

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

Robert Clarke<sup>1\*</sup>, Huaidong Du<sup>1,2\*</sup>, Om Kurmi<sup>1\*</sup>, Sarah Parish<sup>1,2\*</sup>, Meng Yang<sup>3</sup>, Matthew Arnold<sup>1</sup>, Yu Guo<sup>4</sup>, Zheng Bian<sup>4</sup>, Liang Wang<sup>3</sup>, Yuexin Chen<sup>5</sup>, Rudy Meijer<sup>6</sup>, Sam Sansome<sup>1</sup>, John McDonnell<sup>1</sup>, Rory Collins<sup>1</sup>, Liming Li<sup>4,7\*</sup>, Zhengming Chen<sup>1\*</sup>  
for the China Kadoorie Biobank Study Group

<sup>1</sup>Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Richard Doll Building, Oxford OX3 7LF, UK; <sup>2</sup>MRC Population Health Research Unit, University of Oxford, Richard Doll Building, Oxford OX3 7LF, UK; <sup>3</sup>Division of Ultrasound Diagnosis, Peking Union Medical College Hospital, Peking Union Medical College Hospital, Beijing, China; <sup>4</sup>Chinese Academy of Medical Sciences, Beijing, China; <sup>5</sup>Center of Vascular Surgery, Peking Union Medical College Hospital, Beijing, China; <sup>6</sup>Department of Radiology, University Medical Centre Utrecht, Netherlands; and <sup>7</sup>Department of Epidemiology and Statistics, School of Public Health, Peking University Health Science Center, Beijing, China

\* These authors contributed equally

**Source of Support:** This work was supported by the UK Medical Research Council (Clinical Trial Service Unit A310); the British Heart Foundation (CH/1996001/9454); Cancer Research UK (C500/A16896); the Kadoorie Charitable Foundation (during 2002-2009); the Wellcome Trust (104085/Z/14/Z); and the Chinese National Natural Science Foundation (81390541).

**Disclaimers:** None

## **Corresponding author:**

Professor Robert Clarke, Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, Richard Doll Building, University of Oxford, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK.  
Email: robert.clarke@ndph.ox.ac.uk  
Tel: +44-1865-743743; Fax: +44-1865-743985

Reprints of this article will not be made available.

**Word count: 4380 (abstract, text & references)**

3 November 2016

## **Abstract**

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

**Design:** Cross-sectional studies of carotid artery atherosclerosis in 24,822 Chinese adults from the China Kadoorie Biobank (CKB) and 2579 Europeans from the UK Biobank.

**Methods:** Mean intima-media thickness (cIMT) of the common carotid arteries, and presence of carotid artery plaque were examined in the CKB study. The cIMT findings in Chinese (mean age 59 years) were compared with a European population (mean age 62 years).

**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 63% at 70-89 years) and 4-fold by region (range, 14%-57%). After adjustment for age, sex and region, plaque prevalence was higher in smokers than in non-smokers (36% vs 28%) and 2-fold higher in individuals with SBP $\geq$ 160 mmHg than those with SBP<120 mmHg (44% vs 22%) in the CKB study. Mean cIMT was similar in the younger Chinese and European adults, but increased more steeply with age in the Chinese ( $p=0.002$ ).

**Conclusions:** About one-third of Chinese adults had carotid plaques. The rate of progression of carotid atherosclerosis with age was more extreme in the Chinese compared with the European population, highlighting the need for more intensive strategies for cardiovascular disease prevention in China.

**Word count:** 238

**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.<sup>1</sup> Age standardised CVD mortality rates have increased exponentially in China over recent decades, in contrast with Western populations where CVD mortality rates have declined over this period.<sup>1</sup> Indeed, cardiovascular diseases (CVD), including stroke and ischaemic heart disease (IHD), are now the leading causes of premature death in both Chinese and Western populations.<sup>2</sup> 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.<sup>3-5</sup>

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,<sup>5,6</sup> but carotid plaques (focal thickening >1.5 mm of the intima layer of the carotid arteries) are stronger predictors of CVD than cIMT.<sup>6,7</sup> Both cIMT and carotid plaques have been widely used in population-based surveys in Western populations for prediction of risk of CVD.<sup>8-14</sup> Previous studies of carotid atherosclerosis in Chinese adults have reported associations of cIMT and plaque with CVD risk factors,<sup>15-18</sup> but few studies in China have included a sufficient number of participants to reliably assess the age-specific burden of atherosclerosis in the Chinese population.

Technological advances in edge detection software in carotid artery ultrasound imaging platforms allow automated methods to measure cIMT and semi-automated methods to measure plaques that have facilitated their use in large-scale

observational studies and clinical trials.<sup>5-7</sup> 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. 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 those in Europeans from the UK Biobank (UKB) study 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.<sup>19,20</sup> 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 2<sup>nd</sup> resurvey in 2013-2014 (~8-10 years after baseline), and 24,822 attended (76% response rate). All participants attending the re-survey had a repeat interview and had physical measurements recorded. Participants also provided blood and urine samples (for long-term storage for future laboratory assays) and underwent carotid imaging. 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*

All participants had a carotid ultrasound examination conducted on a single occasion. 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  $>1.0 \leq 1.5$  mm.<sup>6</sup> The number and location (i.e. segment) of plaques or pre-plaques were also recorded by the sonographers. Cross-sectional scanning of the carotid arteries was used to record the thickness of the largest plaque or pre-plaque. 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 cIMT had been measured correctly at 4 CCA segments, and that presence and number of plaques and the thickness of the maximum plaque had been located and counted satisfactorily in each of the 10 CCA segments. This provided a quality score for the cIMT and plaque thickness measurements recorded by sonographers in each region. (See Supplementary methods for additional details).

### *UK Biobank (UKB) study population*

UK Biobank (UKB) study is a prospective study of 500,000 UK individuals, aged between 40-69 years, who were recruited during 2006-10.<sup>21</sup> The data from the UK-Biobank resource are publically accessible for scientific research.<sup>21</sup> The UKB study conducted ultrasound imaging of the carotid arteries in a subset of participants in

2013-2014 using a Panasonic CardioHealth Station similar to the machines used in CKB. Data for the UKB were restricted to results for cIMT on 2579 participants for the pilot phase of the imaging programme (and no data for carotid plaques are currently available).<sup>22</sup>

### *Statistical methods*

Spearman correlation coefficients were used to compare the associations between different carotid measures. Linear regression was used for comparisons of mean cIMT by risk factor levels. Comparisons of percentages of participants with plaque, with adjustments as indicated, were derived from logistic regression estimates of odds ratios for plaque relative to the overall odds of plaque. Carotid plaque burden was derived by standardising the plaque number and maximum size (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 millimetre units. Comparisons of the odds ratios for the prevalence of CVD by risk factor levels were estimated by logistic regression with likelihood ratio  $X^2$  tests for trend with category levels. The prevalence of plaques, ischaemic stroke, and ischaemic heart disease in 5-year age groups in CKB were used to project the likely numbers of additional events that will occur in the next 0-5 and 5-10 years in the subset aged 40-84 years at re-survey. 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 137 (21) mmHg (Table 1). Overall, 47% of men and 1% of women were current cigarette smokers, 10% had diabetes, 8% had prior ischaemic heart disease and 5% had prior stroke at the time of the examination (Table 1). Selected population characteristics in the Chinese are compared with the Europeans in Table 1.

### *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 radiologists confirmed that the sonographers 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 97% (range 87% to 100%: eTable 1). 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 Spearman correlation coefficients between right and left sides were 0.69 for cIMT, 0.50 for presence of plaque, 0.58 for plaque number and 0.57 for maximum plaque thickness, respectively.



### *Associations with age and region*

Mean cIMT was 0.70 (SD 0.16) mm overall and increased by about 0.08 (SE 0.008) mm per 10-year older age (Table 2). Overall, 31% had a carotid plaque, 9% had a pre-plaque and 60% had no plaques detected. The unadjusted prevalence of plaques also increased with age, from 6%, 21%, 41% to 63% with decades of age from 40-49 years to 70-89 years (Table 2). 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 detected 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). The mean cIMT varied by 0.13 mm between the 10 geographic regions (range, 0.59 to 0.82 mm: Table 2). Likewise, the percentage with plaque varied by almost 4-fold by region (range, 14% to 57%: Table 2; eFigure 1). Analysis of the regional variation in the presence of plaques indicated no particular north-south gradient, but there was a tendency for a higher prevalence of plaques in urban than in rural regions (eFigure 1). When the 10 geographic regions were classified into 3 groups by percentage with plaque: <20%, 20-40%, and >40% the mean values of cIMT increased steadily with age even in geographic regions with low average prevalence 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 ( $r = 0.45$ : eFigure 2). Hence, to combine information from both measures, we devised a weighted average score referred to as the carotid plaque burden (see Statistical Methods). The overall mean cIMT thickness was only moderately

correlated with the carotid plaque burden, with a correlation coefficient of 0.51, overall, and 0.36 excluding cases with no plaque (eFigure 3).

#### *Associations with systolic blood pressure*

Overall, 34% of study participants had hypertension (SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg). Mean values of cIMT varied substantially by levels of SBP (Table 2) from 0.67, 0.69, 0.72 and 0.74 mm for those with SBP < 120 mmHg, 120-139 mmHg, 140-159 mmHg, 160 mmHg or greater, respectively. Likewise, the proportions with plaque varied 2-fold from 22%, 28%, 35% and 43% for those in the corresponding SBP categories after adjustment for other covariates (Table 2).

#### *Comparison of cIMT values in Chinese versus European populations*

Mean cIMT was similar in the younger Chinese and European adults, but increased more steeply with age in the Chinese ( $p=0.002$ ; Figure 3). Among participants aged 70-74 years, mean cIMT was 0.05 (95% CI: 0.04-0.07) mm higher in the Chinese. Mean values of SBP at ages 45-54 years, 55-64 years and 65-74 years were slightly higher in CKB (130 mmHg, 137 mmHg and 144 mmHg) than in UKB (130 mmHg, 135 mmHg, and 140 mmHg), respectively (eFigure 4).

#### *Discriminating power of different plaque measures for prior CVD*

All carotid plaque measures varied by the presence of diagnosed prior CVD at the time of the examination (eTable 3). The results show the extent to which the presence of plaques, the number of carotid plaques, size of the largest plaque and plaque burden varied by the presence or absence of diagnosed CVD at the time of the examination, after adjustment for age, sex and region. Comparison of the  $\chi^2$  test results for the associations of individual plaque measures with CVD demonstrated

that the plaque burden was more strongly associated with CVD than either presence of plaque, number of plaques or the size of the largest plaque (92.9 vs 55.2 vs 78.8 vs 77.0), respectively.

*Projection 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, 29.8% had a carotid plaque (Table 3). We projected the numbers of additional incident cases of plaque, stroke or IHD events likely to occur in the next 0-5 years and 5-10 years, respectively, after this examination. Incident plaques were projected to be ~6-times more frequent than either incident ischaemic stroke or IHD events (1973 vs 372 vs 410, respectively) in the next 0-5 years (i.e., by the time of the next planned resurvey in 2018) and similarly increased in 5-10 years by 2023 (1934 vs 340 vs 401, 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 63% in individuals aged 40-49 years to 70-89 years, respectively. Likewise, the burden of subclinical atherosclerosis varied almost 4-fold by geographic region and 2-fold by extreme blood pressure categories. Mean cIMT was similar in the younger Chinese and European adults but increased more steeply with age in the Chinese ( $p=0.002$ ). 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.<sup>8-14, 23-25</sup> While a previous report acknowledged that methodological differences in recording cIMT between studies make it difficult to define age and sex-specific normative percentile values for Western and Asian populations,<sup>26</sup> the between population comparisons in the present report were based on use of an identical carotid ultrasound protocol to record cIMT in both the CKB and UKB studies. Results from UKB are currently limited and may not be representative of the UK population as a whole, and although the CKB study encompasses diverse regions of China it also may not be fully representative of the Chinese population. Hence, some of the between-study differences could also reflect differences in socioeconomic factors of the respondents between UKB and CKB. Nevertheless, the results suggests that in many regions of China, people at high risk are likely to continue to suffer high absolute risks of CVD over the next few decades unless more intensive strategies for cardiovascular prevention are implemented now.

The age-specific prevalence of carotid plaques observed in CKB 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.<sup>14</sup> 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.<sup>14</sup> The substantial variation in cIMT and plaque prevalence 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 in the Chinese population.

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.<sup>10,11</sup> 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.<sup>27,28</sup>

Consistent with previous reports, it is likely that much of the between-study heterogeneity in cIMT values may reflect differences in the prevalence of established risk factors.<sup>26</sup> An additional limitation of the present study was that there were no data on characteristics of “vulnerable” plaques (i.e. those with a necrotic centre including a high lipid and macrophage content detectable as echo-lucent plaques).<sup>29-</sup>

<sup>31</sup> Previous studies have demonstrated that echo-lucent plaques were more strongly predictive for stroke than echogenic plaques.<sup>29-31</sup>

The substantial burden of carotid plaques in the CKB population, and 4-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 carotid measures. The burden of atherosclerosis in Chinese is substantial, suggesting future high absolute risks of stroke in the Chinese population. 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.

### **Acknowledgements**

This research was undertaken (in part) using the UK Biobank Resource.

### **Declaration of Conflicting Interests**

The authors declare that there is no conflict of interest.

### **Author contributions**

RC, SP, ZC contributed to conception, analysis, and interpretation, and drafted the manuscript. HD and OK contributed to design, acquisition and critical review of the manuscript. MA contributed to analysis and critical review of the manuscript. MY, YO, ZB, LW, YC, RM, SM, JMcD contributed to data acquisition and critical review of the manuscript. RCo and LL contributed to conception, interpretation and analysis and critical revision of the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

## References

1. People's Republic of China health system review. The World Health Organization. Regional Office for the Western Pacific. Health Systems in Transition, vol. 5, no. 7; 2015.
2. Global Burden of Disease Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 385: 117–171.
3. Pignoli P, Tremoli E, Poli A, et al. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation* 1986; 74: 1399–1406.
4. O'Leary DH and Bots ML. Imaging of atherosclerosis: carotid intima-media thickness. *Eur Heart J* 2010; 31: 1682–1689.
5. Bots ML, Evans GW, Riley WA, et al. Carotid intima-media thickness measurements in interventional studies. Design options, progression rates, and sample size considerations: a point of view. *Stroke* 2003; 34: 2985–2994.
6. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr* 2008; 21: 93–111.
7. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. *Circulation* 2010; 122: 2748–2764.

8. Den Ruijter HM, Peters SA, Anderson TJ, et al. Common carotid-intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA* 2012; 308: 796–803.
9. Lorenz MW, Polak JF, Kavousi M, et al. Carotid intima media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *Lancet* 2012; 379: 2053-2062.
10. Inaba Y, Chen JA and Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. *Atherosclerosis* 2012; 220: 128–133.
11. Polak JF, Szklo M, Kronmal RA, et al. The value of carotid artery plaque and intima-media thickness for incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. *JAMA* 2013; 2(2):e00008710.
12. Plichart M, Celermajer DS, Zureik M, et al. Carotid intima-media thickness in plaque-free site, carotid plaques and coronary heart disease risk prediction in older adults. The Three-City Study. *Atherosclerosis* 2011; 219: 917-924.
- 13) Ohira T, Shahar E, Iso H, et al. Carotid artery wall thickness and risk of stroke subtypes: the Atherosclerosis Risk in Communities study. *Stroke* 2011;42:397-403.
14. Li R, Duncan BB, Metcalf PA, et al. for the Atherosclerosis Risk in Communities (ARIC) Study Investigators. B-mode-detected carotid artery plaque in a general population. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Stroke* 1994; 25: 2377-2383.



15. Niu L, Zhang Y, Qian M, et al. Impact of multiple cardiovascular risk factors on carotid artery intima-media thickness and elasticity. *PLoS One* 2013; 8:e67809.
16. Liang Y, Yan Z, Sun B, et al. Cardiovascular risk profiles for peripheral artery disease and carotid atherosclerosis among Chinese older people: a population-based study. *PloS One* 2014; 9:e85927.
17. Ren L, Cai J, Liang J, et al. Impact of cardiovascular risk factors on carotid intima-media thickness and degree of severity: a cross-sectional study. *PloS One* 2015; 10:e0144182.
18. Xie W, Liu J, Wang W, et al. Five-year change in systolic blood pressure is independently associated with carotid atherosclerosis progression: a population-based cohort study. *Hypertens Res* 2014; 37: 960-965.
19. Chen Z, Li L, Chen Y, et al. Cohort profile: the Kadoorie Study of Chronic Disease in China (KSCDC). *Int J Epidemiol* 2005; 34: 1243-1249.
20. Chen Z, Chen J, Collins R, et al. China Kadoorie Biobank of 0.5 million people: survey methods, baseline characteristics and long-term follow-up. *Int J Epidemiol* 2011; 40: 1652-1666.
21. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 2015; 12(3): e1001779.
22. UK Biobank imaging modality: carotid ultrasound.  
[http://biobank.ctsu.ox.ac.uk/crystal/docs/carult\\_explan\\_doc.pdf](http://biobank.ctsu.ox.ac.uk/crystal/docs/carult_explan_doc.pdf). (2015, accessed 24 May 2016)

23. Sillesen H, Muntendam P, Adourian A, et al. Carotid plaque burden as a measure of subclinical atherosclerosis. *JACC Cardiovasc Imaging* 2012; 5: 681-689.
24. Engelen L, Ferreira I, Stehouwer CD, et al, on behalf of the Reference Values for Arterial Measurements Collaboration. Reference intervals for common carotid intima-media thickness measured with echotracking: relation with risk factors. *Eur Heart J* 2013; 34: 2368-2380.
25. Lim TK, Lim E, Dwivedi G, et al. Normal value of carotid intima-media thickness — a surrogate marker of atherosclerosis: quantitative assessment by B-mode carotid ultrasound. *J Am Soc Echocardiogr* 2008; 21: 112-116.
26. Liao X, Norata GD, Polak JF et al. Normative values for carotid intima media thickness and its progression: Are they transferrable outside of their cohort of origin? *Eur J Prev Cardiol* 2016; 23: 1165–1173.
27. Bis JC, Kavousi M, Franceschini N, et al. Meta-analysis of genome-wide association studies from the CHARGE consortium identifies common variants associated with carotid intima media thickness and plaque. *Nat Genet* 2011; 43 :940-947.
28. den Hoed M, Strawbridge RJ, Almgren P, et al. GWAS-identified loci for coronary heart disease are associated with intima-media thickness and plaque presence at the carotid artery bulb. *Atherosclerosis* 2015; 239: 304–1027.
29. Mathiesen EB, Børnaa KH and Joakimsen O. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis: the Tromsø study. *Circulation* 2001; 103: 2171-2175.

30. Peters SAE, Bots ML, Lind L, et al. on behalf of the METEOR study group. The impact of variability in ultrasound settings on the measured echolucency of the carotid intima-media. *J Hypertens* 2013; 31: 1861-1867.

31. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. *Cerebrovasc Dis* 2012; 34: 290-296.

## Legends

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

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

**Figure 3: Comparison of the increase in mean carotid intima-media thickness (cIMT) with age in Chinese and UK populations aged 45-74 years.** Overall means are adjusted for sex. CKB: China Kadoorie Biobank; UKB: UK Biobank. Numbers of individuals are shown in brackets.

**Table 1: Distribution of demographic, medical history, physical measurements and carotid measurements in the China Kadoorie Biobank and UK Biobank studies**

<b>Mean (SD) or n (%)</b>	<b>China Kadoorie Biobank (n=24822)</b>	<b>UK Biobank (n=2579)</b>
<b>Demographic/medical history</b>		
Age, years	59.0 (10.2)	61.9 (7.5)
Sex, % male	9496 (38.3)	1254 (48.6)
Ever regular smoker, n (%)	9126 (36.8)	703 (27.3)
Prior ischaemic heart disease, n (%)	1852 (7.5)	143 (5.5)
Prior stroke, n (%)	1330 (5.4)	25 (1.0)
Diabetes		
Diagnosed, n (%)	1837 (7.4)	93 (3.6)
Screen detected, n (%)	590 (2.4)	-
<b>Physical measurements</b>		
Height, cm	158 (8.3)	169 (9.4)
Weight, kg	60.4 (11.0)	76.6 (15.2)
BMI, kg/m <sup>2</sup>	24.2 (3.5)	26.7 (4.2)
SBP, mm Hg	137 (21)	138 (18)
DBP, mm Hg	78 (11)	79 (10)
<b>Carotid measurements</b>		
cIMT	0.70 (0.16)	0.68 (0.13)
Any plaque, n (%)	7668 (30.9)	-

**Table 2: 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.

		<b>N</b>	<b>cIMT, mm Mean (SD)</b>	<b>Any plaque, % (SD)</b>	<b>Any plaque, adjusted % (SD)</b>
Age (years)	40 - 49	5471	0.59 (0.10)	6% (24%)	7% (26%)
	50 - 59	7678	0.67 (0.13)	21% (41%)	22% (41%)
	60 - 69	7389	0.74 (0.16)	41% (49%)	40% (49%)
	70 - 89	4284	0.82 (0.18)	63% (48%)	61% (49%)
Sex	Men	9496	0.73 (0.18)	39% (49%)	35% (48%)
	Women	15326	0.68 (0.15)	26% (44%)	28% (45%)
SBP (mmHg)	<120	5442	0.67 (0.13)	22% (41%)	22% (42%)
	120-139	9461	0.69 (0.15)	28% (45%)	28% (45%)
	140-159	6594	0.72 (0.16)	36% (48%)	35% (48%)
	160+	3325	0.74 (0.19)	44% (50%)	43% (50%)
Diabetes	No	22395	0.70 (0.16)	30% (46%)	30% (46%)
	Yes	2427	0.74 (0.18)	43% (49%)	40% (49%)
Ever regular smoker	No	15696	0.69 (0.15)	28% (45%)	28% (45%)
	Yes	9126	0.71 (0.18)	36% (48%)	36% (48%)
Residence	Rural	14154	0.69 (0.15)	24% (43%)	25% (43%)
	Urban	10668	0.72 (0.17)	39% (49%)	39% (49%)
Geographic region	Hunan	2880	0.70 (0.17)	14% (34%)	13% (34%)
	Zhejiang	2922	0.68 (0.15)	19% (39%)	19% (39%)
	Sichuan	2775	0.64 (0.13)	20% (40%)	20% (40%)
	Suzhou	2804	0.68 (0.15)	22% (41%)	21% (41%)
	Qingdao	1592	0.72 (0.16)	26% (44%)	26% (44%)
	Gansu	2481	0.71 (0.14)	27% (44%)	29% (45%)
	Henan	3096	0.70 (0.16)	42% (49%)	43% (49%)
	Liuzhou	2746	0.71 (0.16)	46% (50%)	46% (50%)
	Haikou	1377	0.73 (0.19)	51% (50%)	52% (50%)
	Harbin	2149	0.76 (0.19)	57% (50%)	55% (50%)
<b>All</b>		<b>24822</b>	<b>0.70 (0.16)</b>	<b>31% (46%)</b>	<b>31% (46%)</b>

**Table 3: Estimated number of additional cases of plaque, ischaemic stroke and ischaemic heart disease in the 0-5 and 5-10 year periods following resurvey.**

Values were based on prevalence in 23,896 participants aged 40-84 at resurvey.

	At resurvey		Extra cases in years post-resurvey	
	N	Prevalence	0-5	5-10
Any plaque	7117	29.8%	1973	1934
Ischaemic stroke	1190	5.0%	372	340
Ischaemic heart disease	2437	10.2%	410	401
Total	8921	37.3%	2755	2675

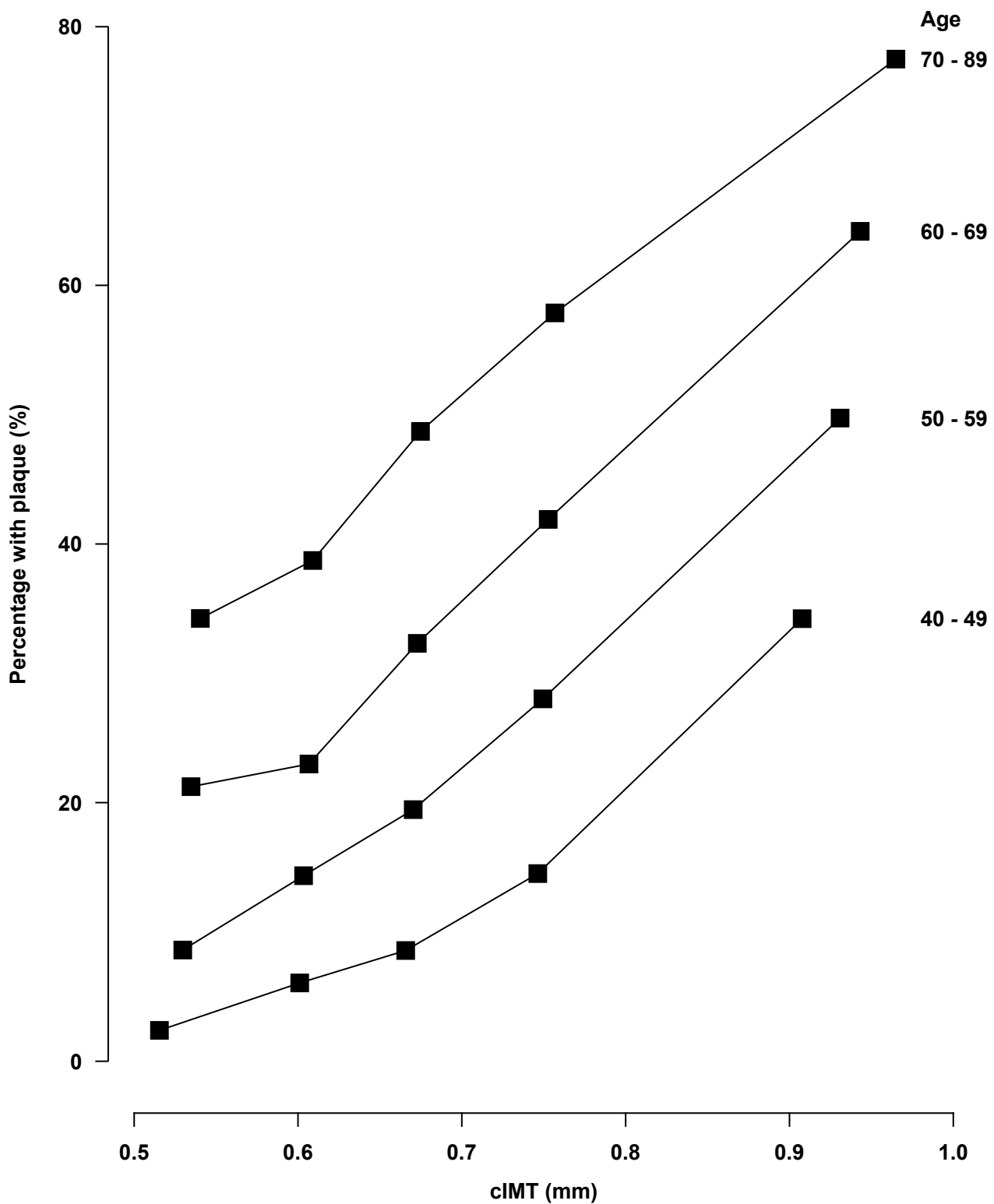
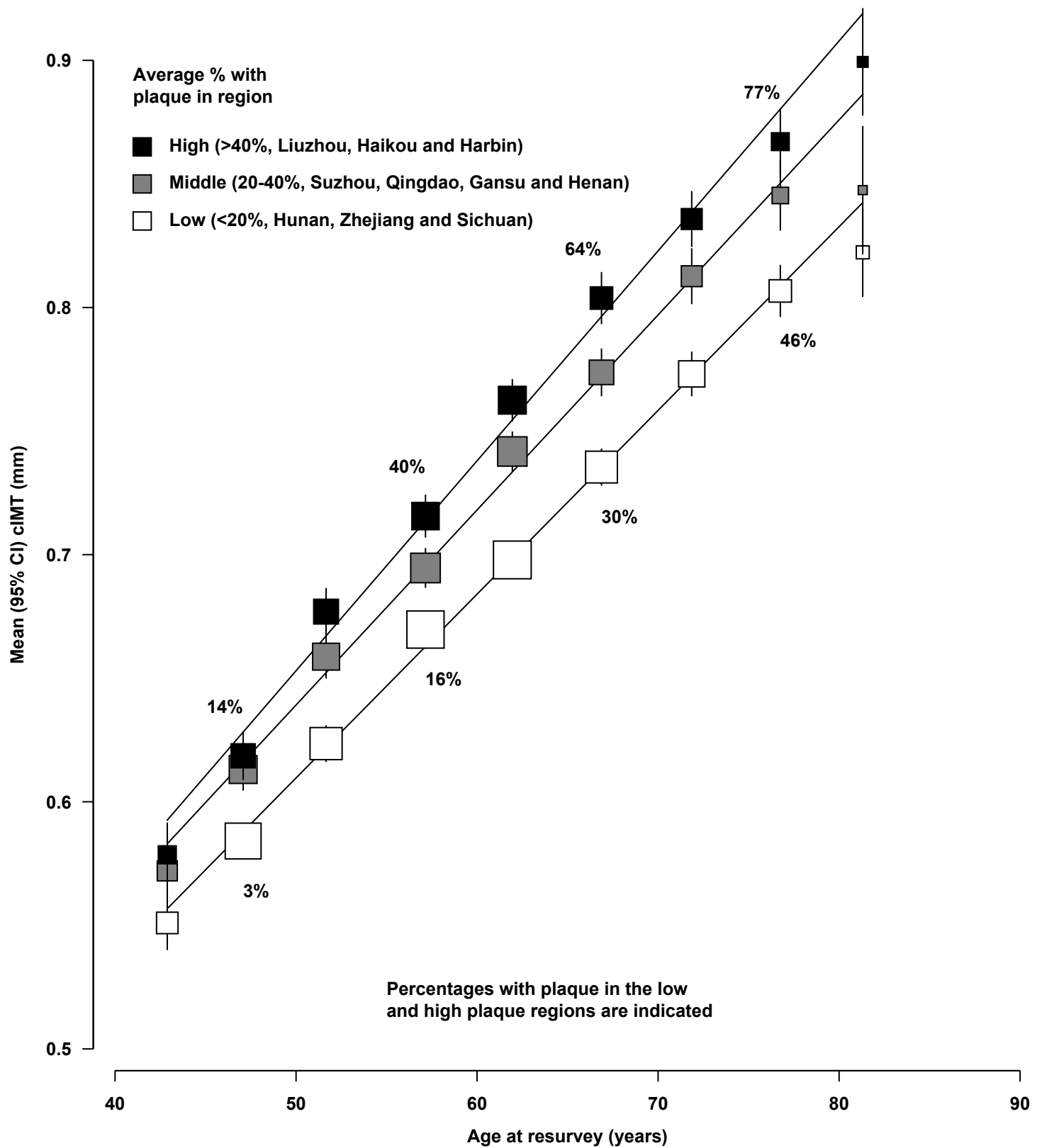
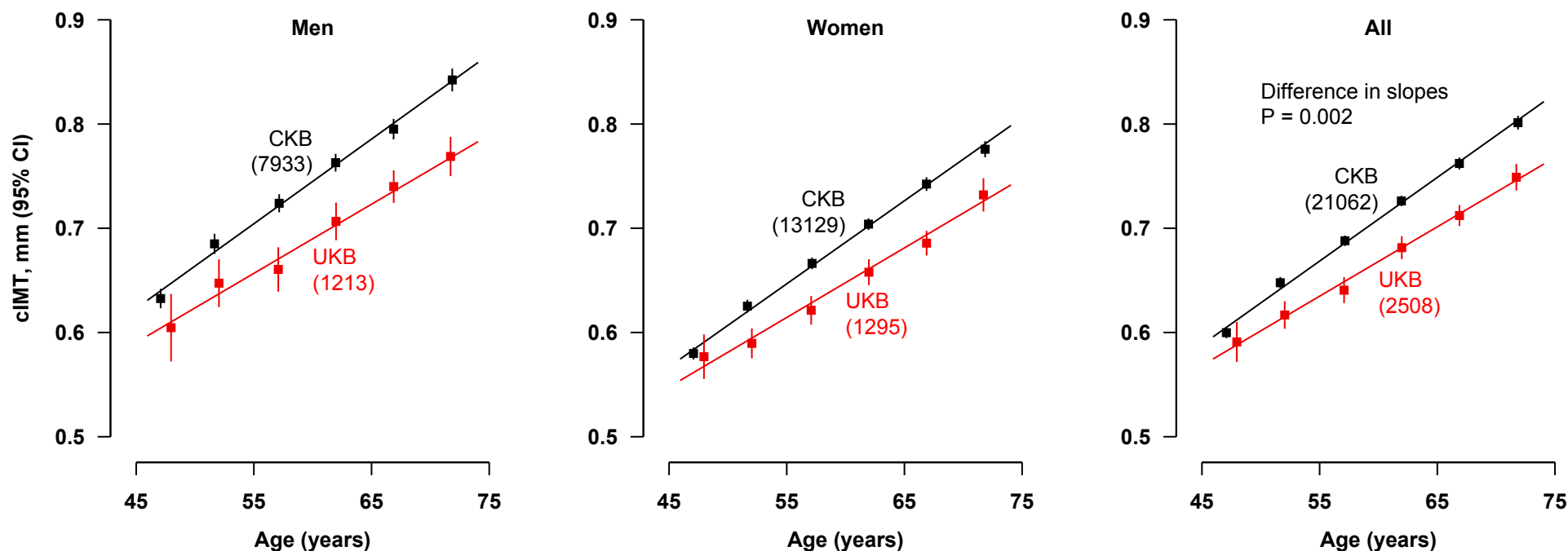


Figure 1: Age-specific percentage with carotid plaque, by quintiles of cIMT. Values are adjusted for sex and geographic region.





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



**Figure 3: Comparison of the increase in mean carotid intima-media thickness (cIMT) with age in Chinese and UK populations aged 45-74 years. Overall means are adjusted for sex. CKB: China Kadoorie Biobank; UKB: UK Biobank. Numbers of individuals are shown in brackets.**

# Supplementary Material for “Burden of carotid artery atherosclerosis in Chinese adults: implications for future risk of cardiovascular diseases”

	Page
Table of Contents	1
Supplementary Methods	2
eTable 1: Assessment of the quality of ultrasound measures of cIMT and carotid plaque burden, by geographic regions.	3
eTable 2: Agreement of carotid measures between right and left sides in all participants at resurvey (n=24,822).	4
eTable 3: Association of presence of plaque, plaque number and size and carotid plaque burden with cardiovascular disease (CVD) at resurvey. Odds ratios for CVD (n=4150) were conducted in all 24,822 participants with carotid measures at resurvey after adjustment for age, sex and region.	5
eFigure 1: Regional variation in percentage of participants with carotid plaque. Regions are ordered by decreasing % with plaque, after adjustment for age and sex.	6
eFigure 2: Correlation of the number of plaques by maximum plaque thickness.	7
eFigure 3: Correlation of carotid intima-media thickness against carotid plaque burden.	8
eFigure 4: Age-specific distribution of systolic blood pressure (SBP) in Chinese and UK populations. Values for Chinese are shown in black and UK in red.	9

## Supplementary Methods

### *Blood pressure:*

Blood pressure was recorded at the same visit as when the carotid measures were recorded. Blood pressure was measured twice by trained staff using an Omron UA-779 digital sphygmomanometer after participants had remained at rest in the seated position for at least 5 minutes. If the difference between the two measurements was greater than 10 mm Hg for the SBP, a third measurement was obtained and the last two measurements were recorded and the mean of the two recorded values of SBP were used in all analyses.

### *cIMT and carotid plaque acquisition*

The study participants were examined in the supine position with their head tilted at approximately 45° to the contralateral side while resting their head using a triangular pillow. Longitudinal images of the far wall of the carotid artery were recorded using a high resolution linear ultrasound probe. B-mode ultrasound displays cIMT as a double line pattern on the far vessel wall of the common carotid artery. The cIMT was measured in the distal 1cm of the CCA just before the bifurcation at four predefined angles (two on each side) based on the Meijer Carotid Arc, using an in-built electronic transducer position guidance, including the right CCA at 150° and 120° and the left CCA at 210° and 240°. Hence, mean cIMT was estimated as the mean of four measurements per person. The Panasonic device automatically recorded cIMT measurements at end-diastole using real-time arterial distension data from the target segment of the CCA. Measurements were recorded by trained sonographers that were supervised by one of three radiologists, based in China, who were experienced in the conduct and interpretation of carotid ultrasound examinations. In consultation with experts with experience in analyses and interpretation of carotid ultrasound measures in studies conducted in Western populations, the one-week training programme included a written protocol and video of the examination procedures providing detailed instructions on the optimum methods to record cIMT and plaque measurements. A random sample was selected to derive an overall quality score, based on the quality checking that cIMT had been measured correctly at 4 CCA segments, and that plaques had been located and counted satisfactorily in each of the 10 CCA segments.

### *Statistical methods*

Cigarette smokers were classified into ever-regular and never cigarette smokers. The mean cIMT and percentage with plaques were compared between population sub-groups defined by age, sex, geographic region and presence of cardiovascular risk factors. The age-specific percentages with carotid plaque were presented for quintiles of cIMT in 4 age groups (40-49, 50-59, 60-69 and 70-89 years, respectively) after adjustment for sex and geographic region. Pearson correlation coefficients were used to assess the agreement between the number of plaques and maximum plaque thickness and between plaque score and cIMT

**eTable 1: Assessment of the quality of ultrasound measures of cIMT and carotid plaque burden, by geographic region**

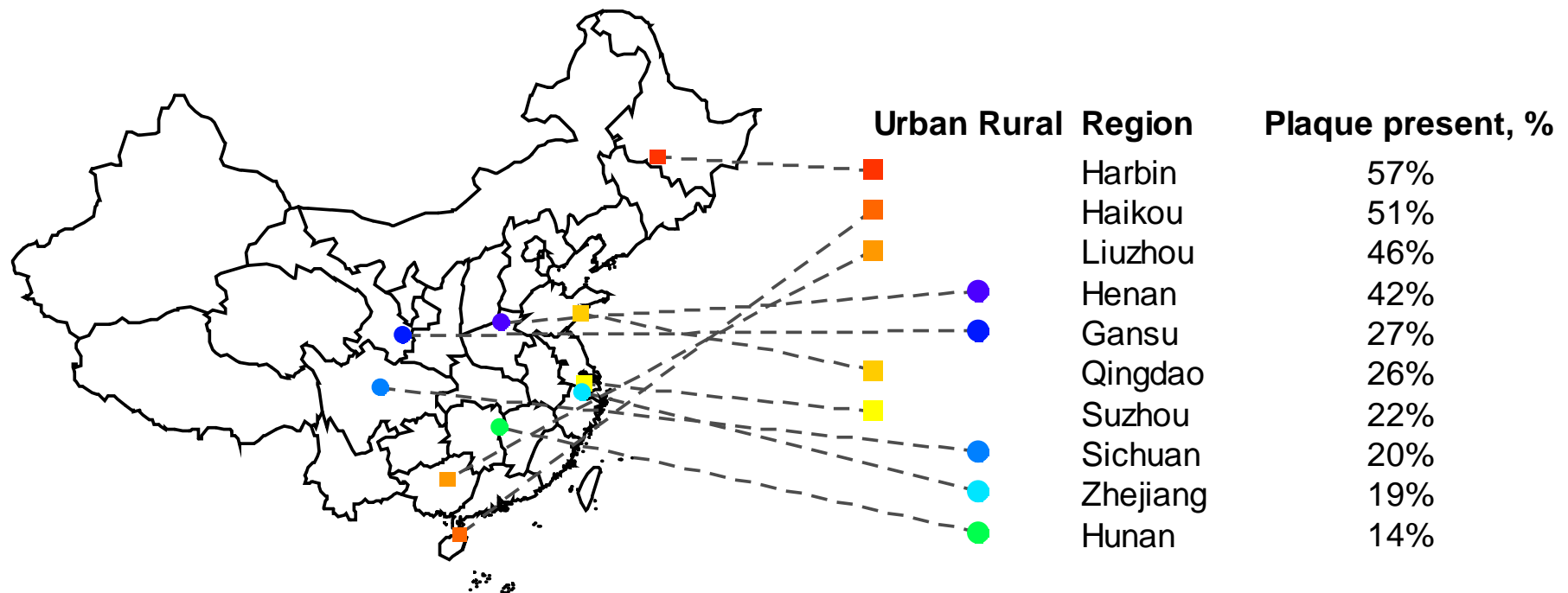
<b>Region</b>	<b>No. of quality assessments</b>	<b>Overall quality score (%)</b>	<b>cIMT correctly measured at 4 locations (%)</b>	<b>Plaque located satisfactorily (%)</b>	<b>Plaque count accuracy (%)</b>
Suzhou	67	93	96	98	98
Haikou	36	92	100	100	100
Gansu	61	90	98	100	100
Henan	31	87	100	100	100
Qingdao	78	86	100	100	87
Zhejiang	81	84	100	100	100
Hunan	137	84	100	100	98
Harbin	134	83	99	89	95
Sichuan	45	78	100	90	100
Liuzhou	24	75	100	100	100
<b>All</b>	<b>694</b>	<b>85</b>	<b>99</b>	<b>96</b>	<b>97</b>

**eTable 2: Agreement of carotid measures between right and left sides in all participants at resurvey (n=24822).** Mean cIMT over left and right; maximum plaque thickness over left and right. 13% had plaque on both left and right arteries.

<b>Carotid measure</b>	<b>Left Mean (SD)</b>	<b>Right Mean (SD)</b>	<b>Left and right combined* Mean (SD)</b>	<b>Left/right correlation</b>
cIMT, mm	0.70 (0.19)	0.70 (0.18)	0.70 (0.16)	0.69
Plaque present, %	23	22	31	0.50
No. of plaques	0.42 (0.75)	0.40 (0.72)	0.82 (1.32)	0.58
Max. plaque thickness, mm	0.61 (1.00)	0.59 (0.99)	0.83 (1.14)	0.57

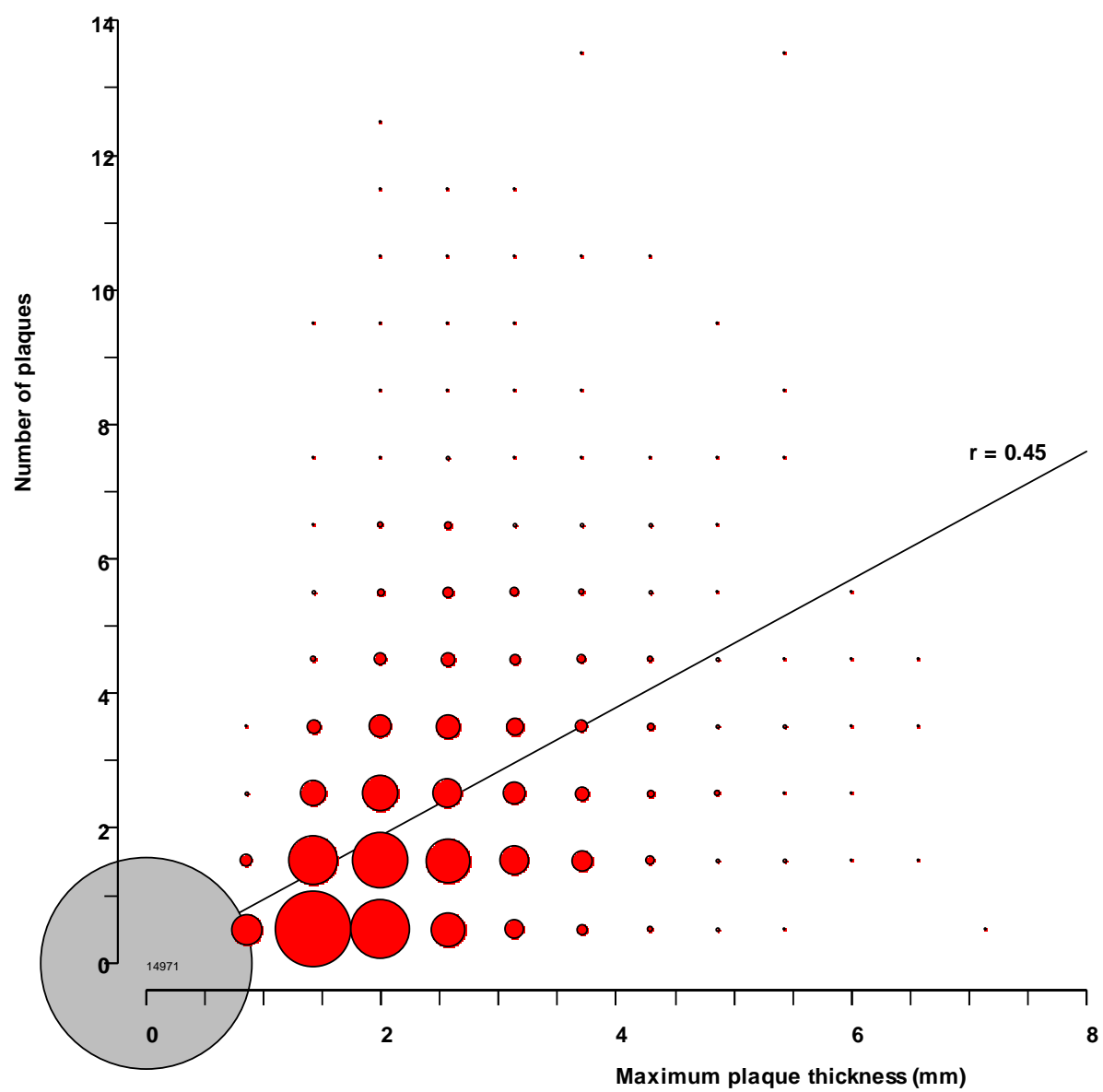
**eTable 3: Association of presence of plaque, plaque number and size and carotid plaque burden with cardiovascular disease (CVD) at resurvey. Odds ratios for CVD (n=4150) were conducted in all 24,822 participants with carotid measures at resurvey after adjustment for age, sex and region. 2189 participants had largest plaque size  $\leq 1.5$ mm and were recorded as having one or more plaques.**

<b>Plaque measure</b>	<b>N with CVD / N at risk</b>	<b>Odds ratio (95% CI) for CVD at resurvey</b>	<b><math>\chi^2</math> (P value) for trend</b>
<b>Plaque (<math>&gt;1.5</math>mm) present</b>			<b>55.2 (<math>1 \times 10^{-13}</math>)</b>
No	2149/17154	1.00	
Yes	2001/7668	1.35 (1.25,1.47)	
<b>Number of plaques</b>			<b>78.8 (<math>7 \times 10^{-19}</math>)</b>
0	1807/14971	1.00 (0.94,1.07)	
1	758/4172	1.09 (1.00,1.18)	
2	776/3133	1.24 (1.14,1.35)	
3+	809/2546	1.72 (1.57,1.89)	
<b>Size of largest plaque</b>			<b>77.0 (<math>2 \times 10^{-18}</math>)</b>
$\leq 1.5$ mm	2149/17154	1.00 (0.94,1.06)	
$>1.5$ mm and $\leq 2$ mm	644/3027	1.20 (1.10,1.31)	
$>2$ mm and $\leq 3$ mm	931/3444	1.38 (1.27,1.49)	
$>3$ mm	426/1197	1.75 (1.54,1.99)	
<b>Plaque burden</b>			<b>92.9 (<math>6 \times 10^{-22}</math>)</b>
$\leq 1.5$ mm	2429/18486	1.00 (0.94,1.06)	
$>1.5$ mm and $\leq 2$ mm	547/2608	1.08 (0.98,1.19)	
$>2$ mm and $\leq 3$ mm	804/2753	1.42 (1.31,1.55)	
$>3$ mm	370/975	2.00 (1.74,2.30)	

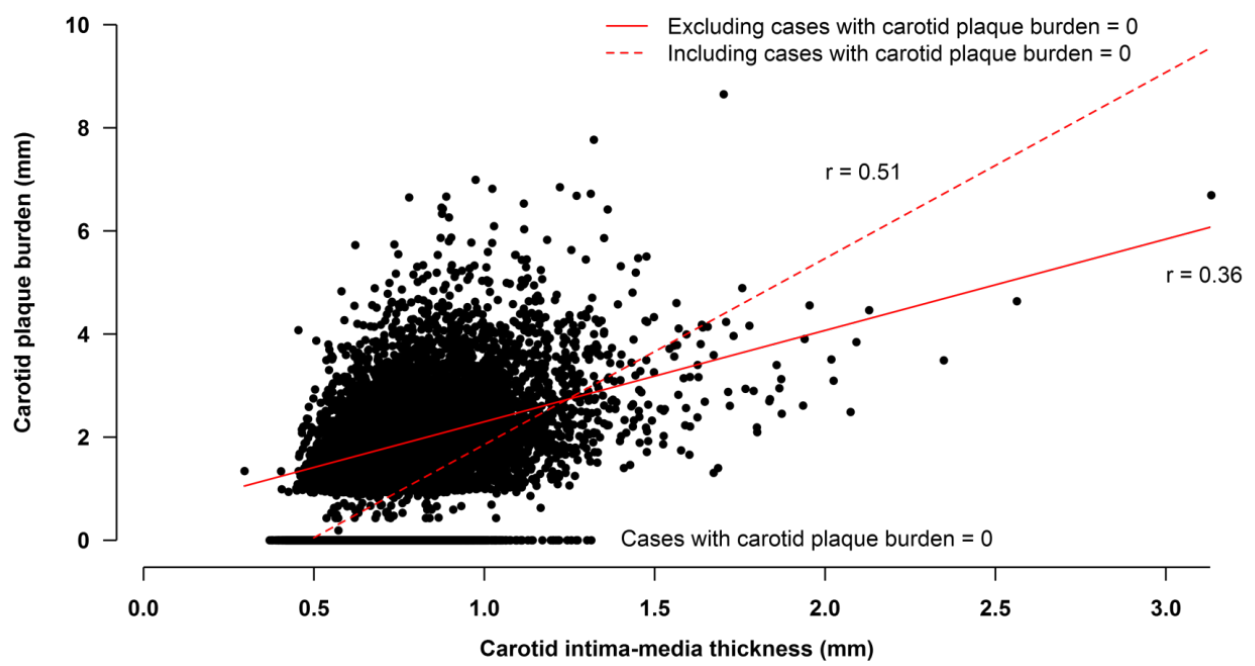


**eFigure 1: Regional variation in percentage of participants with carotid plaque. Regions are ordered by decreasing % with plaque, after adjustment for age and sex.**

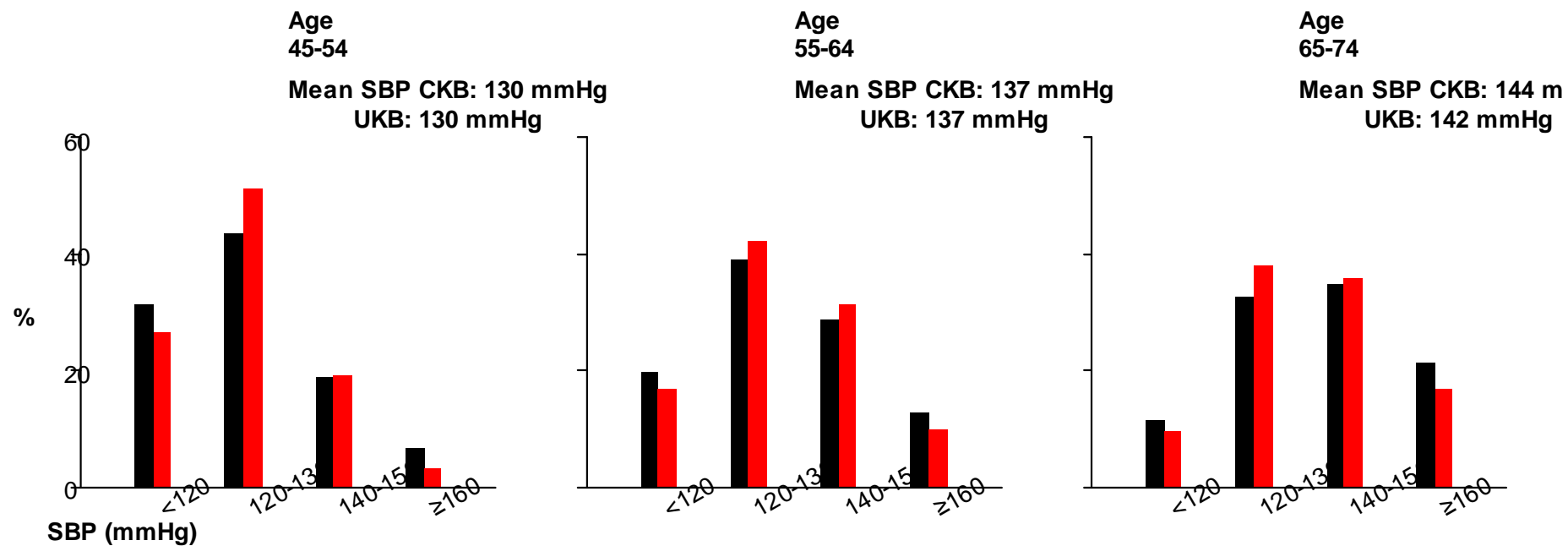




eFigure 2: Correlation of the number of plaques by maximum plaque thickness.



eFigure 3: Correlation of carotid intima-media thickness against carotid plaque burden.



**eFigure 4: Age-specific distribution of systolic blood pressure (SBP) in Chinese and UK populations. Values for Chinese are shown in black and UK in red.**