males than in females during both childhood and adulthood (Table II: 4.6–4.7 versus 4.6–5.2 mmol/l in childhood and 4.7–5.0 versus 4.7–5.4 mmol/l in adulthood). Because cardiovascular risk factors during childhood/adolescence are sex-specific, we may adopt a different strategy for preventing

progression to subclinical atherosclerosis in men compared with women.

In this study, five cardiovascular risk factors (i.e., BMI, SBP, DBP, plasma cholesterol and glucose levels) in both childhood and adulthood were positively associated with CIMT in adulthood. Consistently, BMI, SBP, DBP, fasting glucose and total cholesterol levels in childhood were all significantly correlated with respective factors in adulthood, according to the tracking of respective values between 1992–2000 and 2006–2008. The associations between childhood and adulthood cardiovascular risk factors may explain why their presence in childhood contributes to the development of subclinical atherosclerosis in young adults. However, in the multiple linear regression model, only male sex, BMI, DBP, plasma cholesterol and glucose levels were positively associated with CIMT during adulthood. Comparing the childhood and adulthood risk factors between Taiwanese and people in Western countries [4, 12], both BMI and plasma cholesterol levels were the common risk factors in different ethnic populations. However, SBP and smoking are considered significant risk factors for preclinical atherosclerosis in Western countries, but not in Taiwan.

The multivariate logistic regression analysis shows that higher BMI, higher DBP, and hypertension status in childhood were the major determinants of adulthood subclinical atherosclerosis (CIMT ≥ 75th percentile). A cross-sectional school-based study in Eastern Turkey also demonstrated significant relationships between atherosclerosis and central obesity, DBP, and chronic inflammation in school-aged children [29]. Obesity in adolescents needs to be considered, since it generally persisted into adulthood [29, 30]. Studies have shown that children with obesity are at greater risk of developing hypertension compared with their normal weight counterparts, and the risk progresses into adulthood if obesity persists [31–33]. Hypertension is also a major risk factor for carotid atherosclerosis [23, 34]. A meta-analysis for one million adults in 61 prospective studies showed that the risk of coronary artery disease was estimated to begin at 115/75 mm Hg and double with the increment of 20/10 mm Hg [35]. Endothelial dysfunction is one of the earliest arterial atherosclerotic changes. A 21-year follow-up of the Cardiovascular Risk in Young Finns study showed that the elevated blood pressure in adolescent boys predicted endothelial dysfunction, which suggested that hypertension in adolescence may affect biological processes to regulate endothelium-dependent flow-mediated vasodilation capacity [36]. Individuals with hypertension persisting from childhood to adulthood are at an increased risk of carotid atherosclerosis. However, the risk can be reduced if hypertension is controlled during adulthood [37]. The American Heart Association has recently reported that the prevalence of adult cardiovascular disease decreased from 49.2% to 9.3% in those with or without hypertension [38]. A systemic study with data from diverse populations showed that blood pressure tracking from childhood into adulthood is strong, emphasizing the need for early intervention [39]. Therefore, identifying and treating childhood hypertension has the potential of a substantial effect on the prevention of cardiovascular disease during adulthood. The Student Health Checkup Guidebook of Senior & Junior High School and Elementary School of Taiwan (2020 Version, Ministry of Education, Republic of China (Taiwan)) requires the measure of BMI, blood pressure, spot urine examination, and other biochemical parameters (i.e., CBC, liver function, renal function, cholesterol, HBsAg, anti-HBs, urine routine) for school-aged children and adolescents. The nationwide regular health check-up for students can detect higher BMI, higher DBP and hypertension status in children and adolescents for further medical advice and treatment. The strategy of early intervention of obesity and hypertension in childhood and adolescence may reduce the incidence of atherosclerotic cardiovascular disease in later life.

Many studies have demonstrated that cardiovascular risk factors in children/adolescents are associated with the early stages of coronary atherosclerosis [4, 7, 26–28]. However, very few studies have investigated whether cardiovascular risk factors in childhood or adolescence have different impacts on development of subclinical atherosclerosis in young adults. In the subgroup analysis, we found that adolescence but not childhood cardiovascular risk factors could predict young adulthood subclinical atherosclerosis. The most important predictors were cholesterol, fasting plasma glucose, DBP, and BMI in both adolescents and young adults. However, most of the childhood cardiovascular risk factors were not significant determinants of subclinical atherosclerosis in adolescence. One previous study assessed CIMT in healthy children aged 1–15 years old, and showed that CIMT is constant in healthy children younger than 10 years, and then CIMT increases after the age of 10 years, independent of sex and BMI [40]. It implied that the progression of intimal thickening is not prominent before the age of 10 years, which may explain why cardiovascular risk factors in childhood during Period I are not associated with CIMT in adolescence during Period II in our study.

Another cross-sectional study also showed that CIMT was stable from childhood (age 6–11 years) into adolescence (age 12–18 years), and BMI in childhood was not associated with childhood CIMT. However, both BMI and CV risk score in ado-

lescence had small, but significant positive correlations with CIMT in adolescence [41]. These results were compatible with the findings in our subgroup analysis. However, small numbers of children (6–11 y/o, n = 105) were recruited in this cohort, which may not have enough power to predict thickened CIMT in adolescence according to the five cardiovascular risk factors in childhood. Further studies with larger cohorts are needed to validate whether cardiovascular risk factors in childhood or adolescence have different impacts on the development of subclinical atherosclerosis in young adults.

There were several limitations of this study. First, the recruited participants were positive for proteinuria or glycosuria during the urinary screening program in this study. Therefore, the identified risk factors for subclinical atherosclerosis in young adults may not be generalizable to all young populations. However, all current participants were relatively healthy in adulthood and exhibited similar characteristics to a similar age group in the general population in Taiwan [42]. Therefore, the results obtained in this study can still have a strong impact on policy making for early prevention of atherosclerotic heart disease since childhood. Second, because the longitudinal observational cohort study conducted from 1992 to 2000 only assessed anthropometric measures, fasting blood test for total cholesterol, albumin, blood urea nitrogen, serum creatinine, C3 complement, anti-streptolysin O, and blood pressure [14], we can only include total cholesterol, rather than LDL or non-HDL, as a covariate in the trajectory analysis. Third, because we did not measure uric acid levels in the longitudinal observational cohort study conducted from 1992 to 2000 [14], we did not include uric acid as a covariate in the trajectory analysis. The strength of this study is that the participants were recruited from a large population of school-aged children and adolescents in Taiwan during 1992–2000, and demonstrated the characteristics of a representative population for a long-term cohort study to investigate the risk factors during childhood and young adults to predict preclinical atherosclerosis in young adulthood.

In conclusion, exposure to cardiovascular risk factors in childhood, especially higher BMI, higher DBP, and hypertension, predicts the development of thickened CIMT (i.e. ≥ 75th percentile) during adulthood in the Taiwanese population. Therefore, these findings suggest that cardiovascular risk intervention during childhood/adolescence is effective for mitigating illness onset later in life.

Acknowledgments

We thank the third core laboratory of National Taiwan University Hospital for laboratory examination support.

Funding

This study was supported by grants from the National Health Research Institute of Taiwan (NHRI-EX97-9721PC, EX98-9721PC, EX99-9721PC, EX100-9721PC; NHRI-EX95-9531PI, EX96-9531PI, EX97-9531PI).

Ethical approval

Ethics approval for this study was obtained from the institutional review boards at National Taiwan University and China Medical University.

Conflict of interest

The authors declare no conflict of interest.

References

1. Reddy KS. Cardiovascular disease in non-Western countries. N Engl J Med 2004; 350: 2438-40.
2. He J, Gu D, Wu X, et al. Major causes of death among men and women in China. N Engl J Med 2005; 353: 1124-34.
3. Yusuf S, Reddy S, Ounpuu S, et al. Global burden of cardiovascular diseases: Part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. Circulation 2001; 104: 2855-64.
4. Raitakari OT, Juonala M, Kahonen M, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. JAMA 2003; 290: 2277-83.
5. Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking. A preliminary report from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. JAMA 1990; 264: 3018-24.
6. McGill HC Jr, McMahan CA, Herderick EE, et al. Effects of coronary heart disease risk factors on atherosclerosis of selected regions of the aorta and right coronary artery. PDAY Research Group. Pathobiological Determinants of Atherosclerosis in Youth. Arterioscler Thromb Vasc Biol 2000; 20: 836-45.
7. Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 1998; 338: 1650-6.
8. Simon A, Megnien JL, Levenson J. Detection of preclinical atherosclerosis may optimize the management of hypertension. Am J Hypertens 1997; 10: 813-24.
9. Zureik M, Ducimetiere P, Touboul PJ, et al. Common carotid intima-media thickness predicts occurrence of carotid atherosclerotic plaques: longitudinal results from the Aging Vascular Study (EVA) study. Arterioscler Thromb Vasc Biol 2000; 20: 1622-9.
10. Simon A, Gariepy J, Chironi G, et al. Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. J Hypertens 2002; 20: 159-69.
11. Atwa H, Gad K, Hagrasy H, et al. Is subclinical atherosclerosis associated with visceral fat and fatty liver in adolescents with type 1 diabetes? Arch Med Sci 2018; 14: 1355-60.
12. Li S, Chen W, Srinivasan SR, et al. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. JAMA 2003; 290: 2271-6.

13. Daniels SR, Arnett DK, Eckel RH, et al. Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment. Circulation 2005; 111: 1999-2012.
14. Liao CC, Su TC, Chien KL, et al. Elevated blood pressure, obesity, and hyperlipidemia. J Pediatr 2009; 155: 79-83.
15. Juonala M, Magnussen CG, Berenson GS, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N Engl J Med 2011; 365: 1876-85.
16. Must A, Jacques PF, Dallal GE, et al. Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. N Engl J Med 1992; 327: 1350-5.
17. Baker JL, Olsen LW, Sorensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. N Engl J Med 2007; 357: 2329-37.
18. Franks PW, Hanson RL, Knowler WC, et al. Childhood obesity, other cardiovascular risk factors, and premature death. N Engl J Med 2010; 362: 485-93.
19. Su TC, Liao CC, Chien KL, et al. An overweight or obese status in childhood predicts subclinical atherosclerosis and prehypertension/hypertension in young adults. J Atheroscler Thromb 2014; 21: 1170-82.
20. Tsai CW, Kuo CC, Wu CF, et al. Associations of renal vascular resistance with albuminuria in adolescents and young adults. Nephrol Dial Transplant 2011; 26: 3943-9.
21. Wei JN, Sung FC, Lin CC, et al. National surveillance for type 2 diabetes mellitus in Taiwanese children. JAMA 2003; 290: 1345-50.
22. Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: a working group report from the National High Blood Pressure Education Program. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. Pediatrics 1996; 98: 649-58.
23. Su TC, Jeng JS, Chien KL, et al. Hypertension status is the major determinant of carotid atherosclerosis: a community-based study in Taiwan. Stroke 2001; 32: 2265-71.
24. Su TC, Chien KL, Jeng JS, et al. Age- and gender-associated determinants of carotid intima-media thickness: a community-based study. J Atheroscler Thromb 2012; 19: 872-80.
25. Lin CY, Lin LY, Wen TW, et al. Association between levels of serum perfluorooctane sulfate and carotid artery intima-media thickness in adolescents and young adults. Int J Cardiol 2013; 168: 3309-16.
26. Newman W, 3rd, Freedman DS, Voors AW, et al. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis. The Bogalusa Heart Study. N Engl J Med 1986; 314: 138-44.
27. McGill HC Jr, McMahan CA, Malcom GT, et al. Effects of serum lipoproteins and smoking on atherosclerosis in young men and women. The PDAY Research Group. Pathobiological Determinants of Atherosclerosis in Youth. Arterioscler Thromb Vasc Biol 1997; 17: 95-106.
28. Urbina EM, Srinivasan SR, Tang R, et al. Impact of multiple coronary risk factors on the intima-media thickness of different segments of carotid artery in healthy young adults (The Bogalusa Heart Study). Am J Cardiol 2002; 90: 953-8.
29. Elkiran O, Yilmaz E, Koc M, et al. The association between intima media thickness, central obesity and diastolic blood pressure in obese and overweight children: a cross-sectional school-based study. Int J Cardiol 2013; 165: 528-32.
30. Singh AS, Mulder C, Twisk JW, et al. Tracking of childhood overweight into adulthood: a systematic review of the literature. Obes Rev 2008; 9: 474-88.
31. Shi Y, de Groh M, Morrison H. Increasing blood pressure and its associated factors in Canadian children and adolescents from the Canadian Health Measures Survey. BMC Public Health 2012; 12: 388.
32. Hou Y, Wang M, Yang L, et al. Weight status change from childhood to early adulthood and the risk of adult hypertension. J Hypertens 2019; 37: 1239-43.
33. Ghomari-Boukhatem H, Bouchouicha A, Mekki K, et al. Blood pressure, dyslipidemia and inflammatory factors are related to body mass index in scholar adolescents. Arch Med Sci 2017; 13: 46-52.
34. Shi X, Zhang K, Wang P, et al. Association of masked uncontrolled hypertension and cardiovascular diseases in treated hypertensive patients. Arch Med Sci 2020; 16: 538-44.
35. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13.
36. Juonala M, Viikari JS, Ronnemaa T, et al. Elevated blood pressure in adolescent boys predicts endothelial dysfunction: the cardiovascular risk in young Finns study. Hypertension 2006; 48: 424-30.
37. Juhola J, Magnussen CG, Berenson GS, et al. Combined effects of child and adult elevated blood pressure on subclinical atherosclerosis: the International Childhood Cardiovascular Cohort Consortium. Circulation 2013; 128: 217-24.
38. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. Circulation 2021; 143: e254-743.
39. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. Circulation 2008; 117: 3171-80.
40. Baroncini LA, Sylvestre Lde C, Pecoits Filho R. Assessment of intima-media thickness in healthy children aged 1 to 15 years. Arq Bras Cardiol 2016; 106: 327-32.
41. Gooty VD, Sinaiko AR, Ryder JR, et al. Association between carotid intima media thickness, age, and cardiovascular risk factors in children and adolescents. Metab Syndr Relat Disord 2018; 16: 122-6.
42. Su TC, Bai CH, Chang HY, et al. Evidence for improved control of hypertension in Taiwan: 1993-2002. J Hypertens 2008; 26: 600-6.