



Neurological diseases in China 2

Stroke in China: advances and challenges in epidemiology, prevention, and management

Simiao Wu*, Bo Wu*, Ming Liu, Zhengming Chen, Wenzhi Wang, Craig S Anderson, Peter Sandercock, Yongjun Wang, Yining Huang, Liying Cui, Chuanqiang Pu, Jianping Jia, Tong Zhang, Xinfeng Liu, Suming Zhang, Peng Xie, Dongsheng Fan, Xunming Ji, Ka-Sing Lawrence Wong, Longde Wang, on behalf of the China Stroke Study Collaboration†

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*Joint first authors

†Other members are listed at the end of Review

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Department of Neurology (S Wu PhD, Prof B Wu PhD, Prof M Liu PhD), Center of Cerebrovascular Diseases (Prof M Liu), and State Key Laboratory of Biotherapy (Prof M Liu), West China Hospital, Sichuan University, Chengdu, China; Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK (Prof Z Chen DPhil); Department of Neuroepidemiology, Beijing Neurosurgical Institute (Prof W Wang MD), Department of Neurology, Beijing Tiantan Hospital (Prof Y Wang MD), Innovation Center for Neurological Disorders, Department of Neurology, Xuanwu Hospital (Prof J Jia PhD), Faculty of Rehabilitation Medicine (Prof T Zhang PhD), and Department of Neurosurgery, Xuanwu Hospital (Prof X Ji PhD), Capital Medical University, Beijing, China; Neurorehabilitation Department, China Rehabilitation Research Center, Beijing, China (Prof T Zhang); The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia (Prof C S Anderson PhD); The George Institute China at Peking University Health Science Center, Beijing, China (Prof C S Anderson); Neurology Department, Royal Prince Alfred Hospital, Sydney, NSW, Australia (Prof C S Anderson); Centre for Clinical Brain

With over 2 million new cases annually, stroke is associated with the highest disability-adjusted life-years lost of any disease in China. The burden is expected to increase further as a result of population ageing, an ongoing high prevalence of risk factors (eg, hypertension), and inadequate management. Despite improved access to overall health services, the availability of specialist stroke care is variable across the country, and especially uneven in rural areas. In-hospital outcomes have improved because of a greater availability of reperfusion therapies and supportive care, but adherence to secondary prevention strategies and long-term care are inadequate. Thrombolysis and stroke units are accepted as standards of care across the world, including in China, but bleeding-risk concerns and organisational challenges hamper widespread adoption of this care in China. Despite little supporting evidence, Chinese herbal products and neuroprotective drugs are widely used, and the increased availability of neuroimaging techniques also results in overdiagnosis and overtreatment of so-called silent stroke. Future efforts should focus on providing more balanced availability of specialised stroke services across the country, enhancing evidence-based practice, and encouraging greater translational research to improve outcome of patients with stroke.

Introduction

Stroke is the second leading cause of death in the world and the leading cause of death in China, where a fifth of the world's population resides.^{1–3} A previous Review, which summarised existing data on the epidemiology, prevention, and management of stroke in China before 2007, called for further research to update the knowledge of disease burden, clinical course, outcomes, and patterns of care.⁴ Subsequently, a surge in research on stroke has occurred over the past decade in China, leading to improved understanding of its causes, and advances in stroke prevention and management.^{5–12} Notably, evidence-based stroke care has been incorporated into the national health-care system and in-hospital outcomes have improved, with no increase in mortality despite the rising prevalence and incidence in the past decade.⁵

In this Review, we provide an update on the epidemiology, prevention, and management of stroke in China. We focus on modifiable risk factors and interventions that are affordable and potentially widely applicable for prevention and treatment of stroke. We identify gaps in the delivery of evidence-based stroke care and elucidate possible reasons for these gaps. We also discuss the variations in stroke care across the country that are different from the more uniform practices in high-income countries.¹³ On the basis of current progress and ongoing challenges, we provide suggestions for policy makers and health-care providers to address, and reduce, the rising burden of stroke in China.

Epidemiology

Nationwide studies and periodic governmental reports indicate a high and increasing burden of stroke.^{5,6,14,15} For

example, the National Epidemiological Survey of Stroke in China (NESS-China) involved 480 687 individuals (aged ≥ 20 years) from 31 provinces between 2012 and 2013, reporting an age-standardised stroke prevalence of 1115 cases per 100 000 people, and annual age-standardised incidence of 247 cases per 100 000 and mortality of 115 cases per 100 000.⁵ These data indicated annual estimates of 11 million prevalent cases of stroke, 2.4 million new strokes, and 1.1 million stroke-related deaths in China in 2013, consistent with long-term trends (figure 1).^{6,14,15} The China National Stroke Screening Survey, done between 2013 and 2014, reported higher stroke prevalence and incidence (in adults older than 40 years) than in the NESS-China study.⁶ All of these data highlight a marked increase in stroke prevalence and incidence yet a generally stable mortality compared with the values reported in the past decade.⁴ Such temporal trends are similar to the general trend in low-income and middle-income countries, where the incidence of stroke is increasing, in contrast to the decreasing incidence in high-income countries (figure 1).³ Given that China had the highest number of prevalent cases of stroke in the world, as reported in 2014,³ and more recently indicated by results of the Global Burden of Disease Study 2017 (unpublished data), more vigorous and effective actions are needed to reduce the burden of stroke.

In China, the prevalence of stroke still surpasses that of ischaemic heart disease; however, the Healthcare Access and Quality (HAQ) index ranks stroke as the second lowest among 32 diseases or conditions from which death is preventable in China,¹³ indicating inadequate social and medical investments to stroke care compared with other diseases. As stroke incidence and mortality increase with age,¹⁶ the absolute number of patients who have stroke

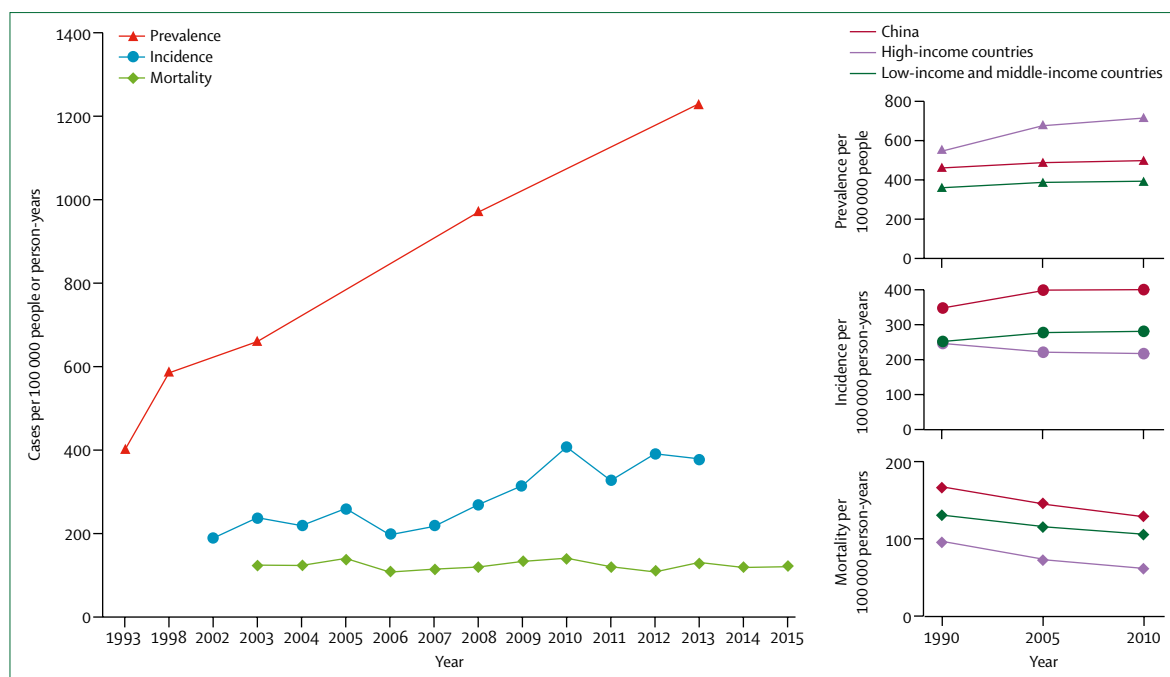


Figure 1: Prevalence, incidence, and mortality of stroke in China and in comparison with those of other countries.

Prevalence data are the crude prevalence of cerebrovascular diseases on Chinese people of all ages (due to absence of age-specific prevalence) per 100 000 people. Sample sizes: year 1993 (n=215 163), 1998 (n=216 101), 2003 (n=193 689), 2008 (n=177 501), and 2013 (n=273 688).⁴ Incidence data are age-standardised stroke incidence on Chinese people aged 40–74 years (standardised by the China 2000 census population) per 100 000 person-years. Real data sample sizes (the study also provided retrospective estimates for 2002–12, not presented here): year 2013 (n=633 859 people) and 2014 (n=726 451).⁶ Mortality data are age-standardised mortality of cerebrovascular diseases on Chinese people of all ages (standardised by the China 2010 census population) per 100 000 person-years, extracted from China's Public Health Statistical Yearbooks from 2004 to 2016 (note: each yearbook reports numbers for the preceding year).¹⁵ Sample size is based on the national population: year 2003 (1292 million people), 2004 (1300 million), 2005 (1308 million), 2006 (1314 million), 2007 (1321 million), 2008 (1328 million), 2009 (1335 million), 2010 (1341 million), 2011 (1347 million), 2012 (1354 million), 2013 (1361 million), 2014 (1368 million), 2015 (1375 million). Data in the graphs showing comparisons with other countries are from the Global Burden of Disease Study 2010.³

and die from it can be expected to increase steadily as the Chinese population continues to grow and age, further increasing the pressure on the Chinese health system.

Over half of the Chinese population lives in rural areas, where overall stroke incidence is higher (298 cases per 100 000 person-years) than in urban areas (204 cases per 100 000 person-years).⁵ The prevalence of stroke in rural areas increased sharply between 2003 and 2013, whereas in urban areas the prevalence was relatively stable over the same period (figure 2A). The marked increase in rural prevalence probably reflects a rising incidence of stroke and increased detection. By contrast, stroke-related mortality was relatively stable between 2003 and 2015; notably, these rates were consistently higher in rural areas than urban areas (figure 2B). A north-to-south geographical gradient in stroke incidence and mortality is apparent, with numbers being highest in the northeast and lowest in the south of China.⁵ However, the estimated mortality-to-incidence ratio (MIR) of stroke based on data from the NESS-China study⁵ shows a different pattern, with the highest MIR in the southwest and the lowest along the eastern and southern coasts (figure 3A). These regional differences in MIR indicate striking disparities in both access to and quality of stroke care across the country;

such disparities are consistent with the regional distribution pattern of the HAQ index of stroke (highest in Beijing, lowest in Tibet).¹³ The distribution of MIR and HAQ might be associated with variation in the proportion of registered medical doctors per 1000 of the population, being highest in northern and eastern China and lowest in the southwest of China (figure 3B); and with variation in the proportion of secondary and tertiary hospitals that have certified stroke centres, being relatively high in eastern and southern China, and low in northeast and western China (figure 3C). As the MIRs we report here are based on a secondary analysis of published data, more reliable data from future studies are needed to confirm these observed discrepancies in MIR between and within regions, and to explore the underlying reasons.

Risk factors and primary prevention strategies

Hypertension, dyslipidaemia, diabetes, smoking, alcohol consumption, air pollution, diets low in fruit and vegetables, and high sodium intake are the most common and modifiable risk factors for stroke in China.^{5,6} Hypertension, the most important modifiable risk factor for stroke, was estimated to affect approximately 300 million adults in China between 2013 and 2014 (a prevalence of 28%), which

Sciences, University of Edinburgh, Edinburgh, UK (Prof P Sandercock DM); Department of Neurology, Peking University First Hospital, Beijing, China (Prof Y Huang MD); Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China (Prof L Cui MD); Department of Neurology, Chinese PLA General Hospital, Beijing, China (Prof C Pu MD); Department of Neurology, Jinling Hospital, Medical School of Nanjing University, Nanjing, China (Prof X Liu PhD); Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (Prof S Zhang PhD); Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China (Prof P Xie MD); Department of Neurology, Peking University Third Hospital, Beijing, China (Prof D Fan PhD); Key Laboratory for Neuroscience, Ministry of Education/National Health Commission, Peking University, Beijing, China (Prof D Fan); Division of Neurology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China (Prof K-S L Wong MD); and Stroke Prevention Project Committee of National Health Commission of the People's Republic of China, Beijing, China (Prof L Wang MD)

Correspondence to: Prof Ming Liu, Department of Neurology, West China Hospital, Sichuan University, Chengdu 610041, China
wyplmh@hotmail.com

For more on the Global Burden of Disease Study 2017 results see <http://ghdx.healthdata.org/gbd-results-tool>

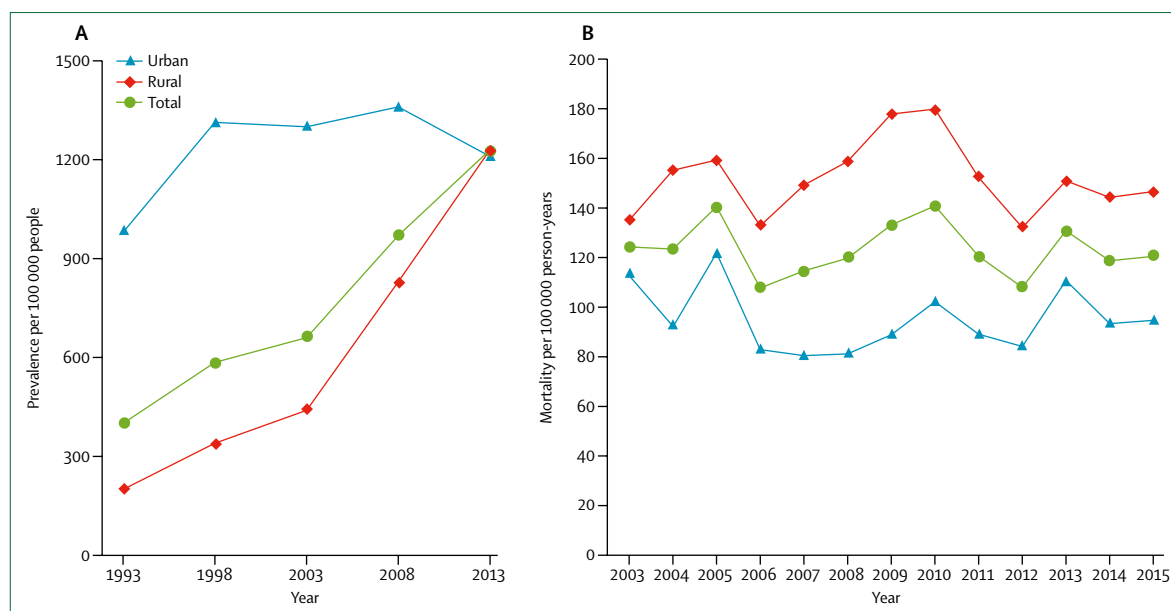


Figure 2: Prevalence and mortality of stroke in urban and rural areas of China

(A) Prevalence data are the crude prevalence of cerebrovascular diseases in Chinese people of all ages (due to lack of age-specific prevalence) per 100 000 people.¹⁴ (B) Mortality data are age-standardised mortality of cerebrovascular diseases in Chinese people of all ages (standardised by the China 2010 census population) per 100 000 person-years, extracted from China's Public Health Statistical Yearbooks from 2004 to 2016 (note: each yearbook reports numbers for the preceding year).¹⁵

represents an almost 50% increase from the 153 million estimated in 2002.¹⁷ A geographical gradient can be noted in the prevalence pattern of hypertension, which is highest in northeast, northern, and southwest China.¹⁸ Although improvements in patient awareness and the treatment and control of hypertension are encouraging, the proportion of people whose hypertension is controlled is under 20% in China, which is considerably lower than in the UK or the USA.^{18–20} The figures regarding awareness, treatment, and control of hypertension are lower in rural areas, despite an absence of a clear urban–rural difference in the prevalence of hypertension.^{17,18} Similarly, dyslipidaemia (prevalence 34%) and diabetes (prevalence 11%) are relatively common and poorly controlled in China.^{21,22} For both conditions, the prevalence and amount of awareness, access to treatment, and proportion of patients whose condition is controlled are lower in rural areas than urban areas.^{21,22}

New evidence has emerged from large prospective studies about the relevance of a range of lifestyle factors for stroke in Chinese adults, which might account for the north-to-south differences in prevalence of stroke. Smoking and heavy alcohol consumption contribute to an increased risk of stroke, particularly among men, of whom up to two-thirds are smokers and more than a third drink alcohol on a weekly basis (compared with <5% of women).^{7,8} High frequencies of smoking and alcohol consumption in the northeast correlate with high incidence of and mortality related to stroke.⁵ Of note, smoking prevalence has been consistently high in the past decade, and is higher among rural residents than urban residents.²³

Air pollution continues to be a great public health challenge in China, which has the second highest concentration of fine particulate matter (PM_{2.5}) among 79 countries, and showed consistent increases in PM_{2.5} from 1990 to 2013.²⁴ Compared with the use of clean fuels (such as gas and electricity), the domestic use of solid fuels (such as coal and wood), which is common in rural areas, is a major source of PM_{2.5} and is associated with higher stroke-related mortality.²⁵ Although the stroke-related mortality attributable to PM_{2.5} has decreased at the national level, the geographical belt of regions with high correlation between stroke mortality and PM_{2.5} has gradually moved from northern and western China to central and southwestern regions between 1990 and 2015.²⁶

The traditional northern Chinese diet (characterised by high intakes of refined cereal products and salted vegetables) is associated with an elevated risk of stroke compared with the traditional southern Chinese diet (characterised by high intakes of rice, vegetables, and fruit, and lower salt intake).²⁷ Although personal daily consumption of vegetables and fruit among the Chinese population has gradually increased since the 1980s, consumption is still below national recommended amounts, and consistently lower in rural areas than urban areas.²⁸ High sodium intake is associated with increased risk of both hypertension and stroke, and the daily individual intake in the north of China is about twice of that in the south.²⁹ In consideration of the high prevalence of hypertension and stroke in northern China, a cluster randomised controlled trial (NCT02092090) is currently evaluating a potentially widely applicable diet intervention—a potassium-enriched,

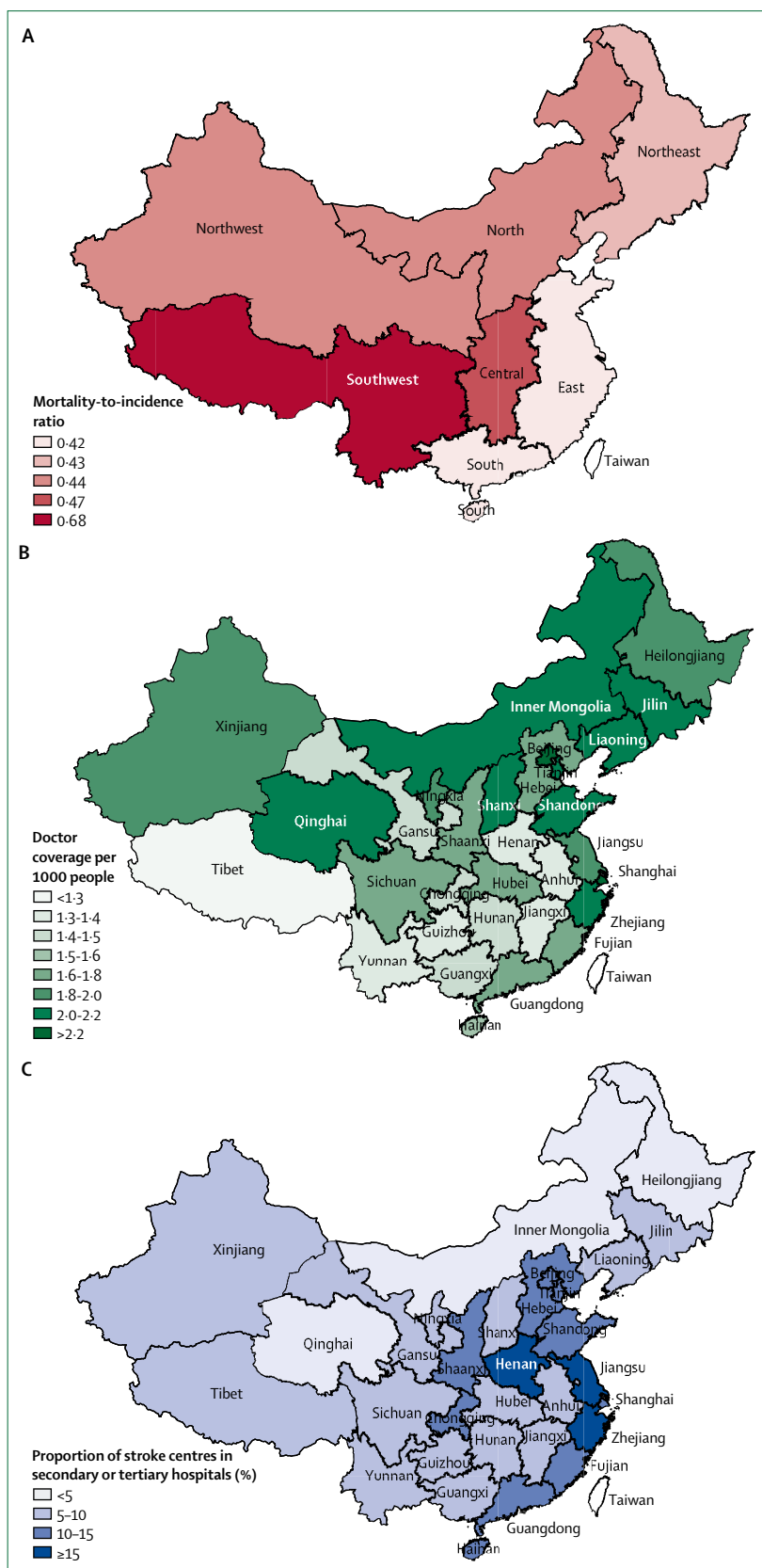
low-salt substitute—for the prevention of stroke in 600 villages across five northern provinces. Other regional-specific interventions that should be promoted might include more intensive smoking restrictions in the areas with high smoking frequency spanning northeast and central China;²³ the promotion of clean fuel use in rural areas;²⁵ and increasing the supply of fresh vegetables and fruit in the north.²⁷

The current high incidence of stroke indicates that primary prevention strategies are not sufficiently effective. Improved control of risk factors requires not only more effective public education and greater responsibilities of individuals, but also changes in government laws and regulations related to taxation, advertising, urban development, and construction of more healthy cities (a concept of the WHO Healthy Cities project). For example, the Chinese Government launched the Stroke Screening and Intervention for High-risk Population (in Chinese) programme in 2011, as part of a national non-communicable diseases (NCDs) programme, in which 6 million people across 31 provinces were screened for vascular risk factors by 2016, and nearly 1 million high-risk individuals have received appropriate intervention.³⁰ In 2017, the State Council of China released a national, medium-to-long term plan on the prevention and treatment of NCDs, with an aim to reduce mortality related to cerebrovascular diseases by 15% by 2025, through an emphasis on promoting healthy lifestyles, public education, early screening for chronic diseases, and the development of national platforms for quality control of health care. Stroke societies (panel 1) have been actively leading public education and academic activities to raise awareness of stroke, particularly since the foundation of the Chinese Stroke Society in 2002. In conjunction with the World Stroke Organisation, the Chinese Stroke Society, the Chinese Stroke Association, and other stroke initiatives (panel 1) have organised regular public education events across the country, which are maximised around the time of World Stroke Day.

Stroke aetiology

Reliable assessment of pathological and aetiological subtypes of acute stroke is pivotal for appropriate treatment

Figure 3: Geographical distribution of mortality-to-incidence ratio, coverage of registered medical doctors, and proportion of hospitals with a stroke centre among secondary and tertiary hospitals in mainland China
(A) Mortality-to-incidence ratios for seven geographical regions of mainland China were calculated from the stroke incidence and mortality data in the National Epidemiological Survey of Stroke in China.⁵ (B) Doctor coverage (per 1000 people) was calculated from the number of registered medical doctors and the population in each of the 31 provinces and municipalities in China, obtained from the National Bureau of Statistics of China. (C) The number of certified stroke centres was retrieved from the websites of the National Stroke Center and the China Stroke Center Alliance, which are two qualified organisations to officially certify stroke centres in China. The number of secondary or tertiary hospitals was extracted from the National Bureau of Statistics of China. Data were not available for Taiwan (A-C).



For more information of the WHO Healthy Cities project see https://www.who.int/healthy_settings/types/cities/en/
For the relevant webpages of the National Bureau of Statistics of China see <http://data.stats.gov.cn/index.htm>

Panel 1: Stroke societies and initiatives in China

- Chinese Stroke Society (founded in 2002), affiliated to the Chinese Medical Association
- Stroke Prevention and Control Society (founded in 2010), affiliated to the Chinese Preventive Medicine Association
- Stroke Prevention Project Committee (founded in 2011), affiliated to the National Health Commission
- Chinese Stroke Association (founded in 2015), affiliated to the China Association for Science and Technology

and secondary prevention of stroke. However, data on stroke aetiology specifically pertaining to Chinese patients are too scarce or heterogeneous to be conclusive,⁴ although more reliable data are becoming available from large community-based and hospital-based studies. The nationwide community-based study, NESS-China, indicated that ischaemic stroke accounts for approximately 70% of all incident stroke cases, with intracerebral haemorrhage accounting for 24%, subarachnoid haemorrhage accounting for 4%, and undetermined or other types accounting for the remaining 2% of cases;⁵ these proportions are similar to those in multicentre hospital-based studies.^{31,32} Although the proportional frequency of intracerebral haemorrhage among patients with stroke is higher in Chinese populations than those in high-income countries, wide variation exists across China, with greater frequency in central China and lower frequencies in coastal regions.³³ A markedly high proportion (50–61%) of individuals affected by intracerebral haemorrhage was repeatedly reported in Changsha, a city in central China, for a period of more than 25 years (between 1986 and 2013), for reasons still not fully understood.³⁴

Hospital-based studies have revealed variation regionally and nationally in the aetiological subtypes of acute ischaemic stroke (Trial of Org 10172 in Acute Stroke Treatment [known as TOAST] classification), with an increase in large arterial atherosclerosis and decline in undetermined subtypes from 2002 to 2015 (appendix).^{35–39} These trends are in line with those in other Asian populations,⁴⁰ and probably reflect the increased access to vascular imaging.³⁹ The proportion of ischaemic stroke caused by small artery occlusion is about 30% on average,^{35–39} and even higher from lacunar infarction specifically,⁴¹ whereas the proportion of cardioembolic stroke remains low in Chinese patients (about 10%) (appendix) compared with patients in high-income countries (about 30%).⁴⁰ This discrepancy might be due in part to the underdiagnosis of atrial fibrillation in Chinese patients. The wide variation in the aetiological subtypes of stroke might be explained by the discrepancies in study design, subtype definitions, and the different times at which different studies were conducted. Future large-scale studies are needed to provide more reliable and precise data on the proportions of subtypes and temporal changes, by repeating assessments in the same stroke population across different time periods.

Subtypes of intracerebral haemorrhage are less well reported than subtypes of ischaemic stroke. One multicentre study assessed subtypes of non-traumatic intracerebral haemorrhage and reported that hypertensive angiopathy was the most common aetiology, followed by undetermined aetiology, cerebral amyloid angiopathy, vascular structural lesions, medication-derived haemorrhage, and systemic diseases.⁴² Largely consistent with a study in Taiwan,⁴³ these findings suggested that Chinese people have higher proportions of hypertensive angiopathy and structural lesions, and lower proportions of medication-derived haemorrhage and cerebral amyloid angiopathy, than populations in high-income countries.⁴⁴

Patients with stroke or those who die from stroke in low-income and middle-income countries, including China, have lower mean ages (mid-60s) than those in high-income countries (mid-70s), partly reflecting the differences in demography and risk factors between different populations.^{3,45} These differences might explain the lower proportions of cardioembolic stroke and cerebral amyloid angiopathy in China because these conditions are more common in elderly people. The low proportion of medication-related intracerebral haemorrhage in China^{42,43} might be related to the underuse of anticoagulant and thrombolytic therapies. Given that the ageing population will prompt a foreseeable increase in the use of anticoagulant and thrombolytic therapies for indicated patients (those with atrial fibrillation and ischaemic stroke) in the future, cerebral amyloid angiography and medication-related intracerebral haemorrhage are likely to increase. In addition, evidence is consistently highlighting the higher proportional frequencies of intracerebral haemorrhage^{33,34} and small artery occlusion^{35–39} in Chinese patients as two subtypes of stroke that share a common underlying mechanism of hypertension-related cerebral small vessel disease. The features and management of these events are currently under investigation in observational studies (ChiCTR-OOC-17010562 and ChiCTR-COC-17013056 [in Chinese]).

Neuroimaging and diagnosis of stroke

Non-contrast CT is widely available in Chinese hospitals, where around 90% of patients with ischaemic stroke receive brain CT (table). About 50% of patients receive MRI.⁵¹ As neuroimaging is increasingly being used for routine health screening and in general clinics in cities (eg, CT, MRI, or ultrasound for headache or dizziness), the increased detection of silent pathological signs can cause overdiagnosis of stroke and cause uncertainty for doctors in their decision whether to prescribe secondary prevention medication. For example, about a fifth of community-dwelling Chinese residents (≥ 20 years old) have silent cerebral infarcts on brain CT or MRI,⁵ 10% have silent cerebral microbleeds on MRI,⁵⁴ and approximately a third have carotid atherosclerotic plaques on ultrasound assessment.⁵⁵ If these silent pathological signs are

See Online for appendix

	Chen et al (1997) ⁴⁶	Chengdu Stroke Registry ³⁵	China Quality Evaluation of Stroke Care and Treatment study ³⁶	China National Stroke Registry I ⁴⁷	China National Stroke Registry II ⁴⁷	INTERSTROKE study ⁴⁸	GOLDEN BRIDGE-Acute Ischaemic Stroke intervention ⁴⁹
Study period	1993–94	2002–06	2006	2007–08	2012–13	2007–15	2014–15
Participants	1095 doctors from 247 hospitals	2070 patients with ischaemic stroke, 882 patients with intracerebral haemorrhage, 72 patients with subarachnoid haemorrhage, and 99 patients with transient ischaemic attack	4782 ⁵¹ or 4783 ³⁶ patients* from 62 hospitals	12 173 patients from 131 hospitals	19 604 patients from 219 hospitals	5859 patients from upper-middle-income countries (3987 from China [68% of total cohort])† ⁴⁵	4800 patients from 40 hospitals (2400 patients in control group)
Admission time (onset to door)	..	<3 h: 10% (214/2070) <6 h: 22% (448/2070)	<3 h: 21% (1019/4783)	<3 h: 22% (2514 of 11 675 patients with known time) ⁵⁰	..	..	<2 h: 10% (492/4800)
CT accessibility	88% (683/775) of doctors in 171 hospitals with CT scanners	97% (3028/3123) of all patients with stroke and transient ischaemic attack	89% (4267/4782) ⁵¹	..	..	..	..
Stroke unit care	..	..	30% (1449/4782) ⁵¹	..	..	23% (1323/5859)†	63% (25/40) of hospitals
Intravenous thrombolysis	4% (41/1095)‡	1% (20/2070)	2% (91/4783)	1% (120/12 173) of all patients; 10% (120/1203) of eligible patients§	1% (243/19 604) of all patients; 18% (243/1326) of eligible patients§	3% (168/5859)†	Control group: 1% (23/2400) of all patients; 11% (23/204) of eligible patients§
Antiplatelet therapy	54% (590/1095)‡	83% (1719/2070)	81% (3853/4783)	<48 h: 80% (9706/12 090) of eligible patients§; at discharge: 71% (8285/11 677) of eligible patients§	<48 h: 85% (16 149/19 093) of eligible patients§; at discharge: 90% (16 021/17 743) of eligible patients§	87% (5121/5859)†	Control group: <48 h: 97% (2253/2330) of eligible patients§; at discharge: 93% (2141/2305) of eligible patients§
Lipid-lowering drugs	..	12% (246/2070)	30% (1444/4783)	43% (2402/5634) of eligible patients§	66% (8475/12 791) of eligible patients§	72% (4222/5859)†	Control group: 93% (1439/1547) of eligible patients§
Chinese herb products	66% (728/1095)‡	90% (1857/2070)	79% (3784/4783)	..	..	..	..
Neuroprotective drugs	..	68% (1410/2070)	76% (3632/4783)	..	..	..	..
Glycerol or mannitol	68% (750/1095)‡	23% (486/2070)	Intravenous diuretics: 36% (1738/4782) ⁵¹	..	..	..	..
Antihypertension therapy	33% (365/1095)‡ immediately after admission	34% (702/2070)	62% (2945/4782) ⁵¹	56% (4620/8196) of eligible patients§	66% (9684/14 758) of eligible patients§	66% (3881/5859)†	Control group: 77% (1372/1771) of eligible patients§
Anticoagulation therapy	1% (11/1095)‡	14% (52/366) of eligible patients ⁵² ¶ (2002–08)	12% (37/314) of eligible patients ⁵² ¶	20% (221/1124) of eligible patients§	21% (332/1578) of eligible patients§	..	Control group: 28% (39/137) of eligible patients§
In-hospital rehabilitation	..	..	28% (1331/4782) ⁵¹	49% (5757/11 677)	59% (11 396/19 382) of eligible patients§	..	..
Decompressive hemicraniectomy	..	14% (31/219) of eligible patients ⁵³ (2007–11)	..	..	..	..	..

*Numbers from the original reports of this study (the reason for the differing total number of patients was not specified). †Chinese data not reported separately and therefore percentages of the total cohort are reported. ‡The proportion of doctors who would routinely provide the therapy to patients after admission. §Eligible patients were those without any medical contraindications documented as reasons for nontreatment for each of the applicable measures. ¶Eligible patients were those who had atrial fibrillation. || Eligible patients were those who had malignant middle cerebral artery infarction (patients with infarction of more than two-thirds of the middle cerebral artery territory on brain imaging with neurological evidence of local brain swelling).

Table: Clinical studies assessing in-hospital management of patients with acute ischaemic stroke in China

misinterpreted as cerebral infarcts or even overt stroke, it can lead to the over prescribing of antiplatelets and statins, which might also affect the epidemiological data for surveillance of stroke prevalence. Whether silent cerebral infarcts should be treated with aspirin for secondary prevention is under investigation (NCT03318744) and

studies on treatments for asymptomatic carotid plaques are ongoing (appendix).

Management of acute stroke

The Chinese Stroke Society and the Chinese Society of Neurology have together published a series of national

For more on the **National Stroke Centre** see <http://sinosc.org/Home/Home>

For more on the **China Stroke Centre Alliance** see <http://cscsa.chinastroke.net/>

clinical guidelines to promote evidence-based stroke care,^{56–59} and two nationwide register platforms serve to monitor and evaluate the quality of stroke care: the National Stroke Centre of the Stroke Prevention Project Committee (since 2011) and the China Stroke Centre Alliance of the Chinese Stroke Association (since 2015). Other stroke registers and studies have also provided data on the quality of stroke care in China (table),^{35,36,45–53} and confirm that the use of evidence-based therapies (ie, stroke unit care, thrombolysis, antiplatelets, lipid-lowering agents, antihypertensives, and anticoagulants) has gradually increased from 1993 to 2015, although therapies with a high perceived risk of bleeding (eg, thrombolysis and anticoagulation) and those requiring specific facilities (ie, stroke units) and skills (eg, decompressive hemicraniectomy) are still underused.

Acute management of ischaemic stroke

Antiplatelets and statins are the most commonly prescribed medications in the acute phase of ischaemic stroke in China; about 90% of patients commence antiplatelet treatment within 48 h of admission and are maintained on this at discharge.^{47,49} The prescription of statins to hospitalised patients with stroke has dramatically increased from 2002 to 2015. Despite scarce evidence for their efficacy, Chinese herbal products, neuroprotective drugs, and dehydrating anticerebral oedema drugs are widely used in clinical practice. Several studies are underway to clarify the efficacy of Chinese herbal products and neuroprotective drugs in acute stroke (appendix). Although stroke unit care is an accepted standard of care to improve outcome worldwide, few studies have investigated its use and organisation in China.^{48,49,51} Whether the facilities and quality of care in Chinese stroke units meet the international standards is uncertain; a study showed that only a third of patients with stroke receive such care,⁵¹ and even fewer receive care that satisfies key organisational and staffing parameters (eg, discrete wards, staff specialised in stroke care, regular multidisciplinary team meetings, established protocols for care, staff education and training, and educational information for patients and carers).⁴⁸ Data are scarce on decompressive hemicraniectomy⁵³ and rehabilitation.⁶⁰ Although the safety and efficacy of mechanical clot retrieval have been well established in several randomised controlled trials,^{61–65} minimum standards of training and quality control reporting have yet to be established in China.

Effective therapies for hyperacute treatment of ischaemic stroke rely on timely restoration of blood supply to salvageable brain tissue. Currently, only 10 to 20% of patients with stroke reach hospital within 3 h in China (table). Delays in admission are associated with several factors, particularly that of early recognition of the symptoms of acute stroke.^{66,67} Only about one in five patients recognise the initial symptoms as stroke, and a similar proportion of all patients call an emergency

number.⁶⁷ To address this awareness issue, a stroke 1-2-0 educational programme was launched in China to educate the public on recognising symptoms of stroke and on accessing emergency medical services,⁶⁸ and efforts to increase public awareness of stroke symptoms are ongoing (NCT03167346). Many cities and provinces have released stroke maps to help patients and relatives locating the nearest stroke centre, which have been widely disseminated to the public through mass and social media. Additionally, a national telestroke centre platform was initiated in 2014, and the network is under development to guide timely stroke care in rural hospitals.⁶⁹ In terms of hyperacute therapy, less than 3% of patients with ischaemic stroke in China received intravenous thrombolysis, a proportion much lower than that in high-income countries (table).^{48,49} Although admission delay is an explanation for this low amount, the treatment is given to less than 20% of eligible patients admitted in time (table). Apart from the high cost for patients, the main reason for the underuse of intravenous thrombolysis is high concern over the bleeding risk among patients, families, and doctors.⁵⁰ However, these data, reported in 2015,^{48,49} might not accurately reflect the current situation, as clinics have observed an increasing use of intravenous thrombolysis in practice since 2015. Given the promising results of late-window reperfusion trials,^{70–72} Chinese doctors are now cautiously applying intravenous thrombolysis and endovascular interventions to a broader range of eligible patients. Therefore, the proportion of patients who have received reperfusion therapies in practice might be higher than the frequencies reported in the existing studies, which thus need to be updated.

Acute management of intracerebral haemorrhage

Approximately two-thirds of Chinese patients with intracerebral haemorrhage receive early antihypertensive therapy, more than 90% receive intravenous haemodiluting medications, and 10% receive some type of neurosurgical intervention.⁷³ Open surgery for haematoma evacuation is done in many city hospitals with access to neurosurgery, whereas minimally invasive surgery is more widely used in local hospitals with restricted access to neurosurgery.

Secondary prevention

Medications for secondary prevention are initiated in hospital for most patients after stroke, but adherence is poor among community-dwelling individuals after discharge from hospital.^{74–76} For example, in a multicentre observational study of 1913 patients with minor ischaemic stroke, 835 (92%) of 905 patients with large arterial atherosclerosis, 421 (91%) of 461 patients with small artery occlusion, and 63 (72%) of 88 patients with cardioembolic stroke received antiplatelets in hospital, but less than half of these patients had maintained the medication 1 year later.⁷⁷ Socioeconomic factors such as inadequate

health insurance and reimbursement policies, and an unawareness of the need for long-term use of these medications by patients and doctors are two of the main reasons precluding long-term use of such treatment.^{74,76} More research is required to explore more affordable strategies and to improve adherence in the secondary prevention of stroke.⁷⁸ For example, use of a single pill that contains several cardiovascular medications for secondary prevention is a promising strategy to improve adherence, as more than 90% of community-dwelling individuals after a stroke required at least two types of medication for secondary prevention.⁷⁹

About 2% of Chinese adults older than 40 years had atrial fibrillation between 2014 and 2015, which had increased from less than 1% noted 10 years earlier (2004–5).⁸⁰ About 10% of Chinese patients with stroke had atrial fibrillation,⁵² but this proportion was higher as indicated by a study that monitored patients by Holter electrocardiography for more than 6 days after admission to hospital.⁸¹ However, prolonged cardiac monitoring for patients with stroke is scarcely used in practice, despite recommendations by Chinese and international guidelines, which possibly results in the underdiagnosis of atrial fibrillation in China.

Although the proportion of patients with ischaemic stroke and atrial fibrillation who receive oral anti-coagulation in hospital or at discharge is steadily increasing, still only 30% received anticoagulants at discharge and 10% at 1 year after stroke; by contrast, more than 60% of patients with stroke and atrial fibrillation receive antiplatelets in hospital, despite a decrease in use by 10% over the past 10 years (appendix).^{49,52,77,82–86} A nationwide community-based survey for stroke screening involved 1 252 703 adults older than 40 years and identified 5588 patients with ischaemic stroke and atrial fibrillation, who showed a preference for use of antiplatelets over oral anticoagulants; only 2% of these patients used anticoagulants (compared with 16% on antiplatelets), and most of the patients receiving anticoagulants used warfarin, while fewer than 2% were on novel oral anticoagulants.⁸⁵ The main reason for this underuse of oral anticoagulation is the concern over bleeding risk among doctors and patients, with the perception that this risk is much higher in Asian populations than other populations.⁸⁷

The total number of carotid angioplasty and stenting procedures done for patients with carotid atherosclerosis has increased from 2014 to 2016. In 2016, 9310 patients received carotid artery stenting in 100 selected Chinese hospitals with advanced interventional facilities, which was notably greater than the 3668 patients who received carotid endarterectomy,⁸⁸ indicating the current situation that carotid artery stenting is preferred for reasons that are as yet unclear. Unlike in high-income countries, where extracranial carotid atherosclerosis is more common, Chinese people have a greater prevalence of intracranial atherosclerosis.⁸⁹ This prevalence has led to the exploration of better targeting for those who might benefit from

Panel 2: Priorities of research on stroke in China

- Multicentre observational studies in community and rural areas to explore stroke outcome and management patterns, to allow comparisons between patients in urban and rural areas, and between China and developed nations
- Longitudinal studies to explore temporal trends of risk factors, treatment patterns, and stroke outcomes
- Prospective studies and clinical trials on the natural history and management of silent cerebral infarcts and asymptomatic carotid artery plaques
- Studies on the cause and management of cerebral small vessel disease, including intracerebral haemorrhage
- Data on the status of the implementation of emergency services and stroke unit care according to international, national or regional quality standards
- Development of widely accessible and affordable strategies for long-term secondary prevention and rehabilitation
- Early identification of patients at high risk of bleeding to provide individualised treatment on blood flow restoration
- High-quality clinical trials to address the efficacy of widely used Chinese herb products and neuroprotective drugs

Panel 3: Regional-specific needs to combat stroke in China

- Northeast China: more intensive action (eg, in public education, screening, and monitoring) to control hypertension, smoking, and heavy alcohol drinking, and to promote diets that are low in sodium and high in fruits and vegetables
- Northern China: more intensive action in public education to control hypertension, and in advertising regulation and dietary guidelines to promote diets that are low in sodium and high in fruits and vegetables
- Central China: more intensive action in public education, advertising regulation, tax policies, and governmental intervention to control smoking and air pollution; more research to explore mechanisms underlying the high prevalence of intracerebral haemorrhage
- Southwest China: more investment to improve access to and quality of stroke care; more intensive action, for example in public education and governmental action, to control hypertension and air pollution

intra-arterial interventions, for which adequate safety has been shown in small-scale studies,⁹⁰ and trials are ongoing (appendix).

Rehabilitation

A three-stage rehabilitation network for patients with stroke was launched in China in the early 2000s. Since then, the proportion of patients with stroke who receive in-hospital rehabilitation has increased, and this rehabilitation is often considered part of routine stroke care.⁴⁷ However, about 30 to 60% of patients still do not have access to rehabilitation in hospital (table), and of those

Search strategy and inclusion criteria

We searched PubMed, Cochrane Library, the Chinese National Knowledge Infrastructure, and the Chinese Science and Technology Journals Database for articles published in Chinese and English between Jan 1, 2007, and Oct 31, 2018, using the terms “stroke”, “cerebral haemorrhage”, “cerebral vascular diseases”, “epidemiology”, “risk factors”, “subtypes”, “outcome”, “prognosis”, “prevention”, “treatment”, “rehabilitation”, and “management”. We also inspected reference lists of articles and reviews, consulted experts in the field, and searched ClinicalTrials.gov and the Chinese Clinical Trial Registry. Additionally, we browsed the annual reports and websites of the National Bureau of Statistics of China and of the National Health Commission of the People's Republic of China. The final reference list was generated according to relevance and quality.

who do receive some type of therapy, they most often receive acupuncture, passive massage, or isolated physical therapy for motor function, with only less than 10% of patients receiving physiotherapy, occupational therapy, speech-language therapy, or psychotherapy.^{60,91} This limited access indicates that rehabilitation areas related to maximise recovery in speech and cognitive and emotional function are neglected in China, despite Chinese patients with stroke expressing high demand for psychological support.⁹² About 20% of patients receive rehabilitation after hospital discharge but whether, and to what extent, any professional guidance is involved is uncertain.⁶⁰ The evidence on rehabilitation is scarce and further investigation is needed.

Outcomes after stroke

Hospital-based studies have provided data on outcomes within 1 year after stroke, which were not available before 2007.⁴ For acute ischaemic stroke, the reported case fatality increases from less than 5% at 1 month to 10% at 3 months and 15% at 1 year, and about a third of patients are either dead or disabled by both 3 months and 1 year (appendix).^{31,35,47,51,93–97} The continuously increasing risk of death after stroke emphasises the need to explore the causes of death and improve care for severe stroke, which is under investigation (NCT03222024).⁹⁸ For intracerebral haemorrhage, the reported case fatality varies from about 10% at 1 month to 25% at 3 months and 30% at 1 year, and about half of patients with intracerebral haemorrhage are either dead or disabled by both 1 month and 3 months, and the proportion slightly decreases by 1 year (appendix).^{31,35,73,93,95,97,99–101}

With consistent, albeit slow, improvement in the quality of stroke care, outcomes for patients with stroke have gradually improved from 2002 to 2013 (appendix).⁴⁷ This improvement in outcomes is reflected in the relatively stable or even slightly decreased mortality of stroke patients from 1985 to 2013, despite the increase in

incidence.⁵ Generally, the prognosis for patients with acute stroke appears to be better in China than in high-income countries,¹⁰² likely, in part, related to the differing demographic characteristics (younger age),^{3,45} milder neurological severity, and differences in distribution of aetiological subtypes^{35–40} among Chinese patients. The earlier occurrence of stroke in Chinese people than in other populations might be related to the general unhealthy lifestyle of young Chinese individuals, such as the high prevalence of adolescent smoking and alcohol consumption.²³ However, the data on stroke outcomes in Chinese patients might be biased in relation to the type of hospitals involved in research studies, mainly being those for tertiary care, which are located in large cities, and within which access to health and other services is greater than in rural areas in China. Thus, the case fatality and functional outcome patterns might be underestimated, and more data are required across time and regions, particularly for rural areas, to provide an unbiased overview of stroke outcomes in China.

Conclusions and future directions

The prevalence and incidence of stroke are increasing in China, and substantial geographical and rural–urban variations in prevalence and mortality exist, reflecting the regional disparities in the prevalence of risk factors, and in access to and quality of stroke care.^{5,6} Public awareness of healthy lifestyles and the control of risk factors are still suboptimal and need further intensive action for public education, screening for those at high risk who need targeted therapy, and population-wide control of risk factors through promotion of healthy lifestyles and cities. The increasing use of brain imaging technology raises challenges relating to the diagnosis and treatment of silent pathological signs.^{5,54,55} Chinese patients with stroke are younger^{3,45} and have more small vessel and intracranial atherosclerotic diseases⁴⁰ than patients in high-income countries. Stroke outcomes appear to have improved from 2002 to 2013 (appendix),⁴⁷ in line with the relatively stable mortality from stroke despite the increase in incidence,^{5,6,15} possibly due to improvements in in-hospital stroke care.

However, a number of challenges remain and require further research and action (panels 2 and 3). Although a framework of evidence-based stroke care has been incorporated into the existing health-care system, how well organisational and staffing requirements are being met and interventions are being implemented are generally unknown. Evidence-based stroke care has improved in urban areas, particularly for interventions with a low risk of adverse effects (eg, antiplatelet agents and lipid lowering drugs^{47,49}). Neuroprotective drugs and Chinese herbal products, despite scarcity of evidence of efficacy, are commonly used. By contrast, stroke unit care and other proven interventions (eg, intravenous thrombolysis, anticoagulation, and decompressive hemicraniectomy for patients with indications^{49,53}) are underused, often due to organisational challenges and unnecessarily high

perceived risk of adverse effects. Early secondary prevention and rehabilitation in hospital have improved, but long-term adherence is unsatisfactory. As most stroke research has been done in urban areas, data on treatment patterns and stroke outcomes in rural areas are scarce. Additionally, data on community-based stroke care are unavailable. To fill these gaps in evidence-based practice, an increasing number of studies on stroke management are ongoing (appendix). Coordinated efforts by government, local and hospital leaders, and doctors are required to support more high-quality research that explores interventions that are affordable and widely applicable for the prevention and treatment of stroke, and to provide more balanced resources and evidence-based stroke care across the country, with sensitivity to specific regional needs.

Contributors

ML, SW, BW, PS, WW, and ZC conceived the Review. ML designed and drafted the outline of the Review and coordinated the writing process. SW did the literature search, data collection, analysis, and checking, and made the tables and figures. ML, SW, and BW evaluated the quality of the included studies, wrote the first draft, and revised each version of the manuscript. YW, YH, LC, CP, JJ, TZ, XL, SZ, PX, DF, XJ, and K-SLW sourced data from key publications in their expertised areas and commented on the manuscript. ML, ZC, CSA, PS, and LW interpreted data and revised the manuscript following major changes. All authors contributed to critical appraisal of the content, and approved the final version.

Other members of the China Stroke Study Collaboration

Chenchen Wei, Yanan Wang, Yajun Cheng, Dong Zhou, Li He, Junfeng Liu, Shuting Zhang, Wendan Tao, Zilong Hao, Deren Wang, Shihong Zhang (Department of Neurology, West China Hospital, Sichuan University, Chengdu); Yunhai Liu (Department of Neurology, Xiangya Hospital, Central South University, Changsha); Xin Li (Department of Neurology, The Second Hospital of Tianjin Medical University, Tianjin); Qiang Dong (Department of Neurology, Huashan Hospital, Fudan University, Shanghai); Jinsheng Zeng (Department of Neurology and Stroke Center, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou); Bin Peng (Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing); Yun Xu (Department of Neurology, Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing); Yi Yang (Department of Neurology, The First Hospital of Jilin University, Changchun); Yilong Wang, Zixiao Li (Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing); Gang Zhao (Department of Neurology, Xijing Hospital, The Fourth Military Medical University, Xi'an); Wei Wang (Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan); Yuming Xu (Department of Neurology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou); Qingwu Yang (Department of Neurology, Xinqiao Hospital, The Third Military Medical University, Chongqing); Zhiyi He (Department of Neurology, The First Affiliated Hospital of China Medical University, Shenyang); Shaoshi Wang (Neurology Department, Shanghai No 4 People's Hospital, Tongji University, Shanghai); Chao You (Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu); Ying Gao (Department of Neurology, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing); Jie Yang (Department of Neurology and Stroke Center, The First Affiliated Hospital of Chengdu Medical College, Chengdu); Department of Neurology and Stroke Center, Nanjing First Hospital, Nanjing Medical University, Nanjing); Chunyan Lei (Department of Neurology, The First Affiliated Hospital of Kunming Medical University, Kunming); Yuhua Zhao (The People's Hospital of Tibet Autonomous Region, Lhasa).

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