Original Article

Associations of Cardiovascular Risk Factors with Carotid Intima-Media Thickness in Middle-Age Adults and Elders

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Aims: Elevated carotid intima-media thickness (cIMT) is a preclinical phenotype of atherosclerotic diseases. There are significant sex differences in the morbidities of cardiovascular diseases and their major determinants, and we explored the sex-specific effects of cardiovascular factors on cIMT by a community-based study.

Methods: We measured the cIMT and cardiovascular profiles of 1579 residents aged $40-74$ years in northern Taiwan. Multivariate regression analyses were used to assess the effects and contributions of these factors on cIMT.

Results: Males had significantly higher mean ($\pm$ SD) of cIMT than females (0.668 ± 0.113 vs. 0.632 ± 0.100 nm, $p < 0.0001$). The common factors of the best-fit regression models in both sexes were age, BMI, and LDL-/HDL-C ratio; however, their contributions and effects were different. The partial coefficients of determination (r^2) were 17.9, 5.8, and 4.1%, respectively, for males and were 27.8, 1.4, and 1.2%, respectively, for females. Test statistics showed that the regression coefficients of BMI and LDL-/HDL-C ratio of males were significantly higher than those of females. As compared with females, per 1.0 SD increases of BMI and LDL-/HDL-C in males resulted in 0.0971 ($p = 0.030$) and 0.1177 ($p = 0.0087$), respectively, SD increases in cIMT. There was no difference in the means of cIMT between pre- and post-menopausal women of the same age groups.

Conclusions: There was a significant sex difference in cIMT. The contributions and effects of LDL-/HDL-C ratio and BMI on cIMT were more profound in males. Our findings indicate that sex-specific factors, but possibly not menstrual status-related factors, contribute to thicker cIMT.

> **See editorial vol. 24: 673-674**

Introduction

The structure of blood vessels largely affects the function of them. Many parameters have been tested for their abilities to detect change in blood vessel structure and to predict risk of cardiovascular diseases (CVD)[1]. The carotid wall thickness, which can be detected non-invasively using B-mode carotid ultrasound, is wildly accepted as a valid indicator of vascular aging[2]. It was significantly correlated with risks of myocardial infarction and stroke[3, 4]. Recently, the measurement of carotid intima-media thickness (cIMT) was considered as reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk[5].

CVD are highly prevalent in developed countries and are emerging as one of the major burden of diseases in developing countries[6]. It had been estimated that cardiovascular and circulatory diseases accounted for 12% of the global disability-adjusted life years in 2010[6]. Several traditional modifiable cardiovascular risk factors, including obesity, high blood pressure,

high blood sugar, dyslipidemia, and cigarette smoking, had been correlated with elevated cIMT by population-based studies[7, 8]. It is anticipated that reducing the morbidities of determinants of cIMT can produce significant impacts on global health.

To achieve more extensive control on CVD, it is essential to formulate preventive programs being targeted on subpopulations of different attributes. There were significant age, sex, and ethnic variations in the means of cIMT[8, 9] and the morbidities of cardiovascular risk factors[9, 10]. However, only a few studies demonstrated the sex-specific relationships for cardiovascular risk factors with cIMT. We therefore conducted this community-based study to investigate whether there were sex differences in the effects and contributions of cardiovascular risk factors on cIMT.

Methods

The study subjects were from a community-based cohort enrolled by the Mitochondria-Aging in Northern Taiwan (MAGNET) study[10]. During September 2010 and May 2012, 1607 residents aged 40-to-74 years voluntarily provided informed consent and were enrolled[10]. One male had no blood pressure reading and another 10 males and 17 females were excluded due to the lack of good quality of recorded carotid ultrasound imaging, leaving 635 males and 944 females in the cIMT association study. The study complied with the 1975 Helsinki Declaration on ethics in medical research and was reviewed and approved by the Institution Review Board of Mackay Medicine College (No. P990001).

All participants received standardized questionnaire interviews and anthropometric and laboratory measurements. Body weight and height were measured by a digital system (BW-2200; NAGATA Scale Co. Ltd., Tainan, Taiwan). Waist circumference (WC) was measured at the level of mid-distance between the bottom of the rib cage and the top of the iliac crest. Body mass index (BMI) was calculated as (body weight)/(body height)^2 (kg/m^2). Body shape index (BSI) were calculated as $WC/(BMI^{2/3} \times body\ height^{1/2})$ (m$^{11/6} \times$ kg$^{-2/3}$)[11]. Blood pressure was measured three times by a digital system (UDEX-Twin; ELK Co., Daejon, Korea) in the morning after 10 min of rest. The averages of three measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were used for analyses.

Venous blood samples were collected after ≧8 hours of fasting for cardiovascular profile analyses. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting triglycerides (FTG), fasting plasma glucose (FPG), HbA1c, and uric acid (UA) were determined by an autoanalyzer (Toshiba TBA c16000; Toshiba Medical System, Holliston, MA, USA) with commercial kits (Denka Seiken, Tokyo, Japan). Fasting insulin level was determined by a chemiluminescence immunoassay with commercial kit (IMMULITE 2000 Insulin; Siemens Healthcare Global, Erlangen, Germany). The atherogenic index of plasma (AIP) was calculated as $\log_{10}$ (FTG/LDL-C)[12] and the homeostasis model assessment (HOMA) index was calculated as fasting insulin × FPG/405[13].

In this study, hypertension was defined as SBP ≧140 mmHg, DBP ≧90 mmHg, or a history of taking antihypertensive medications. Diabetes mellitus (DM) was defined as FPG ≧126 mg/dL or the use of insulin or other hypoglycemic agents. Subjects who had ever been diagnosed with coronary artery diseases by physicians were regarded as positive history of CVD. Metabolic syndrome (MetS) was defined as the NCEP-ATP Ⅲ and with the modification of WC cutoff points for Asians[14]. The components include central obesity (WC, >90 cm in male or >80 cm in female); high blood pressure (SBP ≧130 mmHg, DBP ≧85 mmHg, or self-reported treatment with antihypertensive medications); high blood sugar (FPG ≧100 mg/dl, or the use of insulin or other hypoglycemic agents); low HDL-C level (<40 mg/100 ml in male or <50 mg/100 ml in female); high FTG level (≧150 mg/100 ml). Participants with ≧3 of these 5 components were defined as having MetS. The 10-year general CVD risks of each subject were calculated by using the multivariable risk function proposed by D'Agostino *et al.*[15].

The cIMT were measured with high-resolution B-mode ultrasonography systems (GE Healthcare Vivid 7 and Vivid E9; General Electric Company, Milwaukee, USA), equipped with a multi-frequency linear array transducer. The ultrasonographic systems were operated by two experienced technicians, who were blind to patients' clinical characteristics. Both left and right common carotid arteries (CCA) images were obtained and digitally stored according to the protocol recommended by the American Society of Echocardiography[16]. The IMT was defined as the distance between the lumen-intima and media-adventitia interfaces and included plaques. A well-trained technician measured the far-wall IMTs blindly by using automatic contouring software (GE Healthcare EchoPAC version 112.0.2; General Electric-Vingmed, Horten, Norway). The average, minimum, and maximum IMTs of the distal 1-to-2 cm of the left and right CCA were recorded. Mean cIMT was calculated as the mean of the left and right average IMTs and was used for correlation and regression analyses. In the study, plaque,

which was defined as a focal protrusion 50% greater than the surrounding area, was included in the IMT measurements.

To evaluate the repeatability, a sample of 82 subjects was randomly selected one month after the first measurement and re-measured blindly. The intra-class correlation coefficient r of two measurements were 0.974, 0.981 and 0.979 for left, right and mean, respectively, far-wall mean cIMTs. The mean (standard deviation [SD]) differences of two measurements were 0.0050 (0.0052), 0.0091 (0.0056) and 0.0070 (0.0046) mm for left, right and mean, respectively, far-wall cIMTs.

In the study, we used the student's t and the chi-square test to compare whether there were significant differences in the cardiovascular measurements between males and females. For continuous cardiovascular measurements with distributions skewed to the right, log-transformed were performed before correlation and regression analyses. Linear trends with cIMT for cardiovascular measurements were demonstrated by Pearson's product-moment correlation coefficients (r). Factors significantly correlated with cIMT were subjected to multivariate linear regression with backward selection method. The criteria of stay at the regression model was $p < 0.05$. The contributions of potential predictors were manifested by the partial coefficients of determination (r^2). The best fit model for cIMT was defined as which contains the smallest number of significant factors but with the largest model r^2. To test the significance of interaction terms and to reduce the influences of sex differences in continuous measurements, we transformed, separately by sex, these measurements into standardized Z deviates before performing generalized linear model analyses. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

In the study, males had significantly higher means of all, except for age, LDL-C, HbA1c, insulin, and HOMA, anthropological and cardiovascular measurements and 10-year general CVD risks than females (**Table 1**). The cIMTs of males were significantly thicker than those of females. The mean (SD) of far-wall IMTs of the left and right CCA of males were 0.658 (0.124) and 0.677 (0.130) mm, respectively. The corresponding figures for female subjects were 0.626 (0.116) and 0.637 (0.110) mm, respectively.

Males had significantly higher prevalence rates of CCA plaque, cigarette smoking, alcohol drinking, DM, hypertension, and CVD (**Table 1**). The prevalence rates of MetS were non-significantly different between males and females.

Table 2 shows that subjects affected with MetS, DM, and hypertension had significantly thicker cIMTs than unaffected subjects. The presences of CCA plaque were also correlated with thicker cIMTs. Male CVD patients had significantly thicker cIMTs than unaffected subjects, yet mean of cIMTs of female patients was not different from that of unaffected subjects. In males, there was no difference in the mean of cIMT among different groups of cigarette smoking and alcohol drinking. In females, current smokers had significantly thinner cIMT than abstainers. Female smokers were younger than ex-smokers and abstainers (45.9 ± 4.9, 50.0 ± 8.3, and 53.0 ± 8.6 years, respectively; $p < 0.0001$). There was no difference in the means of cIMT after age adjustment.

There were significant associations between cIMT and predicted CVD risks in both sexes (both $r > 0.50$; $p < 0.0001$; **Table 3**). Among all anthropological and clinical characteristics, age was the strongest correlate for cIMT in both sexes. After adjustment for age, all measurements were positively correlated with cIMT except body height, BSI, and HDL-C. In both sexes, HDL-C levels were inversely correlated with cIMTs. In males, LDL-/HDL-C ratio and BMI, followed by total-/HDL-C ratio, WC, LDL-C, and body weight showed stronger linear trends with cIMTs. In females, SBP and LDL-/HDL-C ratio were the top two strongest predictors.

All continuous or categorical variables significantly correlated with cIMT were subjected to multivariate regression analyses. The results showed that approximately 31% of the variability of mean cIMT in males can be explained by the best fit regression model (**Table 4**). Age was the strongest predictor of cIMT (partial $r^2 = 17.9\%$, $p < 0.0001$). Replaced LDL-/HDL-C ratio with total cholesterol alone, total-/HDL-C ratio alone, LDL-C alone, HDL-C alone, or LDL- and HDL-C resulted in lower r^2 (0.282, 0.293, 0.302, 0.274, and 0.307, respectively). Among females, age alone accounted for 28% of the total variability of mean cIMT. The inclusions of SBP, LDL-/HDL-C ratio, and BMI to the regression analyses resulted in significant model improvement. The r^2 for models that replaced LDL-/HDL-C ratio with total cholesterol alone, total-/HDL-C ratio alone, LDL-C alone, HDL-C alone, or LDL- and HDL-C varied slightly (r^2: 0.312, 0.317, 0.315, 0.312, and 0.317, respectively) and the regression coefficients of HDL-C were non-significant.

Table 4 shows that the common predictors of the best fit models in both sexes were age, BMI and LDL-/HDL-C ratio. The male-to-female ratios of the regression coefficients were 0.86, 2.66, and 2.10, respectively, indicating that there might be interac-

Table 1. Baseline characteristics of the study subjects

Continuous variables	Males (n=635)		Females (n=944)		*p*-value
	Mean	SD	Mean	SD	
Age at enrollment (years)	53.5	9.5	52.6	8.6	0.065
Body height (cm)	166.9	6.4	156.3	5.5	<0.0001
Body weight (kg)	70.2	10.2	59.0	9.8	<0.0001
BMI (kg/m²)	25.2	3.2	24.2	3.7	<0.0001
Hip circumference (cm)	95.5	6.0	94.6	8.4	0.017
Waist circumference (cm)	85.7	8.0	77.7	9.2	<0.0001
Waist-to-hip ratio (%)	89.6	5.2	82.0	6.4	<0.0001
Body shape index ($m^{11/6} \times kg^{-2/3}$)	0.077	0.004	0.075	0.005	<0.0001
SBP (mm Hg)	130.3	18.5	125.7	19.9	<0.0001
DBP (mm Hg)	81.4	13.5	77.4	13.3	<0.0001
Total cholesterol (mg/dL)	204.4	38.0	209.9	36.7	0.0053
HDL-C (mg/dL)	50.0	13.1	60.7	15.3	<0.0001
LDL-C (mg/dL)	124.9	33.8	123.1	32.7	0.27
LDL-/HDL-C ratio	2.66	0.96	2.17	0.81	<0.0001
Total-/HDL-C ratio	4.32	1.21	3.64	0.99	<0.0001
FTG (mg/dL)	135.2	111.9	101.9	66.9	<0.0001
FPG (mg/dL)	101.2	28.2	97.7	24.9	0.010
HbA1c (%)	5.38	0.99	5.77	0.74	0.14
Insulin (mIU/L)	6.98	5.10	7.60	6.88	0.065
HOMA index	1.79	1.72	1.89	2.09	0.37
Log (FTG/LDL-C)	0.36	0.32	0.17	0.31	<0.0001
Uric acid (mg/dL)	6.28	1.33	4.82	1.12	<0.0001
Number of metabolic components	1.74	1.31	1.52	1.33	0.0014
10-years CVD risk (%)	17.7	13.9	7.1	6.5	<0.0001
Far-wall CCA IMT (mm)					
Right	0.658	0.124	0.626	0.116	<0.0001
Left	0.677	0.130	0.637	0.110	<0.0001
Mean	0.668	0.113	0.632	0.100	<0.0001
Dichotomous variables	n	%	n	%	
CCA plaque	78	12.3	40	4.2	<0.0001
Metabolic syndrome	178	28.0	225	23.8	0.061
Diabetes mellitus	69	10.9	72	7.6	0.028
Hypertension	285	44.9	316	33.5	<0.0001
History of CVD	25	3.9	15	1.6	0.0036
Cigarette smoking	303	48.0	72	7.6	<0.0001
Alcohol drinking	170	26.8	61	6.5	<0.0001

Note: BMI, body mass index; CCA, common carotid artery; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FTG, fasting triglycerides; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

tions for sex with BMI and LDL-/HDL-C ratio on cIMT. Because there were sex differences in the means of most continuous measurements, sex-specific Z deviates but not their absolute values were used for generalized linear model analyses. As compared with females, per 1.0 SD increases of BMI and LDL-/HDL-C ratio in males resulted in additional 0.0971 (SE=0.0448; *p*=0.030) and 0.1177 (SE=0.0448; *p*= 0.0087), respectively, SD increases in cIMT (**Table 5**). Replacing LDL-/HDL-C ratio with other blood lipid indicators, we found the interaction between sex and LDL-C was statistically significant. There was no significant interaction between sex and total cholesterol, HDL-C, and total-/HDL-C ratio.

When we restricted analyses to 1461 CCA plaque-free subjects, per 1.0 SD increases of BMI and LDL-/

Table 2. Comparisons of means of far-wall mean CCA IMT

	Males				Females			
	n	Mean	SD	p-value	n	Mean	SD	p-value
CCA plaque				<0.0001				<0.0001
No	557	0.653	0.103		904	0.625	0.091	
Yes	78	0.771	0.124		40	0.784	0.160	
Metabolic syndrome				<0.0001				<0.0001
No	457	0.653	0.103		719	0.619	0.094	
Yes	178	0.705	0.127		225	0.672	0.109	
Diabetes mellitus				<0.0001				<0.0001
No	566	0.661	0.110		872	0.691	0.097	
Yes								
Newly diagnosed	31	0.699	0.124		25	0.654	0.091	
Previously diagnosed	38	0.738	0.115		47	0.712	0.130	
Hypertension				<0.0001				<0.0001
No	350	0.641	0.103		628	0.611	0.090	
Yes								
Newly diagnosed	132	0.688	0.114		172	0.664	0.096	
Previously diagnosed	153	0.711	0.117		144	0.682	0.118	
History of CVD				<0.0001				0.81
No	610	0.664	0.111		929	0.632	0.101	
Yes	25	0.753	0.136		15	0.638	0.078	
Cigarette smoking				0.31				0.0023
Never	328	0.661	0.108		865	0.634	0.101	
Ex-smokers	121	0.669	0.117		24	0.625	0.113	
Current smokers	182	0.677	0.119		48	0.583	0.064	
Alcohol drinking				0.55				0.39
Never	464	0.668	0.116		875	0.630	0.100	
Ex-drinkers	97	0.674	0.090		39	0.639	0.106	
Current drinkers	73	0.655	0.118		22	0.658	0.097	

HDL-C ratio in males resulted in additional 0.0968 (SE=0.0436; $p=0.027$) and 0.1064 (SE=0.0437; $p=0.015$), respectively, SD increase in cIMT. For further exclusion subjects who were affected with CVD, DM, and hypertension, the corresponding regression coefficients changed slightly (0.0935 and 0.1385, respectively).

In the study, all females had provided information associated menopausal status (pre-menopausal, $n=386$; post-menopausal, $n=486$; irregular menstrual cycles, $n=72$). However, menopausal status was nearly perfectly correlated with subject's age. 94% of females aged 51-to-74 years were post-menopausal; in contrast, 98% of females aged 40-to-46 years had regular menstrual cycles. Due to the significant age effects on menopausal status and cIMT, it would be impossible to assess the effect of menopausal status on cIMT when all females were included. Consequently, we focused on individuals aged 47-to-50 years. In the age subgroup, there were 86 males, 43 post-menopausal and 87 pre-menopausal females. The means (SD) of

multivariate-adjusted cIMT were 0.637 (0.030), 0.616 (0.031), and 0.617 (0.029), respectively. The adjusted cIMT of males was significantly thicker than those of females and was not different between pre- and post-menopausal women.

Discussions

Measurement of cIMT had been considered as reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk. It is also well-known that sex differences exist in the morbidities of cardiovascular risk factors as well as CVDs. However, only a few studies reported the sex-specific relationships of cardiovascular risk factors with cIMTs. In the community-based study, we measured cIMTs and cardiovascular profiles of 1579 middle-age adults and elders and systematically assessed the modification effects of sex. We confirmed that cIMTs were significantly correlated with predicted CVD risks and all tra-

ditional cardiovascular risk factors in both sexes. Moreover, multivariate analyses showed that age, BMI, and LDL-C/HDL-C ratio were the common predictors of cIMT in both sexes; nonetheless, their contributions and effects on cIMT showed significant sex differences.

The determinants of cIMT have been reported by several population-based studies[17-24]. However, most studies treated sex as a regressor or correlate that needs to be controlled for and only a few of them showed the sex-specific relationships of cardiovascular risk factors with cIMT. To our knowledge, only a recent work of multicenter study had assessed the modification effects of sex. Engelen *et al.* (2013) combined data from 18, 3, 2, and 1 centers from Europe, north America, south America, and Asia, respectively, and reported that the effects of BMI on cIMT were more profound in males than in females in two subpopulations. They found the effects of total-/HDL-C ratio were similar between two sexes[17]. However, only pooled estimates were shown by the study, since it was not sure that these findings held for different ethnic populations. In the present study, we observed similar results. Additionally, we first revealed that the effects of LDL-/HDL-C ratio or LDL-C on cIMT were stronger in males than in females. These findings indicate that the blood vessels of males are more susceptible to damage resulting from LDL-C or there are factors in males that tend to transform LDL-C to more pathogenic forms. The underlining mechanisms deserve further explorations.

The findings of population studies, which demonstrated the sex-specific relationships of cardiovascular risk factors with cIMT, were inconsistent[17, 19-24]. All reports including ours have indicated that age is the most consistent and strongest determinant. Hypertension, LDL-C, cigarette smoking[19, 20], hypertriglyceridemia[19], low HDL-C[20], BMI[17, 20, 21], and SBP[17, 21, 23], were the common factors in both sexes. Factors reported to associate with males only were impaired glucose tolerance[19] and LDL-C[20, 21]. On the other hand, HDL-C[19] and FPG[22] were restricted to females. The inconsistent findings might be attributable to differences in the prevalence rates of these cardiovascular risk factors and lifestyles among different populations. Additionally, it might also imply that the underlining mechanisms of cIMT thickening were different among different populations. Further study is necessary to verify this hypothesis.

We found that the effects of BMI and LDL-C/HDL-C ratio on cIMTs were more profound in males. One possible mechanism underlines the sex differences in cIMT is the effects of sex hormones. Experimental and clinical evidences have demonstrated the protective effects of estrogen against cardiovascular events[25]. However, among study subjects aged 47-to-

Table 3. Correlation analyses for the far-wall mean CCA IMTs with anthropological and clinical characteristics[a]

Variables	Males	Females
Log (10-years CVD risks)	0.501***	0.502***
Age	0.423***	0.527***
Body height	−0.041	0.016
Body weight	0.206***	0.138***
BMI	0.264***	0.139***
Hip circumference	0.185***	0.073*
Waist circumference	0.224***	0.110**
Waist-to-hip ratio	0.165***	0.078*
Body shape index	−0.012	−0.028
SBP	0.143**	0.183***
DBP	0.093*	0.132***
Total cholesterol	0.149**	0.075*
HDL-C	−0.167***	−0.114**
LDL-C	0.212***	0.124**
LDL-/HDL-C ratio	0.283***	0.172***
Total-/HDL-C ratio	0.256***	0.162***
Log (FTG)	0.108*	0.070*
Log (FPG)	0.184***	0.109**
Log (HbA1c)	0.159**	0.066*
Log (Insulin)	0.064	0.044
HOMA index	0.102*	0.047
Log (FTG/LDL-C)	0.147**	0.092*
Uric acid	0.100*	0.121**

[a]Numbers in the table, except for age, are age-adjusted Pearson's correlation coefficients.
*, $0.001 < p < 0.05$; **, $0.0001 < p < 0.001$; ***, $p < 0.0001$

50 years, we found that means of multivariate-adjusted cIMTs were significantly thicker in males than in females and there was a non-significant difference between pre- and post-menopausal women. Our findings indicated that menstrual status-related factors might not be the primary determinants of cIMT thickening. Other sex-specific factors possibly play more important roles in the responses of blood vessels to stresses. Our hypothesis was further supported by the inconsistent findings of several clinical researches of estrogen replacement on cIMT[26, 27].

Alternatively, androgen deficiency is emerging as an independent determinant of CVDs and cardiovascular risk factors[28]. It is known that testosterone levels fall with advancing age. Observational studies depicted that obese males and those who affected with chronic conditions, including DM and MetS, had significantly lower levels of testosterone[29, 30]. There were evidently positive effects, including improvement of lipid profiles[31] and reversal of fat accumulation with significant improvement in lean body mass[32], in individuals receiving testosterone therapy. A recent meta-analysis,

Table 4. The best-fit multiple regression models on the far-wall mean CCA IMT in male and female subjects

	Males ($n=635$)			Females ($n=944$)		
	Partial r^2	β	(95% CI)	Partial r^2	β	(95% CI)
Intercept		-0.0565	$(-0.2299 \sim 0.1168)$		0.1960***	$(0.1474 \sim 0.2445)$
AGE (per 10 years)	0.179	0.0467***	$(0.0387 \sim 0.0547)$	0.278	0.0541***	$(0.0476 \sim 0.0607)$
BMI (per 5 kg/m²)	0.058	0.0242***	$(0.0119 \sim 0.0365)$	0.014	0.0091*	$(0.0014 \sim 0.0167)$
LDL-/HDL-C ratio (per 1.0)	0.041	0.0250***	$(0.0171 \sim 0.0329)$	0.012	0.0119**	$(0.0049 \sim 0.0189)$
Log$_{10}$ FPG (per 10 mg/dL)	0.018	0.1517**	$(0.0687 \sim 0.2347)$		$-$	
Hypertension (Yes vs No)	0.015	0.0298**	$(0.0141 \sim 0.0454)$		$-$	
SBP (per 10 mmHg)		$-$		0.014	0.0065***	$(0.0036 \sim 0.0094)$
Model r^2	0.311			0.318		

Note: CI, confidence interval; +, $0.05 < p < 0.1$; *, $0.001 < p < 0.05$; **, $0.0001 < p < 0.001$; ***, $p < 0.0001$

Table 5. Generalized linear regression model on the far-wall mean CCA IMT in the whole subjects and subgroups

	Whole subjects ($n=1579$)		CCA plaque-free subjects ($n=1461$)		CCA plaque-, CVD-, DM-, and hypertension-free subjects ($n=879$)	
	Standardized β	(95% CI)	Standardized β	(95% CI)	Standardized β	(95% CI)
SEX (Male vs. Female)	-0.0193	$(-0.1040 \sim 0.0655)$	-0.0385	$(-0.1201 \sim 0.0432)$	-0.0468	$(-0.1511 \sim 0.0575)$
Age	0.4299***	$(0.3863 \sim 0.4735)$	0.4047***	$(0.3619 \sim 0.4475)$	0.4249***	$(0.3693 \sim 0.4805)$
LDL-C/HDL-C	0.0953**	$(0.0385 \sim 0.1522)$	0.0815*	$(0.0275 \sim 0.1355)$	0.0378	$(-0.0301 \sim 0.1057)$
SBP	0.0483+	$(-0.0068 \sim 0.1034)$	0.0636*	$(0.0099 \sim 0.1173)$	0.0754*	$(0.0024 \sim 0.1485)$
BMI	0.0443	$(-0.0138 \sim 0.1023)$	0.0327	$(-0.0222 \sim 0.0876)$	0.0364	$(-0.0347 \sim 0.1075)$
Hypertension (Yes vs. No)	0.1665*	$(0.0520 \sim 0.2805)$	0.0992+	$(-0.0123 \sim 0.2107)$	Not included	
BMI × Sex (per SD increase in males vs. that of in females)	0.0971*	$(0.0093 \sim 0.1850)$	0.0968*	$(0.0112 \sim 0.1824)$	0.0935	$(-0.0235 \sim 0.2105)$
LDL-C/HDL-C × Sex (per SD increase in males vs. that of in females)	0.1177*	$(0.0298 \sim 0.2056)$	0.1064*	$(0.0207 \sim 0.1920)$	0.1385*	$(0.0330 \sim 0.2440)$
Log$_{10}$ FPG	0.0790**	$(0.0355 \sim 0.1226)$	0.0610*	$(0.0176 \sim 0.1045)$	0.1269*	$(0.0346 \sim 0.2192)$
Model adjusted r^2	0.310		0.298		0.276	

Note: CI, confidence interval; +, $0.05 < p < 0.1$; *, $0.001 < p < 0.05$; **, $0.0001 < p < 0.001$; ***, $p < 0.0001$

which included 5 randomized controlled trials with a total of 351 participants, on the metabolic effects of testosterone replacement therapy in hypogonadal diabetic men showed that testosterone treatment significantly reduced fasting plasma glucose and triglyceride levels, fasting serum insulin levels, and HbA1c%[33]. In addition, several observational studies consistently depicted significantly thicker carotid IMTs in males with reduced testosterone levels[34, 35]. It is therefore reasonable to hypothesize that the modification effects of sex on the relationships between cIMTs and BMI or LDL-/HDL-C ratio are primarily attributable to decreased levels of testosterone in males. Due to the lack of large prospective and clinical studies on metabolic effects of sex hormones, further explorations are required to distinguish the major and critical determinants of sex differences in cIMT.

The present study and a recent Japanese study[36] showed that LDL-C/HDL-C ratio predicts cIMT better than LDL-C or HDL-C alone. On the contrary, most previous studies regarded LDL-C and HDL-C as independent determinants of elevated cIMT. None of the population-based studies had assessed the sex-specific relationships of LDL-/HDL-C with cIMT[18-24]. Yet, the importance of LDL-C/HDL-C ratio was demonstrated by several clinical evidences. The Framingham Heart Study concluded that individuals with similar LDL-C/HDL-C ratios had similar CVD risks regardless of their LDL-C levels[37]. LDL-C/HDL-C ratio has remained an important measure for CVD risk assessment even though having high levels of apolipoprotein[38]. Based on our results, we concurred with

such statement and found LDL-C/HDL-C an important determinant of elevated cIMT in both sexes.

There were several strengths in the study. The first study recruited subjects from the northern coastal areas, an area of limited health care resource. None of the cohort members had ever received a carotid ultrasonographic scan. Therefore, the distribution of cIMT was more likely to reflect the natural spectrum. Secondly, to obtain valid measurement of cIMT, we strictly followed the protocol which was recommended by a group of experts and endorsed by the Society of Vascular Medicine and measured blindly. Thirdly, we used structured questionnaire to obtain information associated with personal attributes. The confounding effects of established determinants on cIMT were sufficiently adjusted. Finally, to reduce the influence of measurement variation, all cIMT were measured by a well-trained technician. A random sample of 82 (5%) subjects was re-measured one month after the first measurement to assess the extent of the intra-observer variability. Our cIMT measurements were of great repeatability, which was manifested by high intra-class correlation coefficients and negligible mean differences between two repeated measurements.

There were potential limitations of the study. Firstly, the cross-sectional nature of the study limited pathophysiological speculations. In addition, due to the complexity of equipment setup, some of the eligible residents had to travel a long distance to the study sites. It was likely that the voluntary participants of the study might be different from the whole population of the study area, e.g., more concerned about their health. To evaluate the representativeness of the study sample, we obtained vital statistics from the housing office of the study area. Test statistics showed that the age distribution, the most important determinant of cIMT, of the study subjects was not significantly different from that of the target population (age groups: 40−44, 45−49, 50−54, 55−59, 60−64, 65−69, and 70−74 years; $\chi^2_6 = 12.01$, $p = 0.062$). Thirdly, the data of durations of treatments of hyperlipidemia and hypertension were not available in the study. Therefore, we were not able to assess the effects of these treatments on cIMT. However, all participants had never received carotid ultrasonographic scans before and both ultrasonographic system operators and the technician who measured the carotid IMTs were blind to examinees' personal histories of common diseases and clinical profiles. Consequently, our measurement error tended to be non-differential and our findings were more likely to be conservative. Lastly, although the model r^2 of the present study were larger than previous studies[7, 8, 20], there were unmeasured variables which might influence our findings. However, confounding effects would be obvious only when such unmeasured variables strongly correlated with sex and cIMT. To minimize their potential influences, we used the Z deviates but not the absolute values of continuous measurements in the generalized linear models. We found that the interactions between sex and BMI or LDL-/HDL-C ratio were statistically significant even when restricting analyses to plaque-free subjects. The slight variations in the r^2 and regression coefficients of different models further implied the validity of our findings.

In conclusion, this study revealed that approximately the same proportions of the total variability in the cIMT in the middle-aged adults and elderly can be attributed to age, BMI, and LDL-/HDL-C ratio, but their contributions were different. Our results indicated the existence of sex-specific factors affecting cIMTs. Attentions on different risk factors should be made differently based on gender and the cause of such differences require further investigation.

Acknowledgments

Conflict of Interest

None.

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