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Impact of Multiple Cardiovascular Risk Factors on the Carotid Intima-media Thickness in Young Adults: The Kangwha Study

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Objectives : Although risk factors for coronary artery disease are also associated with increased carotid intima-media thickness (IMT), there is little information available on the asymptomatic, young adult population. We examined the association between multiple cardiovascular risk factors and the common carotid IMT in 280 young Korean adults.

Methods : The data used for this study was obtained from 280 subjects (130 men and 150 women) aged 25 years who participated in the Kangwha Study follow-up examination in 2005. We measured cardiovascular risk factors, including anthropometrics, blood pressure, blood chemistry, carotid ultrasonography, and reviewed questionnaires on health behaviors. Risk factors were defined as values above the sex-specific 75th percentile of systolic blood pressure, body mass index, total cholesterol/high-density lipoprotein cholesterol ratio, fasting blood glucose and smoking status.

Results : The mean carotid IMT±standard deviation observed was 0.683±0.079 mm in men and 0.678±0.067 mm in women (p=0.567) and the evidence of plaque was not observed in any individuals. Mean carotid IMT increased with an increasing number of risk factors(p for trend <0.001) and carotid IMT values were 0.665 mm, 0.674 mm, 0.686 mm, 0.702 mm, and 0.748 mm for 0, 1, 2, 3, and 4 to 5 risk factors, respectively. The odds ratio for having the top quartile carotid IMT in men with 3 or more risk factors versus 0-2 risk factors was 5.09 (95% CI, 2.05-12.64).

Conclusions : Current findings indicate the need for prevention and control of cardiovascular risk factors in young adults and more focus on those with multiple cardiovascular risk factors.

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Key words : Young adult, Cardiovascular disease, Risk factors, Atherosclerosis, Carotid arteries, Ultrasonography

INTRODUCTION

The first clinical manifestation of cardiovascular disease often appears at an advanced stage of atherosclerosis [1] and the higher the coronary heart disease (CHD) mortality and morbidity rates are in a population, the more extensive a the lesions of atherosclerosis in autopsied persons [2]. However, arterial vessel wall changes occur during long subclinical lap phases characterized by endothelial dysfunction and gradual thickening of the intima.

Recent research on atherosclerosis has been mainly focused on identifying various markers of early atherosclerosis. IMT is a good marker of early atherosclerotic changes and its progression [3]. IMT measurement of large artery walls by B-mode ultrasound is relatively simple, safe, inexpensive, precise and reproducible. B-mode ultrasonography is increasingly being used noninvasively to measure the intima-media thickness of carotid and femoral arteries in epidemiologic and clinical studies [4].

IMT of the carotid artery is a sonographic parameter that may reflect the degree of atherosclerosis [5] and has been found to be increased in groups of patients with several cardiovascular risk factors [6]. It has been proven to be an independent risk factor for cardiac infarction and stroke [5,7-9]. There is a strong correlation between atherosclerosis of carotid arteries and coronary arteries and carotid IMT is a good predictor of the presence and extent of coronary artery disease [10]. A close relationship between IMT and a number of cardiovascular risk factors has been found. Traditional cardiovascular risk factors, such as being male, aging, overweight, elevated blood pressure, high blood cholesterol, diabetes and insulin resistance, and cigarette smoking are positively associated with carotid IMT in observational and epidemiological studies performed on patients at cardiovascular risk and among the general population [11,12].

Atherosclerosis occurring later in the common carotid segment than in the internal carotid or carotid bulb segment suggests variations in susceptibility to atherosclerosis among different segments of the carotid artery [1-3]. But the common carotid artery is

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examined more frequently than the internal carotid artery or the bulbus [13]. High quality scans of the common carotid artery, unlike the internal carotid artery and the carotid bulb, can be obtained from nearly every patient [14].

Fatty streaks begin to appear in the aorta before the age of 3 [15] and atherosclerotic lesions appear in other vascular beds early in adolescence [16]. Although the clinical manifestations of cardiovascular diseases occur during and after middle age, autopsy studies in adolescence have shown that cardiovascular risk factors are related to the early stages of coronary atherosclerosis [17,18].

Importantly, the risk of atherosclerosis is greatly increased by multiple factors [19]. Epidemiologic studies, such as the Framingham Study, have stressed the importance of the multivariate risk profile on the prediction and prevention of coronary artery disease [20]. We have noted that the information on the impact of multiple risk factors on the IMT of the carotid artery in young adults is found to be limited although risk factors for coronary artery disease in middle-aged and older persons are associated with increased carotid artery IMT as measured by B-mode ultrasonography. The present study investigated the association of IMT at the common carotid with multiple cardiovascular risk factors in young adults in the early stages of atherosclerosis.

Table 1. Characteristics of study participants by sex

	Total (N=280)	Men (N=130)	Women (N=150)	p value
Body mass index (kg/m²)	21.80± 3.04	22.75± 2.97	20.98± 2.87	<0.001
Waist circumference (cm)	82.59± 6.62	83.94± 6.40	81.42± 6.61	<0.001
Hip circumference (cm)	94.90± 5.85	96.47± 5.83	93.53± 5.54	<0.001
Waist-hip ratio	0.87± 0.04	0.87± 0.04	0.87± 0.05	0.900
Fat (%)	23.45± 6.79	19.42± 5.63	26.94± 5.70	<0.001
Systolic blood pressure (mmHg)	118.69±14.40	127.44±13.07	111.10±10.75	<0.001
Diastolic blood pressure (mmHg)	69.89± 8.40	73.07± 8.32	67.13± 7.46	<0.001
Pulse pressure (mmHg)	48.80± 9.87	54.37± 9.57	43.97± 7.24	<0.001
Total cholesterol (mg/dL)	163.75±27.68	168.07±28.98	160.00±26.01	0.015
HDL-cholesterol (mg/dL)	57.59±12.12	53.44±10.52	61.18±12.29	<0.001
Triglycerides (mg/dL)	90.48±56.58	113.93±64.34	70.15±38.90	<0.001
Fasting blood glucose (mg/dL)	84.95± 6.78	86.88± 7.01	83.27± 6.12	<0.001
Common carotid IMT (mm)	0.681±0.073	0.683±0.079	0.678±0.067	0.567
Cigarette smoking				
Yes	102 (36.4)	82 (63.1)	20 (13.3)	
No	178 (63.6)	48 (36.9)	130 (86.7)	<0.001
Alcohol intake				
Yes	241 (86.1)	122 (93.8)	119 (79.3)	
No	39 (13.9)	8 (6.2)	31 (20.7)	<0.001
Regular exercise				
Yes	75 (26.8)	39 (30.0)	36 (24.0)	
No	205 (73.2)	91 (70.0)	114 (76.0)	0.258

Values are Mean±SD or No.(%).
HDL, high-density lipoprotein; IMT, intima media thickness.

MATERIALS & METHODS

Ⅰ. Subjects

The 2005 study was conducted as a part of a community-based prospective cohort study called "the Kangwha Study" on hypertension and related factors, which started in 1986 in Kangwha County with 430 school children (6-year-old, 211 males, 219 females).

The number of Kangwha Study subjects increased three-fold and consists of 1,223 people (586 males, 637 females). The follow-up methods and study details are described in previous reports [21,22]. As of March 1, 2005, the study subjects were 25 years old. This report is an analysis of the follow-up cross-sectional examination of 280 participants (130 males and 150 females) in 2005.

To promote and conduct the 2005 follow-up survey, we used regular postal service, phone calls, and Web sites. The cover letter of the survey and the smoking and drinking habits questionnaire were first mailed to 784 out of 1,223 people, whose addresses had been confirmed from the previous study. For those who did not reply by mail or surveys that were returned due to a change of address, we contacted them by telephone and were able to obtain replies from 288 people. Because the subjects were young adults of 25 years of age, we contacted them through the Internet using "Cyworld(http://www.cyworld.com)", a South Korean web community site with 13 million members as of March 2005, and launched a "Kangwha Study Club" Web site. We have searched Cyworld members using the subject names and their birth dates and sent requests for them to join the club. Each subscriber was screened and confirmed as a study subject.

We measured cardiovascular risk factors, including anthropometrics, blood pressure, blood chemistry, carotid ultrasonography, and questionnaires on health behaviors. This follow-up study was conducted between April 23 - September 12, 2005, and total of 281 people participated (130 men, 151 women), among which a total of 280 (130 men, 150 women) with carotid IMT data were included in the analysis. One subject data was excluded from the analyses due to missing ultrasound data. Informed consent forms were obtained from each participant. The protocol was approved by the Institutional Review Board of Severance Hospital at the Yonsei University College of Medicine.

Ⅱ. General Examinations

After obtaining the informed consent forms, family history/health habits questionnaires, blood pressure, and anthropometric data were collected according to defined protocol. Subjects were asked to complete questionnaires regarding personal health, behavioral lifestyle (including tobacco and alcohol use), and family history. Blood pressure was measured on the right arm with the subject in a relaxed, sitting position. The average of two measurements with an automatic sphygmomanometer (Dinamap 1846 SX/P, USA) was used in all analyses. Pulse pressure is defined as the

Table 2. Distribution of carotid intima-media thickness (mm)

	Men (N=130)	Women (N=150)
5 th percentile	0.560	0.580
25 th percentile	0.640	0.625
50 th percentile	0.675	0.675
75 th percentile	0.730	0.720
95 th percentile	0.830	0.780
Mean ± SD	0.683 ± 0.079	0.678 ± 0.067

difference between systolic and diastolic pressure. Replicate measures of height to the nearest 0.1 cm and weight to the nearest 0.1 kg were made. Body mass index (BMI) in kg/m^2 was used as a measure of overall adiposity.

Ⅲ. Laboratory Analyses

Venipuncture was performed after an 8-hour fast. Blood glucose was measured based on a glucose oxidase method. Fasting serum concentrations of total cholesterol and triglycerides were measured using commercially available kits on a Hitachi 7600 Autoanalyzer (Hitachi Ltd. Tokyo, Japan). High-density lipoprotein cholesterol (HDL-C) was measured based on a direct enzymatic assay with accelerator selective detergent methodology.

Ⅳ. Measurement of Carotid Intima-media Thickness

The carotid arteries were evaluated by high-resolution B-mode ultrasonography using a 10 MHz probe (LOGI9, General Electric Medical Systems, USA). Both common carotid arteries were thoroughly scanned from proximal to distal to the bifurcation. Frozen photocopies of end-diastolic images taken from a longitudinal view showing the bifurcation were captured. All images were taken when the inner echoes of both near and far walls were clearly visible. Carotid IMT was measured at the far wall of both common carotid arteries about 1 cm proximal to the carotid bulb. The distance between the leading edge of first and second echogenic line was obtained using Intima Scope software (MediaCross, Tokyo, Japan). A plaque was defined as an area where the IMT was 1.5 mm [23]. The IMT of the common carotid artery was defined as the mean of the maximal IMT of each common carotid artery [24]. All measurements were taken by one examiner. The intraobserver coefficient of variation (CV) in our laboratory was 2.1%.

Ⅴ. Statistical Analyses

Partial Pearson correlation coefficients were used to assess the bivariate relation between IMT measures and risk factor variables. Unfavorable levels of blood cholesterol and blood pressure, cigarette smoking, overweight /obesity, and diabetes are well established as the major causal factors for CHD [25]. Obesity is associated with elevated blood pressure, blood lipids and blood glucose [26,27], and changes in body weight are coincident with changes in these risk factors for disease [28]. Thus we identified key variables that assess traditional cardiovascular risk factors: tobacco use, fasting plasma glucose, systolic blood pressure, total cholesterol/HDL-C ratio, and body mass index. Risk factors were defined as values above the sex-specific 75th percentile of systolic blood pressure, BMI, total cholesterol/ HDL-C ratio, and fasting blood glucose along with smoking status. The top quartile systolic blood pressure in men and women was 137.5 mmHg and 117.5 mmHg. The top quartile BMI in men and women was 25.03 kg/m^2 and 22.21 kg/m^2. The top quartile total cholesterol/ HDL-C ratio in men and women was 3.66 mg/dL and 2.98 mg/dL. The top quartile fasting blood glucose in men and women was 91.0 mg/dL and 87.0 mg/dL. The ratio of total cholesterol to HDL-C was used as a measure of dyslipidemia for coronary artery disease risk and to reflect the balance between atherogenic and antiatherogenic lipoproteins [29]. The association between multiple risk factors and high quartile carotid IMT risk were estimated with the OR and 95% CI using logistic regression. The effect of multiple risk factors on IMT of common carotid artery was examined by comparing the mean IMT values of individuals with 0, 1, 2, 3, and 4 more risk factors.

RESULTS

Ⅰ. Characteristics of Study Participants

The characteristics of the 280 study participants are given in Table 1. BMI, waist circumference, systolic blood pressure, diastolic blood pressure, pulse pressure, fasting plasma glucose, total cholesterol, triglycerides were higher, and HDL-C level was lower among men versus women ($p<0.05$). Smokers were defined as people who have smoked more than 100 cigarettes in their lifetime. Fewer women smoked than men (13.3 % vs. 63.3 %), respectively. Past alcohol use was reported by 93.8 % of men compared to 79.3 % of women. In addition, 30 % of men and 24 % of women reported to exercise regularly and there was no sex difference ($p=0.258$).

The mean carotid IMT ± SD observed was 0.683 ± 0.079 mm in men and 0.678 ± 0.067 mm in women, and there was no sex difference for carotid IMT, respectively, ($p=0.567$). Mean and selected percentiles of carotid IMT by sex are listed in Table 2. The top quartile carotid IMT in men was 0.730 mm and 0.720 mm in women. Plaque was not observed in any of the individuals.

Ⅱ. Carotid IMT Relation to Cardiovascular Risk Factors

Partial correlations between cardiovascular risk variables and carotid IMT are listed in Table 3. In men, carotid IMT was significantly and positively associated with BMI, waist circumference, hip circumference, systolic blood pressure, pulse pressure, and total cholesterol/HDL-C ratio, but in women, carotid IMT was positively associated with pulse pressure only. The magnitude of correlation was relatively higher between pulse pressure and carotid IMT. HDL-C was negatively correlated with the carotid IMT, but it was not significant.

Table 3. Correlation between carotid intima-media thickness and cardiovascular risk factors

	Total (N=280)		Men (N=130)		Women (N=150)	
	Coefficient	p value	Coefficient	p value	Coefficient	p value
Body mass index (kg/m²)	0.202	0.001	0.305	0.001	0.091	0.266
Waist circumference (cm)	0.197	0.001	0.246	0.005	0.144	0.078
Hip circumference (cm)	0.193	0.001	0.251	0.004	0.127	0.121
Waist-hip ratio	0.071	0.238	0.080	0.367	0.068	0.410
Fat (%)	-0.046	0.448	-0.094	0.290	0.030	0.718
Systolic blood pressurere (mmHg)	0.183	0.002	0.251	0.004	0.138	0.100
Diastolic blood pressure (mmHg)	0.071	0.239	0.083	0.345	0.039	0.648
Pulse pressure (mmHg)	0.208	0.001	0.271	0.002	0.160	0.050
Total cholesterol (mg/dL)	0.121	0.043	0.134	0.129	0.099	0.230
HDL chlolesterol (mg/dL)	-0.069	0.247	-0.141	0.111	0.005	0.949
Triglycerides (mg/dL)	0.113	0.059	0.128	0.148	0.079	0.336
Total/HDL-C* ratio	0.163	0.006	0.227	0.010	0.069	0.401
Fasting blood glucose (mg/dL)	0.086	0.152	0.060	0.499	0.102	0.213
Cigarette smoking	0.102	0.087	0.115	0.192	0.077	0.352

HDL-C*, high-density lipoprotein cholesterol.

Table 4. Odds ratio for high carotid Intima-media thickness* according to number of cardiovascular risk factors

Number of risk factors	Men (N=130)		Women (N=150)	
	N	OR (95% CI)	N	OR (95% CI)
0	21	1.00	54	1.00
1	51	1.77 (0.34-9.11)	48	1.49 (0.56- 3.97)
2	31	3.30 (0.63-17.44)	33	1.88 (0.66- 5.35)
3	15	8.31 (1.41-49.03)	13	2.22 (0.56- 8.82)
4~5	12	13.29 (2.08-84.92)	2	5.00 (0.29-87.55)
3~5 vs 0~2		5.09 (2.05-12.64)		1.83 (0.58- 5.77)
per one risk factor increase		1.92 (1.36- 2.70)		1.35 (0.94- 1.95)

* High carotid IMT ≥ 75 th percentile.
CI, confidence interval.

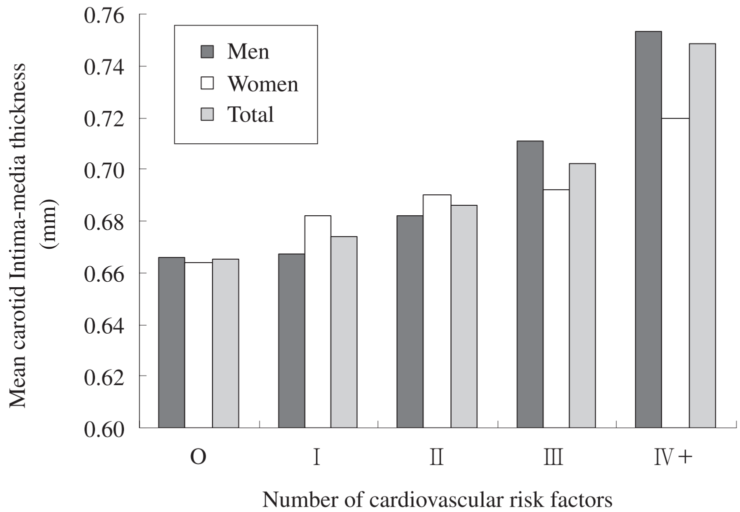

Figure 1. Mean carotid intima-media thickness according to number of cardiovascular risk factors.

Ⅲ. Carotid IMT Relation to Multiple Risk Factors

Risk factors included were systolic blood pressure, BMI, total cholesterol/HDL-C ratio, smoking status, and fasting blood glucose (≥ 75th percentile specific for sex). Analyses of joint effects of risk factors as in Table 4 showed that compared to the reference group with no exposure to any of the aforementioned risk factors, in men with 1, 2, 3, and 4 or more of the risk factors, the ORs of high quartile carotid IMT were 1.77, 3.30, 8.31, and 13.29 respectively. The finding supports the view that multiple risk factors have a synergistic effect on the risk for CVD as has been demonstrated by others [19,20].

Mean carotid IMT values were 0.665 mm, 0.674 mm, 0.686 mm, 0.702 mm, and 0.748 mm for 0, 1, 2, 3, and 4 to 5 risk factors. Adding a term for interaction between IMT and sex to the above model did not result in significant effect in any of the models (p>0.8). The mean carotid IMT data for subjects with different numbers of risk factors (0, 1, 2, 3, and 4≥) are shown in Figure 1. A significant trend of increasing thickness is shown with greater numbers of risk factors in both men (p for trend <0.001)(Figure 1) and women (p for trend =0.036)(Figure 1). The mean carotid IMT increased significantly with greater numbers of risk factors in all the subjects (p for trend <0.001)(Figure 1).

DISCUSSION

Ⅰ. Carotid IMT Relation to Multiple Risk Factors in Young Adults

The present study shows an adverse impact of multiple cardiovascular risk factors on carotid IMT in an asymptomatic, healthy population of young adults. Furthermore, another recent study using electron beam computed tomography showed an association between coronary calcification, an indicator of coronary atherosclerosis, and cardiovascular risk factors in young adults [30]. The noninvasive ultrasonographic evaluation of carotid IMT in this study expands earlier autopsy findings from the Bogalusha Heart Study and the Pathobiological Determinants of Atherosclerosis in Youth Study, showing a strong relationship between early phases of atherosclerosis and cardiovascular risk factors in young adults [18,19]. Also, current findings signify the need for prevention and control of cardiovascular risk factors in young patients. Although carotid ultrasonographic examination may not be recommended in routine mass screenings of the general population, the assessment of carotid IMT may assist in characterizing the extent of atherosclerosis in young individuals with multiple cardiovascular risk factors.

Ⅱ. Carotid IMT Related Factors

In general, the topographic findings seem to indicate the following sequence of development: the atherosclerotic process starts at the bifurcation and in the sinus region and from there progresses proximally along the common carotid artery and distally to the proximal portions of the internal carotid artery [27]. The atherosclerotic changes, as measured by ultrasonography, have been reported to be more advanced in the femoral artery than in the carotid artery. The examination of both arterial segments may provide more accurate information on the extent of atherosclerosis [31]. Although the carotid bulb IMT is associated more closely with coronary artery disease than the common carotid IMT [32], the common carotid artery is examined more frequently than the internal carotid artery and the bulbus [13]. The magnitude of associations of risk factors with carotid IMT and carotid bulb IMT were also similar [32] and high quality scans of common carotid artery can be obtained from nearly every patient in contrast to those of the internal carotid artery and the carotid bulb [14]. We restricted the measurement of IMT to common carotid to examine the impact of multiple risk factors for its greater reproducibility of measurements from this site and because it is more difficult to obtain measurements from bifurcation or from the internal carotid artery in some populations [14].

The mean carotid IMT observed in this study was 0.683 mm in men and 0.678 mm in women (p=0.567). In a sample of 518 black and white subjects (mean age 32 years) enrolled in the Bogalusa Heart Study, the mean carotid IMT observed in white men and white women was 0.67 mm (N=137) and 0.65 mm (N=220), respectively (p=0.001). In the Bogalusa Heart Study, trained sonographers performed ultrasound examinations with a Toshiba Sonolayer SSH160A, a 7.5-MHz linear array transducer on subjects [32]. In 2,264 white adults from eastern Finland aged 24 to 39 years, the mean carotid IMT observed in men and women was 0.601 mm and 0.583 mm, respectively. In the Young Finns Study, ultrasound experiments were performed using Sequoia512 ultrasound mainframes (Acuson) [33]. The mean carotid IMT values with respect to age in men and women were 0.57 mm vs. 0.57 mm in those aged 30 to 39, respectively in the Korean population [34]. A comparison of carotid IMT in the population of this study to those of major American and European studies indicates that there is not much difference between the carotid IMT of Korean and white young adults even though there are several differences in the study procedures and conditions.

In the Bogalusa Heart Study, systolic blood pressure was found to be the major contributor to the explained variance of common carotid IMT followed by race (black more than white), age, LDL cholesterol, and an inverse association of HDL-C in that order [32]. In the Tromso Study, age, blood pressure, total cholesterol, HDL-C and BMI were independent long-term predictors of IMT in elderly men and women. Triglyceride levels were associated with an increase in IMT in women only while physical activity and smoking were predictors on IMT in men [32]. Several population-based studies have found cross-sectional associations between IMT and unfavorable levels of systolic blood pressure, total cholesterol, HDL-C, BMI, age and smoking [34,35]. An inconsistent relation of carotid IMT to triglycerides, fasting blood glucose and sex has been reported in these cross-sectional studies [33-36].

In the present study, no risk factors were independently associated with an increase in carotid IMT of both men and women when we included systolic blood pressure, BMI, total cholesterol/HDL-C ratio, glucose and smoking status in the multiple linear regression model (data not shown). This study has a relatively small sample size and thus may not have sufficient credibility to detect a meaningful, independent association between single cardiovascular risk factor and mean carotid IMT. In a study from the Atherosclerosis Risk in Communities (ARIC) cohort of 2,073 subjects aged 31 to 52 years at baseline, active smoking was associated with increased IMT 12 to 14 years later [37]. Thus the lack of association of carotid IMT with smoking status may be due to the lack of sufficient years of exposure and a misclassification of smoking status.

The weaker relation of carotid IMT and multiple risk factors in women than in men is clear-cut (Table 4) and raises questions about the nature of its mechanism. The involvement of female sex hormones in the relative protection from cardiovascular disease may play a role [38].

Ⅲ. Limitations of the Study

Several aspects of the present study need to be addressed. First, carotid IMT measured by B-mode ultrasonography can not be unequivocally attributed to local atherosclerosis because this technique cannot distinguish between the incipient atherosclerotic transformation of the arterial wall and other forms of medial thickening, such as hyperplasia or hypertrophy [39]. However, an increased carotid IMT has been shown to relate to atherosclerosis elsewhere in the arterial system, suggesting that an increased carotid IMT reflects generalized atherosclerosis [40]. Second, as the relation between subclinical atherosclerosis and cardiovascular risk factors was studied cross-sectionally, it does not allow determinations of temporal relationships, such as changes in cardiovascular risk profile and carotid IMT. Our findings should therefore be confirmed in longitudinal studies with repeated measurements of carotid IMT. Third, this study has a relatively small sample size and may not have sufficient credibility to detect some meaningful, independent association. Dyslipidemia, high blood pressure, obesity, and fasting blood glucose are metabolically linked

[26,27]. Additional studies were needed to examine the association between metabolic syndrome and IMT in early life. Differences in age distribution in the study samples, sample sizes, and different methods in assessment of smoking status and IMT measurements may contribute to the inconsistent findings. It is necessary to compare different study samples, sample sizes, and IMT measurement methods. Finally, because of the biological variation in the risk factor variables between subjects, the single measurement available for each subject in this study will reflect long-term average less precisely than multiple measurements.

We found that carotid IMT in asymptomatic healthy young adults is associated with traditional cardiovascular risk factors. The observed deleterious trend of increasing carotid IMT with an increasing number of risk factors in asymptomatic young adults underlines the importance of profiling multiple risk factors in early life. Current findings indicate the need for prevention and control of cardiovascular risk factors in young adults and focus on multiple cardiovascular risk factors rather than a specific risk factor. To reduce the future burden of CHD, we need to define prevention and intervention strategies early in life that decrease the prevalence of cardiovascular risk factors in children and young adults. Major gains will likely accrue from public health strategies targeting overweight, exercise and cigarette smoking. Individualized atheroprotective strategies in childhood will initially focus on the highest risk children with such factors as dyslipidemia, diabetes mellitus, hypertension and obesity. Although carotid ultrasonographic examination may not be recommended in routine mass screening for the general population, it may be valuable in selected high-risk populations.

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