Westernization of Chinese Adults and Increased Subclinical Atherosclerosis

Kam S. Woo, Ping Chook, Olli T. Raitakari, Brendan McQuillan, Jiang Zheng Feng, David S. Celermajer,

Abstract—Cardiovascular event rates are much lower in China compared with developed countries. “Westernization” of diet and lifestyle in the Chinese, however, may lead to an increased prevalence of atherosclerosis-related diseases. Because carotid intima-media thickness (IMT) is a marker of subclinical atherosclerosis, we examined IMT and vascular risk profile in community-based groups of rural Chinese, Westernized urban Chinese, and urban whites. Mean IMT of the common carotid artery was measured in 348 healthy adults, aged 42±13 years (range 21 to 71 years); 116 subjects from rural China, 116 urban Chinese subjects living in Hong Kong or in Australia, and 116 urban Caucasians living in Australia. These 3 groups were matched for age, sex, and cigarette smoke exposure. Urban Chinese subjects had slightly better risk factor profile (higher HDL-cholesterol and lower blood pressure) compared with rural Chinese subjects. Despite this, however, the mean IMT was lowest in rural Chinese (0.50±0.10 mm), intermediate in urban Chinese (0.56±0.12 mm), and highest in urban whites (0.64±0.13 mm) (P<0.001 for comparisons between all groups). These differences in IMT were not altered after adjustment for the major traditional cardiovascular risk factors (serum lipids, smoking, and blood pressure or for body mass index). The influence of vascular risk factors on atherosclerosis between urban versus rural Chinese subjects was studied by multivariate regression models and by comparing the steepness of regression slopes between risk factors and IMT in the subject groups. The effects of smoking, HDL-cholesterol, and triglycerides on IMT were significantly greater in the urban compared with the rural Chinese (P<0.01). These data suggest that Westernization of Chinese subjects is associated with greater susceptibility to the pro-atherogenic effects of traditional vascular risk factors, such as lipids and smoking, and with evidence of increased IMT as a marker of subclinical atherosclerosis. (Arterioscler Thromb Vasc Biol. 1999;19:2487-2493.)

Key Words: atherosclerosis □ diet □ Chinese □ intima-media thickness

In China, the risk of coronary heart disease has been exceptionally low compared with other countries. The World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) project showed a 12-fold range between participating countries in the age-standardized coronary event rates for 35- to 64-year-old men, this being lowest in Beijing, China.1 Chinese migrants to Australia have low cardiovascular mortality rates during their first 10 years of residence, but their mortality rates rise thereafter.2 Similar increases in mortality rates have also been observed in other Asian populations after migration to developed countries.3 It is not known, however, whether the progressive Westernization of diet and lifestyle that are occurring inside China will similarly affect the pathogenesis of atherosclerosis or cardiovascular event rates. Because approximately one quarter of the world’s population (1.2 billion people) live in China, the public health implications of such a situation would be considerable.

Noninvasive measurements of subclinical atherosclerosis have been described in community-based studies.4,5 Intima-media thickness (IMT) of the common carotid artery, for example, can be measured noninvasively by ultrasound; it correlates with traditional vascular risk factors and with the extent of atherosclerotic lesions in the coronary, carotid, aortic, and femoral circulations; and it may predict the future risk of myocardial infarction.5,6 To assess the impact of Westernization on subclinical atherosclerotic disease, we measured carotid IMT and traditional vascular risk factors in communities in rural China, urban China (Hong Kong), and urban Australia.

Methods

Subjects
We studied 348 healthy subjects who were 42±13 years of age. These subjects were from 3 prespecified population groups: 116 Chinese from a rural village in Southern China, 116 urban Chinese

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2487
from Hong Kong (n=44) or Sydney (n=72), and 116 urban whites from Perth, Australia. Subjects were recruited from community volunteers and were included if they met prespecified criteria: age 18 to 75 years, no clinical evidence of atherosclerosis, no history of diabetes mellitus or hypertension, and taking no regular cardiovascular medications or specific antioxidant supplements. Thirty-one percent of the women were postmenopausal (20 of the 65 women in each of the 3 groups). The study was approved by the appropriate institutional ethics committees, and subjects gave informed consent in their native language.

The rural Chinese subjects were studied in Shek Kei Village, on the outskirts of Pan Yu, in Guangdong province, Southern China. The population of this village is approximately 3000 people. People from this village are not geographically isolated, and intermarriage with inhabitants of Pan Yu is common. Adults in Shek Kei Village are similar to the other inhabitants of Guangdong province in body size, lifestyles (diet, smoking habits, and physical activities), personal income, and disease patterns. Most of the villagers still have a traditional Chinese diet based on vegetables, rice, fish, and green tea. The annual rate of acute myocardial infarction in this region of China is approximately 35 per 100 000 persons.7 In a 2-week visit there by the study investigators, we examined 142 rural Chinese adults, of whom 116 met the inclusion criteria (as above).

The urban Chinese subjects were studied in Hong Kong or in Sydney. These subjects were recruited as part of an ongoing study of community atherosclerosis risk in urban-dwelling Chinese in these 2 centers (n=270), where annual rates of myocardial infarction significantly exceed those in rural China.3 Subjects were included if they had been living in Hong Kong or Sydney for at least 10 years and were originally of Southern Chinese heritage. They generally had a much lower consumption of vegetables and green tea and greater intake of eggs and dairy products, on the basis of detailed dietary questionnaires completed by all the Chinese participants. For example, compared with rural Chinese, the subjects living in Hong Kong consumed fewer vegetables (161±102 vs 279±158 g per day), less green tea (646±399 vs 1024±794 mL per day), and more dairy products (36±83 vs 11±20 g per day) (P<0.01 for all comparisons). By contrast, aspects of dietary intake were more comparable between Westernized Chinese living in Hong Kong and those in Sydney (for example, vegetables 161±102 vs 175±144 g per day and eggs 18.5±18.7 vs 16.7±14.5 g per day, respectively, P=NS). The urban whites had all been living in Perth, Australia (a city of 1.1 million people) for at least 10 years and were also recruited as part of a large community-based study of risk factor prevalence (n=1100).

For each subject studied in rural China, the most closely matched subject was selected from the database of urban Chinese or whites, on the basis of sex, age (±3 years), and history of cigarette smoking (never, former, or current smoking, the latter groups matched for lifetime exposure to cigarettes, as previously described by our group).8

To minimize any selection bias resulting from the use of community volunteers, we applied similar strategies for subject recruitment in China and Australia. Posters advertising the study projects were placed in the community in the vicinity of the hospital or health center. All advertising material was written only in the local language in each center.

Study Design

Each subject had 1 visit to the study center, during which a medical history was taken, including an assessment of smoking history. Height and weight were recorded, routine physical examination was performed, supine resting blood pressure was measured after at least 10 minutes of rest, and the carotid arteries were scanned with the use of external vascular ultrasound. Body mass index was calculated as weight (kg) divided by height^2 (m^2). Venous blood was sampled after a 14-hour fast for analysis of serum lipoproteins on the same day or within 1 week of the ultrasound studies.

Ultrasound Imaging

B-mode ultrasound examinations were performed with an Acuson 128XP/10 mainframe with a 7-MHz scanning frequency linear array transducer, an ATL 3000 mainframe with a high-resolution, linear array scanner (medium frequency 7.5 MHz), or an Interspec Apogee CX200 mainframe with a 7.5-MHz transducer. All ultrasound systems therefore used similar scanning frequency and had similar resolution (≈0.12-mm theoretical resolution in each case). All scans were performed by operators after a predetermined, standardized scanning protocol for the right and left carotid arteries as described by Salonen and Salonen and Blankenhorn et al,9 using images of the far wall of the distal 10 mm of the common carotid arteries. Three scanning angles were used in each case; anterior oblique, lateral, and posterior oblique. The image was focused on the posterior (far) wall, and images were recorded from the angle showing the greatest distance between the lumen-intima interface and the media-adventitia interface as described previously.3 All scans were recorded on super-VHS videotape for subsequent off-line analysis.

Ultrasound Analysis

All scans were analyzed with the use of identical methodology in each of the study centers, with a common computerized edge-detection system that we have previously described and validated.10 Observers were blinded to the subject’s identity and demographic features. Two end-diastolic frames were selected, digitized, and analyzed for mean IMT, and the average reading from these 2 frames was calculated for both right and left carotid arteries. Images were digitized with the use of a frame grabber (Video Associates Labs) and an IBM-compatible computer interfaced with a Panasonic AG7350 super-VHS videocassette recorder. Edge-detection software automatically identifies intimal and medial points from the region of interest of the far wall of the common carotid artery as defined by the observer.10 Automated computerized edge tracking of this type has been shown to reduce measurement variability 2-fold to 4-fold compared with manual methods, and we have previously reported good intraobserver and interobserver repeatability values and within-subject reproducibility with the use of this method.10 Images from 30 randomly selected subjects were independently analyzed by operators in China, Sydney, and Perth, and this showed an excellent between-center measurement reliability. The mean difference of repeated measurements between 2 centers was 0.02±0.04 mm, and the coefficient of variation for mean IMT measurements was 3.0%.

Serum Lipoproteins

Fasting serum cholesterol and triglycerides were assayed enzymatically with the use of the Boehringer Mannheim Hitachi 747 (Sydney and Perth laboratories) or 911 (Hong Kong laboratory) analyzer. Samples from rural Chinese subjects were analyzed in the Hong Kong laboratory. HDL cholesterol was measured after precipitation with phosphotungstate-magnesium. All laboratories are currently accredited with intra-assay imprecision of their cholesterol measurement <3% and accuracy as standardized by the Center for Disease Control–National Heart, Lung, and Blood Institute (US) program (for example, the absolute bias from the Abell-Kendall method was −0.1 mmol/L at 5.2 and 6.2 mmol/L at the time of this study). LDL cholesterol was calculated according to the Friedewald formula.11

Statistical Analysis

Descriptive data are expressed as mean±SD unless otherwise stated. Comparisons among the 3 subject groups (rural Chinese, urban Chinese, and urban Australians) for continuous variables were performed by ANOVA, followed by Bonferroni’s multiple comparison procedure to allow pairwise testing for significant differences between the groups. Significance of differences in proportions across groups was assessed by χ^2 statistics (χ^2 test). Mean values for IMT were adjusted for other study variables by use of the least-squares method, and significance of differences between the adjusted means were tested by ANCOVA. Univariate association between IMT and risk factors were examined with the use of linear regression models. Multivariate linear regression models were used to examine if the associations between IMT and risk factors were similar between urban and rural Chinese. The models included IMT as the dependent variable and group, sex, specific risk factor, and risk factor × group interaction term as independent variables. The linear relations between IMT and risk variables were also studied separately in Chinese subjects by regression analysis. The significance of differences between the
regression coefficients of the 2 subject groups was tested according to the formula

$$z = (B_1 - B_2) / \sqrt{SE_1^2 + SE_2^2},$$

where $B_1$ and $B_2$ are the regression coefficients and $SE_1$ and $SE_2$ are the respective standard errors.\(^{12}\) The statistical tests were performed with the Statistical Analysis System (SAS), and statistical significance was inferred at a 2-tailed value of $P<0.05$.

### Results

#### Baseline Characteristics

The average age for all subjects was $42 \pm 13$ years (range 21 to 71), with similar ages in the 3 study groups. Forty-four percent of the subjects were men, with equal numbers of men and women in each group. The characteristics of subject groups are shown in Table 1. Urban Chinese had significantly higher mean values for HDL cholesterol ($P<0.01$) and lower systolic blood pressure ($P<0.01$) compared with the rural Chinese; these latter groups were similar to each other. Urban whites had greater height, weight, body mass index ($P<0.001$), and total cholesterol ($P<0.001$), compared with the rural or urban Chinese; these latter groups were similar to each other.

#### Comparison of IMT Values

The distribution of unadjusted IMT values among the subject groups is shown in Figure 1. The mean IMT value was lowest in the rural Chinese, intermediate in the urban Chinese, and highest in urban whites ($P<0.001$ for all between-group comparisons) (Table 2). Similar differences were seen in the left and right IMT values, and the differences in the mean IMT values remained highly significant after adjusting for all the other measured study variables (Table 2). The IMT values were similar between the 2 subgroups of urban Chinese in Hong Kong (0.54±0.11 mm) and in Sydney (0.58±0.12 mm) ($P=0.11$).

#### Associations Between IMT and Risk Factors

In all subjects pooled together, IMT was significantly related to age ($R^2=0.26$, $P<0.001$), study group ($R^2=0.20$, $P<0.001$), body mass index ($R^2=0.13$, $P<0.001$), mean arterial blood pressure ($R^2=0.06$, $P<0.001$), total cholesterol ($R^2=0.05$, $P<0.001$), LDL cholesterol ($R^2=0.05$, $P<0.001$), pack-years of cigarettes ($R^2=0.04$, $P<0.001$), triglycerides ($R^2=0.02$, $P<0.01$), HDL cholesterol ($R^2=0.01$, $P<0.05$), and sex ($R^2=0.01$, $P<0.05$). On stepwise multivariate regression analysis, the IMT remained significantly associated with the study group ($P<0.001$), age ($P<0.001$), body mass index ($P<0.001$), and sex ($P<0.05$).

![Figure 1. Comparison of carotid IMT values in 116 rural Chinese subjects, 116 urban Chinese subjects, and 116 urban whites. For each study group, the box represents the interquartile range (between 25th and 75th percentiles), with the median value shown as a horizontal bar within each box. Bars outside each box show the range of 95% of values.](image-url)
TABLE 2. Left, Right, and Mean IMT Values in Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Rural Chinese</th>
<th>Urban Chinese</th>
<th>Urban Whites</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left IMT</td>
<td>0.51 (0.11)</td>
<td>0.56 (0.14)</td>
<td>0.64 (0.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right IMT</td>
<td>0.49 (0.11)</td>
<td>0.57 (0.13)</td>
<td>0.65 (0.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean IMT</td>
<td>0.50 (0.10)</td>
<td>0.56 (0.12)</td>
<td>0.64 (0.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>†Adjusted IMT</td>
<td>0.50</td>
<td>0.57</td>
<td>0.63</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean (SD).
*Difference in all pairwise comparisons.
†Mean IMT, adjusted for age, pack-years smoked, body mass index, serum lipoproteins, and blood pressure (see “Methods”).

Effect of Risk Factors in Rural Versus Urban Chinese

To test whether risk factors have similar influence on IMT in Chinese subjects regardless of their environment, we calculated the regression coefficients for IMT separately for rural and urban Chinese (Table 3). Age (P<0.001) and total cholesterol (P<0.05) were directly associated with IMT in both groups. Smoking, triglycerides, and body mass index were positively associated and HDL cholesterol inversely associated with IMT in urban Chinese but not in the rural Chinese subjects. Urban Chinese had significantly steeper slopes for IMT by pack-years of cigarettes smoked (P<0.01), HDL cholesterol (P<0.001), and triglycerides (P<0.01) (Figure 2), suggesting a greater impact of these risk factors on subclinical atherosclerosis in urban compared with rural Chinese adults. These interactions were further analyzed by regression models. These multivariate models indicated significant study group × risk factor interaction effects for group × smoking (P=0.01), group × triglycerides (P=0.01), and group × HDL cholesterol (P=0.04), consistent with the findings from the comparisons of regression slopes shown in Figure 2.

Discussion

The risk of atherosclerotic disease has been very low in rural China compared with Westernized nations, but this situation may be rapidly changing along with the modernization processes now taking place in China as well as in most other Asian countries. Recent data show that cardiovascular diseases have become one of the leading causes of death worldwide, and the emergence of atherosclerosis as a major cause of morbidity and death in the world’s most populous regions in Asia has prompted proposals for action to halt this process.

Studies in Asian people have shown that migration from rural to urban environments is associated with modifications in diet and lifestyle, often leading to undesirable changes in lipid and blood pressure profiles and to an increase in the risk of cardiovascular events. We now report increased arterial wall thickness, a marker of subclinical atherosclerosis in urban compared with rural Chinese adults. These data suggest that environmental factors may significantly affect the atherogenic process in the early, presymptomatic stages of the disease across entire community groups with prolonged exposure to Western diet and lifestyle. Carotid IMT was
greater still in urban white subjects, however, suggesting that atherosclerosis may also be importantly influenced by ethnic or genetic factors.18,19

In this study, the difference in IMT level between Chinese subjects could not be explained by the levels of serum lipoproteins or blood pressure; in fact, the overall risk factor profile was slightly better in the urban Chinese subjects, who had higher levels of HDL cholesterol and lower systolic blood pressure compared with rural Chinese. There is no clear explanation for these findings; however, the results are consistent with an increased susceptibility of urban Chinese to the proatherogenic effects of traditional risk factors. Using 2 separate analytical models, we have shown that the risk factors of smoking, low HDL cholesterol, and high triglycerides were significantly associated with increased IMT in urban Chinese but not in rural Chinese. Consistent with the concept of different susceptibility to the atherogenic effects of risk factors in different populations, we have also recently demonstrated that rural Chinese are less susceptible than whites to the deleterious effects of cigarette smoking20 and aging21 on arterial endothelial function, a marker of vascular reactivity. These data may be consistent with a protective factor or factors in the rural Chinese environment. Thus, although urban migration may be associated with potential health benefits, such as less morbidity from infectious diseases, some protection against atherosclerosis may be lost.

The mechanism underlying increased subclinical atherosclerosis in urban Chinese (and whites) is not currently known. It is possible that certain unmeasured factors, such as susceptibility of LDL to oxidation, an important determinant of IMT,22 may be different between Chinese living in different environments within China. Rural Chinese have high consumption of green teas, which are rich in antioxidant flavonoid compounds,23 and the intake of dietary antioxidants has been shown to be inversely associated with IMT.24 Other differences in their diet include increased consumption of vegetables and fish, accompanied by lower consumption of saturated fat. Recent data have also implicated possible vascular protective roles for the high levels of soy protein25 and plant phytoestrogens26 found in the rural Chinese diet.

As a marker of subclinical atherosclerosis, we measured IMT in the far wall of the distal part of the common carotid artery, as described by us10 and many other groups.5,6,9,27 Although actual plaque formation is more often seen in the internal compared with the common carotid artery,28 there are potential problems in assessing the IMT of the internal carotid artery because it cannot be measured precisely in a large proportion of patients and therefore may result in missing data.29 In some investigators’ experience, however, a more complex carotid IMT score involving both internal and common carotid observations may have better predictive value than either measure taken alone.30 By contrast, IMT of the common carotid artery has been shown to be easily visualized and a highly reproducible measurement, and previous validation data support its use in studies of risk factor associations and in cohort studies.31,32 The association of carotid and coronary atherosclerosis is only marginally increased when information of IMT from the internal carotid and carotid bulb are added to the common carotid IMT, supporting that the use of common carotid IMT may be preferable for certain analyses.31

IMT measurements of the common carotid artery correlate significantly with traditional risk factors,2,33–35 with the occurrence of cerebrovascular disease,5,36 and with the severity and extent of coronary heart disease.10 Although IMT values cannot be used to predict the risk of coronary heart disease on an individual basis,10 they can nevertheless predict the likelihood of cardiovascular events in population groups.5,6 Recent prospective studies have suggested that every 0.1-mm increase in common carotid IMT may increase the subsequent risk of acute myocardial infarction by 11% to 30% in high-risk asymptomatic subjects.5,6 With the use of this noninvasive measure, it is therefore now possible to detect early changes of atherosclerosis long before clinical manifestations of cardiovascular disease. We are unaware of any previous reports of carotid IMT in Chinese populations. The highly significant differences that we have observed in IMT values between rural and urban Chinese therefore suggest that the future risk of cardiovascular diseases may be substantially increased across the population of Chinese subjects living in urban environments, both inside and outside of China. To date, this possibility has received little public health response, even within Asian countries.13

The current study is limited by its cross-sectional nature. Serial studies of cardiovascular risk factors and measures of atherosclerosis would be logistically difficult, however, because of the need to identify subjects in China prospectively, before emigration from or Westernization within China. Furthermore, “Westernization” is difficult to quantify, and the concepts of urbanization and Westernization are difficult to distinguish because both involve changes in diet and lifestyle associated with increasing affluence and modernization. We studied groups of Chinese who had been living in a rural, “unspoiled” environment all their lives or in the environment of a modern Westernized city (Hong Kong or Sydney) for at least 10 years. As an example of lifestyle changes related to Westernization, we found significant differences in the dietary habits between the rural and urban Chinese and certain dietary similarities between the “Westernized” Chinese in Hong Kong and Sydney. Although some measured aspects of diet were comparable between the urbanized Chinese in Hong Kong and Australia, other diet and/or lifestyle factors may be important (and difficult to quantify). The observation of a nonsignificant trend toward increased IMT in urban Chinese living in Sydney compared with Hong Kong (0.58 vs 0.54 mm, P=0.11) also may be consistent with an effect of Westernization on IMT. In future studies, larger numbers of subjects will need to be investigated to reveal differences in IMT between groups of urban Chinese living inside and outside of China.

The influence of hypertension on carotid wall thickness was also considered. Although hypertension-related stroke is a common public health problem in Northern China,17 this is unlikely to have influenced our measurements of IMT because only nonhypertensive subjects were studied. Furthermore, the pathogenesis of stroke in this population is most commonly related to small-vessel changes and hemorrhage rather than to large-vessel atherosclerosis with ischemia.38 Techniques for data collection and analysis were standardized among all participating centers, and we attempted to minimize any potential differences in recruitment bias (which is inherent in the use of consenting volunteers, presuming
literacy, willingness to participate, and so on). The number of subjects in the rural study group was relatively small because only volunteers meeting prespecified entry criteria were recruited from this countryside village; however, these rural subjects were carefully matched with urban control subjects for their age, sex, and cigarette smoke exposure. Despite these factors, significant differences in IMT were observed between groups, consistent with an increased prevalence of subclinical atherosclerosis in urban compared with rural Chinese (although still lower in both groups compared with urban whites).

Cardiovascular disease is poised to become the greatest cause of morbidity and death worldwide in the 21st century, despite falling rates in developed nations. The demonstration of increased atherosclerotic burden in healthy Chinese in urban settings (both inside and outside of China) compared with rural Chinese has important public health implications because China and other Asian nations are undergoing rapid economic growth, progressive Westernization, and consequent changes in diet and lifestyle. Further study will be required to elucidate which environmental factors operative in rural China, if any, may be affording possible cardiovascular protection in these subjects.

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References


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