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Burden of carotid artery atherosclerosis in Chinese adults: implications for future risk of cardiovascular diseases

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Abstract

Background—Population-based studies of ultrasound measures of carotid atherosclerosis are informative about future risks of cardiovascular disease.

Objectives—To conduct carotid ultrasound screening in a random sample of 24,822 Chinese adults from 10 diverse regions in the China Kadoorie Biobank study (CKB) in 2013–2014.

Methods—Mean intima-media thickness (cIMT) of the common carotid arteries, number of plaques and maximum plaque thickness were examined in various population subgroups in CKB. The cIMT findings in Chinese (mean age 59 years) were compared with those from 2579 Europeans (mean age 63 years) from the UK Biobank.

Results—Overall, the mean cIMT in Chinese was 0.70 mm (SD 0.16) and increased with age by 0.08 mm (SE 0.008) per 10-years older age. About 31% of the Chinese had carotid plaques and the prevalence varied 10-fold with age (6% at 40–49 to 58% at 70–89 years) and 5-fold by region of China (range, 11%–50%). Plaque burden and cIMT were only moderately correlated with each other ($r=0.40$). After adjustment for age, sex and region, plaque prevalence was 50% higher in smokers than in non-smokers (34% vs 23%) and over 2-fold higher in individuals with SBP ≥ 160

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mmHg than those with SBP<120 mmHg (39% vs 19%) in CKB. The overall mean (SE) cIMT values were higher in Chinese than in Europeans (0.70 [0.001] vs 0.66 [0.003] mm, $p<0.001$).

Conclusions—About one-third of Chinese adults had carotid plaques and the overall burden of carotid atherosclerosis was comparable with Europeans, but was even more extreme in some regions of China.

Keywords

Atherosclerosis; plaques; carotid intima-media thickness

Introduction

The health status of the Chinese population, which accounts for one fifth of the global population, has improved substantially over the last half century, with a 50% increase in life expectancy from 49 years in 1949 to 75 years in 2012 (1). In contrast with Western populations where cardiovascular disease (CVD) mortality rates have declined over recent decades, CVD mortality rates have increased exponentially in China over this period (1). Stroke and ischaemic heart disease (IHD) are now the leading causes of premature death in both Chinese and Western populations (2). Since atherosclerosis develops silently over several decades before presentation as a clinical CVD event, population-based studies using carotid artery ultrasound examinations should be informative about future risks of CVD (3–5). Carotid intima-media thickness (cIMT: reflecting hypertrophy of both the intima and media layers of the arterial wall) provides the first morphological evidence of atherosclerosis (5,6), but carotid plaques (focal thickening >1.5 mm of the intima layer of the carotid arteries) are stronger predictors of CVD than cIMT (6,7). Both cIMT and carotid plaques have been widely used in population-based surveys in Western populations for prediction of risk of CVD (8–14). Previous studies of carotid atherosclerosis in Chinese adults have also reported associations of cIMT and plaque with CVD risk factors (15–18), but few population-based studies in China included a sufficient number of participants to reliably assess the age-specific burden of atherosclerosis.

Technological advances in edge detection software in carotid artery ultrasound imaging platforms allow semi-automated methods to measure cIMT and plaques that have facilitated their use in large-scale observational studies and clinical trials (5–7). Automated methods typically locate the carotid bifurcation and measure the thickness of the far wall of the artery at a fixed point proximal to the bifurcation of the common carotid artery to record cIMT. However, detection of carotid plaques is not fully automated and requires a sonographer to acquire ultrasound images bilaterally to include four main segments of the carotid arteries (distal common carotid artery [CCA], carotid artery bifurcation [carotid bulb], proximal internal carotid artery [ICA] and proximal external carotid artery [ECA]) to record the location and number of plaques and measure their maximum thickness.

We conducted B-mode ultrasound imaging of both extra-cranial carotid arteries using such semi-automated methods to measure cIMT, and recorded the presence and number of any of carotid plaques in a random sample of 24,822 participants in the China Kadoorie Biobank (CKB) study. We compared the cIMT findings in Chinese with 2579 age-matched Europeans

from the UK Biobank (UKB) study. The aims of the present report were: (i) to estimate the prevalence of various measures of carotid atherosclerosis in population sub-groups defined by age, region and CVD risk factors; and (ii) and to compare mean cIMT values in the Chinese (CKB) with a European population (UKB) recorded using identical methods and (iii) to review the implications for future risk of CVD in China.

Methods

CKB study population

The CKB study is a prospective study of 0.5 million adults, aged 30-79 years, who were recruited from 10 geographical regions in China that were chosen to include a wide range of behavioural, lifestyle and environmental risk factors (19,20). In each region, temporary assessment clinics were set up in residential centres. A representative 5-6% sample of survivors (i.e. about 33,000) were invited for the 2nd resurvey in 2013-2014 (~8 years after baseline), and 24,822 attended (76% response rate). All participants attending the re-survey underwent a repeat interview and had physical measurements recorded and provided biological samples. Ethics approval was obtained from the appropriate UK authorities (University of Oxford Tropical Research Ethics Committee) and Chinese authorities (Chinese Academy of Medical Sciences). All participants provided written informed consent.

Carotid intima-media thickness (cIMT)

A Panasonic CardioHealth Station was used to acquire and record ultrasound images for four segments of the carotid arteries each involving about 1 cm distance (distal CCA, carotid bifurcation, proximal ICA, and proximal ECA) on both left and right sides. The cIMT measures were recorded only in the distal 1 cm of the CCA, but all 4 segments were screened for the presence or absence of plaques (Supplementary Material: Supplementary methods).

Carotid plaques

Longitudinal scanning of the entire length of the carotid arteries (from the base of the neck to the angle of the jaw) was conducted bilaterally to screen for plaques and pre-plaques in each of the 4 segments of the carotid arteries. Consistent with the Mannheim consensus, a plaque was defined as any focal thickening or protrusion from the wall into the lumen with cIMT >1.5 mm thickness and a pre-plaque was defined as any focal thickening of cIMT >1.0-1.5 mm (6). The number and location (i.e. segment) of plaques or pre-plaques were also recorded. Horizontal scanning of the carotid arteries was used to record the thickness of the largest plaque or pre-plaque.

Carotid imaging quality control

The average time for completion of carotid artery image acquisition, including both cIMT and plaque assessments, was 10 minutes per participant. Random samples (~3%) of carotid ultrasound examinations were checked for quality assessment by one of three radiologists who confirmed that measurements of cIMT, presence and number of plaques and the thickness of the maximum plaque were correctly recorded (Supplementary Material:

Supplementary methods). The radiologists provided a quality score for cIMT and plaque thickness measurements recorded by the sonographers in each of the 10 geographic regions in China.

UKB study population

The UK Biobank (UKB) study is a prospective study of 500,000 UK individuals, aged between 40-69 years, who were recruited during 2006-10 (21). The data from the UK-Biobank resource are publically accessible for scientific research (21). The UKB study conducted ultrasound imaging of the carotid arteries in a subset of participants in 2014-2015, using a Panasonic CardioHealth Station, which involved identical ultrasound devices and procedures to those used in CKB. Data available for the UKB study participants were restricted to results for cIMT on 2579 participants from the pilot phase of the imaging programme (22) (and no data for carotid plaques are currently available).

Statistical methods

Mean values of cIMT, carotid plaque thickness and plaque number were compared between the left and right sides, and the agreement between these measurements was assessed using Pearson correlation coefficients. Linear and logistic regressions were used to assess levels of cIMT and presence of plaque, respectively, by 10-year age groups and standard systolic blood pressure (SBP) groups (<120, 120-139, 140-159, 160 mmHg) after appropriate adjustments (specified for particular results). F-statistics, which indicate the extent to which a risk factor accounts for variance in the outcome of a regression model, were used to compare the strength of associations of carotid measures with the different risk factors. Carotid plaque burden was derived by first standardising the plaque number and maximum width (i.e. dividing each by its standard deviation [SD]) and estimating the average, then multiplying the average value by the SD of the maximum plaque thickness to provide a plaque burden recorded in millimetres units (i.e. interpretable as an enhanced estimate of the maximum plaque thickness). All analyses used SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

Population characteristics

Among the 24,822 CKB participants with carotid ultrasound measures, the mean (SD) age at measurement was 59 (10) years, 38% were men and the mean SBP was 136 (21) mmHg. Overall, 7% had diabetes, 47% of men and 1% of women were current cigarette smokers, and 16% had a prior history of stroke or IHD at the time of the examination.

Quality assurance of carotid measures

Among the 24,822 participants, 694 (3%) had quality assessments of the carotid ultrasound measurements recorded (eTable 1). The overall quality score, reflecting the extent to which the radiologist confirmed that the sonographer had correctly recorded cIMT and plaques, was 85% (range, 75% to 93%) for the 10 centres (eTable 1). The cIMT was correctly measured in 99% (range: 96% to 100%). Plaques were satisfactorily located in 96% (range: 89-100%) and counted accurately in 96% (range 87% to 100%: eTable 1).

Left versus right side measurements

There were no significant differences in the mean values of cIMT, proportions with plaque, number of plaques or maximum plaque thickness between the left and right sides (eTable 2). Likewise, the correlation coefficients between right and left sides were 0.60 for cIMT, 0.50 for presence of plaque, 0.62 for plaque number and 0.58 for maximum plaque thickness, respectively.

Associations with age and region

Mean cIMT was 0.70 (SD 0.16) mm overall and it increased with age by about 0.08 mm (SE 0.008) per 10-year older age (Table 1). Overall, 31% had a carotid plaque, 9% had a pre-plaque and 60% had neither detected. The prevalence of plaques also increased with age, from 6%, 20%, 38% to 58% in the 10-year groups from 40 to 69 and 70-89 (Table 1). The prevalence of plaques also increased with increasing cIMT (Figure 1). Among the 4 carotid artery segments examined, plaques were most frequently located in the carotid bulb (61%) and CCA (35%), and were rarely present in the ICA (3%) or in the ECA (1%).

Both the number of plaques and the maximum plaque thickness also increased linearly with increasing age (Data not shown). In addition to the variation by age, the mean cIMT and percentage with plaque also varied substantially by geographic region (Figure 2, Table 1). The mean cIMT varied by 0.12 mm between the 10 geographic regions (range, 0.64 to 0.76 mm: Table 1). Likewise, the percentage with plaque varied 5-fold by region (range, 11% to 50%: Table 1) after adjustment for other covariates. The 10 geographic regions were classified by percentage with plaque into 3 groups: <20%, 20-40%, and >40% and the mean values of cIMT increased steadily with age even in geographic regions with low average rates of plaque (Figure 2).

Associations of number of plaques with maximum plaque thickness

The maximum plaque thickness was only moderately correlated with the number of plaques ($r = 0.40$: eFigure 1). Hence, we devised a score to combine both measures, referred to as the carotid plaque burden score (see Statistical methods). The overall mean cIMT thickness was only moderately correlated with this carotid plaque burden, with a correlation coefficient of 0.40, overall, and 0.55 excluding cases with no plaque (eFigure 2).

Associations with SBP

Overall, 42% of study participants had hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg). Mean values of cIMT varied substantially by levels of SBP (Table 1) from 0.67 to 0.74 mm for those with SBP < 120 mmHg to those with SBP ≥ 160 mmHg or greater. Likewise, the proportions with plaque varied over 2-fold from 19%, 24%, 31% and 39% for those in the corresponding SBP categories after adjustment for other covariates (Table 1).

Comparison of cIMT values in Chinese versus European populations

The distribution of mean levels of SBP in CKB and UKB is shown for individuals aged 45-54 years, 55-64 years and 65-74 years, respectively in eFigure 3. Mean values of SBP were slightly higher in CKB (130 mmHg, 137 mmHg and 144 mmHg) compared with UKB

(130 mmHg, 135 mmHg, and 140 mmHg) in the corresponding age groups (eFigure 3). The increase in mean level of cIMT with increasing age and blood pressure was more extreme in the Chinese population, CKB, compared with the European population in UKB (Figure 3). At all ages, the overall mean (SE) cIMT values were significantly greater in CKB than in UKB (0.70 [0.001] vs 0.66 [0.003] mm; $p < 0.001$) in this age-sex-adjusted comparison of the sub-set of overlapping age groups in both studies.

Discriminating power of different plaque measures

All carotid plaque measures in CKB also varied by region, and by categories of CVD risk factors, including hypertension and cigarette smoking (eTable 3). The results show the extent to which the number of carotid plaques, plaque thickness and plaque burden varied by these determinants in all participants and in the sub-set with no prior history of CVD at the time of the examination, after adjustment for age, sex and region. The plaque burden showed slightly greater heterogeneity than either the maximum plaque thickness or the number of plaques for hypertension categories (F statistics: 127 vs 112 vs 113, respectively, in participants with no history of CVD).

Prediction of incident cases with carotid plaque versus ischaemic stroke or IHD

Among the sub-set of 23,896 participants aged 40-84 years at re-survey (i.e. excluding those outside this age range), 29.8% had a carotid plaque (Table 2). Using the observed prevalence of carotid plaques and of ischaemic stroke and IHD events in each 5-year age groups, we estimated the projected numbers of additional incident cases of plaque (among people with no plaque), stroke or IHD events likely to occur in the next 0-5 years and 5-10 years, respectively, after this examination. The projected results demonstrated that incident plaques are likely to be ~6-times more frequent than either incident ischaemic stroke or IHD events (1970 vs 296 vs 347, respectively) in the next 0-5 years by the time of the next planned resurvey in 2018, and similarly increased in 5-10 years by 2023 (1926 vs 289 vs 350, respectively).

Discussion

One-third of the Chinese adult study population in CKB had evidence of carotid plaques, and the age-specific prevalence of plaques increased progressively from 6% to 57% in individuals aged 40-49 years to 70-89 years, respectively. The prevalence of plaques varied 5-fold by geographic region and the mean prevalence of plaques was 48% in 3 of the 10 geographic regions studied (Haikou, Harbin and, Liuzhou). Likewise, the prevalence of plaques varied over 2-fold by extreme blood pressure categories. The overall mean cIMT levels in Chinese were slightly greater than those in age-matched European populations assessed using similar methods over the same calendar period. The present study demonstrated the burden of carotid atherosclerosis was even more extreme in several regions in China compared with European populations, suggesting that much of the Chinese population is likely to continue to suffer high absolute risks of CVD over the next few decades.

The age-specific prevalence of carotid plaques observed in CKB in the regions with highest plaque prevalence was comparable to that observed in the Atherosclerosis Risk In Communities (ARIC) study in the USA in the early 1990's, prior to the widespread use of LDL-lowering therapy for the prevention of CVD (14). The ARIC study had reported that 34% of their study population (aged 45-64 years) had a carotid plaque and the prevalence of plaques varied from 22% to 47% among those aged 40 to 64 years, respectively (14). The substantial variation in cIMT and prevalence of plaques by age and region in CKB highlights the importance of studying associations of cardiovascular risk factors (and particularly blood pressure) with both cIMT and carotid plaque and, subsequently, with CVD events across diverse regions of China. The higher age-specific mean values of CIMT observed in the CKB than the UKB population and other Western populations may reflect the higher proportions with untreated CVD risk factors in the Chinese population (8-14, 23-25).

The chief strength of the CKB study population was the availability of measures of both plaque thickness and plaque number, in addition to cIMT measures, in a large population which permitted analysis across a wide range of age groups and diverse urban and rural regions in China. The present study highlights the relevance of carotid plaque burden as a measure of atherosclerosis for between and within-population surveys and in studies assessing associations with genetic and plasma biomarkers for CVD. Consistent with previous reports in Western populations, plaque burden was only modestly correlated with cIMT. The evidence from Western populations suggests that plaque number and plaque thickness are stronger predictors than cIMT for both stroke and IHD (10,11). Future studies will compare the predictive value of cIMT and plaque for incident stroke and IHD events in this population. As a quantitative trait for CVD, measurement of plaque burden should also be particularly informative for future studies examining associations with genetic and plasma biomarkers, as this measure is likely to have much greater statistical power compared with studies using incident stroke or IHD events alone as outcomes (26,27).

One of the limitations of the present study is that data on plaque were limited to presence of plaques, plaque thickness and plaque number. Atherosclerotic plaques leading to stroke events may not necessarily be multiple or unduly large plaques, but plaques with a necrotic centre (including a high lipid and macrophage content) detectable as an echolucent plaques are believed to have a particularly high risk of rupture (28-30). Previous studies have demonstrated that echo-lucent plaques were more strongly predictive for stroke than echogenic plaques (28-30). Future analyses in the present cohort may assess the feasibility of using grey scale median analysis software to quantify grading of echolucent plaques (30).

Conclusions

The substantial burden of carotid plaques in the CKB population, and 5-fold difference observed by region, suggests that other factors (in addition to established CVD risk factors) remain to be discovered that account for differences in measures of atherosclerosis. The burden of carotid atherosclerosis was substantial in the Chinese and comparable with European populations and worse in some regions of China, suggesting future high absolute risks of CVD in China as in European populations. Moreover, unless concerted efforts are

made to lower levels of established risk factors in China, the age-specific death rates from CVD in China are likely to continue to increase over the next few decades.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Abbreviations

CCA	Common carotid artery
cIMT	Carotid-intima media thickness
CKB	China Kadoorie Biobank study
cPLQ	Carotid plaque score
CVD	Cardiovascular disease
ECG	Electrocardiogram
IHD	Ischaemic heart disease
SD	Standard deviation
SE	Standard error
SBP	Systolic blood pressure
UKB	UK-Biobank study

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Perspectives

Competency in Medical Knowledge 1: While both cIMT and carotid plaques increase with age, the mean levels of each are only moderately correlated with the other.

Competency of Medical Knowledge 2: Overall, one-third of the Chinese population had carotid plaques with two-thirds of these present in the carotid bulb and one-third present in the distal 1 cm of the common carotid artery.

Competency in Patient Care: Carotid artery ultrasound should assess both plaque number and maximum plaque width in addition to the more widely measured cIMT.

Competency in Interpersonal and Communication Skills: It is important to discuss the available options for individuals who are undergoing carotid artery ultrasound examinations.

Translational Outlook 1: The burden of carotid atherosclerosis in Chinese population was comparable with European populations, suggesting future high absolute risks of cardiovascular disease in the Chinese comparable with those in European populations.

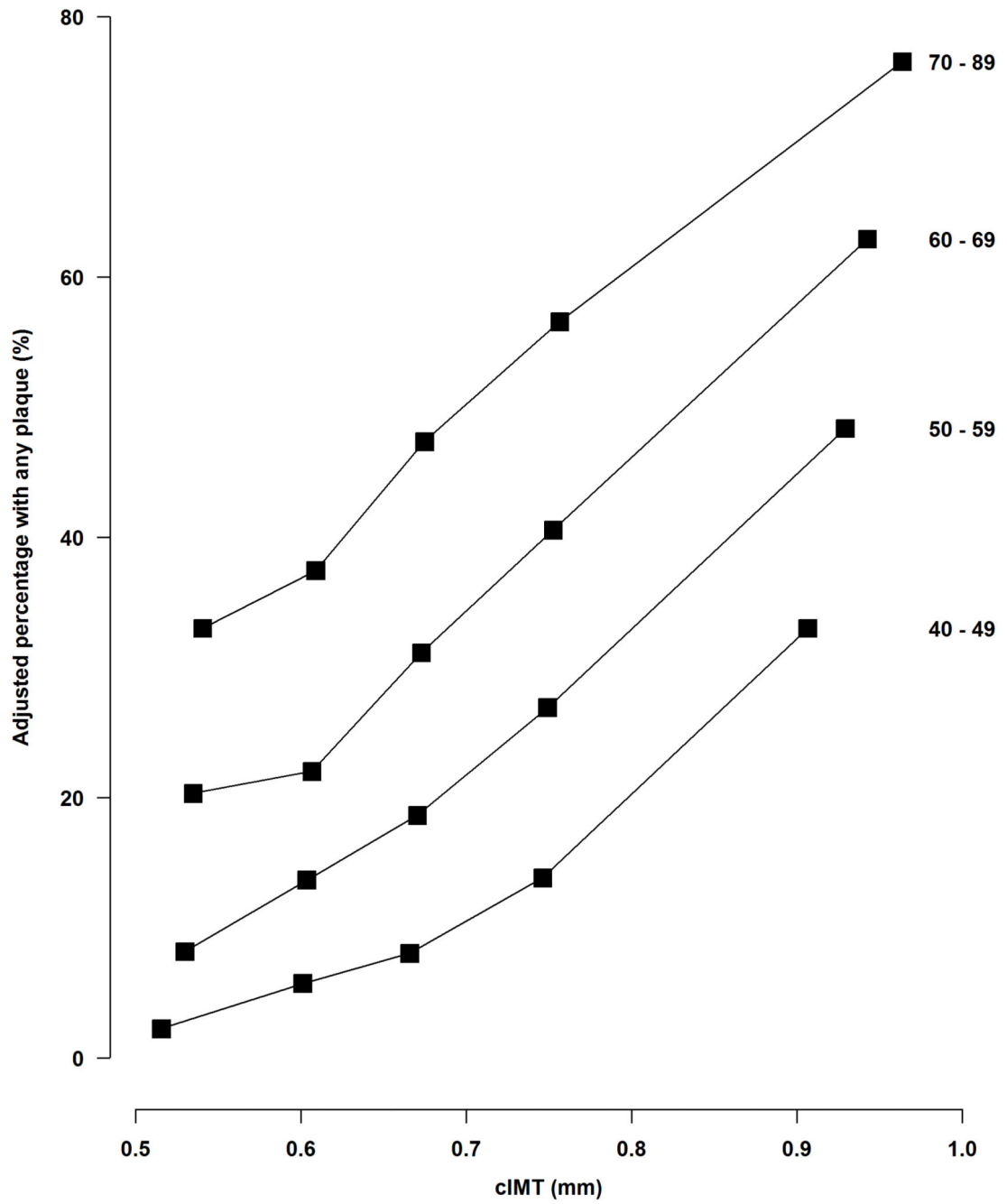


Figure 1. Age-specific percentage with any carotid plaques, by quintiles of cIMT.
 Values are adjusted for sex and geographic region.

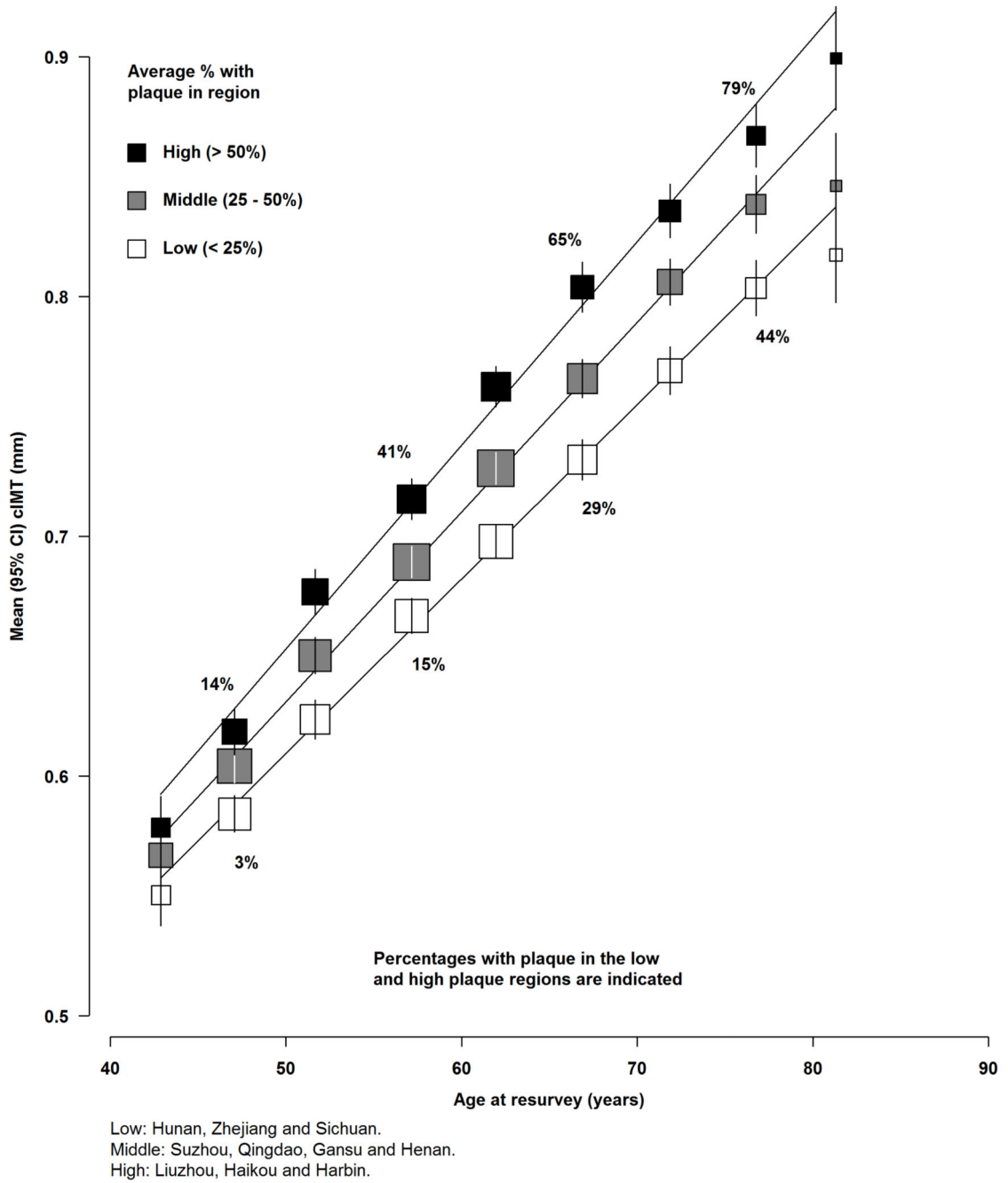


Figure 2. Mean values of cIMT and percentage with plaque by geographic region. Values for geographic region are classified into 3 groups (low, middle and high) and adjusted for sex.

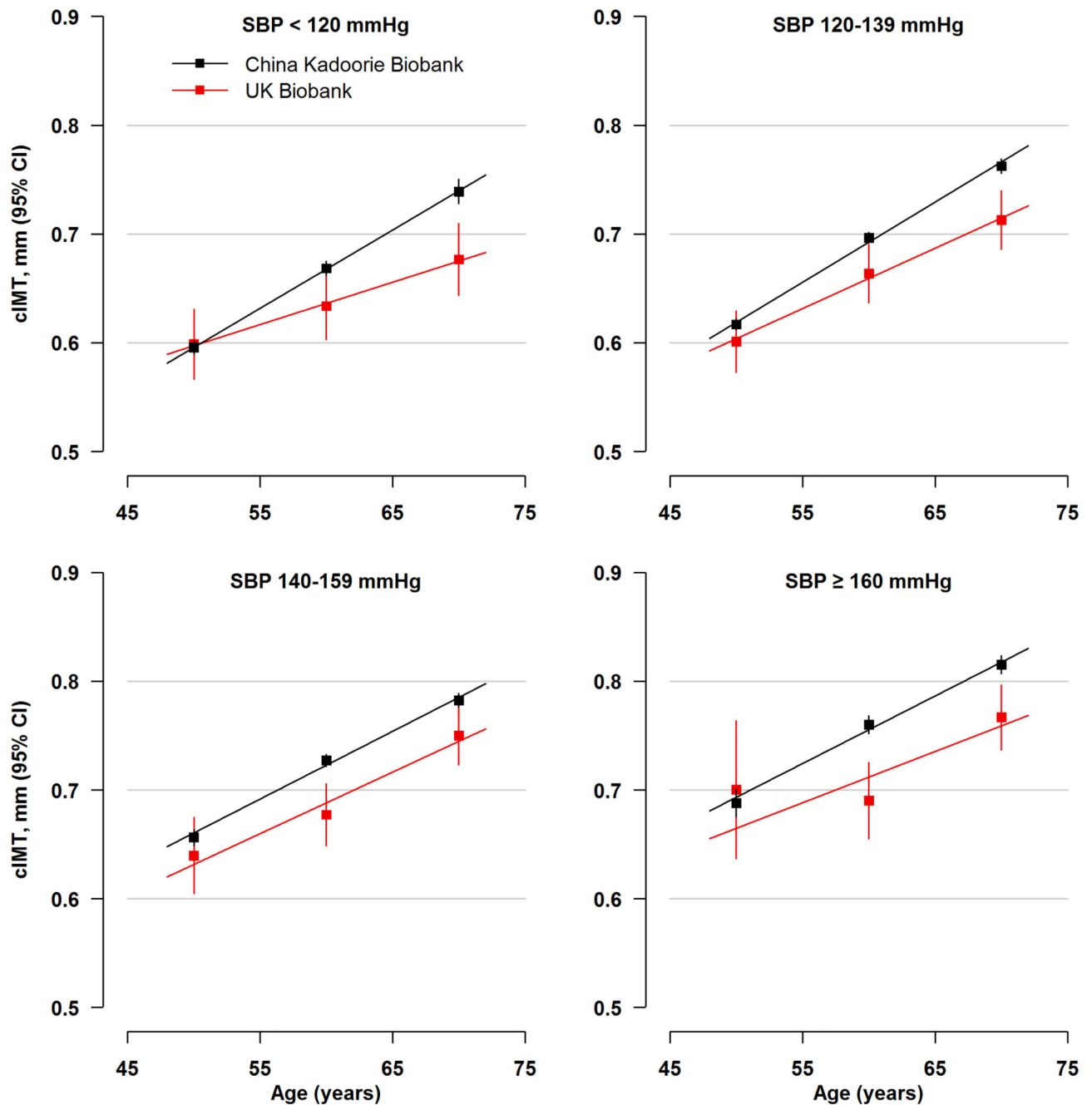


Figure 3. Mean (95%CI) values of cIMT by age and hypertension groups in the Chinese and UK populations aged 45-74 years.

The values for cIMT in the Chinese were based on 21,062 individuals (mean age, 59 years) and in the UK population were based on 2579 individuals (mean age 63 years). The mean (SE) values in the Chinese (0.70 [0.001] mm) were greater than in the UK population (0.68 [0.003] mm, $p < 0.001$)

Table 1

Distribution of mean (SD) values of cIMT and percentage with plaque, by age, sex, hypertension, cigarette smoking and geographic region, after adjustment for age, sex and region as appropriate. Values for plaque in the final column are additionally adjusted for all other group variables. Values for systolic blood pressure (SBP) and current cigarette smoking are the average of those at baseline and at resurvey

		N	cIMT, mm Mean (SD)	Any plaque, % Mean (SD)	Any plaque, % Adjusted mean (SD)
Age (years)	40 - 49	5469	0.59 (0.10)	6% (5%)	6% (6%)
	50 - 59	7680	0.67 (0.13)	20% (13%)	20% (14%)
	60 - 69	7388	0.74 (0.16)	39% (16%)	38% (18%)
	70 - 89	4285	0.82 (0.18)	62% (16%)	58% (17%)
Sex	Men	9496	0.73 (0.18)	33% (24%)	28% (24%)
	Women	15326	0.68 (0.15)	21% (20%)	23% (21%)
SBP (mmHg)	< 120	5442	0.67 (0.13)	19% (15%)	19% (15%)
	120-139	9461	0.69 (0.15)	25% (20%)	24% (20%)
	140-159	6594	0.72 (0.16)	31% (23%)	31% (23%)
	160+	3325	0.74 (0.19)	39% (24%)	39% (24%)
Ever regular smoker	No	15696	0.69 (0.15)	23% (21%)	23% (22%)
	Yes	9126	0.71 (0.18)	35% (24%)	34% (24%)
Residence	Rural	14154	0.69 (0.15)	21% (17%)	21% (18%)
	Urban	10668	0.72 (0.17)	36% (21%)	35% (21%)
Geographic region	Hunan	2880	0.70 (0.17)	12% (15%)	11% (15%)
	Zhejiang	2922	0.68 (0.15)	17% (17%)	16% (17%)
	Sichuan	2775	0.64 (0.13)	17% (16%)	16% (18%)
	Suzhou	2804	0.68 (0.15)	19% (17%)	18% (18%)
	Qingdao	1592	0.72 (0.16)	23% (19%)	23% (20%)
	Gansu	2481	0.71 (0.14)	24% (19%)	25% (20%)
	Henan	3096	0.70 (0.16)	38% (21%)	38% (22%)
	Liuzhou	2746	0.71 (0.16)	42% (22%)	41% (23%)
	Haikou	1377	0.73 (0.19)	46% (24%)	47% (26%)
Harbin	2149	0.76 (0.19)	53% (23%)	50% (24%)	
All		24822	0.70 (0.16)	31% (46%)	31% (46%)

Table 2

Estimated number of additional cases of plaque, ischaemic stroke and ischaemic heart disease in the 0-5 and 5-10 year periods following resurvey

	At resurvey		Extra cases in years post-resurvey	
	N	Prevalence	0-5	5-10
Any plaque	7117	29.8%	1970	1926
Ischaemic stroke	943	3.9%	296	289
Ischaemic heart disease	2215	9.3%	347	350
Total	8726	36.5%	2614	2565

Values were based on prevalence in 23896 participants aged 40-84 at resurvey.