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Original research

Intracranial arterial stenosis in Caucasian versus Chinese patients with TIA and minor stroke: two contemporaneous cohorts and a systematic review

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► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2020-325630).

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Received 11 November 2020
Revised 21 December 2020
Accepted 4 January 2021

To cite: Leng X, Hurford R, Feng X, *et al*. *J Neurol Neurosurg Psychiatry* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnnp-2020-325630

ABSTRACT

Background Intracranial arterial stenosis (ICAS) is an important cause of stroke worldwide. Separate reports in Caucasians and Asians with stroke/transient ischaemic attack (TIA) have suggested lower ICAS prevalence in Caucasians, but there has been no direct comparisons of the two ethnic groups with the same criteria to define ICAS.

Methods Acute minor stroke or TIA patients in two cohorts respectively recruiting patients in Oxford (2011–2018, predominantly Caucasians) and Hong Kong (2011–2015, predominantly Chinese) were compared. ICAS was defined as ≥50% stenosis/occlusion in any major intracranial artery in MR/CT angiography. Prevalence, distribution and risk factors of ICAS were compared between the two cohorts. We also systematically reviewed literature on ICAS prevalence in stroke/TIA patients in different populations.

Results Among 1287 patients from Oxford and 691 from Hong Kong (mean age 69 vs 66), ICAS prevalence was higher in Chinese than in Caucasians (43.0% vs 20.0%; OR 3.02; 95% CI 2.47 to 3.70; p<0.001), independent of age (age-adjusted OR 3.73; 95% CI 3.00 to 4.63; p<0.001) and vascular risk factors (multivariable-adjusted OR 3.21; 95% CI 2.56 to 4.02; p<0.001). This ethnic difference was greater (p interaction=0.005) at age <70 years (OR 5.33; 95% CI 3.79 to 7.50; p<0.001) than at ≥70 years (OR 2.81; 95% CI 2.11 to 3.74; p<0.001). ICAS prevalence increased with age and with vascular risk factors in both cohorts, with equivalent prevalence in Chinese aged <60 years and Caucasians aged ≥80, and in Chinese with no vascular risk factor and Caucasians with two vascular risk factors. ICAS locations also differed between Chinese and Caucasian patients.

Conclusions Chinese are more susceptible to ICAS than Caucasians, with an earlier onset age and a higher prevalence, independent of vascular risk factors.

INTRODUCTION

Intracranial arterial stenosis (ICAS), predominantly atherosclerotic, is an important cause of ischaemic stroke worldwide.[1] Patients with minor stroke or transient ischaemic attack (TIA) with ICAS face a high risk of recurrence despite timely medical treatment; for instance, minor stroke or TIA patients with ICAS had a significantly higher risk of recurrent stroke within 90 days than those without ICAS (12.5% vs 5.4%, p<0.001; HR 2.39, 95% CI 1.57 to 3.66, p<0.001), treated within 24 hours with dual or mono antiplatelet therapies in the Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial.[2]

Indirect comparisons of separate studies have suggested large ethnic differences between Caucasians and Asians in ICAS prevalence among both TIA/ischaemic stroke patients and asymptomatic populations, with significantly higher ICAS prevalence in Asians.[1 3] However, these studies were heterogeneous in the recruitment period, subjects (eg, mean age, stroke severity) and in imaging modalities/methods to define ICAS. To our best knowledge, there has been no direct comparison between Caucasians and Chinese in the prevalence and risk factors of ICAS in TIA/stroke patients, based on data from contemporaneous cohorts using the same imaging modalities and the same criteria to define ICAS.

To compare the risk factors of ICAS in Caucasians and Asians, to estimate the yields of routine imaging of cerebral arteries, and to understand the impact of imaging on ischaemic stroke subtyping, it is important to reliably determine these ethnic differences and the extent to which they are independent of age and vascular risk factors. Therefore, in the current study, we compared two contemporaneous cohorts of acute TIA and minor stroke patients recruited in Oxford, UK (predominantly Caucasian) and in Hong Kong SAR, China (predominantly Chinese) using MR angiography (MRA) and/or CT angiography (CTA) for the diagnosis of ICAS. We also systematically reviewed existing literature on ICAS prevalence in TIA and ischaemic stroke patients in different populations around the world.

METHODS AND MATERIALS

Subjects

In a cross-sectional study, patients with acute TIA or minor ischaemic stroke with brain MRA/CTA at baseline from two prospective, contemporaneous cohorts were investigated: all eligible patients enrolled in Oxford Vascular Study (OXVASC) from January 2011 to December 2018, and all eligible

patients admitted within 24 hours of symptom onset enrolled in the Chinese University of Hong Kong Stroke Registry (CUHK-SR) from January 2011 to December 2015. TIA was defined as a transient episode of neurological dysfunction caused by focal brain or retinal ischaemia that completely resolved within 24 hours. Minor ischaemic stroke was defined as sudden onset of neurological deficits caused by brain ischaemia lasting longer than 24 hours, with a National Institutes of Health (NIH) Stroke Scale (NIHSS) ≤3.

OXVASC is an ongoing population-based study recruiting all patients with acute vascular events (including TIA and ischaemic stroke; predominantly Caucasian patients), in about 93 000 individuals registered with about 100 primary care physicians in 9 general practices in Oxfordshire, UK.[4–6] CUHK-SR is an ongoing stroke registry at Prince of Wales Hospital, a regional hospital in Hong Kong with a comprehensive stroke service team; all acute stroke or TIA patients (predominantly Chinese) in the catchment area requiring inpatient or outpatient treatment were registered in the stroke registry.

Intracranial vascular imaging was done routinely in all patients in OXVASC from April 2010 onwards. We attempted to obtain as high an imaging rate as possible by using MRA as first choice, CTA if MRI was contraindicated, and transcranial Doppler (TCD) if CTA was also contraindicated.[5 6] In CUHK-SR, MRA was also the first-choice imaging modality, CTA was used if MRI was contraindicated or to confirm MRA findings; Occasionally, patients had both brain MRI and CT exams for clinical purposes; TCD was conducted in most patients especially when MRA and CTA were both contraindicated or unavailable.

In both studies, we collected demographic data, history of smoking, hypertension, diabetes, dyslipidaemia, ischaemic stroke, TIA and ischaemic heart disease, history of atrial fibrillation (AF) and newly diagnosed AF after an index TIA/stroke, and stroke severity by NIHSS. History of hypertension, diabetes or dyslipidaemia was defined as being previously diagnosed or taking relevant medications at the index stroke/TIA.

Imaging protocol and assessment of ICAS

MRI exam included T1/T2-weighted imaging, diffusion-weighted imaging and time-of-flight MRA. MRI exams for OXVASC patients were conducted with a Verio V.3.0 Tesla scanner (Siemens, Germany) at Advanced Vascular Imaging Centre, University of Oxford; and for CUHK-SR patients Achieva V.3.0 Tesla scanner (Philips, Netherlands) at Prince of Wales Hospital, Hong Kong. Brain CT and single-phase CTA were performed with a 64-slice CT scanner (Toshiba Aquilion 64) at John Radcliffe Hospital, Oxford, for OXVASC patients; or a 64-slice CT scanner (Lightspeed VCT, GE Healthcare, USA) at Prince of Wales Hospital, Hong Kong, for CUHK-SR patients.

Presence of ICAS was defined as ≥50% stenosis or occlusion in any of the 11 major intracranial arteries in MRA/CTA: bilateral intracranial internal carotid arteries (ICA), middle cerebral arteries (MCA, M1 and M2), anterior cerebral arteries (ACA, A1 and A2), posterior cerebral arteries (PCA, P1 and P2), vertebral arteries (VA, V4) and basilar artery (BA). The percentage of stenosis was defined by the Warfarin-Aspirin Symptomatic Intracranial Disease method, which was the percent reduction in vessel diameter at the stenotic throat comparing with a proximal normal vessel diameter.[7] We attempted to exclude cases with ICAS due to definite Moyamoya disease, arterial dissection, or vasculitis. We assessed interobserver agreement for presence of ICAS in 60 patients randomly selected from each study: OXVASC (XL and RH) and CUHK-SR (XL and XF).

Statistical analyses

We compared patients' characteristics between the two cohorts, and characteristics of those with and without ICAS in each cohort. We compared ICAS prevalence between the two cohorts in different age categories (<60, 60–69, 70–79 and ≥80 years), and in patients with 0, 1, 2 or 3 vascular risk factors (histories of hypertension, diabetes and dyslipidaemia). We compared prevalence of common vascular risk factors between the two cohorts in different age categories. We also compared distribution of ICAS lesions (in anterior/posterior circulations and in individual arteries) between the two cohorts. Means (SD) or medians (IQR) were used for describing continuous variables and numbers (percentage) for categorical variables. Student's t-tests were used for comparison of continuous variables between two groups and χ^2 tests for categorical variables. Interobserver agreement for presence of ICAS was assessed with Cohen's kappa.

Univariate and multivariate logistic regression analyses were conducted for risk factors of ICAS in each cohort; crude and adjusted ORs and the 95% CI were presented. We also conducted subgroup analyses for independent risk factors of ICAS in patients aged< or ≥70 years in each cohort. Moreover, the difference between the two cohorts in ICAS prevalence was presented with crude, age-adjusted and multivariable-adjusted ORs (95% CI), among all patients, and in those aged< or ≥70 years; p for study centre–age (<or ≥70 years) interaction was obtained. All statistical analyses were conducted using SPSS Statistics V.22.0 (IBM). Two-tailed $p<0.05$ was considered statistically significant.

Systematic review of ICAS prevalence in TIA/ischaemic stroke patients

The systematic review was carried out according to the Meta-analysis Of Observational Studies in Epidemiology[8] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[9] statements. We searched PubMed and OVID on 14 October 2019, for primary studies reporting ICAS prevalence in TIA and/or ischaemic stroke patients, with full-text article published in English since 1 January 1990. Briefly, the search terms included ICAS, ischaemic stroke, TIA and prevalence (search strategy provided in online supplemental etables 1 & 2). We also manually searched references in pertinent review articles.

The inclusion criteria were studies reporting prevalence of ICAS (> or ≥50% stenosis or occlusion) in TIA and/or ischaemic stroke patients with a sample size ≥100. Studies were excluded if it reported ICAS prevalence in highly selective (eg, non-cardioembolic) stroke patients; prevalence of complete occlusion (rather than stenosis and occlusion) of intracranial arteries; or ICAS in certain (eg, anterior-circulation arteries only) rather than all major intracranial arteries. The study quality was assessed with a modified version of the Newcastle-Ottawa Scale, with a total score of 0–5 and score of ≥3 or <3, respectively, indicating low and high risk of bias (more details provided in the Appendix).[10 11] We collected the following information from relevant studies: country/region, enrolment period, sample size, mean age, male percentage, TIA and/or ischaemic stroke patients involved, imaging modality and criteria to define ICAS, and prevalence of any ICAS and/or symptomatic ICAS.

Data availability statement

Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as (online supplemental information). Requests for access to anonymised data

Table 1 Baseline characteristics of patients in OXVASC and CUHK-SR

Characteristics	OXVASC (n=1287)	CUHK-SR (n=691)	P value
Age, years	69 (13.9)	66 (12.3)	<0.001
Age ≥70 years	715 (55.6)	279 (40.4)	<0.001
Male sex	667 (51.8)	441 (63.8)	<0.001
Ever-smoker	688 (53.5)	270 (39.1)	<0.001
Male smoker	431 (64.7)	174 (39.5)	<0.001
Female smoker	257 (41.5)	96 (38.4)	0.407
History of hypertension	707 (54.9)	454 (65.6)	<0.001
History of diabetes	169 (13.1)	181 (26.2)	<0.001
History of dyslipidaemia	436 (33.9)	354 (51.2)	<0.001
Atrial fibrillation*	191 (14.9)	78 (11.3)	0.028
History of ischaemic stroke or TIA	192 (14.9)	144 (20.8)	0.001
History of ischaemic heart disease	166 (12.9)	54 (7.8)	<0.001
Event type			<0.001
TIA	842 (65.4)	208 (30.1)	
Minor stroke	445 (34.6)	483 (69.9)	
Presence of ICAS	257 (20.0)	297 (43.0)	<0.001
No of arteries† affected			<0.001
0	1030 (80.0)	394 (57.0)	
1	162 (12.6)	148 (21.4)	
≥2	95 (7.4)	149 (21.6)	

Values are means (SD) or medians (IQR) or numbers (%); Student's t-tests were used for comparison of continuous variables and χ^2 tests for categorical variables.
*History of atrial fibrillation and newly diagnosed atrial fibrillation after the index stroke or TIA.
†Including 11 cerebral arteries: bilateral intracranial internal carotid arteries, middle/anterior/posterior cerebral arteries, intracranial vertebral arteries and basilar artery.
CUHK-SR, the Chinese University of Hong Kong Stroke Registry; ICAS, intracranial atherosclerotic stenosis; OXVASC, Oxford Vascular Study; TIA, transient ischaemic attack.

reported in this paper will be considered by the corresponding author.

RESULTS

Patient recruitment and investigation in the two studies are shown in (online supplemental efigure 1). Of 1579 potentially eligible patients in OXVASC, 1368 (86.6%) underwent intracranial vascular imaging (1033/65.4% MRA; 254/16.1% CTA; 81/5.1% TCD only), whereas 154 (9.8%) had only carotid ultrasound imaging (often due to contraindications to MRA and CTA) and 57 (3.6%) did not undergo any vascular imaging. Of 1099 potentially eligible patients in CUHK-SR, 953 (86.7%) underwent intracranial vascular imaging (673/61.2% MRA; 99/9.0% CTA; 81/7.4% MRA and CTA; 262/23.8% TCD only; 1/0.1% digital subtraction angiography (DSA) only), 38 (3.5%) had only carotid ultrasound imaging and 107 (9.7%) did not undergo any vascular imaging (details in (online supplemental etable 3). In both cohorts, patients who did not receive intracranial MRA/CTA were older with a higher burden of vascular risk factors (details in (online supplemental etable 4).

Among the 1287 TIA and minor stroke patients in OXVASC and 691 in CUHK-SR with brain MRA and/or CTA, CUHK-SR patients were younger (66 vs 69 years old; p<0.001) and more of them were male (63.8% vs 51.8%; p<0.001). More OXVASC patients had TIA as an index ischaemic event (65.4% vs 30.1%; p<0.001). More CUHK-SR patients had histories of hypertension, diabetes, dyslipidaemia and previous ischaemic stroke or TIA, while more OXVASC patients had history of ischaemic heart disease, and more of them had AF (table 1). Additionally, more male patients in OXVASC had ever smoked than male patients in CUHK-SR (64.7% vs 39.5%; p<0.001), irrespective of age, while the ever-smoking rates were similar between the two cohorts in females (online supplemental efigure 2). When classified to four age groups, more CUHK-SR patients had histories of hypertension, diabetes and dyslipidaemia than OXVASC patients in each age group (all p<0.05;online supplemental efigure 2).

Interobserver agreement for presence of ICAS was good in both cohorts (both kappa=0.82). ICAS prevalence was higher in Chinese (CUHK-SR) than in Caucasians (OXVASC): 43.0% vs 20.0% (OR 3.02; 95% CI 2.47 to 3.70; p<0.001). More Chinese patients had ≥2 cerebral arteries with ICAS than Caucasians (21.6% vs 7.4%; p<0.001; table 1).

Chinese patients with ICAS were younger than Caucasians (68 vs 75 years; p<0.001). The ethnic difference in ICAS prevalence was independent of age (age-adjusted OR 3.73; 95% CI 3.00 to 4.63; p<0.001), which existed in those aged <60, 60–69, 70–79 and ≥80 years (figure 1A). However, the difference was greater (p-interaction=0.005) at age <70 years (36.7% vs 9.8%; OR 5.33; 95% CI 3.79 to 7.50; p<0.001) than at ≥70 years (52.3% vs 28.1%; OR 2.81; 95% CI 2.11 to 3.74; p<0.001). Only in Caucasians aged ≥80 did the prevalence of ICAS (35.5%; 95% CI 30% to 41%) reach that of Chinese patients aged <60 years (35.1%; 95% CI 29% to 42%).

Table 2 shows multiple factors associated with presence of ICAS in both cohorts, including older age, histories of hypertension, diabetes, dyslipidaemia and ischaemic stroke or TIA; while AF and history of ischaemic heart disease were associated with ICAS in OXVASC but not CUHK-SR. In addition, more patients with ICAS had minor stroke as the index ischaemic event than those without ICAS in OXVASC (39.7% vs 33.3%; p=0.054); but the ischaemic event types were similar between those with or without ICAS in CUHK-SR.

After adjusting for age, histories of hypertension, diabetes and dyslipidaemia were significantly associated with ICAS in both cohorts, while male sex was significantly associated with ICAS in OXVASC only. Multivariate logistic regression identified older age, and histories of hypertension and diabetes as independent risk factors of ICAS in both cohorts; male sex was an independent risk factor of ICAS in OXVASC; history of dyslipidaemia tended to be independently associated with ICAS in CUHK-SR (table 3).

Subgroups analyses (online supplemental etable 5) showed that in patients aged ≥70 years, older age was an independent risk factor of ICAS in both cohorts; in addition, history of hypertension and history of diabetes were respectively independent risk factors of ICAS in OXVASC and CUHK-SR. In those younger than 70 years, male sex (p=0.079) and history of hypertension (p=0.090), and history of diabetes (p=0.054) tended to be, respectively, independently associated with ICAS in OXVASC and CUHK-SR.

ICAS prevalence was equivalent in Chinese patients with no vascular risk factors (27.1%; 95% CI 20% to 36%) and Caucasians with two vascular risk factors (26.2%; 95% CI 21% to 32%; figure 1B). The higher ICAS prevalence in Chinese than Caucasians was independent of vascular risk factors (multivariable-adjusted OR 3.21; 95% CI 2.56 to 4.02; p<0.001), which existed in subgroups of patients with 0–3 vascular risk factors (figure 1B).

ICAS locations were also different between the two cohorts. The anterior and posterior circulations (both 12.0%) were similarly involved with ICAS in Caucasian patients, while Chinese

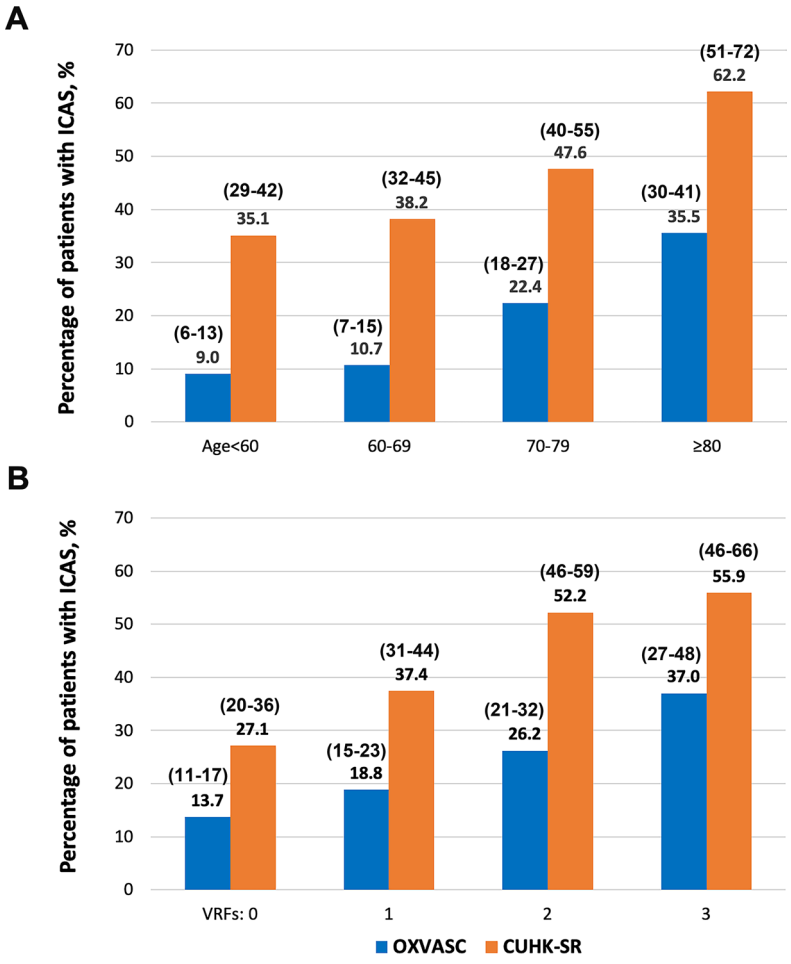

Figure 1 Prevalence of ICAS in minor stroke and TIA patients in Caucasians (OXVASC) and Chinese (CUHK-SR) in subgroups. (A) Prevalence of ICAS in OXVASC and CUHK-SR in different age groups; p<0.001 for χ^2 tests in the comparison between OXVASC and CUHK-SR in each age group. Larger differences in ICAS prevalence are seen in younger patients. (B) Prevalence of ICAS in OXVASC and CUHK-SR by different numbers (0, 1, 2 or 3) of vascular risk factors including histories of hypertension, diabetes and dyslipidaemia; p<0.001 for χ^2 tests in the comparison between OXVASC and CUHK-SR in subgroups of patients with 0, 1 or 2 vascular risk factors, and p=0.008 in the subgroup of patients with three vascular risk factors.95% CIs of ICAS prevalence in these subgroups are provided within parentheses in the figure. CUHK-SR, the Chinese University of Hong Kong stroke Registry; ICAS, intracranial atherosclerotic stenosis; OXVASC, Oxford vascular study; TIA, transient ischaemic attack; VRFs, number of vascular risk factors.

patients had more ICAS lesions in the anterior than posterior circulation (35.9 vs 17.6%). Overall, more Chinese patients than Caucasians had ICAS lesions in either or both circulations (all p<0.05; table 4).

In OXVASC, PCA (percentage of arteries with ICAS, 3.8%), VA-V4 (3.8%), MCA (3.6%) and intracranial ICA (3.5%) were similarly affected by ICAS, while ACA (1.2%) and BA (1.0%) were less frequently affected (table 4). In CUHK-SR, the most commonly affected cerebral artery was MCA (16.5%), followed by PCA (8.4%), intracranial ICA (7.7%), ACA (5.4%), BA (3.3%) and VA-V4 (2.8%). Per-patient and per-artery data of ICAS locations are presented in table 4.

Systematic review of ICAS prevalence in TIA/ischaemic stroke patients

Of the 889 records retrieved from literature search, we identified 32 studies reporting ICAS prevalence in TIA and/or ischaemic stroke patients in various populations published in the last three decades (online supplemental efigure 3). Studies conducted in different continents are, respectively, summarised in (online supplemental etables 6–9). Different methods/criteria were used to define ICAS: various velocity criteria by TCD, and/or arterial luminal narrowing by MRA/CTA/DSA. Among the four European studies with over 1000 patients (mostly Caucasians),[12–15] ICAS was diagnosed by TCD alone in most or all patients,[14 15] or screened by TCD and confirmed with MRA/CTA/DSA only in those with suspected ICAS in TCD (online supplemental etable 6).[12 13] In large-scale studies in Asia, MRA or MRA/CTA were used in most or all patients (online supplemental etable 7).[16–18] In the worldwide TIAregistry.org project,[19] 67%, 46% and 15% of the patients had TCD, MRA and CTA, respectively, when ICAS was diagnosed with one or more of these imaging modalities (online supplemental etable 9). Among the 32 studies included, 26 (81.3%) had a modified Newcastle-Ottawa Scale of 3 or 4, indicating a low risk of bias (online supplemental etable 6–9).

Overall, the prevalence of any ICAS or symptomatic ICAS was higher in Asian than European patients: 22%–65% vs 7%–36% and 17%–36% vs 0.5%–31%, respectively (online supplemental etables 6 and 7). Studies in the USA mostly involved patients with multiple ethnic backgrounds (online supplemental etables 8). There was no direct comparison between Caucasian and Asian (or Chinese) TIA/stroke patients in ICAS prevalence in any individual study. Although higher ICAS prevalence in 345 Japanese TIA/minor stroke patients than 4238 non-Japanese

Table 2 Baseline characteristics of patients with or without ICAS in OXVASC and CUHK-SR

Characteristics	OXVASC (n=1287)			CUHK-SR (n=691)		
	Any ICAS (n=257)	No ICAS (n=1030)	P value	Any ICAS (n=297)	No ICAS (n=394)	P value
Age, years	75 (12.2)	68 (13.8)	<0.001	68 (12.3)	64 (11.9)	<0.001
Age ≥70 years	201 (78.2)	514 (49.9)	<0.001	146 (49.2)	133 (33.8)	<0.001
Male sex	141 (54.9)	526 (51.1)	0.276	184 (62.0)	257 (65.2)	0.375
Ever-smoker	138 (53.7)	550 (53.4)	0.943	116 (39.1)	154 (39.1)	0.994
Male smoker	90 (63.8)	341 (65.0)	0.804	76 (41.3)	98 (38.1)	0.502
Female smoker	48 (41.4)	209 (41.5)	0.986	40 (35.4)	56 (40.9)	0.375
History of hypertension	180 (70.0)	527 (51.2)	<0.001	219 (73.7)	234 (59.4)	<0.001
History of diabetes	49 (19.1)	120 (11.7)	0.002	101 (34.0)	80 (20.3)	<0.001
History of dyslipidaemia	111 (43.2)	325 (31.6)	<0.001	173 (58.2)	181 (45.9)	0.001
Atrial fibrillation*	59 (23.0)	132 (12.8)	<0.001	30 (10.1)	48 (12.2)	0.392
History of ischaemic stroke or TIA	59 (23.0)	133 (12.9)	<0.001	77 (25.9)	67 (17.0)	0.004
History of ischaemic heart disease	59 (23.0)	107 (10.4)	<0.001	28 (9.4)	26 (6.6)	0.170
Event type			0.054			0.814
TIA	155 (60.3)	687 (66.7)		88 (29.6)	120 (30.5)	
Minor stroke	102 (39.7)	343 (33.3)		209 (70.4)	274 (69.5)	

Values are mean (SD) or median (IQR) or number (%); Student's t-tests were used for comparison of continuous variables and χ^2 tests for categorical variables.
*History of atrial fibrillation and newly diagnosed atrial fibrillation after the index stroke or TIA.
CUHK-SR, the Chinese University of Hong Kong Stroke Registry; ICAS, intracranial atherosclerotic stenosis; OXVASC, Oxford Vascular Study; TIA, transient ischaemic attack.

patients (20 vs 13%; p=0.01) was reported in the TIAregistry.org cohort, there were at least 912 patients of Asian, African or Hispanic ancestry in the non-Japanese patients; moreover, no data were reported in this study for the locations and risk factors of ICAS in different ethnic groups.[20]

DISCUSSION

To our knowledge based on the systematic review, the current study was the first to directly compare the prevalence, distribution and risk factors of ICAS between Caucasian and Chinese patients with TIA/minor stroke, based on two contemporaneous cohorts (1287 patients from Oxford and 691 from Hong Kong), with similar imaging modalities (MRA/CTA) and criteria to define ICAS. Overall, ICAS prevalence was higher among Chinese TIA/minor stroke patients than Caucasians (43.0% vs 20.0%; p<0.001), and Chinese patients with ICAS were younger than Caucasians. This ethnic difference in ICAS prevalence was independent of age and vascular risk factors, but was most marked at younger ages. ICAS prevalence was equivalent in Chinese aged <60 years and Caucasians aged ≥80, and in Chinese with no vascular risk factors and Caucasians with two vascular risk factors.

The higher ICAS prevalence and younger age of patients with ICAS in Chinese than Caucasian patients in the current study corroborated the higher susceptibility of Chinese to ICAS than Caucasians. Interestingly, the independent associations between vascular risk factors and presence of ICAS was weaker in patients aged <70 years than ≥70 years in the Chinese cohort. Therefore, the higher prevalence of vascular risk factors in Chinese patients cannot explain all of the ethnic difference in ICAS prevalence, especially in younger patients.

Previous studies in Asia indicated stronger association of atherosclerosis in extracranial and coronary arteries, than that in intracranial and coronary arteries, independent of vascular risk factors, among subjects with or without ischaemic stroke.[21–24] Therefore, we speculated that atherosclerosis of intracranial arteries might be a relatively independent and earlier process in systemic atherosclerosis in Asians.[24] In addition to the effects of modifiable vascular risk factors (eg, hypertension, diabetes and dyslipidaemia), genetic factors play an important role in early ICAS development in Asians.[25]

Large-scale genome-wide association studies and subsequent meta-analyses have revealed genetic variants associated with large artery atherosclerotic (LAA) stroke.[26 27] For instance, MEGASTROKE, the most valuable multiancestry genome-wide association study in stroke patients (with 40 585 and 17 369 stroke cases, respectively, in the European and East Asian cohorts) have indicated some genetic loci associated with LAA stroke shared across continents by transancestral meta-analysis, while there are also genetic loci associated with LAA stroke in European cohorts only.[27] These findings have implied genetic differences underlying LAA stroke among populations. However, atherosclerotic disease of extracranial and intracranial arteries was not differentiated in such analyses, and mostly, only symptomatic (rather than 'any') large artery disease was studied.[26 27] Thus far, evidence is insufficient regarding the genetic background of higher ICAS prevalence in Asians than in Caucasians. Some Korean and Japanese studies showed that over 20% of patients with non-Moyamoya intracranial stenosis had ring finger protein 213 gene variants (particularly the p.R4810K variant), which could lead to vascular fragility.[28] The p.R4810K variant is commonly seen in East Asian populations but rarely seen in Caucasians.[29–31] This may be a contributing factor for the higher ICAS prevalence in Asians than Caucasians. In addition, geographical and environmental factors, such as the climate, food, social and cultural habits, may also underlie the ethnic differences in ICAS prevalence. There is indeed geographic difference between North (higher) and South China in ICAS prevalence among ischaemic stroke and TIA patients.[32]

Although lower than that in Chinese, ICAS prevalence in Caucasians was higher than previously estimated in European studies of TIA/ischaemic stroke patients (online supplemental etable 6), but this will partly reflect the reliance on TCD only in many previous studies. In the current study, ICAS presented in 22.4% of Caucasians aged 70–79 years and 35.5% aged ≥80 (figure 1). Intracranial vascular imaging might, therefore, be

Table 3 Risk factors for presence of ICAS in the two cohorts

Risk factors	OXVASC (n=1287)					CUHK-SR (n=691)				
	Crude OR (95% CI)	P value	Age-adjusted OR (95% CI)	P value	Multivariable-adjusted OR (95% CI)	P value	Crude OR (95% CI)	P value	Age-adjusted OR (95% CI)	P value	Multivariable-adjusted OR (95% CI)	P value
Age (every 10 years increment)	1.65 (1.46 to 1.87)	<0.001	–	–	1.62 (1.42 to 1.84)	<0.001	1.33 (1.17 to 1.52)	<0.001	–	–	1.23 (1.08 to 1.41)	0.003
Male sex	1.17 (0.89 to 1.53)	0.276	1.40 (1.05 to 1.86)	0.022	1.36 (1.01 to 1.84)	0.042	0.87 (0.64 to 1.19)	0.375	0.91 (0.66 to 1.25)	0.555	0.96 (0.70 to 1.33)	0.810
Ever-smoker	1.01 (0.77 to 1.33)	0.943	1.12 (0.84 to 1.48)	0.445	0.98 (0.73 to 1.32)	0.910	1.00 (0.73 to 1.36)	0.994	1.01 (0.74 to 1.38)	0.967	1.02 (0.74 to 1.40)	0.894
History of hypertension	2.23 (1.66 to 2.99)	<0.001	1.67 (1.23 to 2.27)	0.001	1.51 (1.09 to 2.08)	0.012	1.92 (1.38 to 2.66)	<0.001	1.64 (1.17 to 2.31)	0.004	1.43 (1.00 to 2.03)	0.047
History of diabetes	1.79 (1.24 to 2.57)	0.002	1.74 (1.19 to 2.53)	0.004	1.46 (0.98 to 2.16)	0.057	2.02 (1.44 to 2.85)	<0.001	1.86 (1.32 to 2.64)	<0.001	1.67 (1.17 to 2.38)	0.005
History of dyslipidaemia	1.65 (1.25 to 2.18)	<0.001	1.42 (1.06 to 1.89)	0.017	1.17 (0.86 to 1.58)	0.319	1.64 (1.21 to 2.23)	0.001	1.50 (1.10 to 2.05)	0.010	1.34 (0.98 to 1.85)	0.069

CUHK-SR, the Chinese University of Hong Kong Stroke Registry; ; ICAS, intracranial atherosclerotic stenosis; OXVASC, Oxford Vascular Study.

justified in elderly Caucasian patients presenting with TIA/stroke with multiple vascular risk factors, for better understanding of the stroke aetiology.

The current study indicated more involvement of the anterior circulation by ICAS in Chinese stroke/TIA patients, with MCA as the most common lesion location, consistent with previous Chinese studies.[33–35] For Caucasian patients, our study indicated same involvement rates of the anterior and posterior circulations by ICAS, with PCA, VA-V4, MCA and ICA similarly affected. Distribution of ICAS lesions in anterior vs posterior circulations in European Caucasians varied in previous studies. A study in Netherlands (n=786) reported higher ICAS prevalence in posterior circulation in TIA/ischaemic stroke patients, with PCA and distal VA most commonly affected,[36] while other European studies reported higher ICAS prevalence in the anterior circulation.[13 14 37] Previous American (multiple ethnic backgrounds) and Chinese studies suggested that atherosclerosis might affect arteries in the anterior circulation earlier in life, and vascular risk factors and genetic factors might interface differently with endothelium of cerebral arteries with different haemodynamic and structural features.[35 38] Yet, these inferences need further investigations.

Our study had limitations. First, although we attempted to exclude non-atherosclerotic stenosis of intracranial arteries, we used MRA/CTA to define ICAS, which might not accurately differentiate the etiologies of ICAS; even with DSA, the currently gold standard to define ICAS, it is difficult to differentiate ICAS and early-stage Moyamoya disease. Therefore, there might be contamination from non-atherosclerotic stenosis (eg, early-stage Moyamoya disease or arterial dissection) in ICAS in the current study, especially in younger Chinese patients without vascular risk factors. Moreover, to determine the degree of luminal stenosis in ICAS, time-of-flight MRA, with a flow-dependent nature, tends to overestimate the severity, while good-quality CTA is more precise.[39 40] Second, stroke subtyping and symptomatic/asymptomatic ICAS were prospectively determined as soon as possible after patient recruitment in OXVASC,[6] while retrospective classification was needed in a considerable proportion of TIA patients in CUHK-SR with atypical neurological symptoms without cerebral infarctions, or those with multiple possible stroke etiologies, which might be unreliable. We, therefore, reported the prevalence of any ICAS but did not differentiate symptomatic and asymptomatic ICAS, or the stroke aetiologies, in the current study. Moreover, a considerable proportion of patients did not have complete V4 scanned in MRA/CTA in CUHK-SR, who were not counted in the analyses of ICAS locations; thus, the prevalence of V4 stenosis in Chinese patients may need further verification. Finally, data were not available for extracranial carotid and vertebral artery stenosis for the Chinese patients, hence we did not compare prevalence of extracranial arterial stenosis between the two cohorts; also, without considering the extracranial artery status, accuracy in grading the degree of intracranial stenosis as well as determining the compensatory effects mimicking an intracranial stenosis in the presence of extracranial occlusion might have been underestimated or misinterpreted. Future longitudinal studies with both extracranial- and intracranial vascular imaging, and with a more comprehensive profile of patients' characteristics (eg, peripheral artery disease, chronic kidney disease, medications and vascular risk factor management status) and environmental factors (eg, climate, food, social and cultural habits), will better delineate and explain the ethnic difference in cervicocerebral arterial stenosis between the two populations.

In conclusion, among TIA and minor stroke patients, Chinese are more susceptible to ICAS than Caucasians, with an earlier

Table 4 Distribution of ICAS lesions in the two cohorts

	OXVASC (n=1287)		CUHK-SR (n=691)	
	No of patients with the arteries affected/no of patients with the artery imaged (%)	No of arteries affected/total no of arteries imaged (%)	No of patients with the arteries affected/ no of patients with the artery imaged (%)	No of arteries affected/total no of arteries imaged (%)
Any ICAS in anterior circulation	155/1287 (12.0)*		248/691 (35.9)*	
Any ICAS in posterior circulation	155/1287 (12.0)†		121/689 (17.6)†	
ICAS in both anterior and posterior circulations	53/1287 (4.1)‡		72/689 (10.4)‡	
ICAS in individual arteries				
Intracranial ICA	68/1287 (5.3)	90/2574 (3.5)	83/691 (12.0)	107/1382 (7.7)
ACA (A1+A2)	30/1287 (2.3)	31/2574 (1.2)	68/691 (9.8)	75/1382 (5.4)
MCA (M1+M2)	85/1287 (6.6)	93/2574 (3.6)	184/691 (26.6)	228/1382 (16.5)
PCA (P1+P2)	83/1287 (6.4)	98/2574 (3.8)	102/691 (14.8)	116/1382 (8.4)
VA (V4)	82/1287 (6.4)	97/2574 (3.8)	15/334 (4.5)	19/668 (2.8)
BA	13/1287 (1.0)	13/1287 (1.0)	23/689 (3.3)	23/689 (3.3)

*P<0.001 for comparison between the two cohorts.
†P=0.001 for comparison between the two cohorts.
‡P<0.001 for comparison between the two cohorts.
ACA, anterior cerebral artery; BA, basilar artery; CUHK-SR, the Chinese University of Hong Kong Stroke Registry; ICA, internal carotid artery; ICAS, intracranial atherosclerotic stenosis; MCA, medial cerebral artery; OXVASC, Oxford Vascular Study; PCA, posterior cerebral artery; VA, vertebral artery.

onset age and a higher prevalence, independent of vascular risk factors. ICAS prevalence was equivalent in Chinese aged <60 years and Caucasians aged ≥80. There are also significant differences between Chinese and Caucasians in ICAS locations. Overall, ICAS shared similar risk factors in Chinese and Caucasian patients, but vascular risk factors were not independently associated with ICAS in Chinese patients aged <70 years, supporting an important role of genetic factors underlying the ethnic difference. On the other hand, ICAS burden in Caucasians might be higher than previously estimated, especially in the elderly.

Acknowledgements We thank the participants of the study, and clinical and research staff in Oxford and Hong Kong who contributed to patient recruitment and data collection. We acknowledge the use of the facilities of the Acute Vascular Imaging Centre (AVIC), Oxford.

Contributors XL and PMR planned the study, analysed the data, interpreted the findings and wrote the manuscript; RH, XF, KLC, FJW, LL and YS contributed to data collection and analyses; KSLW, VM and TWL provided critical comments/revisions of the manuscript. PMR is responsible for the overall content.

Funding This work was supported by the Lee Hysan Postdoctoral Fellowship in Clinical Neurosciences (no reference number); Direct Grant for Research, the Chinese University of Hong Kong (Reference No. 2018.035); the Oxford Vascular Study is funded by the Wellcome trust, Wolfson Foundation, British Heart Foundation, Stroke Association and the National Institutes of Health (NIHR) Biomedical Research Centre (no reference numbers), Oxford.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by ethics committee in Hong Kong and in Oxford: the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (2017.591), and the Oxfordshire Research Ethics Committee (OREC A: 05/Q1604/70).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as online supplemental information. Requests for access to anonymised data reported in this paper will be considered by the corresponding author.

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Supplemental materials

Leng X, *et al. J Neurol Neurosurg Psychiatry* 2021;0:1–8. doi: 10.1136/jnnp-2020-325630

eTable 1. Search strategy for PubMed, conducted on 14 October 2019

Search #	Search queries	Number of items found
#1	Search (intracranial arter* steno* OR intracranial steno* OR intracranial large artery steno* OR intracranial occlusi* OR intracranial arter* occlusi* OR intracranial large artery occlusi* OR intracranial atherosclero* OR intracranial large artery atherosclero*) [All Fields]	2,388
#2	Search (prevalence OR incidence OR frequency OR epidemiology OR burden) [All Fields]	3,831,047
#3	Search (ischemic stroke OR ischaemic stroke OR minor stroke OR minor ischemic stroke OR minor ischaemic stroke OR transient ischemic attack OR transient ischaemic attack OR TIA) [All Fields]	113,316
#4	Search #1 AND #2 AND #3	373
#5	Search #4 AND ("1990/01/01" [Date - Publication]: "2019/10/14" [Date - Publication]) AND English [Language]	324

eTable 2. Search strategy for OVID, conducted on 14 October 2019 [a]

Search #	Search queries	Number of items found
#1	(intracranial arter* steno* or intracranial steno* or intracranial large artery steno* or intracranial occlusi* or intracranial arter* occlusi* or intracranial large artery occlusi* or intracranial atherosclero* or intracranial large artery atherosclero*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]	8,452
#2	(prevalence or incidence or frequency or epidemiology or burden).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]	10,186,862
#3	(ischemic stroke or ischaemic stroke or minor stroke or minor ischemic stroke or minor ischaemic stroke or transient ischemic attack or transient ischaemic attack or TIA).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]	231,419
#4	#1 AND #2 AND #3	1293
#5	limit #4 to yr="1990 -Current"	1283
#6	limit #5 to (English) AND (full text) AND (human)	563

[a] The following databases were searched via OVID: Embase 1910 to Present; Ovid MEDLINE(R) 1946 to October 14, 2019; and Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations 1946 to October 14, 2019.

eTable 3: Details of imaging received by study patients

Imaging modality	OXVASC	CUHK-SR
	n (%) N= 1579	n (%) N= 1099
Intracranial vascular imaging		
MR angiography	1035 (65.5)	673 (61.2)
CT angiography	253 (16.0)	99 (9.0)
MR and CT angiography	0	81 (7.4)
Transcranial Doppler only	81 (5.2)	262 (23.8)
Digital subtraction angiography only	0	1 (0.1)
Extracranial vascular imaging only		
Carotid Doppler ultrasound	154 (9.8)	38 (3.5)
No vascular imaging	57 (3.6)	107 (9.7)
Known atrial fibrillation	25	62
Previously investigated or imaged elsewhere	8	0
Other clinical or logistical issue [a]	24	45

Abbreviations: OXVASC, Oxford Vascular Study; CUHK-SR, the Chinese University of Hong Kong Stroke Registry.

[a] Such as older than 90 years, gastrointestinal bleeding, trauma, dementia.

eTable 4: Baseline characteristics of study population, stratified by intracranial vascular imaging.

Characteristics	OXVASC			CUHK-SR		
	Intracranial MRA/CTA (n= 1,287)	***No intracranial MRA/CTA (n= 292)***	**p-value**	***Intracranial MRA/CTA (n= 691)***	***No intracranial MRA/CTA (n= 408)***	**p-value**
Age, years	69 (13.9)	75 (12.8)	<0.0001	66 (12.3)	72 (11.9)	<0.001
Age ≥70 years	715 (55.6)	209 (71.6)	<0.0001	279 (40.4)	243 (59.6)	<0.001
Male sex	667 (51.8)	143 (49.0)	0.38	441 (63.8)	213 (52.2)	<0.001
Ever-smoker	688 (53.5)	162 (56.3)	0.40	270 (39.1)	154 (37.7)	0.662
History of hypertension	707 (54.9)	194 (67.4)	<0.0001	453 (65.6)	286 (70.1)	0.121
History of diabetes	169 (13.1)	62 (21.6)	<0.0001	181 (26.2)	116 (28.4)	0.420
History of dyslipidemia	436 (33.9)	109 (38.1)	0.17	354 (51.2)	169 (41.4)	<0.002
Atrial fibrillation [a]	191 (14.9)	70 (24.3)	<0.0001	78 (11.3)	95 (23.3)	<0.001
History of ischemic stroke/TIA	192 (14.9)	88 (30.4)	<0.0001	144 (20.8)	90 (22.1)	0.633
History of ischemic heart disease	166 (12.9)	65 (22.5)	<0.0001	54 (7.8)	52 (12.7)	0.007
Event type						0.015
TIA	842 (65.4)	158 (54.1)	<0.0001	208 (30.1)	152 (37.3)	
Minor stroke	445 (34.6)	134 (45.9)		483 (69.9)	256 (62.7)	

Abbreviations: OXVASC, Oxford Vascular Study; CUHK-SR, the Chinese University of Hong Kong Stroke Registry; MRA, magnetic resonance angiography; CTA, computed tomography angiography; TIA, transient ischemic attack.

[a] History of atrial fibrillation and newly diagnosed atrial fibrillation after the index stroke or TIA.

eTable 5. Risk factors of ICAS in younger and older patients in the 2 cohorts

Risk factors	OXVASC (n=1287)				CUHK-SR (N=691)			
	Patients <70 years old (n=572)		Patients ≥70 years old (n=715)		Patients <70 years old (n=412)		Patients ≥70 years old (n=279)	
	Multivariable adjusted OR (95% CI)	p-value	Multivariable adjusted OR (95% CI)	p-value	Multivariable adjusted OR (95% CI)	p-value	Multivariable adjusted OR (95% CI)	p-value
Age (every 10-year increment)	0.97 (0.72-1.30)	0.818	1.79 (1.37-2.35)	<0.001	1.00 (0.78-1.28)	0.973	1.86 (1.10-3.15)	0.020
Male sex	1.72 (0.94-3.16)	0.079	1.28 (0.90-1.82)	0.173	1.01 (0.65-1.55)	0.980	1.05 (0.63-1.74)	0.858
Ever-smoker	1.01 (0.57-1.79)	0.965	0.98 (0.69-1.39)	0.909	0.94 (0.62-1.43)	0.774	1.19 (0.72-1.98)	0.494
History of hypertension	1.68 (0.92-3.06)	0.090	1.48 (1.00-2.18)	0.048	1.40 (0.90-2.20)	0.138	1.68 (0.93-3.02)	0.086
History of diabetes	1.67 (0.77-3.61)	0.191	1.40 (0.88-2.23)	0.155	1.63 (0.99-2.66)	0.054	1.86 (1.09-3.18)	0.023
History of dyslipidemia	1.05 (0.55-2.02)	0.873	1.24 (0.87-1.77)	0.230	1.23 (0.80-1.87)	0.342	1.57 (0.96-2.59)	0.074

Abbreviations: ICAS, Intracranial atherosclerotic stenosis; OXVASC, Oxford Vascular Study; CUHK-SR, the Chinese University of Hong Kong Stroke Registry; OR, odds ratio; CI, confidence interval.

eTable 6. Prevalence of ICAS in patients with ischemic stroke or TIA in Europe

Study	Country/ Region	Enrolment period	Sample size	Mean age, years	Male, %	IS/TIA	Cerebrovascular imaging to define ICAS [a]	Cerebral vascular workups of the patients				Prevalence of ICAS, %		Modified NOS [b]
								TCD, % or n (%)	MRA, % or n (%)	CTA, % or n (%)	DSA, % or n (%)	Any ICAS	Symptomatic ICAS	
Weimar 2006 [1]	Germany	2000-2002	4,157	67	57	IS/TIA	TCD/MRA/ CTA/DSA	97	24	3	4	—	15	4
Holzer 2009 [2]	Germany	2000-2004	176	63	38	TIA	TCD	176 (100)	NA	NA	NA	12	—	2
Meseguer 2010 [3]	France	2003-2007	1,823	62	50	TIA	TCD/MRA/ CTA/HR-MRI	1,823 (100)	1,248 (69)	82 (5)	NA	9	4	3
Homburg 2011 [4]	Netherlands	—	786	62	56	IS/TIA	CTA	786 (100)	NA	NA	NA	10	3	3
Ovesen 2013 [5]	Denmark	2009-2011	652	67	56	IS/TIA	CTA	652 (100)	NA	NA	NA	7	0.5	3
von Sarnowski 2013 [6]	Pan-European countries	2007-2010	1,612	46	82	Young IS/TIA (age 18-55)	TCD	1,612 (100)	NA	NA	NA	20% in IS; 7% in TIA	14% in IS; 4% in TIA	4
Ssi-Yan-Kai 2013 [7]	France	2009-2011	129	64	57	Minor IS/ TIA	MRA	NA	129 (100)	NA	NA	—	12	2
Wolff 2014 [8]	France	2005-2010	159	37	51	Young IS (age 18-45)	TCD/MRA/ CTA/DSA	157 (99)	144 (91)	47 (30)	68 (44)	—	31	2
Logallo 2014 [9]	Norway	2010-2011	607	72	55	IS/TIA	TCCS/MRA/ CTA	TCCS: 607 (100)	533 (88)	227 (37)	NA	11	7	3

Tsivgoulis 2014 [10]	Greece	2009-2011	467	58	60	IS/TIA	TCD/MRA/ CTA/DSA	467 (100)	Only in those suspected of ICAS by TCD; numbers not reported			11	9	4
Baracchini 2016 [11]	Italy	2011-2013	1,134	71	59	IS	TCD/TCCS/ MRA/CTA	TCD/ TCCS: 1,134 (100)	844 (74)	290 (26)	113 (10)	9% (uncertain if it was any ICAS or symptomatic ICAS)		4
Sorgun 2017 [12]	Turkey	2012-2014	619	69	54	IS	MRA/CTA/ DSA	—	—	—	—	12	11	3
Hoshino 2018 [13]	France	2005-2008	403	62	74	IS	TCD/MRA/ CTA	399 (99)	289 (72)	53 (13)	NA	36	18	3

Abbreviations: ICAS, intracranial atherosclerotic stenosis or intracranial arterial stenosis of any etiology as defined in different studies; TIA, transient ischemic attack; IS, ischemic stroke; TCD, transcranial Doppler, MRA, magnetic resonance angiography; CTA, computed tomographic angiography; DSA, digital subtraction angiography; NOS, Newcastle-Ottawa Scale; HR-MRI, high-resolution magnetic resonance imaging; TCCS, transcranial color-coded Doppler sonography.

[a] ICAS was defined by velocity criteria in TCD or >/≥50% stenosis or occlusion in MRA/CTA/DSA, if not specified otherwise.

[b] With a total score of 0-5; scores of ≥3 or <3 respectively indicating low and high risk of bias.

"—" indicates unclear or not reported; "NA" indicates not applicable.

eTable 7. Prevalence of ICAS in patients with ischemic stroke or TIA in Asia

Study	Country/ Region	Enrolment period	Sample size	Mean age, years	Male, %	IS/TIA	Cerebrovascular imaging to define ICAS [a]	Cerebral vascular workups of the patients				Prevalence of ICAS, %		Modified NOS [c]
								TCD, n (%)	MRA, n (%)	CTA, n (%)	DSA, n (%)	Any ICAS	Symptomatic ICAS	
Lee 2002 [14]	Taiwan	1997-2001	170	—	71	Young IS/TIA (age 18-45)	DSA	NA	NA	NA	170 (100)	27	—	2
Shin 2005 [15]	South Korea	2000-2003	901	62	59	IS	MRA/DSA	NA	—	NA	—	28 [b]	22	3
Kim 2010 [16]	South Korea	2006-2009	1,012	64	63	IS/TIA	MRA	NA	1,012 (100)	NA	NA	27	—	3
Niu 2014 [17]	China	2007-2012	197	39	65	Young IS (age 15-49)	TCD/MRA/ CTA/DSA	160 (81)	MRA/CTA/DSA: 159 (81)			51	35	2
Shi 2014 [18]	China	2010-2012	351	47	72	Young IS (age≤55)	MRA/CTA/DSA	NA	315 (90)	24 (7)	12 (3)	35	—	3
Roy 2014 [19]	India	2007-2013	610	49	70	IS	Possibly MRA/CTA	NA	—	—	NA	—	36	3
Kiyohara 2014 [20]	Japan	2007-2012	693	69	62	TIA	MRA/CTA/DSA	NA	672 (97)	158 (23)	57 (8)	22		4
Ojha 2015 [21]	China	2007-2012	123	45	80	Young IS (age ≤50)	MRA	NA	98 (80)	NA	NA	38	—	2
Lee 2017 [22]	South Korea	2011-2016	516	68	52	IS	MRA	NA	516 (100)	NA	NA	43	—	3

Kim 2017 [23]	South Korea	2006-2009	1,081	64	62	IS/TIA	MRA/CTA/DSA	Mostly MRA (numbers not reported)				37	17	3
Park 2017 [24]	South Korea	2013-2013	9,506	66	61	Minor IS/ high-risk TIA	TCD/MRA/CTA/ DSA	6,990 (74)	7,494 (79)	3,255 (34)	945 (10)	—	25	4
Zhang 2019 [25]	China	2017-2018	207	62	66	IS	CTA	NA	NA	207 (100)	NA	65	—	3

Abbreviations: ICAS, intracranial atherosclerotic stenosis or intracranial arterial stenosis of any etiology as defined in different studies; TIA, transient ischemic attack; IS, ischemic stroke; TCD, transcranial Doppler, MRA, magnetic resonance angiography; CTA, computed tomographic angiography; DSA, digital subtraction angiography; NOS, Newcastle-Ottawa Scale.

[a] ICAS was defined by velocity criteria in TCD or >/≥50% stenosis or occlusion in MRA/CTA/DSA, if not specified otherwise.

[b] Prevalence of any ICAS was not reported in this article[15]. This number (28%) was retrieved from another article[26] reporting ICAS prevalence in this cohort but with a smaller sample size (n=512).

[c] With a total score of 0-5; scores of ≥3 or <3 respectively indicating low and high risk of bias.

"—" indicates unclear or not reported; "NA" indicates not applicable.

eTable 8. Prevalence of ICAS in patients with ischemic stroke or TIA in North and South America

Study	Country/ Region	Enrolment period	Sample size	Mean age, years	Male, %	IS/TIA	Cerebrovascular imaging to define ICAS [a]	Cerebral vascular workups of the patients				Prevalence of ICAS, %		Modified NOS [c]
								TCD, % or n (%)	MRA, % or n (%)	CTA, % or n (%)	DSA, % or n (%)	Any ICAS	Symptomatic ICAS	
Sacco 1995 [27]	USA (multi-ethnic)	1990-1993	438	70	46	IS	TCD/MRA/ DSA [b]	75	—	NA	—	—	1% in Caucasians; 6% in African Americans; 11% in Hispanics	4
Wityk 1996 [28]	USA (multi-ethnic)	1993-1995	274	67	50	IS/TIA	TCD/MRA/ DSA	14	49	NA	14	24% in Caucasians; 22% in African Americans	9	3
Koch 2005 [29]	USA (Haitian)	1998-2002	126	60	52	IS	MRA/DSA	NA	MRA/DSA in 81 (64%)			—	9	3
Rincon 2009 [30]	USA (multi-ethnic)	1993-1997	714	60	37	First IS	TCD/MRA/ DSA [b]	54	18	NA	3	—	7	4
Lange 2018 [31]	Brazil	2012-2015	359	64	51	First IS	TCD/MRA/ CTA/DSA	315 (88)	MRA/CTA/DSA in 184 (51%)			—	5	3

Abbreviations: ICAS, intracranial atherosclerotic stenosis or intracranial arterial stenosis of any etiology as defined in different studies; TIA, transient ischemic attack; IS, ischemic stroke; TCD, transcranial Doppler, MRA, magnetic resonance angiography; CTA, computed tomographic angiography; DSA, digital subtraction angiography; NOS, Newcastle-Ottawa Scale.

[a] ICAS was defined by velocity criteria in TCD or >/≥50% stenosis or occlusion in MRA/CTA/DSA, if not specified otherwise.

[b] ICAS was defined by velocity criteria in TCD or >60% stenosis or occlusion in MRA/DSA in this study.

[c] With a total score of 0-5; scores of ≥3 or <3 respectively indicating low and high risk of bias.

"—" indicates unclear or not reported; "NA" indicates not applicable.

eTable 9. Prevalence of ICAS in patients with ischemic stroke or TIA in other countries/regions or worldwide

Study	Country/ Region	Enrolment period	Sample size	Mean age, years	Male, %	IS/TIA	Cerebrovascular imaging to define ICAS [a]	Cerebral vascular workups of the patients				Prevalence of ICAS, %		Modified NOS [c]
								TCD, % or n (%)	MRA, % or n (%)	CTA, % or n (%)	DSA, n (%)	Any ICAS	Symptomatic ICAS	
TIAregistry.org project [32, 33]	World-wide	2009-2011	4,583	66	60	Minor IS/TIA	TCD/MRA/CTA	67	46	15	NA	14% overall; 20% in Japanese; 13% in non-Japanese [b]	—	4
Moustafa 2013 [34]	Egypt	2011	143	62	59	IS	MRA	NA	143 (100)	NA	NA	67	44	3

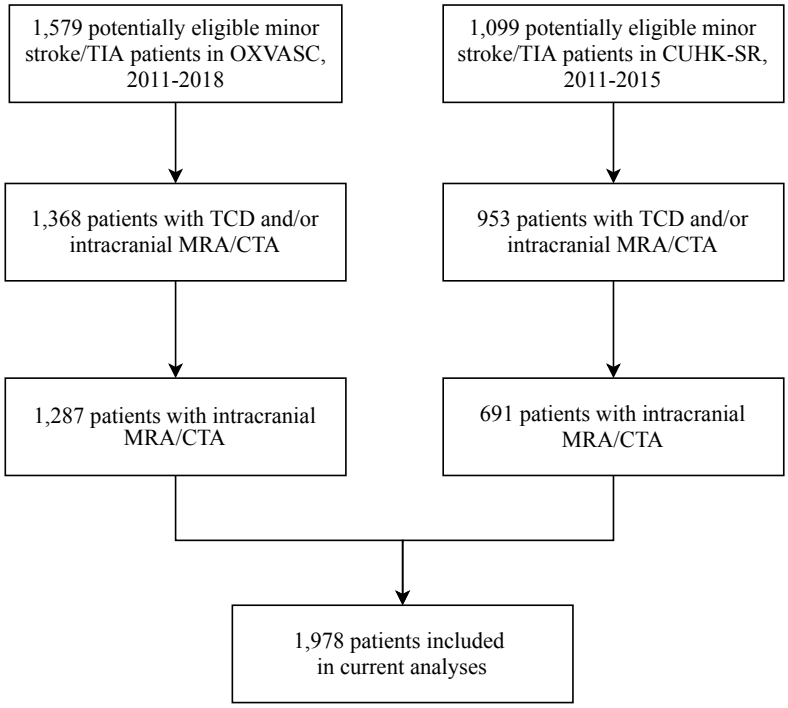
Abbreviations: ICAS, intracranial atherosclerotic stenosis or intracranial arterial stenosis of any etiology as defined in different studies; TIA, transient ischemic attack; IS, ischemic stroke; TCD, transcranial Doppler, MRA, magnetic resonance angiography; CTA, computed tomographic angiography; DSA, digital subtraction angiography; NOS, Newcastle-Ottawa Scale.

[a] ICAS was defined by velocity criteria in TCD or >/≥50% stenosis or occlusion in MRA/CTA/DSA, if not specified otherwise.

[b] 345 (7.5%) patients were Japanese; non-Japanese patients included European native (n = 3,317), Eastern Asian (n = 725), Middle or Proximal Eastern and Maghreb (n = 69), American Hispanic or Latino (n = 63), African American (n = 38), and other (n = 26).[33]

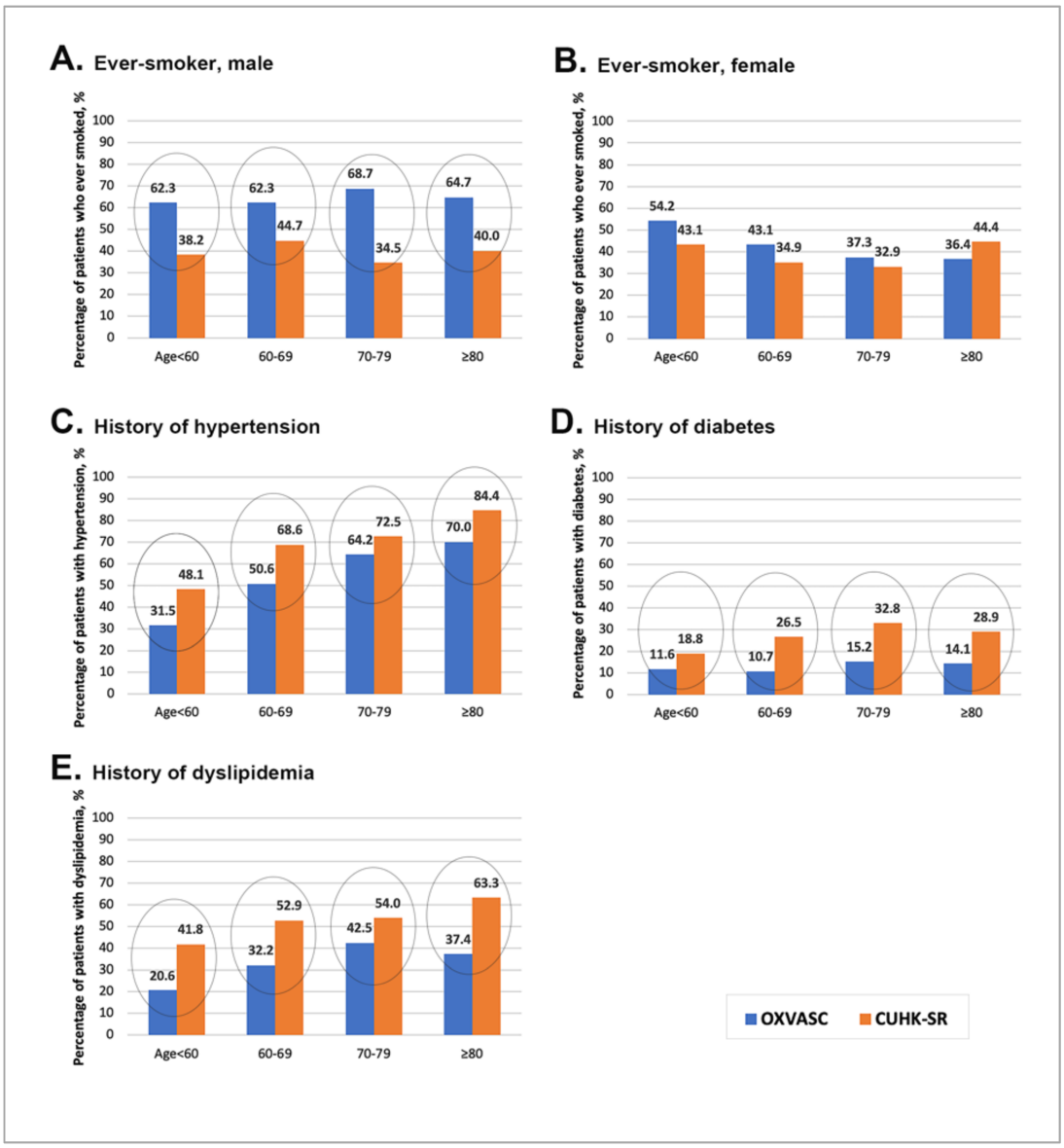
[c] With a total score of 0-5; scores of ≥3 or <3 respectively indicating low and high risk of bias.

"—" indicates unclear or not reported; "NA" indicates not applicable.



eFigure 1. Flow chart for patient screening in the current study.

Abbreviations: TIA, transient ischemic attack; OXVASC, Oxford Vascular Study; CUHK-SR, the Chinese University of Hong Kong Stroke Registry; TCD, transcranial Doppler; MRA, magnetic resonance angiography; CTA, computed tomography angiography.



eFigure 2. Age-specified prevalence of vascular risk factors in the 2 cohorts.

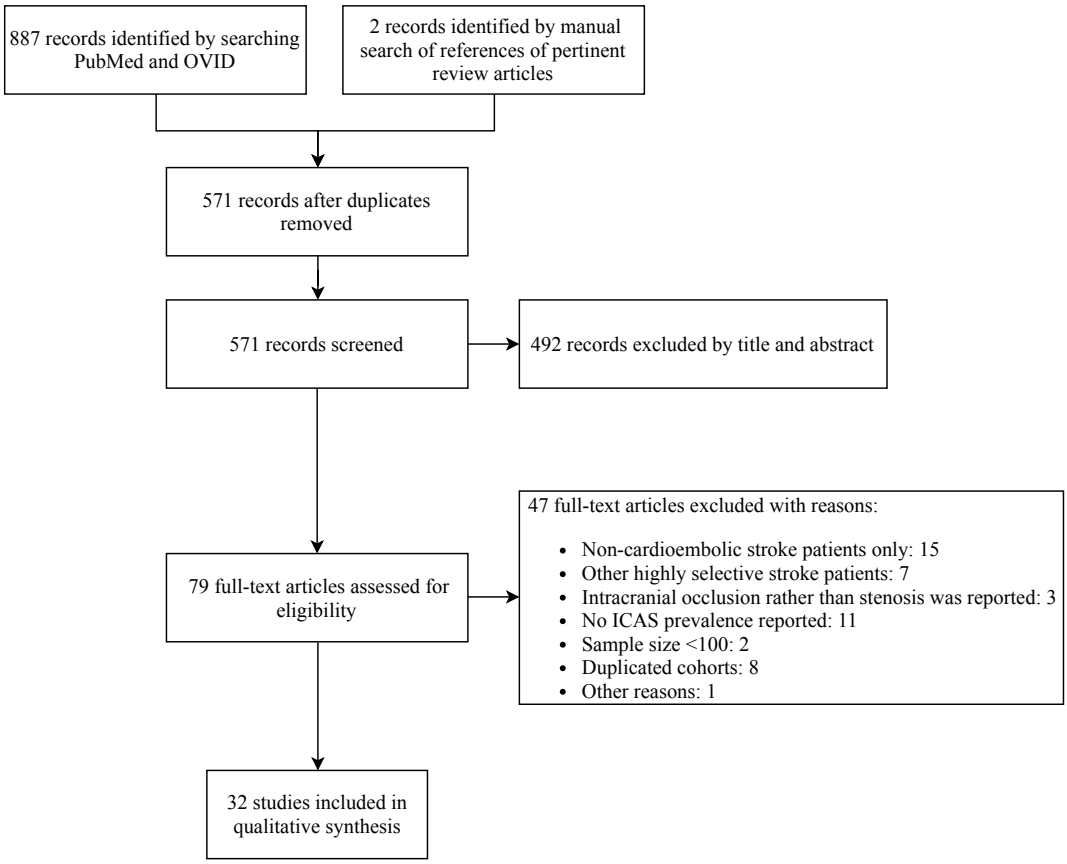
A. More male patients in OXVASC had ever smoked than those in CUHK-SR in each age group.

B. The percentages of female patients who had ever smoked in the two cohorts were not significantly different in any age group.

C/D/E. More patients in CUHK-SR had histories of hypertension, diabetes and dyslipidemia than those in OXVASC, in each age group.

Circles indicate comparisons with $p<0.05$ for chi-square tests.

Abbreviations: OXVASC, Oxford Vascular Study; CUHK-SR, the Chinese University of Hong Kong Stroke Registry.



eFigure 3. Flow chart for study screening and selection in the systematic review.

Abbreviations: ICAS, intracranial atherosclerotic stenosis.

Appendix. Modified Newcastle-Ottawa Scale (NOS) [35, 36] for quality assessment of the primary studies.

(1) Representativeness of the sample:

1 point: Population contained a mixture of specialties or at multiple sites.

0 points: Population contained a single specialty at a single site.

(2) Sample size:

1 point: Sample size was greater than 200 participants.

0 points: Sample size was less than 200 participants or a convenience sample.

(3) Non-respondents:

1 point: Comparability between respondent and non-respondent characteristics was established, and the response rate was satisfactory.

0 points: The response rate was unsatisfactory, the comparability between respondents and non-respondents was unsatisfactory, or there was no description of the response rate or the characteristics of the responders and the non-responders.

(4) Ascertainment of intracranial arterial stenosis (ICAS):

1 point: Independent assessment using objective imaging methods.

0 points: No description/non-standard imaging methods used.

(5) Quality of descriptive statistics reporting:

1 point: Reported descriptive statistics to describe the population (*e.g.*, age, sex) with proper measures of dispersion (*e.g.*, standard deviation, standard error, range).

0 points: Descriptive statistics were not reported, were incomplete, or did not include proper measures of dispersion.

Legend: This scale, ranging from 0 to 5, assesses quality in several domains: sample representativeness and size, comparability between respondents and non-respondents, ascertainment of ICAS, and statistical quality. Studies were judged to be of low risk of bias (≥3 points) or high risk of bias (<3 points).

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