Risk Factors of Subclinical Atherosclerosis and Plaque Burden in High Risk Individuals: Results From a Community-Based Study

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China is going through major change and the incidence of first-ever stroke has increased dramatically. In this study, we aim to determine the ultrasound characteristics of carotid intima-media thickness (CIMT) and carotid plaques (CP) in the Chinese community-based population with high risk of stroke. 1009 stroke-free participants from Datun community were classified at high risk of stroke and included in this cross-sectional study. We performed B-mode carotid ultrasound imaging in all of the study subjects to measure the CIMT in the common carotid artery (CCA) far wall and CP in the CCA, bifurcation and internal carotid artery. Stepwise logistic regression analyses were used to determine factors associated with elevated CIMT and subclinical atherosclerosis, as well as plaque burden (≥2 plaques). Our results showed that traditional risk factors including aging, hypertension, current smoking and the level of high density lipoprotein cholesterol are associated with subclinical atherosclerosis and plaque burden in high-risk community residents. To improve primary prevention in this population, we may consider intense blood pressure and lipid management, and smoking cessation.

Keywords: carotid intima-media thickness, carotid plaque, plaque burden, community-based study, subclinical atherosclerosis

INTRODUCTION

Stroke has become a threatening public health issue in China. Recently, a dramatically increased incidence of first-ever stroke among a low-income population in rural China from 1992 to 2012 has been reported, with an annual increase of 6.5% (Wang et al., 2015). Moreover, the prevalence of traditional risk factors for stroke like obesity and hypertension is also booming in this population over the past several decades, especially in those aged 35–44 years (Ning et al., 2014; Wang et al., 2014), indicating an even heavier disease burden in the near future.

B-mode ultrasound is one of the imaging techniques with the merits of non-invasive, low cost and no contradictions, and offers valuable information such as carotid intima thickness (CIMT) and the presence of plaque. These parameters have been reported to predict cardiovascular disease (CVD) in several large studies (Lorenz et al., 2010; Polak et al., 2011). In 2007, a systematic review...
Identified Subjects at High Risk of Stroke

Screen questionnaire included questions as follows:

1. blood pressure ≥140/90 mmHg,
2. atrial fibrillation or valvular heart disease,
3. smoking,
4. dyslipidemia (triglyceride ≥2.26 mmol/L or total cholesterol ≥6.22 mmol/L or low density lipoprotein cholesterol ≥4.14 or high density lipoprotein cholesterol < 1.04mmol/L),
5. diabetes, defined according to 1999 World Health Organization criteria,
6. lack of exercise, defined as less than 3 times per week and less than 30 min each time,
7. BMI ≥26, (8) having family history of stroke. Those having 3 or more risk factors listed in the screen questionnaire or with a history of stroke were defined as high-risk individuals. Of over 6000 residents screened, 1197 were found to be at high risk. After excluding those with reported history of stroke (n = 159), and those without ultrasound examination (n = 28), a total of 1009 stroke-free participants with the age range of 40–84 years old were included in this study.

Physical Examination and Laboratory Measurements

Height and weight were measured with a standard process using a SECA 813 digital scale (Seca, Vogel & Halle GmbH & Co., Hamburg, Germany) and a flexible anthropometer as we previously reported (Xia et al., 2017). Waist circumference was measured at the midpoint between the lower border of the rib cage and the iliac crest. Body mass index (BMI) was calculated as body weight in kilogram divided by body height squared in meters. Blood pressure (BP) and pulse were measured in triplicate after 10-min rest with Omron electronic sphygmomanometers (Omron Healthcare Co. Ltd., Kyoto Japan).

Venous blood samples were obtained after an overnight fast of at least 8 h. All blood samples were analyzed in a national central laboratory in Beijing using the Olympus auto-analyzer 2700 (Olympus Instruments Inc., Tokyo, Japan), with strict quality control. Fasting glucose, serum triglyceride (TG), low-density lipoprotein cholesterol (LDLC) and high-density lipoprotein cholesterol (HDL-C) concentrations were measured as we previously described (Xia et al., 2017). HbA1c was measured by high-performance liquid chromatography (HPLC) using the Variant II (Bio-Rad, Hercules, CA, United States). Serum levels of homocysteine (HCY) was estimated using commercial kits.
Nonmydriatic Direct Ophthalmoscopy
Ophthalmologists performed direct ophthalmoscopy without mydriasis after a general physical examination. According to Scheie’s classification (Scheie, 1953), Fundus arteriosclerosis was defined as the presence of broadening of the light reflex from artery, arterial narrowing, arteriovenous compression, and “copper” or “silver” wiring. Mild fundus arteriosclerosis were defined as stage 1 in Scheie’s classification and moderate to severe fundus arteriosclerosis was defined as stage 2–4 in Scheie’s classification.

Ultrasound Examination
All subjects were studied lying in supine position with their head turned 45 degrees from the site being scanned, and the operator seated at the head bed, using a Philips HDI 5000 ultrasound system equipped with a 7.5 MHz probe. During ultrasound examination, the common carotid intima-media thickness (CIMT), the presence and type of carotid plaque were recorded. Carotid IMT scanning and reading was performed as suggested by the Mannheim Consensus (Touboul et al., 2004). The IMT was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media adventitia echo. The CIMT was defined as the mean of the right and left IMT of the CCA far wall. Elevated CIMT was defined as CIMT thickening over 1mm, as suggested in literature (Howard et al., 1993). Carotid plaques were defined as a focal region with a thickness >1.5 mm as measured from the media adventitia interface to the lumen-intima interface or as the presence of focal wall thickening that is at least 50% greater than that of the surrounding vessel wall. According to the characteristics of CP echogenicity, CP were categorized into three groups, namely, echogenic (higher content of fibrous tissue and calcification), echolucent (lipid rich), heterogeneous (mixed echolucent and echogenic) (European Carotid Plaque Study Group, 1995; Mathiesen et al., 2001). Presence of carotid plaque was defined as subclinical atherosclerosis.

RESULTS
General Characteristics of Study Population
A total of 1009 individuals (305 males and 704 females) at high risk of stroke were included. The mean age of the subjects was 61.7 ± 9.0 years. The proportion of subjects at subclinical atherosclerosis was 81.5% (822), including 147 (14.6%) subjects with CIMT and 675 (66.9%) subjects with carotid plaque/subclinical atherosclerosis. Among those with carotid plaque, the proportion of having echolucent, echogenic and heterogeneous plaque were 17.9, 22.9, and 59.2%, respectively.

Table 1 showed the clinical characteristics of the subjects. As compared to the reference group (CIMT < 1 mm), subjects with elevated CIMT and subclinical atherosclerosis were older, more likely to be males, current smoker and current drinker, having history of hypertension and diabetes, having moderate-to-severe fundus arteriosclerosis and having less favorable metabolic profiles, such as elevated levels of systolic BP, fasting plasma glucose and homocysteine.

Factors Associated With Elevated CIMT and Subclinical Atherosclerosis
Stepwise logistic regression revealed that current drinker [OR and 95% CI: 3.44 (1.55–7.63), P = 0.002] and moderate-to-severe fundus arteriosclerosis [OR and 95% CI: 3.40 (1.67–6.91), P = 0.001] increased the risk of elevated CIMT, while each 1 mmol/L increase of HDL-C decreased 67% risk. Compared to those with normal CIMT (CIMT < 1mm), for subclinical atherosclerosis, age and current smoker were significantly associated with increased odds and HDL-C was protective factors (OR: 0.40 and 0.51, 95% CI: 0.21–0.75 and 0.29–0.90, respectively). Moreover, moderate-to-severe fundus arteriosclerosis increased 75% risk of having subclinical atherosclerosis. Compared to those with elevated CIMT (1 ≤ CIMT ≤ 1.5 mm), aging was associated with increased risk and females were at lower risk of subclinical atherosclerosis than males, when elevated FPG [OR = 1.31 (1.05–1.65)] and history of hypertension [OR = 1.69 (1.08–2.66)] were risk factors. (Table 2).

Factors Associated With Carotid Plaque Burden (Plaques ≥2)
We further investigated the factors associated with carotid plaque burden (plaques ≥2) using stepwise logistic regression analysis (Table 3). The results showed that sex, age, hypertension, diabetes, current smoker, waist circumference, HDL-C and LDL-C were independently associated with carotid plaque burden, with female gender [OR and 95% CI: 0.40 (0.26–0.63), P < 0.001], waist circumference [OR and 95% CI: 0.98 (0.96–1.00), P = 0.012] and HDL-C [OR and 95% CI: 0.39 (0.20–0.76), P = 0.005] considered protective factors, and age [OR and 95% CI: 1.11 (1.08–1.13), P < 0.001], hypertension [OR and 95% CI: 1.77 (1.25–2.50), P < 0.001], diabetes [OR and 95% CI: 1.68 (1.13–2.50), P = 0.010], current smoking [OR and 95% CI: 2.05 (1.19–3.54), P = 0.010] and LDL-C [OR and 95% CI:...
### TABLE 1 | Characteristics of subjects according to carotid intima-media thickness and subclinical atherosclerosis.

| Variables | Total CIMT < 1 mm | Elevated CIMT (1 mm ≤ CIMT ≤ 1.5 mm) | Subclinical atherosclerosis | P  |
|-----------|-------------------|--------------------------------------|----------------------------|----|
| N (%)     | 1009 (100)        | 187 (18.5)                           | 147 (14.6)                 | 675 (66.9) |
| Age, years| 61.7 ± 9.0        | 56.5 ± 8.4                           | 59.6 ± 8.2                 | 63.7 ± 8.6 | < 0.001 |
| Male, n (%)| 276 (27.4)     | 33 (17.6)                            | 29 (19.7)                  | 243 (36.0) | < 0.001 |
| Current smoker, n (%) | 161 (16.0) | 16 (8.6) | 18 (12.2) | 127 (18.8) | 0.002 |
| Current drinker, n (%) | 207 (20.5) | 23 (12.3) | 32 (21.8) | 152 (22.5) | 0.006 |
| Hypertension, n (%) | 578 (57.3) | 86 (46.0) | 72 (49.0) | 420 (62.2) | < 0.001 |
| Diabetes, n (%) | 229 (22.7) | 29 (15.5) | 24 (16.3) | 176 (26.1) | 0.001 |
| Dyslipidemia, n (%) | 586 (58.1) | 104 (55.6) | 87 (59.2) | 395 (58.1) | 0.743 |

**Plaque composition, n (%)**

- Echolucent: 124 (12.3) vs. 124 (17.9) vs. 104 (55.6)
- Echogenic: 158 (15.7) vs. 158 (22.9) vs. 87 (59.2)
- Heterogeneous: 409 (40.5) vs. 409 (59.2) vs. 395 (58.1)

**Fundus arteriosclerosis, n (%)**

- Normal: 450 (44.6) vs. 100 (53.5) vs. 64 (43.5)
- Mild: 275 (27.2) vs. 62 (33.2) vs. 35 (23.8)
- Moderate to severe: 284 (28.1) vs. 25 (13.3) vs. 48 (32.7)

**Body mass index, kg/m²**: 26.0 ± 3.7 vs. 26.0 ± 4.2 vs. 26.6 ± 3.9

**WC, cm**: 86.4 ± 9.7 vs. 85.2 ± 10.1 vs. 86.7 ± 9.8

**SBP, mmHg**: 126.2 ± 14.5 vs. 123.5 ± 14.2 vs. 125.3 ± 14.4

**DBP, mmHg**: 78.3 ± 7.9 vs. 77.6 ± 8.8 vs. 78.8 ± 7.5

**FPG, mmol/L**: 5.40 ± 1.49 vs. 5.26 ± 1.33 vs. 5.20 ± 1.17

**HbA1c, %**: 6.01 ± 0.91 vs. 6.12 ± 1.06 vs. 5.95 ± 0.85

**TG, mmol/L**: 1.54 (1.10–2.13) vs. 1.56 (2.06–2.34) vs. 1.59 (1.14–2.19)

**TC, mmol/L**: 5.33 ± 1.07 vs. 5.25 ± 1.05 vs. 5.24 ± 1.05

**HDL-C, mmol/L**: 1.30 ± 0.30 vs. 1.34 ± 0.30 vs. 1.28 ± 0.27

**LDL-C, mmol/L**: 3.07 ± 0.86 vs. 2.98 ± 0.83 vs. 3.11 ± 0.84

**HCY, umol/L**: 17.31 ± 5.97 vs. 16.68 ± 5.44 vs. 16.25 ± 3.84

Data are expressed as mean ± SD or number (percentage). SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HCY, homocysteine; WC, waist circumference. P-values were from ANOVA or Chi-square test.

### TABLE 2 | Factors associated with elevated CIMT and subclinical atherosclerosis.

| Variables | 1 ≤ CIMT ≤ 1.5 mm (n = 147) vs. CIMT < 1mm | Subclinical atherosclerosis (n = 675) vs. CIMT < 1mm | Subclinical atherosclerosis (n = 675) vs. 1 ≤ CIMT ≤ 1.5 mm | P-value |
|-----------|--------------------------------------------|-----------------------------------------------|-------------------------------------------------|--------|
| OR (95% CI) | P-value                                    | OR (95% CI) | P-value                                             | OR (95% CI) | P-value |
| Age, years | 1.11 (1.08–1.13) | < 0.001 | 0.40 (0.21–0.75) | 0.004 | 1.04 (1.02–1.07) | 0.002 |
| HDL-C, mmol/L | 0.33 (0.12–0.88) | 0.027 | 0.55 (0.33–0.91) | 0.019 | 0.44 (0.25–0.77) | 0.004 |
| Female gender | 1.11 (1.08–1.13) | < 0.001 | 0.40 (0.21–0.75) | 0.004 | 1.04 (1.02–1.07) | 0.002 |
| Current smoker | 2.65 (1.35–5.20) | 0.005 | 2.65 (1.35–5.20) | 0.005 | 2.65 (1.35–5.20) | 0.005 |
| Current drinker | 3.44 (1.55–7.63) | 0.002 | 3.44 (1.55–7.63) | 0.002 | 3.44 (1.55–7.63) | 0.002 |
| Normal reference | 1.00 (1.00–1.00) | 0.000 | 1.00 (1.00–1.00) | 0.000 | 1.00 (1.00–1.00) | 0.000 |
| Mild | 0.90 (0.49–1.66) | 0.742 | 0.90 (0.49–1.66) | 0.742 | 0.90 (0.49–1.66) | 0.742 |
| Moderate to severe | 3.40 (1.67–6.91) | 0.001 | 3.40 (1.67–6.91) | 0.001 | 3.40 (1.67–6.91) | 0.001 |
| FPG | 1.31 (1.05–1.65) | 0.014 | 1.31 (1.05–1.65) | 0.014 | 1.31 (1.05–1.65) | 0.014 |
| Hypertension | 1.69 (1.06–2.66) | 0.022 | 1.69 (1.06–2.66) | 0.022 | 1.69 (1.06–2.66) | 0.022 |

Variables that resulted statistically significant at p ≤ 0.10 in the univariate analysis, which included sex, age, BMI, SBR, FPG, HbA1C, HDLC, HCY, hypertension, diabetes, fundus arteriosclerosis, current smoking and drinking status, were introduced in a multivariate logistic regression model and a backward selection method was used with a significance level of 0.05.
positively associated with retinal venular caliber in hypertension was negatively associated with retinal arteriolar caliber and subclinical atherosclerosis (Liu et al., 2015). Moreover, CIMT patients aged 40 years or older, the presence of diabetic studies. In a Chinese community-based study of diabetes found in our study has been consistently reported in other association between fundus abnormality and elevated CIMT arteriosclerosis was associated with elevated CIMT. The found that current drinking and moderate-to-severe fundus hyperplasia, which may be induced by pressure overload (namely, CIMT) represents smooth muscle hypertrophy and/or cannot be discriminated by current ultrasound technique. Carotid intima media is composed of smooth muscle cells (media layer, 80%) and endothelium (intima, 20%), which variation in carotid plaque area (Spence et al., 1999). Moreover, these associations are largely unknown, but shared pathophysiological mechanisms beyond traditional cardiovascular risk factors have been suggested (Alonso et al., 2015).

Plaque, on the other hand, is a localized manifestation of atherosclerosis, which represents predominantly intimal thickening and is more likely related to inflammation, oxidation, endothelial dysfunction, and/or smooth cell proliferation (Mathiesen and Johnsen, 2009). In our study, carotid plaque was associated with aging, smoking and level of HDL-C, and carotid plaque burden (≥2 plaques) was associated with aging, smoking, gender, hypertension, and levels of HDL-C and FPG. In consistency with our study, a previous study has shown that factors independently associated with the presence of carotid plaque were age, past smoke, HDL cholesterol, retinopathy and retinopathy plus nephropathy in diabetes patients aged over 45 years (de Kreutzzenberg et al., 2011). David Spence et al also reported that traditional risk factors including age, sex, hyperlipidemia, hypertension and smoking were determinants of carotid plaque area, which accounted for about 60% of the variation in carotid plaque area (Spence et al., 1999). Moreover, Núria Alonso et al recently demonstrated that aging, gender, dyslipidemia and the presence of retinopathy were associated with the presence of ≥2 CP in diabetes patients (Alonso et al., 2015).

Unlike CIMT which has an undetectable change with the annual change roughly 0.01–0.04 mm, CP grow 2.4 times faster in longitudinal view, which allows assessments of the progression of disease in months (Spence and Hackam, 2010). The Tromso Study measured IMT and total plaque area in 3240 men and 3444 women with the age range of 25–84 and followed these participants 10 years. They found that every 1 SD in square-root-transformed plaque area increased the risk of incident ischemic strokes by 9–38% in man and 1–41% in women. Furthermore, the multivariable-adjusted model showed that compared to no plaque, the highest quartile of plaque area increased 0.73- and 0.62-foSeparator
CVD risk and significantly added to CVD risk prediction over conventional risk factors. The study also showed that hazard ratio of incident CVD increased as the number of plaque increased, with plaque at one site predicted 1.5-folds the risk when plaque at two or more sites predicted 1.5-folds the risk (Plichart et al., 2011). Moreover, the Northern Manhattan Study showed that plaque thicker over 1.9 mm was associated with 2.8-fold increased risk of vascular events (Rundek et al., 2008). A recent study also showed that the presence of CP, history of smoking, and statin therapy might be important factors for primary prevention of first atherosclerotic CVD in asymptomatic high-risk patients, especially in middle-aged patients, emphasizing the importance of carotid artery evaluation (Kim et al., 2015).

Smoking was a common risk factor for subclinical atherosclerosis and plaque burden in our study, rising about 1-fold risk than those non-smokers, which was similar to previous studies (McEvoy et al., 2015; Hisamatsu et al., 2016). The evidence linking smoking exposure with various CVD including MI, stroke and peripheral vascular diseases, is clearly present (Ambrose and Barua, 2004). Atherosclerosis is considered as a critical player in the pathophysiology of smoking-induced CVD, and these adverse effects would be reduced by smoking cessation (Johnson et al., 2010). Supporting this notion, recently, the Multi-Ethnic Study of Atherosclerosis (MESA) and the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA), both of which were community-based cohort, have reported the association of current and former smoking to CAC (coronary artery calcium), CIMT and ABI (ankle-brachial index)—subclinical atherosclerosis at 3 anatomically distinct sites—in the western and Japan population, respectively (McEvoy et al., 2015; Hisamatsu et al., 2016). A monotonic relationship was also found between increasing pack-years exposure and elevated inflammatory markers and time since quitting in former-smokers was independently associated with lower inflammation and atherosclerosis in MESA (McEvoy et al., 2015). Similarly, in SESSA, researchers observed dose-response relationships of pack-years and daily consumption, with CIMT, carotid plaque, AoAC (aortic artery calcification), and ABI among both current and former smokers, and even a small amount of pack-years or daily consumption among current smokers was associated with coronary artery calcification and AoAC, whereas time since cessation among former smokers was linearly associated with lower burdens of all atherosclerotic indices (Hisamatsu et al., 2016).

There were some limitation to this study. First, this was a cross-sectional study and was not randomized. Additionally, we did not compare the characteristics of those excluded in the screening process (identified as non-high risk) with those included (identified as high risk) in our study due to lack of data, so our results can only apply to those at high risk of stroke. Second, we only measured the CCA far wall IMT, and used arbitrary cutoff value to define elevated CIMT. However, the cutoff value is widely used, and CCA far wall IMT is validated as representing the true thickness of the vessel wall and its measurement is easier and more reliable than the other three segment. Our study also have some strength. First, we first investigated the determinants of subclinical atherosclerosis and plaque burden in a community-based, Chinese stroke-free but at asymptomatic high-risk population. With the booming incidence of stroke in China, such study is in urgent demand. Second, our result may offer some information for community-based interventions for stroke, which is already a common strategy for chronic diseases in China.

CONCLUSION

In conclusion, our study showed that traditional risk factors including aging, hypertension, current smoking and the level of HDL-C are associated with subclinical atherosclerosis and plaque burden in high-risk community residents. To improve primary prevention in this population, we may consider intense BP and lipid management, and more importantly, smoking cessation.

AUTHOR CONTRIBUTIONS

YH and LB conceived and designed the study. LB, YW, JJ, YZ, DL, and WL acquired the data. LX analyzed and interpreted the data. All authors approved the final version to be submitted for publication.

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