



Diagnostic accuracy of major stroke types in Chinese adults: A clinical adjudication study involving 40,000 stroke cases

Iain Turnbull,^a Robert Clarke,^{a,*} Neil Wright,^a Yu Guo,^b Christina Kartsonaki,^{a,c} Pei Pei,^b Alex Hacker,^a Canqing Yu,^d Simon Gilbert,^a Ling Yang,^{a,c} Jinyi Zhou,^e Sam Sansome,^a Jun Lv,^d Liming Li,^d Zhengming Chen,^{a,c} and Yiping Chen^{a,c,**}, for the China Kadoorie Biobank Collaborative Group¹

^aClinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, Big Data Institute, Old Road Campus, Oxford OX3 7LF, UK

^bChinese Academy of Medical Sciences, Beijing, China

^cMedical Research Council Population Health Research Unit (MRC PHRU), Nuffield Department of Population Health, University of Oxford, UK

^dDepartment of Epidemiology, School of Public Health, Peking University Health Science Center, Peking University Center for Public Health and Epidemic Preparedness and Response, Beijing, China

^eNCDs Prevention and Control Department, Jiangsu CDC, Zhejiang Province, China

Summary

Background Widespread use of brain imaging in suspected stroke cases in Chinese adults has prompted the need for clinical adjudication studies of stroke types. We conducted a clinical adjudication study to assess the reporting and diagnostic accuracy of major stroke types.

Methods The prospective China Kadoorie Biobank recruited >512,000 adults (mean age 52 years, 59% women) from 10 urban and rural areas in China during 2004–2008, and recorded 45,859 first-ever incident stroke cases during an 11-year follow-up. Medical records were retrieved in ~85%, and clinical details were recorded using a handheld computer for specialist physician adjudicators who applied conventional WHO clinical criteria for diagnosis of stroke. The positive predictive value (PPV) for reported and adjudicated stroke cases was examined for major stroke types (ischaemic stroke [IS], intracerebral haemorrhage [ICH], subarachnoid haemorrhage [SAH]), calendar year, area, and hospital type.

Findings Of 38,823 cases with retrieved medical records, the PPV for reported strokes was 91%. Among 29,952 adjudicated cases, the PPV for adjudicated cases was 81%, with higher PPV for ICH ($n = 3391$; 98%) and SAH (364; 98%) than for IS (20,473; 79%). Of 5504 cases with a verified IS diagnosis that was refuted on adjudication, 3763 (68%) had silent lacunar infarcts (LACI). The proportion of cases with silent LACI increased from 7.1% in 2004–2008 to 18.2% in 2016–2017. If cases with silent LACI were classified as IS, as advocated by new International Classification of Diseases (ICD-11) diagnostic criteria for stroke involving imaging and clinical rather than clinical criteria alone, the PPV increased to 93%.

Interpretation While the overall reporting and diagnostic accuracy of stroke types in Chinese adults is high, the recent implementation of new diagnostic criteria for IS has important implications for contemporary clinical practice and research on stroke in Chinese populations.

Funding Kadoorie Charitable Foundation, Hong Kong, China, UK Wellcome Trust (212946/Z/18/Z, 202922/Z/16/Z, 104085/Z/14/Z, 088158/Z/09/Z), Chinese National Natural Science Foundation (91843302), and the National Key Research and Development Program of China (2016YFC0900500, 2016YFC0900501, 2016YFC0900504, 2016YFC1303904). British Heart Foundation, and UK Medical Research Council, and Cancer Research UK.

Copyright © 2022 University of Oxford. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

*Corresponding author.

**Corresponding author at: Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, Big Data Institute, Old Road Campus, Oxford OX3 7LF, UK.

E-mail addresses: robert.clarke@ndph.ox.ac.uk (R. Clarke), yiping.chen@ndph.ox.ac.uk (Y. Chen).

¹ The members of steering committee and collaborative group are listed in the supplementary material.

The Lancet Regional Health - Western Pacific 2022;21: 100415

Published online 5 March 2022

<https://doi.org/10.1016/j.lanwpc.2022.100415>

Keywords: Stroke phenotype; Clinical adjudication; Diagnostic accuracy; Major stroke types

Research in context

Evidence before this study

- Brain imaging in stroke cases has enhanced the ability to distinguish cases due to infarction or haemorrhage and guide the use of appropriate treatment to prevent recurrence or death, but also resulted in increased detection of silent lacunar infarcts.

Added value of this study

- We retrieved medical records on 40,000 first incident stroke cases to evaluate the reporting and diagnostic accuracy of stroke types over an 11-year period, in 5 rural and 5 urban areas of China.
- Using conventional WHO clinical criteria for diagnosis of stroke, the positive predictive value (PPV) for all reported strokes was 91%. Among adjudicated cases, the PPV was 98% for intracerebral haemorrhage (ICH), and subarachnoid haemorrhage (SAH), but only 79% for ischaemic stroke (IS). The proportion of cases with silent LACI increased from 7% to 18% during follow-up. If the reported IS cases were classified as IS using the new International Classification of Diseases, Eleventh Revision (ICD-11) criteria, the PPV for IS was 93%.
- Recognition of the evolving diagnostic accuracy of major stroke types has important implications for contemporary clinical practice and research on stroke types in population studies in China.

Introduction

Stroke is a leading cause of death and disability worldwide, and most cases now occur in low- and middle-income countries.¹ China has a particularly high incidence of stroke, with over 2 million attributable deaths in 2017.² Stroke is defined by the World Health Organisation (WHO) as a “clinical syndrome characterised by rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting more than 24 h or leading to death due a vascular cause”.³ Diagnosis of the major pathological stroke types – ischaemic stroke (IS), intracerebral haemorrhage (ICH), subarachnoid haemorrhage (SAH) or unspecified stroke – requires assessment of symptoms, clinical signs, and brain imaging (computed tomography [CT] and/or magnetic resonance [MR] imaging), carotid and cardiac investigations. Reliable classification of stroke cases by pathological type – and by aetiological subtype for IS^{4–6} – is necessary when assessing differences in the determinants, treatment and prognosis of major stroke pathological types.^{7,8}

Access to high-quality neuroimaging has increased substantially worldwide (including in China) in recent decades, which has improved the diagnostic accuracy and clinical management of stroke types. However, greater use of brain imaging has also led to increased detection of minor cerebral infarcts – including lacunar infarcts – in the absence of focal neurological deficits (so-called “silent lacunar infarcts [LACI]”⁹), which complicates comparisons of stroke incidence within and between populations.¹⁰ Among 12,150 cases with LACI in the China Kadoorie Biobank (CKB),¹¹ two-thirds had neurological symptoms typical of stroke (symptomatic LACI) while one-third had atypical symptoms that were not consistent with the classical definition of stroke (silent LACI).⁹ Importantly, findings from the same study demonstrated that silent and symptomatic LACI stroke cases had comparable risks of recurrent stroke within 5 years (38% vs 25%).

While many previous large studies have reported on the accuracy of stroke diagnosis in high-income settings,^{12–17} little is known about the accuracy of reported strokes in low- and middle-income countries. The aims of the present report from the CKB study were to: (i) assess the feasibility of retrieval of hospital records of reported first-incident stroke cases in a large-scale study in diverse areas in China; (ii) verify the accuracy of reported diagnoses of major stroke pathological types using retrieved hospital records; (iii) validate the diagnostic accuracy of major stroke pathological types by comparing reported stroke diagnoses verified by hospital records with those obtained after clinical adjudication using conventional WHO clinical criteria for stroke; and (iv) examine the consistency of reporting and diagnostic accuracy of major stroke pathological types by reporting source, calendar year, geographic area and hospital type.

Methods

Study population

Details of the study design, methods and participants of the CKB have been described elsewhere.¹¹ Briefly, 512,726 men and women, aged 30 to 79 years, were recruited from 10 diverse (5 urban and 5 rural) areas in China. The baseline survey was conducted during 2004–2008 by trained health workers in local study assessment centers. Information was collected using interview-administered questionnaires including data collection on demographic and socioeconomic status, medical history and lifestyle factors. Measurements of blood pressure, height, weight, and lung function were recorded and a blood sample was collected for long-

term storage. Ethics approval was obtained from all relevant local, national, and international ethics committees prior to enrolment in the study. All participants provided written informed consent to participate in the study and permission for study investigators to access their medical records for research purposes.

Reporting of incident stroke cases

Reporting of incident cases of non-fatal and fatal stroke cases (and other diseases) among study participants was undertaken by electronic linkage, using unique national identifiers, with regional death and disease-specific registries and with national health insurance (HI) agencies for all hospitalisations (over 97% of study participants had HI coverage at enrolment).¹¹ Stroke cases were classified using ICD-10 codes,¹⁸ blinded to personal details recorded in the baseline survey.

For different stroke types, we used ICD-10 codes of I60, I61, I63, and I64 for SAH, ICH, IS, and unspecified stroke, respectively. The codes I69.0, I69.1, I69.3, and I69.4 were used to classify old strokes or sequelae of stroke according to major pathological types. Additionally, R90.8 ("Other abnormal findings on diagnostic imaging of central nervous system") was used for silent LACI in the absence of a specific ICD-10 code. Additional details of ICD-10 and ICD-11¹⁹ codes for stroke, cardiovascular disease (CVD)-related and non-CVD-related outcomes are provided in webTable 1.

Verification of stroke types

To verify the accuracy of reported diagnoses, available medical records for all reported incident stroke cases were retrieved from accessible hospitals. Inaccessible hospitals for which cases were not selected for verification were those that were not successfully identified, closed or merged, located outside study regions, or otherwise could not be accessed (e.g., military hospitals). Verification of retrieved records with matching participant details was conducted by local trained CKB staff using bespoke software (Portable Validation Device [PVD]) on Windows-based tablets with high-resolution cameras to photograph key documents, for example, the initial page, discharge summary, first admission records, and the results of important diagnostic tests including CT and/or MR imaging (either in formal reports or described in the medical notes). Vital status at discharge was also recorded in PVD.²⁰ If diagnostic information relevant to the reported stroke case was not found in participant-matching medical records, any other non-stroke diagnoses were recorded in PVD (as free-text) and later assigned ICD-10 codes using bespoke disease standardisation software. Subsequently, these diagnoses were further classified into CVD-related (other cerebrovascular, ischaemic heart disease [IHD], and other circulatory diseases), non-CVD-

related (neurological and non-neurological), or other unclassified diseases (webTable 1).

Adjudication of stroke diagnoses

All cases with verified primary diagnoses of stroke from retrieved hospital records were adjudicated by an independent team of 39 expert stroke physicians from 11 major hospitals, using a bespoke web-based platform (internet-based Case Adjudication System for clinical Events [*i*-CASE]).¹⁹ Adjudicators were asked to review key medical records and complete a standardised electronic form, which requested specific details on clinical indicators (e.g. symptoms and signs) and diagnostic criteria, including imaging evidence of haemorrhage or ischaemia, laterality and anatomical location of any cerebral lesions, and additional evidence of extra-cranial and intra-cranial arterial disease or sources of embolism for additional phenotyping. Physicians with relevant expertise in stroke care reviewed electronic copies of medical records and adjudicated the diagnoses of stroke as either IS (symptomatic LACI, non-LACI IS), ICH, SAH, or unspecified stroke types.

Cases where brain imaging indicated ischaemic cerebral lesions in the absence of recorded focal neurological dysfunction were classified by physicians as imaging-detected cerebral infarctions without acute focal dysfunction (silent LACI) and refuted as strokes in accordance with the WHO³ and ICD-10 definitions of stroke.¹⁸ Adjudicators designated other refuted cases as either neurological or non-neurological diseases and, where possible, provided free-text diagnoses and recorded additional clinical data in the standardised form. Physician-adjudicated diagnoses were subsequently assigned appropriate ICD-10 codes using bespoke standardisation software and classified as CVD-related (other cerebrovascular, IHD, and other circulatory diseases), non-CVD-related (neurological and non-neurological), or other unclassified diseases (webTable 1).

All reported stroke cases that were refuted or unconfirmed after the adjudication process were reviewed centrally by two research clinicians with relevant training in neurology. A random sample (~%) of confirmed cases was reviewed to check the quality and consistency of adjudication and classification of major stroke types. Discrepancies between expected and adjudicated diagnoses were identified and examined centrally by research clinicians to confirm the final diagnoses.

The present analyses involved hospitalised stroke cases reported between 25 June 2004 and 31 December 2017. Reported cases from participants with self-reported doctor-diagnosed prior stroke or transient ischaemic attack (TIA) ($n = 4926$) at baseline questionnaire were excluded to reduce the risk of inclusion of recurrent stroke cases – with potentially less rigorous clinical assessment and investigation – and evaluation

of diagnostic accuracy of stroke cases was restricted to first-ever incident stroke cases only. Since it was rarely possible to obtain medical records for stroke cases reported to death registries, 4208 stroke cases collected solely from this reporting source were excluded. However, about 20% of reported stroke cases involved fatal cases, which had been reported to disease registries or the HI system, and these fatal cases were included in the present analyses. In addition, stroke cases identified

as comorbid diagnoses from the presenting pages of hospital records ($n = 1921$) were not available for adjudication and were excluded (Figure 1).

Statistical analysis

Baseline characteristics of individuals with and without a diagnosis of stroke were compared after standardisation by sex, age (5-year age groups), and geographic

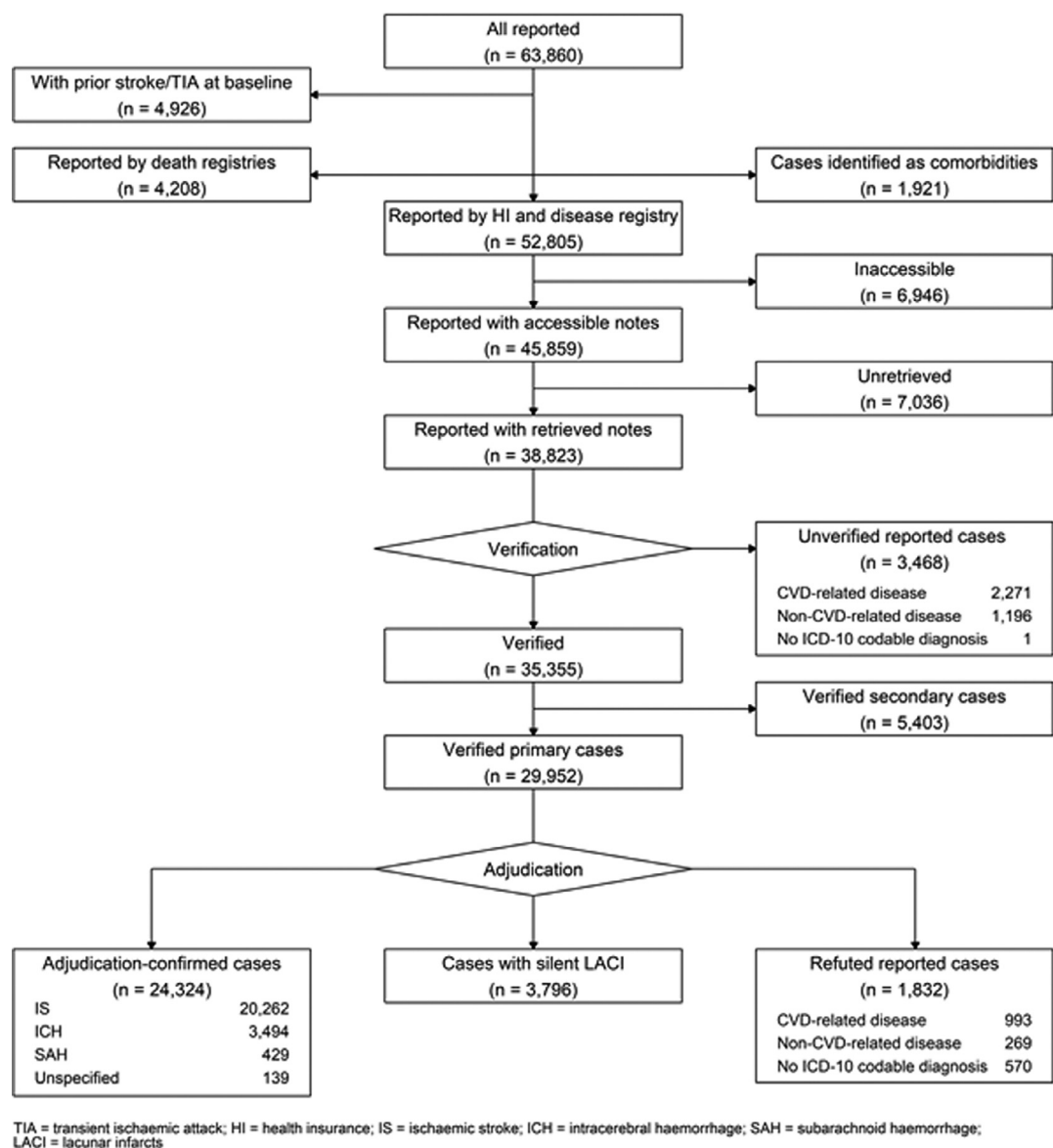


Figure 1. Flow chart of verification and adjudication of all reported stroke cases.

Flow chart summarising the verification and adjudication of reported incident stroke cases. Participants with a prior history of stroke or transient ischaemic attack (TIA) at baseline, with stroke cases reported by death registries, or with stroke cases newly identified from the initial page of hospital records were excluded.

regions. Retrieval rate was defined as the proportion of stroke cases with participant-matching hospital records retrieved among the total number of reported stroke cases from accessible hospitals (excluding fatal stroke cases reported by death registry). Reporting accuracy (i.e., the proportion of reported stroke cases with documented evidence of stroke in hospital records among all reported stroke cases with retrieved participant-matching hospital records) and diagnostic accuracy of stroke (i.e., the proportion of primary stroke diagnoses confirmed by adjudicating physicians among all primary stroke diagnoses documented in hospital records) were estimated using positive predictive values (PPV), overall and by stroke types. The diagnostic accuracy of cases with secondary diagnosis of stroke was not assessed since there were insufficient clinical data in the medical records to confirm or to refute such diagnoses. Chi-squared tests for equal proportions were used to compare PPV between groups, with chi-squared tests for trends in proportions by age, year, and hospital tier. To further validate the accuracy of reported and adjudicated cases of stroke, Cox proportional hazards models were used to compare the strength of associations of major stroke types with usual levels of systolic blood pressure (SBP) after correction for regression dilution bias. All analyses were conducted using publically-available R (version 3.6.2) with the survival package (version 3.1-8) for Cox proportional hazards model and involved data from Release.¹⁷

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. IT, YC and RC had access to all data and had final responsibility for the decision to submit for publication.

Results

Overall, there were 63,860 incident stroke cases reported among study participants during 11 years of follow-up. Among 52,805 eligible first-ever incident stroke cases, 6946 (13.2%) were from inaccessible hospitals, yielding a total of 45,859 stroke cases for the present analyses (Figure 1). The mean (SD) age at baseline was 59.6 (9.7) years, 55% were women, 4% had self-reported IHD, and 10% had screen-detected or self-reported diabetes (webTable 2). Overall, 39,149 (85%) were reported by HI, with the number of cases increasing in later years of follow-up (Table 1). Compared to stroke cases with medical records in accessible hospitals, those in inaccessible hospitals were younger, had lower mean levels of SBP at baseline, and had a higher proportion of IS (87% vs 85% with accessible records: webTable 2).

Among 3467 (9%) cases without a verified diagnosis of stroke in retrieved medical records, 2271 (66%) had

CVD-related diseases, of which 52% (1190) had IHD, 36% (813) had cerebrovascular diseases including TIA, and 12% (268) had other circulatory diseases. The remaining 34% (1196) had non-CVD-related events, among which 85% (1015) were classified as non-neurological diseases (chiefly cancer of the bronchus and lung [ICD-10 C34] or intracranial injury [S06]), and 15% (181) had other neurological diseases (including headache syndromes [G44] and facial nerve disorders [G51]: webTable 4; webTable 11).

Among reported stroke cases from accessible hospitals, participant-matching records were successfully retrieved for 85% from 368 hospitals, with higher retrieval rates in cases from urban areas (92% vs 78% in rural areas), in those reported by HI (87% vs 70% by disease registries), and for later versus earlier years of follow-up (92% in 2016–2017 vs 72% in 2004–2008) (Table 1; webTable 9). The baseline characteristics of retrieved and unretrieved stroke cases were comparable, but a higher proportion of unretrieved cases lived in rural than in urban areas (74% vs 26%: webTable 2). Apart from mean SBP, the baseline characteristics of reported, verified, and adjudication-confirmed stroke cases were similar (webTable 3).

Reporting accuracy of stroke cases

Overall, hospital records were retrieved for 38,823 reported stroke cases (Figure 1). The positive predictive value (PPV) for reported stroke diagnoses was 91.1% (95% CI 90.8–91.4), with higher rates for stroke cases reported by HI than by disease registries (92.0% vs 84.1%), but comparable rates by sex and residence in rural or urban areas. The PPV for reported stroke cases increased with successive calendar years of follow-up (Table 1; webTable 9).

The PPV for reported stroke cases was similar for IS and ICH (91.7% vs 90.4%: Table 2). Overall, 2% of reported ICH cases were verified as having IS, but fewer IS cases were verified as ICH. Over one-third of stroke cases reported as unspecified stroke types had a verified diagnosis of IS (34%), with nearly half (47%) having no verifiable evidence of stroke. For SAH cases, only 78% were verified in retrieved records, with 17% having no evidence of stroke and 2% diagnosed as either IS or ICH (Table 3).

Diagnostic accuracy of stroke cases

After excluding 5403 secondary diagnoses of stroke, which lacked sufficient diagnostic information for further clinical review, a total of 29,952 verified primary stroke cases were adjudicated (Figure 1). Of these cases, 24,324 were confirmed by stroke pathological type, yielding a PPV for adjudicated stroke cases of 81.2% (95% CI 80.8–81.7) for all strokes. The PPV for adjudicated stroke was higher in men than in women (84.1%

	No. of reported cases [†]	% Retrieved	Verified cases		Adjudication-confirmed cases		P-value**
			N	Reporting accuracy (PPV, 95% CI)	N	Diagnostic accuracy (PPV, 95% CI)*	
All	45,859	85	35,355	91.1 (90.8, 91.4)	24,324	81.2 (80.8, 81.7)	
Age, years							
30 – 39	162	47	58	76.3 (66.8, 85.9)	45	86.5 (77.3, 95.8)	
40 – 49	2995	73	1935	88.5 (87.2, 89.9)	1423	82.3 (80.5, 84.1)	
50 – 59	10,442	83	7888	90.9 (90.3, 91.5)	5612	81.6 (80.6, 82.5)	
60 – 69	15,502	86	12,136	91.5 (91.0, 92.0)	8231	80.2 (79.4, 80.9)	
70 – 79	14,544	87	11,556	91.4 (90.9, 91.9)	7857	81.9 (81.1, 82.7)	
80 +	2214	89	1782	90.4 (89.1, 91.7)	1156	80.7 (78.7, 82.8)	0.81
Sex							
Male	20,480	85	15,909	91.7 (91.3, 92.1)	11,518	84.1 (83.5, 84.7)	
Female	25,379	85	19,446	90.6 (90.2, 91.0)	12,806	78.7 (78.1, 79.4)	<0.0001
Region							
Rural	22,553	78	15,854	90.6 (90.2, 91.1)	11,838	83.8 (83.2, 84.5)	
Urban	23,306	92	19,501	91.4 (91.0, 91.8)	12,486	78.9 (78.2, 79.5)	<0.0001
Prior CHD							
No	42,334	84	32,465	91.2 (90.9, 91.5)	22,521	81.4 (81.0, 81.9)	
Yes	3525	92	2890	89.2 (88.1, 90.2)	1803	78.5 (76.8, 80.2)	0.00068
Diabetes							
No	40,252	84	30,794	91.0 (90.7, 91.3)	21,080	80.7 (80.2, 81.2)	
Yes	5607	89	4561	91.5 (90.7, 92.2)	3244	84.6 (83.4, 85.7)	<0.0001
Reporting source							
Disease registry	6710	70	3939	84.1 (83.0, 85.1)	1977	78.4 (76.8, 80.0)	
Health insurance	39,149	87	31,416	92.0 (91.7, 92.3)	22,347	81.5 (81.0, 81.9)	0.00017
Year of reporting							
2004 - 2008	2430	72	1552	89.2 (87.8, 90.7)	1199	86.1 (84.3, 88.0)	
2008	3061	75	2042	89.4 (88.1, 90.7)	1562	87.2 (85.6, 88.7)	
2009	3737	78	2579	88.6 (87.5, 89.8)	1909	84.3 (82.8, 85.8)	
2010	4106	77	2831	89.3 (88.3, 90.4)	2053	83.4 (81.9, 84.9)	
2011	4327	81	3140	89.1 (88.0, 90.1)	2244	83.5 (82.0, 84.9)	
2012	4851	86	3787	90.7 (89.8, 91.5)	2715	81.8 (80.5, 83.1)	
2013	5496	88	4473	92.2 (91.4, 92.9)	3152	82.1 (80.8, 83.3)	
2014	5617	89	4661	92.8 (92.1, 93.5)	3122	81.7 (80.5, 83.0)	
2015	5706	91	4757	92.1 (91.3, 92.8)	3038	77.0 (75.7, 78.3)	
2016 - 2017	6528	92	5533	92.6 (92.0, 93.3)	3330	75.2 (73.9, 76.4)	<0.0001
Hospital tier							
0 (lowest) [§]	2112	63	1132	85.4 (83.5, 87.3)	644	68.4 (65.4, 71.3)	
1	9717	75	6374	87.3 (86.5, 88.1)	4261	78.0 (76.9, 79.1)	
2	12,097	84	9307	91.3 (90.8, 91.9)	7141	83.9 (83.1, 84.7)	
3 (highest)	21,933	91	18,542	92.7 (92.3, 93.1)	12,278	81.7 (81.0, 82.3)	<0.0001

Table 1: Reporting and diagnostic accuracy of all stroke cases reported by health insurance and disease registries overall and by subgroups.

PPV = positive predictive value

* Cases with secondary diagnosis of stroke excluded from diagnostic accuracy assessment since there were insufficient clinical data to confirm diagnoses.

** P-value for chi-squared test of equal proportions (test for trend in proportions for age, year, and hospital tier). After Bonferroni adjustment for multiple testing, all p-values with exception of age were <0.0055.

[†] Reported stroke cases with accessible records.

[§] Includes hospitals of unclassified tier.

vs 78.7%), individuals in rural than in urban areas (83.8% vs 78.9%), and in cases reported by HI than by disease registries (81.5% vs 78.4%) (Table 1; webTable 9). The PPV for adjudicated stroke cases in participants with self-reported prior stroke or TIA at baseline was

higher than in those with first incident stroke cases (89.4% vs 81.2%; $p < 0.001$; webTable 6). The PPV for adjudicated stroke cases was higher in Tier III (81.7%) and II (83.9%) hospitals than in Tier I (78.0%) and small health centers or hospitals with no tier

	No. of reported cases [†]	% Retrieved	Verified cases		Adjudication-confirmed cases	
			N	Reporting accuracy (PPV, 95% CI)	N	Diagnostic accuracy (PPV, 95% CI)*
Ischaemic stroke						
IS**	38,857	87	31,116	91.7 (91.4, 92.0)	20,473	78.7 (78.3, 79.2)
IS + silent LACI [§]					24,222	93.1 (92.9, 93.4)
Haemorrhagic stroke						
ICH	5773	69	3611	90.4 (90.1, 90.7)	3391	98.2 (98.1, 98.4)
SAH	696	75	431	82.7 (82.3, 83.1)	364	98.1 (98.0, 98.3)
Unspecified	533	69	197	53.4 (52.9, 53.9)	96	78.7 (78.2, 79.2)
All stroke	45,859	85	35,355	91.1 (90.8, 91.4)	24,324	81.2 (80.8, 81.7)
All stroke + silent LACI ^{§§}					28,073	93.7 (93.5, 94.0)

Table 2: Reporting and diagnostic accuracy of stroke cases reported by health insurance and disease registries, by stroke type.
 PPV = positive predictive value; IS = ischaemic stroke; ICH = intracerebral haemorrhage; SAH = subarachnoid haemorrhage; LACI = lacunar infarct; Unspecified = stroke, not specified as haemorrhage or infarction.
 * Cases with secondary diagnosis of stroke excluded from diagnostic accuracy assessment, since there were insufficient clinical data to confirm diagnoses.
 † Reported stroke cases with accessible records.
 ** Diagnostic accuracy by ICD-10 classification.
 § Diagnostic accuracy by ICD-11 classification.
 §§ 47 cases where reported or verified non-IS strokes were adjudicated as silent cerebral infarct are not counted as adjudication-confirmed.

	Reported cases, N (%)				(a) Unverified**/ (b) Refuted§ N (%)	Total N
	IS	ICH	SAH	Unspecified		
(a) Verified types						
Reported type†						
IS	30,772 (91%)	88 (0%)	16 (0%)	240 (1%)	2822 (8%)	33,938
ICH	96 (2%)	3395 (85%)	83 (2%)	37 (1%)	384 (10%)	3995
SAH	12 (2%)	12 (2%)	406 (78%)	1 (0%)	90 (17%)	521
Unspecified	124 (34%)	9 (2%)	1 (0%)	63 (17%)	172 (47%)	369
Total	31,004	3504	506	341	3468	38,823
(b) Adjudication-confirmed types						
Verified type*						
IS	20,039 (77%)	256 (1%)	9 (0%)	119 (0%)	5504 (21%)	25,927
ICH	107 (3%)	3189 (94%)	36 (1%)	11 (0%)	54 (2%)	3397
SAH	5 (1%)	34 (8%)	381 (88%)	0 (0%)	12 (3%)	432
Unspecified	111 (57%)	15 (8%)	3 (2%)	9 (5%)	58 (30%)	196
Total	20,262	3494	429	139	5628	29,952

Table 3: Health insurance- and disease registry-reported stroke cases by stroke type for (a) verification and (b) adjudication.
IS = ischaemic stroke; ICH = intracerebral haemorrhage; SAH = subarachnoid haemorrhage; Unspecified = stroke, not specified as haemorrhage or infarction.
† Reported stroke cases with accessible records.
* Cases with secondary diagnosis of stroke excluded from diagnostic accuracy assessment since there were insufficient clinical data to confirm diagnoses.
** No evidence of stroke on review of medical records by public health staff.
§ No clinical evidence of stroke on independent adjudication by expert clinicians.

classifications (68.4%) and decreased in later compared with earlier years of follow-up (86.1% in 2004–2008 vs 75.2% in 2016–2017) (Table 1). The proportion of cases with silent LACI among verified primary stroke cases increased by successive years of follow-up (7.1% during 2004–2008 vs 18.2% during 2016–2017: webTable 7). A corresponding reduction in the PPV for IS during later compared with earlier years of follow-up was observed while the diagnostic

accuracy of ICH remained high throughout the follow-up period (98.2% in 2004–2008 vs 99.0% in 2016–2017: webTable 8) and brain imaging rates increased by calendar year in urban and rural areas alike (89.1% in 2004–2008 vs 94.7% in 2015 for all areas: webTable 10).

For major stroke types, the PPV for adjudicated stroke cases using ICD-10 (excluding cases with silent LACI) was 78.7%, 98.2%, 98.1%, and 78.7% for IS,

ICH, SAH, and unspecified stroke, respectively. However, if cases with silent LACI were classified as stroke cases, consistent with the revised ICD-11 definition of stroke, the PPV for IS increased to 93.1% (Table 2).

At adjudication, 107 (3%) verified ICH cases were reclassified as IS and 256 (1%) IS cases were reclassified as ICH. In addition, 34 (8%) verified SAH cases were reclassified as ICH and only 36 (1%) verified ICH cases as SAH cases. Over half of all cases verified as unspecified stroke (III; 57%) were subsequently adjudicated as having IS (Table 3).

Among 5628 adjudicated cases with verified primary stroke that were refuted by specialist physicians, nearly all (98%) had IS and over two-thirds (3796; 67%) were cases with silent LACI (webTable 5). Of the remaining 1832 (33%) refuted cases, 859 (47%) had IHD, 570 (31%) had no ICD-10 coded diagnoses, and 269 (15%) had non-CVD (15% neurological and 85% non-neurological diseases). The most commonly recorded neurological diagnoses included facial nerve disorders (G51), Parkinson disease (G20), and epilepsy (G40), while unspecified clinical findings, such as 'dizziness and giddiness' (ICD-10 R42) and 'abnormal findings on diagnostic imaging of central nervous system' (R90) were the most frequently identified non-neurological disorders (webTable 5; webTable 12).

Associations of SBP with reported, verified, and adjudication-confirmed stroke

Analyses of the associations of usual SBP with all stroke cases demonstrated stronger associations with adjudication-confirmed vs verified vs reported cases, with adjusted HRs per 10 mmHg higher usual SBP for IS of 1.42, 1.39 and 1.35, respectively (Figure 2). The strength of the associations of usual SBP with reported ICH cases was over 2-fold stronger than for IS (adjusted HRs of 1.89, 1.90, and 1.76, for adjudication-confirmed, verified, and reported cases, respectively; Figure 2). Moreover, the strength of associations of usual SBP with cases with silent LACI was only about half as strong as for adjudication-confirmed IS cases (webFig. 1). The associations of usual SBP with refuted reported cases (other CVD-related diseases, non-CVD-related diseases, or unclassified diseases) were weaker than those with adjudicated IS cases (webFig. 2).

Discussion

This study demonstrated the feasibility of conducting clinical adjudication of major stroke types in large-scale prospective studies in low- and middle-income populations where nationwide disease registries are not typically available. Moreover, this study examined the PPV of reported stroke cases in Chinese adults, and demonstrated that about 91% were verified after review of hospital records. Among the ~30,000 verified primary

stroke cases, over 98% of ICH and SAH cases were confirmed by adjudication. While the reporting accuracy for all stroke cases increased from 89% to 93% between 2004–2008 and 2016–2017, the diagnostic accuracy for all strokes using conventional WHO clinical criteria declined from 86% to 75% over this same period, most likely owing to the increasing proportion of reported stroke cases adjudicated as silent LACI, which is not classified by ICD-10 as stroke. Whereas the overall PPV for adjudicated IS cases was only 79% when assessed using conventional diagnostic criteria, it increased to 93% if cases with silent LACI were considered together with IS cases using newer ICD-11 criteria, which combine clinical and imaging evidence of stroke. Overall, the PPV for reported and verified diagnoses of major stroke types in Chinese adults was high – and similar among rural and urban regions and hospital tiers (Tiers I – III) – and comparable with estimates in Western populations.^{12–17}

Previous validation studies of stroke accuracy were conducted in Europe^{12–15}; North America¹⁶; or East Asia¹⁷ between 1987 and 2014. In contrast with the present study, the number of adjudicated stroke cases was much smaller, ranging from 968¹⁷ to 2308¹⁴ for IS and 120¹⁶ to 436¹⁴ for ICH, respectively. The PPV for stroke in the latter population-based studies varied from 80%¹³ to 83% for IS,¹⁴ from 69%¹⁶ to 87%¹² for ICH, and from 61%¹³ to 87% for SAH.¹⁴ The UK Biobank Stroke Outcomes Group²¹ evaluated the PPV of reported stroke type diagnoses in 37 prospective studies in North America, Europe and Australia, which ranged from 66% to 95% for IS, from 71% to 96% for ICH, and from 86% to 96% for SAH, respectively.

Prospective studies²² and nationally representative surveys^{23–25} have estimated both the prevalence and incidence of total stroke in China. While a previous survey of 480,687 adults²⁴ reported adjudication-confirmed diagnoses of major stroke types of 82.5% for incident stroke and 90.3% for prevalent stroke, it did not report PPV for major stroke pathological types or for stroke overall by reporting source, calendar year, geographic area and hospital type.

The use of neuroimaging for diagnosis of acute stroke has increased in North America (57% in 1980 vs 98% in 2000²⁶), which has enhanced the PPV of adjudicated cases of ischaemic and haemorrhagic stroke types. In China, among >20,000 participants in the Chinese Acute Stroke Trial (CAST), conducted from 1993 to 1997 in 413 hospitals, 87% had had CT brain imaging before randomisation.²⁷

In the CKB, despite overall use of brain imaging in 92% of adjudicated stroke cases – and a positive temporal trend in imaging in rural and urban regions (webTable 10) – the PPV of adjudicated cases of IS declined substantially during follow-up, from 84% in 2004–2008 to 72% in 2016–2017. A North American

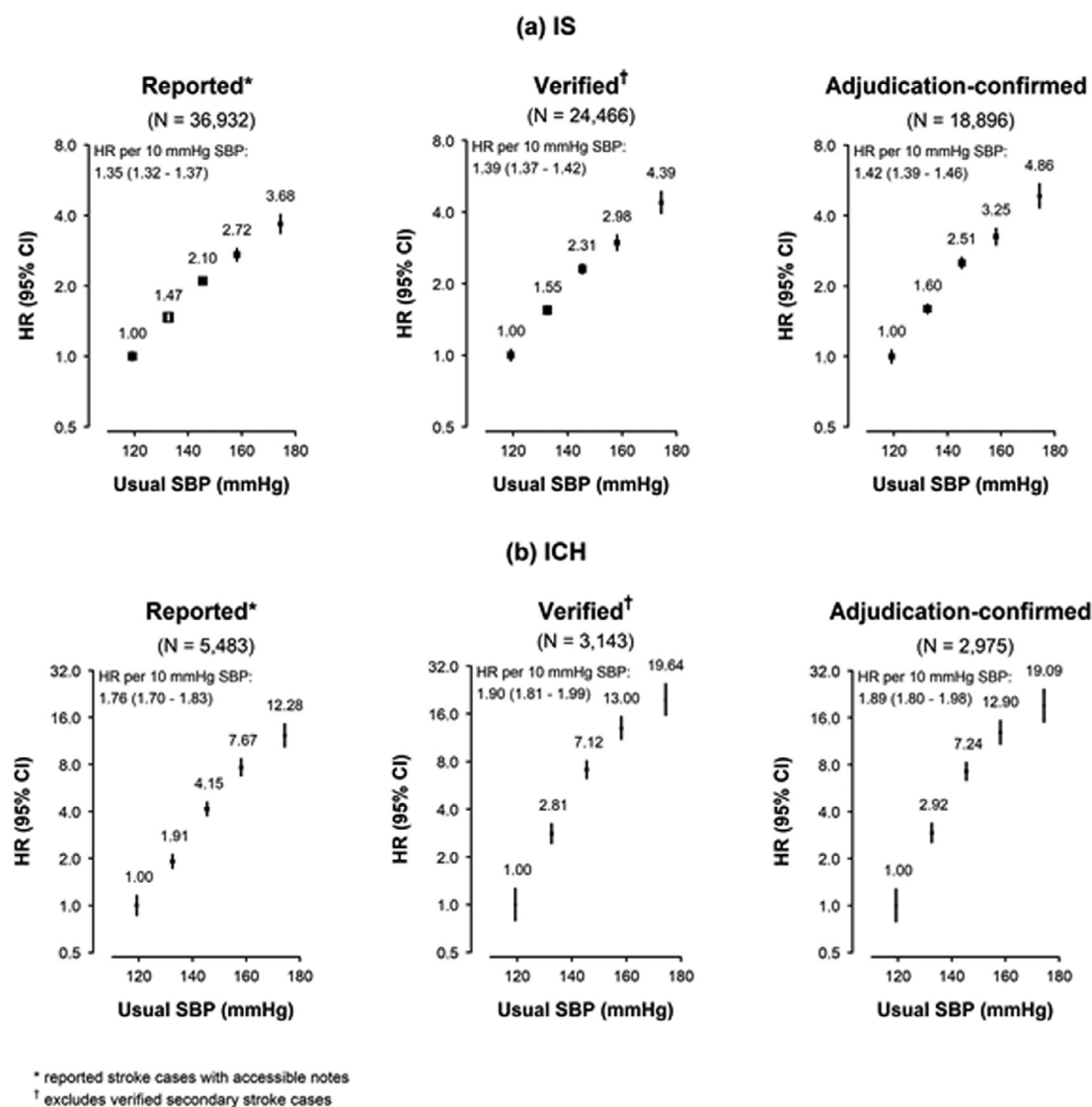


Figure 2. Association of usual SBP with IS and ICH cases, by validation status.

Cox proportional hazards models were used to estimate the strength of associations (HR [95% CI]) of reported, verified, and adjudication-confirmed cases of ischaemic stroke (IS) and intracerebral haemorrhage (ICH) per 10 mmHg higher usual levels of systolic blood pressure (SBP) after correction for regression dilution bias. The HRs were adjusted for age at baseline, sex, and area. The area of each square is inversely proportional to the variance of the log risk, which also determines the 95% CI. The HRs are shown above each square.

study¹⁶ reported no consistent temporal trends for IS, whereas another study in Denmark reported a decline in the PPV for all strokes from 75% during 1994–1999 to 66% during 2005–2009.¹³ The inclusion of the 3763 refuted (false-positive) IS cases reclassified as having silent LACI (consistent with ICD-11 criteria or the recent AHA/ASA classification²⁸ rather than ICD-10 criteria) increased the PPV for IS from 78.7% to 93.1%. In contrast, the Oxford Vascular Study reported an increase in the PPV for IS from 81% between 2002 and 2005 to 93% between 2014 and 2017, when reported cases were

restricted to first admissions with ICD-10 codes for IS (I63).²⁹ The overall diagnostic accuracy for any stroke and IS observed in the present study was comparable with estimates from a validation study of 232 incident stroke cases in the UK Biobank in 2015, which reported PPV of 79% for any stroke and 83% for IS.³⁰

The declining PPV of stroke cases in later years of follow-up in the present study most likely reflects the more frequent classification of silent LACI cases as IS types. Recent reports have also demonstrated increases

in hospitalisation rates for stroke in China after adjustment for differences in socioeconomic status, lifestyle, and comorbidity during 2009–2012, which coincided with expansion of universal health insurance coverage.³¹ Over the same period, reimbursement rates for inpatient care and their maximum thresholds have also increased substantially.³² Moreover, China introduced a critical illness insurance in 2012 for stroke patients to provide additional compensation for treatment costs for stroke and IHD.³³ It is possible that the latter changes in insurance coverage may have contributed to increased detection of silent LACI cases and consequently to the reduced PPV for the WHO definition of IS cases during follow-up.

The validity of stroke diagnoses was assessed by comparing the strengths of associations of major stroke types with usual SBP and demonstrated stronger associations of SBP with adjudication-confirmed cases vs verified or reported stroke cases. The strength of associations for a 10 mmHg higher usual SBP was over 2-fold greater for ICH than for IS in contrast with older studies conducted prior to the widespread use of brain imaging.^{34,35} Importantly, higher levels of usual SBP were also modestly associated with silent LACI (HR 1.23; 1.16–1.30 per 10 mmHg higher SBP). Studies in high-income countries demonstrated a 2-fold higher risk of subsequent symptomatic stroke among those with asymptomatic ischaemic lesions on neuroimaging than those with normal imaging,³⁶ while a recent report from CKB examining cases with silent vs symptomatic LACI demonstrated comparable 5-year risks of recurrent stroke (38% vs 43%) and all-cause mortality (11% vs 14%), respectively.⁹

In addition to determining the diagnostic validity of reported stroke cases, the adjudication process by specialist physicians enabled collection of detailed clinical information for studies of genetic and other associations with stroke types³⁷ or other biomarkers.⁸ Indeed, several genetic variants have been associated with specific subtypes of IS^{38,39} and ICH.^{40,41}

The study had several strengths, including the retrieval of medical records for 46,000 stroke cases from diverse areas in China and the development of bespoke IT platforms for large-scale and cost-effective verification and adjudication, which facilitated better characterisation of major stroke types. While previous large nationally representative surveys^{23–25} have demonstrated the feasibility of large-scale clinical adjudication of stroke cases, direct validation of medical records in the present study avoided recall bias and facilitated the collection of detailed clinical information relevant to hospital admission, including data on almost 4000 imaging-detected cerebral infarcts without focal neurological deficits.

The study also had several limitations, including low use of diffusion-weighted MR (DW-MR) imaging, which limited the ability to distinguish types of silent

small vessel diseases.⁴² Secondly, since recurrent stroke events were not selected for adjudication, analyses of stroke prognosis were limited to reported diagnoses of major stroke types.⁴³ Despite the wide geographical coverage and diversity of study areas, CKB is not representative of the overall Chinese population.

The present study demonstrated the feasibility of conducting clinical adjudication in large-scale studies to resolve diagnostic uncertainties and reliably classify major stroke types (with PPV >93–98% for adjudicated stroke cases using ICD-11 diagnostic criteria) in population studies of Chinese adults. However, greater access to brain imaging for suspected stroke cases has increased the detection during hospitalisation of minor cerebral infarcts without evidence of focal neurological symptoms and signs of stroke, which complicates within- and between-population comparisons of incidence of major stroke types. Recognition of the evolving accuracy of diagnosis of major stroke types has important implications for clinical practice in China and research on stroke types in the CKB study, and has lessons for methodology in similar studies of populations where nationwide stroke registries are unavailable and where additional clinical information is required to classify stroke types.

Author contributions

Preparation of initial draft of present report: IT. Study concept and design: RC, YG, LL, ZC and YC. Data collection: PP, AH, YG, SG, LY, JZ, SS, JL, CY, LL, ZC and YC. Data analysis and interpretation: NW, CK. Critical revision of the manuscript: All authors. Final approval: All authors.

Declaration of interests

No authors declared any conflicts of interests for this report.

Acknowledgments

The CKB baseline survey and the first re-survey were supported by the Kadoorie Charitable Foundation in Hong Kong. The long-term follow-up was supported by grants from Wellcome Trust to Oxford University (212946/Z/18/Z, 202922/Z/16/Z, 104085/Z/14/Z, 088158/Z/09/Z) and grants from the National Key Research and Development Program of China (2016YFC0900500, 2016YFC0900501, 2016YFC0900504, 2016YFC1303904) and from the National Natural Science Foundation of China (91843302). The UK Medical Research Council (MC_UU_00017/1, MC_UU_12026/2 MC_U137686851), Cancer Research UK (C16077/A29186; C500/A16896) and the British Heart Foundation (CH/1996001/9454) provided core funding to the Clinical Trial Service Unit and Epidemiological Studies Unit at Oxford University for this project.

Data access statement

The CKB study group is committed to making selected cohort data available to bona fide scientific researchers worldwide. Details of data available for open access users and how to apply for these are provided on: <http://www.ckbiobank.org/site/Data+Access>.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanwpc.2022.100415.

References

- Feigin VL, Roth GA, Naghavi M, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol*. 2016;15(9):913-924.
- Global Burden of Disease Collaborative Network. Global burden of disease study 2017 (GBD 2017) Results. 2018.
- Aho K, Harmsen P, Hatano S, et al. Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ*. 1980;58(1):113-130.
- Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of org 10172 in acute stroke Treatment. *Stroke*. 1993;24(1):35-41.
- Ay H, Benner T, Arsava EM, et al. A computerized algorithm for etiologic classification of ischemic stroke: the causative classification of stroke system. *Stroke*. 2007;38(11):2979-2984.
- Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol*. 2005;58(5):688-697.
- Lacey B, Lewington S, Clarke R, et al. Age-specific association between blood pressure and vascular and non-vascular chronic diseases in 0.5 million adults in China: a prospective cohort study. *Lancet Glob Health*. 2018;6(6):e641-e649.
- Sun L, Clarke R, Bennett D, et al. Causal associations of blood lipids with risk of ischemic stroke and intracerebral hemorrhage in Chinese adults. *Nat Med*. 2019;25(4):569-574.
- Hao Z, Chen Y, Wright N, et al. Natural history of silent lacunar infarction: 10-year follow-up of a community-based prospective study of 0.5 million Chinese adults. *Lancet Reg Health West Pac*. 2021;17:100309.
- Feigin V, Norrving B, Sudlow CL, Sacco RL. Updated criteria for population-based stroke and transient ischemic attack incidence studies for the 21st century. *Stroke*. 2018;49(9):2248-2255.
- 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(6):1652-1666.
- Li L, Rothwell PM, Oxford Vascular Study. Biases in detection of apparent "weekend effect" on outcome with administrative coding data: population based study of stroke. *BMJ*. 2016;353:i2648.
- Luhdorf P, Overvad K, Schmidt EB, Johnsen SP, Bach FW. Predictive value of stroke discharge diagnoses in the Danish national patient register. *Scand J Public Health*. 2017;45(6):630-636.
- Tolonen H, Salomaa V, Torppa J, et al. The validation of the Finnish hospital discharge register and causes of death register data on stroke diagnoses. *Eur J Cardiovasc Prev Rehabil*. 2007;14(3):380-385.
- Spolaore P, Brocco S, Fedeli U, et al. Measuring accuracy of discharge diagnoses for a region-wide surveillance of hospitalized strokes. *Stroke*. 2005;36(5):1031-1034.
- Jones SA, Gottesman RF, Shahar E, Wruck L, Rosamond WD. Validity of hospital discharge diagnosis codes for stroke: the Atherosclerosis Risk in Communities Study. *Stroke*. 2014;45(11):3219-3225.
- Park TH, Choi JC. Validation of stroke and thrombolytic therapy in Korean national health insurance claim data. *J Clin Neurol*. 2016;12(1):42-48.
- World Health Organization. *International Statistical Classification of Diseases and Related Health Problems*. 10th ed. World Health Organization; 1992.
- World Health Organization. *International Statistical Classification of Diseases and Related Health Problems*. 11th ed. World Health Organization; 2020. <https://icd.who.int/>.
- Chen Y, Clarke R. Verification and adjudication of health outcomes in prospective cohort studies. *Population Biobank Studies: A Practical Guide* 2020:123-143.
- Woodfield R, Grant I, Sudlow CL, UK Biobank Stroke Outcomes Group. UK Biobank Follow-Up and Outcomes Working Group. Accuracy of electronic health record data for identifying stroke cases in large-scale epidemiological studies: a systematic review from the UK Biobank stroke outcomes group. *PLoS One*. 2015;10(10):e0140533.
- Wang T, Lu J, Su Q, et al. Ideal cardiovascular health metrics and major cardiovascular events in patients with prediabetes and diabetes. *JAMA Cardiol*. 2019;4(9):874-883.
- Li Q, Wu H, Yue W, et al. Prevalence of stroke and vascular risk factors in China: a nationwide community-based study. *Sci Rep*. 2017;7(1):6402.
- Wang W, Jiang B, Sun H, et al. Prevalence, incidence, and mortality of stroke in China: results from a nationwide population-based survey of 480 687 adults. *Circulation*. 2017;135(8):759-771.
- Gao Y, Jiang B, Sun H, et al. The burden of stroke in China: Results from a nationwide population-based epidemiological survey. *PLoS ONE*. 2018;13:e0208398.
- Lakshminarayan K, Anderson DC, Jacobs DR, Barber CA, Luepker RV. Stroke rates: 1980-2000: the Minnesota stroke survey. *Am J Epidemiol*. 2009;169(9):1070-1078.
- Chen Z, CAST (Chinese Acute Stroke Trial) Collaborative Group. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. *Lancet*. 1997;349(9066):1641-1649.
- Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(7):2064-2089.
- Li L, Binney LE, Luengo-Fernandez R, Silver LE, Rothwell PM, Oxford Vascular Study. Temporal trends in the accuracy of hospital diagnostic coding for identifying acute stroke: a population-based study. *Eur Stroke J*. 2020;5(1):26-35.
- Rannikmae K, Ngho K, Bush K, et al. Accuracy of identifying incident stroke cases from linked health care data in UK Biobank. *Neurology*. 2020;95(6):e697-e707.
- Levy M, Chen Y, Clarke R, et al. Socioeconomic differences in health-care use and outcomes for stroke and ischaemic heart disease in China during 2009-16: a prospective cohort study of 0.5 million adults. *Lancet Glob Health*. 2020;8(4):e591-e602.
- Meng Q, Xu L, Zhang Y, et al. Trends in access to health services and financial protection in China between 2003 and 2011: a cross-sectional study. *Lancet*. 2012;379(9818):805-814.
- The State Council Information Office of the People's Republic of China Guiding opinions on carrying out major disease insurance for urban and rural residents. 2012.
- Lawes CM, Rodgers A, Bennett DA, et al. Blood pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens*. 2003;21(4):707-716.
- Lewington S. Prospective studies collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies (vol 360, pg 1903, 2002). *Lancet*. 2003;361(9362):1060.
- Gupta A, Giambrone AE, Gialdini G, et al. Silent brain infarction and risk of future stroke: a systematic review and meta-analysis. *Stroke*. 2016;47(3):719-725.
- Bevan S, Traylor M, Adib-Samii P, et al. Genetic heritability of ischemic stroke and the contribution of previously reported candidate gene and genome-wide associations. *Stroke*. 2012;43(12):3161-3167.
- Gretarsdottir S, Thorleifsson G, Manolescu A, et al. Risk variants for atrial fibrillation on chromosome 4q25 associate with ischemic stroke. *Ann Neurol*. 2008;64(4):402-409.

- 39 Markus HS, Mäkelä KM, Bevan S, et al. Evidence HDAC9 genetic variant associated with ischemic stroke increases risk via promoting carotid atherosclerosis. *Stroke*. 2013;44(5):1220–1225.
- 40 Woo D, Falcone GJ, Devan WJ, et al. Meta-analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage. *Am J Hum Genet*. 2014;94(4):511–521.
- 41 Falcone GJ, Woo D. Genetics of spontaneous intracerebral hemorrhage. *Stroke*. 2017;48(12):3420–3424.
- 42 Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12(8):822–838.
- 43 Chen Y, Wright N, Guo Y, et al. Mortality and recurrent vascular events after first incident stroke: a 9-year community-based study of 0.5 million Chinese adults. *Lancet Glob Health*. 2020;8(4):e580–e590.