BMJ Open

Prevalence and distribution of lacunar stroke in China: a cross-sectional study using self-reported survey data

Shangrong Han ,[1,2] Dongling Sun,[3,4] Bin Jiang,[3,4] Haixin Sun,[3,4] Xiaojuan Ru,[3,4] Aoming Jin ,[1,2] Yilong Wang,[1,2] Wenzhi Wang [3,4]

To cite: Han S, Sun D, Jiang B, *et al*. Prevalence and distribution of lacunar stroke in China: a cross-sectional study using self-reported survey data. *BMJ Open* 2022;**12**:e063520. doi:10.1136/bmjopen-2022-063520

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-063520).

SH and DS contributed equally.

SH and DS are joint first authors.

Received 06 April 2022
Accepted 21 November 2022

[1]Department of Neurology, Beijing Tiantan Hospital, Beijing, China
[2]China National Clinical Research Center for Neurological Diseases, Beijing, China
[3]Beijing Neurosurgical Institute, Capital Medical University, Beijing, China
[4]Beijing Municipal Key Laboratory of Clinical Epidemiology, Beijing, China

Correspondence to
Dr Wenzhi Wang; qgnfbwwz@163.com and Professor Yilong Wang; yilong528@aliyun.com

ABSTRACT

Objectives To report the prevalence and distribution of lacunar stroke in different regions of China, as well as the demographical characteristics of symptomatic and asymptomatic lacunar stroke.

Design Cross-sectional study.

Setting Data were derived from NESS-China Study that was conducted in 157 sites covering all 31 provinces, including 64 urban and 93 rural areas in mainland China between 1 September 2013 and 31 December 2013. Lacunar stroke was defined as being previously diagnosed according to the participants' medical history. Patients were further divided into symptomatic or asymptomatic groups, depending on whether they were initially diagnosed with neurological symptoms.

Participants 458 833 participants aged ≥20 years were enrolled in this study.

Results A total of 7520 participants (1.63%) were diagnosed with lacunar stroke. The peak rate of diagnosis was between the ages of 70 and 79 years in both men and women. Geographically, the age-standardised and sex-standardised prevalence was highest in Northeast China (2495.3/100 000 persons) and lowest in Southeast China (599.7/100 000 persons), showing a geographical disparity. Over 90% of patients with lacunar stroke were diagnosed in secondary or tertiary hospitals. Patients with symptomatic lacunar stroke had significantly different demographic characteristics in age, sex and geographical regions compared with those who were asymptomatic.

Conclusions In this study, the prevalence and distribution of lacunar stroke were reported at population level across China. Special attention and prevention should be given to the age, sex and geographical groups that are vulnerable to lacunar stroke.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study was huge in its sample size, with 458 833 adult participants enrolled.
⇒ This study reflected the real-world prevalence and disparities of lacunar stroke at population level in mainland China.
⇒ The study population was collected using a two-stage sampling method covering 157 sites in all 31 provinces in mainland China.
⇒ The limitation of this study is that the diagnoses were collected by self-reporting and confirmed by researchers, with a lack of neuroimaging data.

INTRODUCTION

Lacunar stroke is defined as small subcortical infarcts caused by abnormalities in perforating arterioles. Clinically, patients with lacunar stroke can be symptomatic or asymptomatic. They are at high risk of future strokes.[1–3] The incidence of lacunar stroke ranges from 25 to 50 per 100 000 people worldwide.[4] However, data about its prevalence at population level in a particular country are rare. The overall prevalence and demographic disparities such as sex, age and geographical region of lacunar stroke have not been well investigated. Such data are useful for the planning of prevention and treatment in patients with lacunar stroke. Given the rapid increase in cerebrovascular disease in China, this study is extremely important both for the public health of the people of China and because it shed a light on the change in stroke prevalence as a society's risk factors change.

In this study, we conducted a cross-sectional, national representative, large-scale, door-to-door survey to study the epidemiological characteristics of lacunar stroke in China. We aim to report the prevalence and distribution of lacunar stroke on a national basis, as well as disparities at different levels.

METHODS

Participants and data collection

This study is a post-hoc secondary analysis of the NESS-China Study based on the National Disease Surveillance Points System.[5] It was a national door-to-door survey conducted in 2013. The goal of this study was to examine the stroke burden in China. A total of 157 sites covering all 31 provinces including 64 urban and 93 rural areas in mainland China were included. A two-stage sampling method was used to minimise sampling error and data were collected from 1 September to 31

December 2013. Details of this survey were published elsewhere.[5] In brief, a multistage, stratified cluster sampling technique was used to ensure the representativeness of the local demographic composition. This study included all people who had lived in the region for at least 6 months at the time of the survey. Standardised questionnaires were designed by neurologists and epidemiologists. Participants under 20 years of age were excluded in the original survey. Those who failed to respond to questions on lacunar stroke were excluded in this study. Demographic data and details about the diagnostic history were collected. According to the national policy, the seven geographical regions were classified as Northeast China (Heilongjiang, Jilin and Liaoning), North China (Beijing, Tianjin, Hebei, Shanxi and Inner Mongolia), Northwest China (Shaanxi, Gansu, Ningxia, Qinghai and Xinjiang), East China (Shandong, Jiangsu, Zhejiang, Shanghai, Anhui and Fujian), Central China (Henan, Jiangxi, Hubei and Hunan), South China (Guangdong, Guangxi and Hainan) and Southwest China (Sichuan, Chongqing, Yunnan, Guizhou and Tibet).

All data were collected by trained investigators from the Chinese Center for Disease Control and Prevention. Face-to-face interviews were conducted with the participants or their family members. Data were collected through self-reporting.

Diagnostic criteria and definitions

Lacunar stroke, symptomatic or asymptomatic, was defined as being previously diagnosed by a neurologist and presented on the participants' medical history with neuroimaging data. The diagnostic history was acquired by self-reporting and confirmed by researchers from Chinese Center for Disease Control and Prevention during survey. Patients with a previously diagnosed lacunar stroke were further divided into two groups: symptomatic or asymptomatic. Patients with symptomatic lacunar stroke were defined as having focal neurological

Table 1 General characteristics of the investigated population

Characteristics	Overall	With lacunar stroke	Without lacunar stroke
Participants	458 833 (100.0)	7520 (1.63)	451 313 (98.37)
Sex (men, n (%))	227 458 (49.57)	3881 (51.61)	223 577 (49.54)
Age groups (years), n (%)			
20–29	88 404 (19.27)	77 (1.02)	88 327 (19.51)
30–39	84 070 (18.32)	132 (1.76)	83 938 (18.60)
40–49	104 088 (22.69)	504 (6.70)	103 584 (22.95)
50–59	79 471 (17.32)	1500 (19.95)	77 971 (17.28)
60–69	59 795 (13.03)	2596 (34.52)	57 199 (12.63)
70–79	31 741 (6.92)	2083 (27.70)	29 658 (6.57)
80+	11 264 (2.45)	628 (8.35)	10 636 (2.36)
Ethnicity (Han, n (%))	405 264 (88.36)	7018 (93.39)	398 246 (88.28)
Residence (urban, n (%))	222 650 (48.53)	3545 (47.14)	219 105 (47.75)
Education, n (%)			
Primary school and below	162 806 (35.48)	4294 (57.10)	158 512 (35.12)
Middle school	248 847 (54.23)	2907 (38.66)	245 940 (54.49)
College and higher	46 929 (10.23)	317 (4.22)	46 612 (10.33)
Missing	251 (0.05)	317 (4.22)	249 (0.06)
Marital status, n (%)			
Married	372 170 (81.11)	5972 (79.41)	366 198 (81.14)
Single	55 085 (12.01)	170 (2.26)	54 915 (12.17)
Divorced or widowed	30 955 (6.75)	1361 (18.10)	29 594 (6.56)
Missing	623 (0.14)	17 (0.23)	606 (0.13)
Occupation, n (%)			
Worker	41 471 (9.04)	319 (4.24)	41 152 (9.12)
Farmer	249 334 (54.34)	4055 (53.92)	245 279 (54.35)
Employee	105 357 (22.96)	451 (6.00)	104 906 (23.24)
Retired	62 431 (13.61)	2692 (35.80)	59 739 (13.24)
Missing	240 (0.05)	3 (0.04)	237 (0.05)

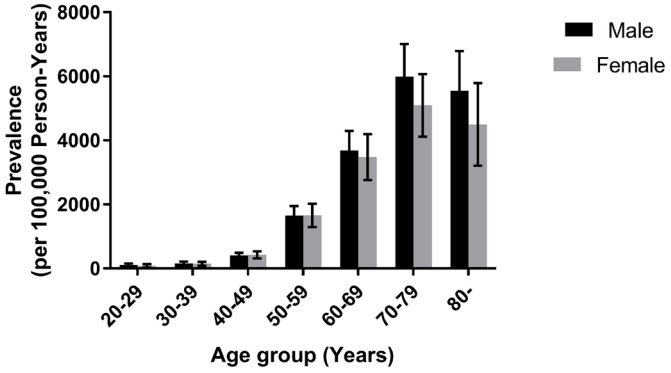

Figure 1 Prevalence of lacunar stroke per 100 000 Chinese adults by age and sex.

symptoms at the time of initial diagnosis, while asymptomatic lacunar stroke was defined as being initially diagnosed based on their neuroimages taken during a regular health check-up or discovered when being treated for other conditions without neurological symptoms. Information such as patients' demographic data, symptoms and the level of hospital care was also collected.

Statistical analyses

Demographic characteristics were described as percentage (%) for categorical variables and as means±SD for continuous variables. Crude prevalence and age-standardised and sex-standardised prevalence were calculated with 95% CIs. Age and sex standardisation was performed using Chinese census data from 2010, which was the up-to-date census data available at the time of survey. Prevalence was described based on patient's age, sex, occupational and geographical difference. Categorical variables were tested by the Wald X^2 test, while continuous variables were tested by Student's t-test. P values were two tailed, and $p<0.05$ was considered statistically significant. All statistical analyses were conducted using the SAS 9.4 software (SAS Institute).

Patient and public involvement

No patient involved.

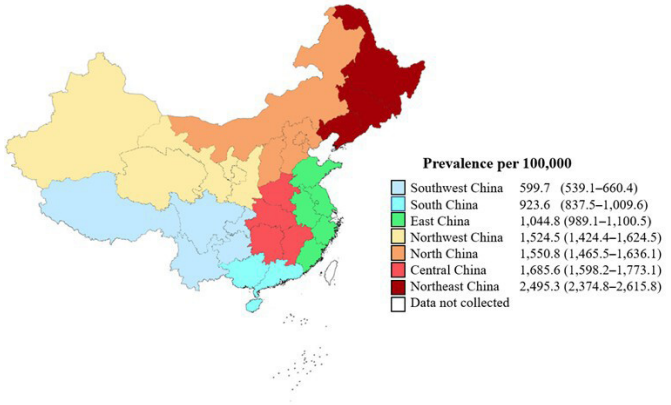

Figure 2 Age-standardised and sex-standardised prevalence of lacunar infarction in the seven major geographical regions of China.

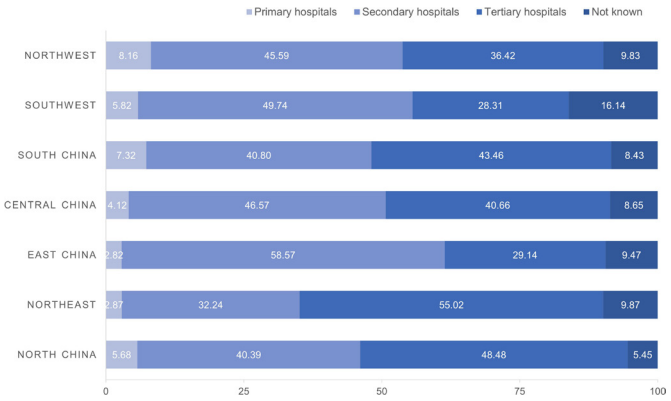

Figure 3 Disparities in the levels of hospital for lacunar stroke diagnoses in the seven major geographical regions in mainland China (%).

RESULTS

The response rate of the original survey was 81.0%, and 480 687 participants were included. Among them, 458 833 participants (95.5%) responded to the questions on lacunar stroke, and 7520 have previously been diagnosed with 'lacunar stroke'. The demographic characteristics of the participants included in this study are listed in table 1.

Among the 7520 participants diagnosed with lacunar stroke, the peak age was between 50 and 79 years, especially in the 70–79 years age group. The mean age of patients with lacunar stroke was 65.18 years, compared with 46.25 years in the group without the diagnosis. Sex distribution was similar in both groups (50%). Among all patients with lacunar stroke, 47.14% were urban dwellers, while 52.86% lived in rural areas. In terms of ethnicity, the percentage of Chinese Han in the lacunar stroke group was slightly higher at 93.39%, while 88.36% among all other ethnicities. The age and sex distributions of patients with lacunar stroke are shown in figure 1. In all age groups, male participants had more lacunar stroke than female participants. The age-specific prevalence of lacunar stroke increased with age in both sexes, except for the age group of 80 years and above, in which both male and female participants reported less lacunar stroke than the age group of 70–79 years, but still higher than all other age groups. Educational level is lower in the lacunar stroke group than in the other groups.

For geographical distribution, the age-standardised and sex-standardised prevalence of lacunar stroke in the seven regions of China ranged from 599.7 to 2495.3 per 100 000 people. The Southwestern region had the lowest prevalence of lacunar stroke, followed by Southern China. The Northeast region had the highest prevalence, with nearly four times the prevalence in the Southwest. The differences among all regions are statistically significant. The seven major geographical regions of China are shown in the map in figure 2.

We also analysed the care levels of hospitals where the participants were diagnosed with lacunar stroke in each region. Most participants were diagnosed in secondary or tertiary hospitals, with more diagnoses in secondary

Table 2 Sociodemographic disparities between symptomatic and asymptomatic lacunar stroke diagnosis

	Lacunar stroke	Symptomatic lacunar stroke	
	Number	Number (%)	P value
Total	7520	5145 (68.42)	
Sex			0.034
Male	3881	2698 (69.52)	
Female	3639	2447 (67.24)	
Age (years)			<0.0001
20–29	77	11 (14.29)	
30–39	132	38 (28.79)	
40–49	504	301 (59.72)	
50–59	1500	1062 (70.80)	
60–69	2596	1842 (70.96)	
70–79	2083	1431 (68.70)	
80+	628	460 (73.25)	
Residence			0.002
Urban	3545	2362 (66.63)	
Rural	3975	2783 (70.01)	
Geographical distribution			<0.0001
North China	1285	1016 (79.07)	
Northeast China	1672	1254 (75.00)	
East China	1383	974 (70.43)	
Central China	1456	923 (63.39)	
South China	451	232 (51.44)	
Southwest China	378	218 (57.67)	
Northwest China	895	545 (60.89)	

hospitals in East China, Central China, Northwest China and Southwest China. In Southern China, Northern China and Northeast China, the majority of participants were diagnosed in a tertiary hospital. In all regions, the diagnoses made in a primary hospital accounted for less than 10% of all diagnoses (figure 3).

Furthermore, 68.42% of patients were diagnosed with one or more neurological symptoms. Male patients were slightly more likely to be symptomatic. The rate of symptomatic lacunar stroke diagnosis was generally increased with age. Rural patients were more often symptomatic when compared with the urban population. Geographically, the percentage of symptomatic lacunar stroke was the highest in Northern China (86.03%) and lowest in Southern China (58.59%). The remaining diagnosed asymptomatically with a lacune found on neuroimages taken during a regular health check-up or discovered when being treated for other conditions (table 2).

DISCUSSION

This population-based study enrolled 458 833 adult participants and provided data for the population-based prevalence of lacunar stroke that is representative of different geographical areas in China. Conducted with a two-stage sampling method covering all 31 provinces in mainland China, this study was representative of the national demographic distribution of lacunar stroke. It showed that the prevalence of lacunar stroke in mainland China was approximately 1.63%. A tendency of increased prevalence in old age can also be concluded and the peak prevalence in both sexes was in their 70s. In people aged >80 years, the prevalence decreased. This can partly be explained by survivor bias, where vulnerable patients may not be able to survive until older age. In all age groups, male participants reported more history of lacunar stroke than their female counterparts, which parallels the age-specific prevalence of stroke.[5]

There are only a few relatively large-scale studies that reported the prevalence of lacunar stroke as an independent diagnosis. One large-scale community-based study conducted in China enrolled nearly half a million participants from 10 sites in different parts of the country, with no stroke history at baseline.[6] This study compared long-term prognosis between patients with symptomatic or asymptomatic lacunar stroke. Although large in sample size, this study was relatively less representative of the demographic distribution throughout China since only 10 sites were selected. Other studies were mostly hospital-based studies in China, South Korea, Japan and the Netherlands. The prevalence of lacunar stroke in the above studies ranged from 2.48% to 8.26%.[6–16] Prior studies focusing on the prevalence of lacunar stroke as an individual disease are listed in table 3.

Our study found a relatively lower prevalence of lacunar stroke compared with other studies. The possible reasons for the difference include the following: (1) our study population data were derived from a huge door-to-door survey in rural and urban communities. We interviewed participants door to door based on the local demographic composition to reflect the real epidemiological characteristics. Thus, a large proportion of our participants were younger and healthier, which may have lowered the prevalence. (2) We also included individuals who did not pay much attention to their health status, neglected their symptoms or never had a neuroimaging scan. These participants might have already had lacunar stroke, but since they had never been to a neurology clinic, they had a negative response in the survey. (3) This study was conducted in 2013 when MRI was not as common, especially in less-developed areas. This might lead to lower rate of detection by CT and result in a lower estimate of prevalence. Future studies will be designed to cover these limitations and reflect the trend of lacunar stroke prevalence.

From this study, we can conclude that the prevalence of lacunar stroke varies in the seven different geographical regions of China, showing a north-to-south disparity. The most prevalent lacunar stroke was in Northeast China, followed by Central China, Northern China and Northwest China. The region with the lowest prevalence (1%) was Southwest China. These findings parallel the

Table 3 Comparisons of studies focusing on the prevalence of lacunar stroke as an individual disease

	Hao *et al*[6]	Chen *et al*[10]	Tabara *et al*[13]	Riba-Llena *et al*[16]	Lee *et al*[12]
Country/region	China	China	Japan	The Netherlands	Korea
Study design	Prospective cohort study	Prospective cohort study	Cross-sectional registry	Retrospective cohort study	Cross-sectional study
Study site	Community	Community	Community	Community	Hospital
Year of publication	2021	2009	2014	2015	2016
Sample size	489 597	477	1308	4905	2326
Participants	Community-based adults with no history of stroke or ischaemic heart disease	Random community residents	Middle-aged to elderly persons for medical check-up	Non-demented elderly individuals	Healthy adults undergoing health check-ups
Age (years)	30–79	60–64	Middle-aged to elderly	55–98	40–79
Prevalence	2.5%	7.8%	8.3%	7.8%	8.1%

distribution in stroke prevalence reported in the same population,[5] as well as the concept of 'stroke belt in China' in previous studies.[17 18] The geographical trend of stroke and lacunar stroke can be partly explained by lifestyle and local habits. In the Northeast and Central parts of China, the local diet includes more salt and fatty food, while in the southern regions, people eat less salt and fatty food.[18] The cold weather in Northeast China limits outdoor physical activities, which may increase the risk of cerebrovascular disease.[19] The prevalence was similar among urban or rural residents and there was no difference in terms of occupation. It is also noteworthy that a lower educational status (below primary schools) was observed in patients with lacunar stroke. This finding is in accordance with previous studies regarding stroke that higher educational levels could protect against stroke independent of one's cognitive function.[20 21] It is also consistent with prior studies that found that lower educational level was associated with subclinical cerebrovascular disease and cerebral small vessel disease markers, including white matter hyperintensities and microbleeds.[22 23] Our finding provides evidence that lower early-life educational level may correlate with higher rates of lacunar stroke as well.

It appeared that the percentage of symptomatic lacunar stroke generally increased with age. This trend is in accordance with the previous studies as well.[8] Younger people may be more health conscious and have a higher level of awareness of diseases; therefore, they seek medical help early for potential strokes. On the other hand, senior people tend to seek medical care until they feel necessary. A north-to-south gradient could also be noticed that people living in the northern parts of China tend to get diagnosed after symptoms occur, while this is less common in the southern parts of China. Lastly, the more prevalent use of MRI in tertiary care hospitals might explain why they are the most common level of hospitals where a patient was initially diagnosed.

Our finding reflects the real-world prevalence of lacunar stroke and disparities among different regions in mainland China. The strength of this study is the large sample size, and the representativeness of the demographical characteristics in all geographical regions and sociological levels in mainland China. In addition, more than 90% of the diagnoses were made in secondary and tertiary hospitals, indicating that the diagnoses were reliable.

Our study has some limitations. We were unable to collect and review all participants' imaging data in this study. All diagnostic data were collected by self-reporting and confirmed by researchers, which might have resulted in recall bias. To minimise the bias, diagnoses of lacunar stroke were confirmed by trained investigators, and the statistics were reconfirmed by our professional epidemiologists. As we lack imaging data upon diagnosis, the prevalence rates estimated in this study are likely to be slightly underestimated compared with the true rate of lacunar stroke. Admittedly, with the lack of imaging data in this cross-sectional study, haemorrhagic and ischaemic pathologies of lacunar stroke cannot be differentiated. Yet, with this method, we were able to include patients with clinically evident lacunar stroke who did not have any remnant-visible small subcortical infarct on imaging by the time of the survey. From this perspective, diagnosis with a medical history might better reflect the real prevalence of past lacunar stroke compared with collecting cross-sectional neuroimaging data, as lesions on neuroimaging could fade with time in patients with previous onset of symptomatic lacunar stroke.[24] Lastly, data regarding the time of diagnosis, mortality, risk factors and socioeconomic status were not collected, and therefore cannot be described. These limitations will be addressed in our future studies.

Acknowledgements The authors would like to thank all the NESS-China investigators and participants.

Contributors SH designed and drafted the manuscript. DS and AJ performed the data analysis. DS, BJ, HS and XR participated in the original design and data collection of the NESS-China Study. YW and WW designed the NESS-China Study and reviewed the manuscript. All authors have read and approved the final version of the manuscript. WW is the guarantor.

Funding This project was supported by the Ministry of Science and Technology, People's Republic of China under Grant No. 2011BAI08B01 of the National Key Technology R&D Program, the National Natural Science Foundation of China (no. 81825007), Beijing Outstanding Young Scientist Program (no. BJJWZYJH01201910025030), Youth Beijing Scholar Program (no. 010), Beijing Talent Project-Class A: Innovation and Development (no. 2018A12), and 'National Ten-Thousand Talent Plan'-Leadership of Scientific and Technological Innovation, National Key R&D Program of China (nos. 2017YFC1307900, 2017YFC1307905).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Obtained.

Ethics approval This study involves human participants and was approved by the Ethics Committees of Beijing Tiantan Hospital (ID: 2011BAI08B00) and all other participating institutes. Interviewers obtained written informed consent from all study participants before collecting their information.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets analysed during the current study are not publicly available due to copyright reasons as a part of the NESS-China Study, but are available from the corresponding author on reasonable request.

ORCID iDs
Shangrong Han http://orcid.org/0000-0003-2608-484X
Aoming Jin http://orcid.org/0000-0002-7221-5444
Wenzhi Wang http://orcid.org/0000-0002-0086-1121

REFERENCES

1 Dhamoon MS, McClure LA, White CL, *et al*. Long-Term disability after lacunar stroke: secondary prevention of small subcortical strokes. *Neurology* 2015;84:1002–8.
2 Makin SDJ, Turpin S, Dennis MS, *et al*. Cognitive impairment after lacunar stroke: systematic review and meta-analysis of incidence, prevalence and comparison with other stroke subtypes. *J Neurol Neurosurg Psychiatry* 2013;84:893–900.
3 Vermeer SE, Prins ND, den Heijer T, *et al*. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med* 2003;348:1215–22.
4 Yaghi S, Raz E, Yang D, *et al*. Lacunar stroke: mechanisms and therapeutic implications. *J Neurol Neurosurg Psychiatry* 2021;92:823–30.
5 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;135:759–71.
6 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.
7 Sun X-G, Wang T, Zhang N, *et al*. Incidence and survival of lacunar infarction in a southern Chinese population: a 7-year prospective study. *Brain Inj* 2015;29:739–44.
8 Fang X-H, Wang W-H, Zhang X-Q, *et al*. Incidence and survival of symptomatic lacunar infarction in a Beijing population: a 6-year prospective study. *Eur J Neurol* 2012;19:1114–20.
9 Kubo M, Kiyohara Y, Ninomiya T, *et al*. Decreasing incidence of lacunar vs other types of cerebral infarction in a Japanese population. *Neurology* 2006;66:1539–44.
10 Chen X, Wen W, Anstey KJ, *et al*. Prevalence, incidence, and risk factors of lacunar infarcts in a community sample. *Neurology* 2009;73:266–72.
11 Sacco SE, Whisnant JP, Broderick JP, *et al*. Epidemiological characteristics of lacunar infarcts in a population. *Stroke* 1991;22:1236–41.
12 Lee JE, Shin DW, Yun JM, *et al*. Insulin resistance is a risk factor for silent lacunar infarction. *Stroke* 2016;47:2938–44.
13 Tabara Y, Okada Y, Uetani E, *et al*. Postprandial hypotension as a risk marker for asymptomatic lacunar infarction. *J Hypertens* 2014;32:1084–90.
14 Otani H, Kikuya M, Hara A, *et al*. Association of kidney dysfunction with silent lacunar infarcts and white matter hyperintensity in the general population: the Ohasama study. *Cerebrovasc Dis* 2010;30:43–50.
15 Kim SH, Shin DW, Yun JM, *et al*. Kidney dysfunction and silent brain infarction in generally healthy adults. *J Neurol Sci* 2017;379:89–93.
16 Riba-Llena I, Koek M, Verhaaren BFJ, *et al*. Small cortical infarcts: prevalence, determinants, and cognitive correlates in the general population. *Int J Stroke* 2015;10 Suppl A100:18–24.
17 Xia F, Yu X, Li Y, *et al*. Geographic variations of stroke incidence in Chinese communities: an 18-year prospective cohort study from 1997 to 2015. *J Stroke* 2020;22:345–56.
18 Xu G, Ma M, Liu X, *et al*. Is there a stroke belt in China and why? *Stroke* 2013;44:1775–83.
19 Boehme AK, Esenwa C, Elkind MSV. Stroke risk factors, genetics, and prevention. *Circ Res* 2017;120:472–95.
20 Xiuyun W, Qian W, Minjun X, *et al*. Education and stroke: evidence from epidemiology and Mendelian randomization study. *Sci Rep* 2020;10:21208.
21 Gill D, Efstathiadou A, Cawood K, *et al*. Education protects against coronary heart disease and stroke independently of cognitive function: evidence from Mendelian randomization. *Int J Epidemiol* 2019;48:1468–77.
22 Backhouse EV, McHutchison CA, Cvoro V, *et al*. Early life risk factors for cerebrovascular disease: a systematic review and meta-analysis. *Neurology* 2017;88:976–84.
23 Backhouse EV, Shenkin SD, McIntosh AM, *et al*. Early life predictors of late life cerebral small vessel disease in four prospective cohort studies. *Brain* 2021;144:3769–78.
24 Loos CMJ, Staals J, Wardlaw JM, *et al*. Cavitation of deep lacunar infarcts in patients with first-ever lacunar stroke: a 2-year follow-up study with Mr. *Stroke* 2012;43:2245–7.