Sex differences in risk factors for stroke: a nationwide survey of 700 000 Chinese Adults

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Running title: Sex differences in the risk factors for stroke

Stroke has become a major public health concern globally.[1] The burden of stroke has increased significantly worldwide in the past two decades. The incidence of stroke has decreased in developed countries, by contrast, it has increased significantly in developing countries.[2] In China, stroke has become the first leading cause of death, and it is the most prominent factor for disability-adjusted life-years lost.[3]

Epidemiological studies of sex disparity in the prevalence, incidence, and mortality of stroke and its risk factors have been conducted in Western countries; [4-8] however, no studies have focused on sex differences in the risk factors for stroke in China. With stroke becoming a great public health issue, findings on sex disparity in stroke risk factors among the Chinese adults are urgently needed to facilitate future personalized healthcare management policy and planning. Thus, we aimed to examine sex differences in the risk factors for stroke based on a nationally representative population-based sample of middle-aged and older Chinese populations.

The China National Stroke Screening and Prevention Project (CNSSPP) was a key national action on stroke prevention and control launched in 2011 by the Chinese government. The rationale, design, and methods of the CNSSPP have previously been described in detail.[9] Our study was based on the data from the CNSSPP in 30 provinces in Mainland China conducted between October 1st 2014 and November 30th 2015. Briefly, a stratified, multistage random sampling method was used to obtain a nationally representative sample of the general Chinese population aged 40 years or older.

Socio-demographic characteristics, stroke history, family history of stroke, medical history, and status of risk factors were collected though trained healthcare workers with a standardized questionnaire. Physical examinations included the assessment of height, weight, and blood pressure (BP) and an electrocardiogram. Laboratory examinations included the measurements of serum lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides) and fasting plasma glucose.

The associations between sex and stroke related risk factors, including stroke history, hypertension, diabetes mellitus (DM), hyperlipidemia, atrial fibrillation (AF), smoking, overweight or obesity, and physical inactivity, were estimated using multivariable logistic regression analysis, respectively. We performed analyses by using SAS version 9.3, and all tests were 2-sided with a significance level of 0.05.

A total of 726,451 respondents (53.27% women) with a mean age of 57.23±11.41 years were investigated in this study. The relatively young mean age among people aged 40 and over in our sample was due to the population structure in China (Figure 1). The age-standardized prevalence rate of stroke was 2.11%. The age-standardized prevalence of stroke was markedly higher in males compared to females (2.30% versus 1.94%).

The sex differences in risk factors associated with stroke are shown in Table 1. Men were less likely than women to have had hypertension (OR=0.87), AF (OR=0.70), and DM (OR=0.88), and to be physical inactive (OR=0.83) and overweight or obese (OR=0.88) in the multivariable adjusted model. Men were more likely than women to have had hyperlipidemia (OR=1.15), stroke (OR=1.27), and be a former or current smoker (OR=18.95) in the multivariable adjusted model.

Intriguingly, men in the 40~49 age group were more likely than women to be overweight or obese (OR=1.09), whereas those in the other age groups had a lower odds of being overweight and obese. The sex differences in AF and cigarette smoking decreased with age, however, the differences in the risk of hyperlipidemia and stroke increased with age (Table 1). In addition, stratified analysis showed that the sex differences were significant in both rural and urban settings; however, the sex differences in the risk of DM and overweight or obesity were significant in rural areas (DM: OR=0.77; overweight or obesity: OR=0.79), but not in urban areas.

Inconsistent with one previous study by Clarke et al.[10], a lower prevalence of stroke was identified in our study (5.4% versus. 2.5%). Notably, the study by Clarke and his colleagues were not based on a nationally-representative survey. The difference might be at least partly attributable to the participants' characteristics, including socio-economic status, geographic regions, and sample size.

Like research findings in other countries,[11-15] our results showed that compared to women, the age-standardized prevalence of stroke was markedly higher in men (2.30% versus 1.94%), which is inconsistent with the results of the study by Wang et al [16] in China in 2013 (1.22% versus 1.01%). Wang and his colleagues indicated that there was no statistically significant difference in the stroke prevalence in both sexes. One possible explanation was that the study by Wang and colleagues included adults aged ≥20 years, whereas the present study included adults aged ≥40 years. Another possible explanation concerns the differences in the relative significance of risk factors for stroke in two studies (such as DM, dyslipidemia, AF, and overweight or obesity). More importantly, in the current study, the multivariable analyses indicate that men have a higher risk of stroke (OR=1.27). Further population and laboratory studies are clearly warranted to assess the potential biological mechanism and difference between the sexes.

Our results were in agreement with previous studies [17-18] showing that there were sex differences in the odds of DM and AF. In contrast to our results, Andersen et al [19] found that men more often had DM (OR=1.22), and AF and smoking were equally frequent in both sexes. One possible reason was that the study by Andersen and colleagues focused on first-ever ischemic stroke patients aged 18 years and older, whereas the present study included general population aged ≥40 years. In addition, a larger sample size may increase the statistical power in our study. Notably, because of the different sampling and analysis methods and temporal differences affected the prevalence estimations, thus, the results across different studies should be interpreted cautiously, and more studies are warranted to confirm the sex differences in stroke risk factors among Chinese adults.

This research is the first study to examine the differences in stroke related risk factors using a nationally representative sample of middle-aged and older Chinese population. The results not only inform Chinese policy makers about priority areas for effective and tailored management strategies for preventing stroke but also enrich the research pool of the topic within the international stroke-related research field.

This study had some limitations. First, this research was a cross-sectional study, thus we cannot refer the causality from the results. Second, because our study focused only on Chinese adults aged ≥40 years, the generalizability of the data to other age groups in China may be limited. Third, the CNSSPP questionnaire did not include some potential stroke-related risk factors, such as the awareness of stroke warning signs, and dietary and psychosocial factors.

In conclusion, compared to women, Chinese men were less likely to have had hypertension, AF, and DM and to be physical inactive and overweight or obese, but more likely to have hyperlipidemia, stroke and to be a smoker. The sex differences in AF, physical inactivity, and cigarette smoking attenuate with age; however, the differences in DM, hyperlipidemia, and stroke increase with age. The sex differences in the risk of DM and overweight or obesity were only significant in rural settings. Considering the variations between women and men in the development of stroke may provide greater insight into the design of prevention strategies and the biological research of both sexes.

Acknowledgements

We thank the 726,451 study participants of the CNSSPP and all staff members involved in this study for their painstaking efforts in conducting the data collection.

Sources of Funding

This study was supported by the Ministry of Finance of the People's Republic of China (Issued by Finance and Social Security [2011] Document No. 61, Ministry of Finance), the Innovation Committee of Shenzhen Science and Technology, "Demonstration Application of Cardiovascular and Cerebrovascular Disease Prevention and Control Based on Functional Community" (KJYY20170413162318686), the Fundamental Research Funds for the Central Universities, Huazhong University of Science and Technology, Wuhan, China (2016YXMS215), and the China Postdoctoral Science Foundation funded project (2018M630870). HJ's time was funded by Australian National Health and Medical Research

Council (APP1141325), Foundation for Alcohol Research and Education and La Trobe Asia. The funding sources played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Authors' contributions

YSJ, YG, ZHW, and ZXL contributed to the conception and design of the study. SJY, YG, LQL, HJ, FJS, XXY, XJW, WZL, CS, SH, CW, WY, FY, and ZHW contributed to the acquisition, analysis and interpretation of data. YG drafted the manuscript. SJY, YG, HJ, FJS, LWC, WNF, CZL, and ZXL critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

Disclosures

We declared that we have no conflicts of interest.

References

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 2017; 135: e146-e603.

2. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2014; 383: 245-254.

3. Yang G, Wang Y, Zeng Y, et al. Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; 381: 1987-2015.

4. Fang MC, Singer DE, Chang Y, et al. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation* 2005; 112: 1687-1691.

5. Touze E and Rothwell PM. Sex differences in heritability of ischemic stroke: a systematic review and meta-analysis. *Stroke* 2008; 39: 16-23.

6. Appelros P, Stegmayr B and Terent A. Sex differences in stroke epidemiology: a systematic review. *Stroke* 2009; 40: 1082-1090.

7. Giralt D, Domingues-Montanari S, Mendioroz M, et al. The gender gap in stroke: a meta-analysis. *Acta Neurol Scand* 2012; 125: 83-90.

8. Gargano JW, Wehner S and Reeves M. Sex differences in acute stroke care in a statewide stroke registry. *Stroke* 2008; 39: 24-29.

9. Wang X, Li W, Song F, et al. Carotid Atherosclerosis Detected by Ultrasonography: A National Cross-Sectional Study. *J Am Heart Assoc* 2018; 7.

10. Clarke R, Du H, Kurmi O, et al. Burden of carotid artery atherosclerosis in Chinese adults:

Implications for future risk of cardiovascular diseases. Eur J Prev Cardiol 2017; 24: 647-656.

11. Boix R, del Barrio JL, Saz P, et al. Stroke prevalence among the Spanish elderly: an analysis based on screening surveys. *BMC Neurol* 2006; 6: 36.

12. Palm F, Urbanek C, Wolf J, et al. Etiology, risk factors and sex differences in ischemic stroke in the Ludwigshafen Stroke Study, a population-based stroke registry. *Cerebrovasc Dis* 2012; 33: 69-75.

13. Melcon CM and Melcon MO. Prevalence of stroke in an Argentine community. *Neuroepidemiology* 2006; 27: 81-88.

14. Geddes JM, Fear J, Tennant A, et al. Prevalence of self reported stroke in a population in northern England. *J Epidemiol Community Health* 1996; 50: 140-143.

15. Proietti M, Mairesse GH, Goethals P, et al. Cerebrovascular disease, associated risk factors and antithrombotic therapy in a population screening cohort: Insights from the Belgian Heart Rhythm Week programme. Eur J Prev Cardiol 2017; 24: 328-334.

16. 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: 759-771.

17. Xu Y, Wang L, He J, et al. Prevalence and control of diabetes in Chinese adults. JAMA 2013; 310: 948-959.

18. Chei CL, Raman P, Ching CK, et al. Prevalence and Risk Factors of Atrial Fibrillation in Chinese Elderly: Results from the Chinese Longitudinal Healthy Longevity Survey. Chin Med J (Engl) 2015; 128: 2426-2432.

19. Andersen KK, Andersen ZJ and Olsen TS. Age- and gender-specific prevalence of

cardiovascular risk factors in 40,102 patients with first-ever ischemic stroke: a Nationwide Danish Study. Stroke 2010; 41: 2768-2774.

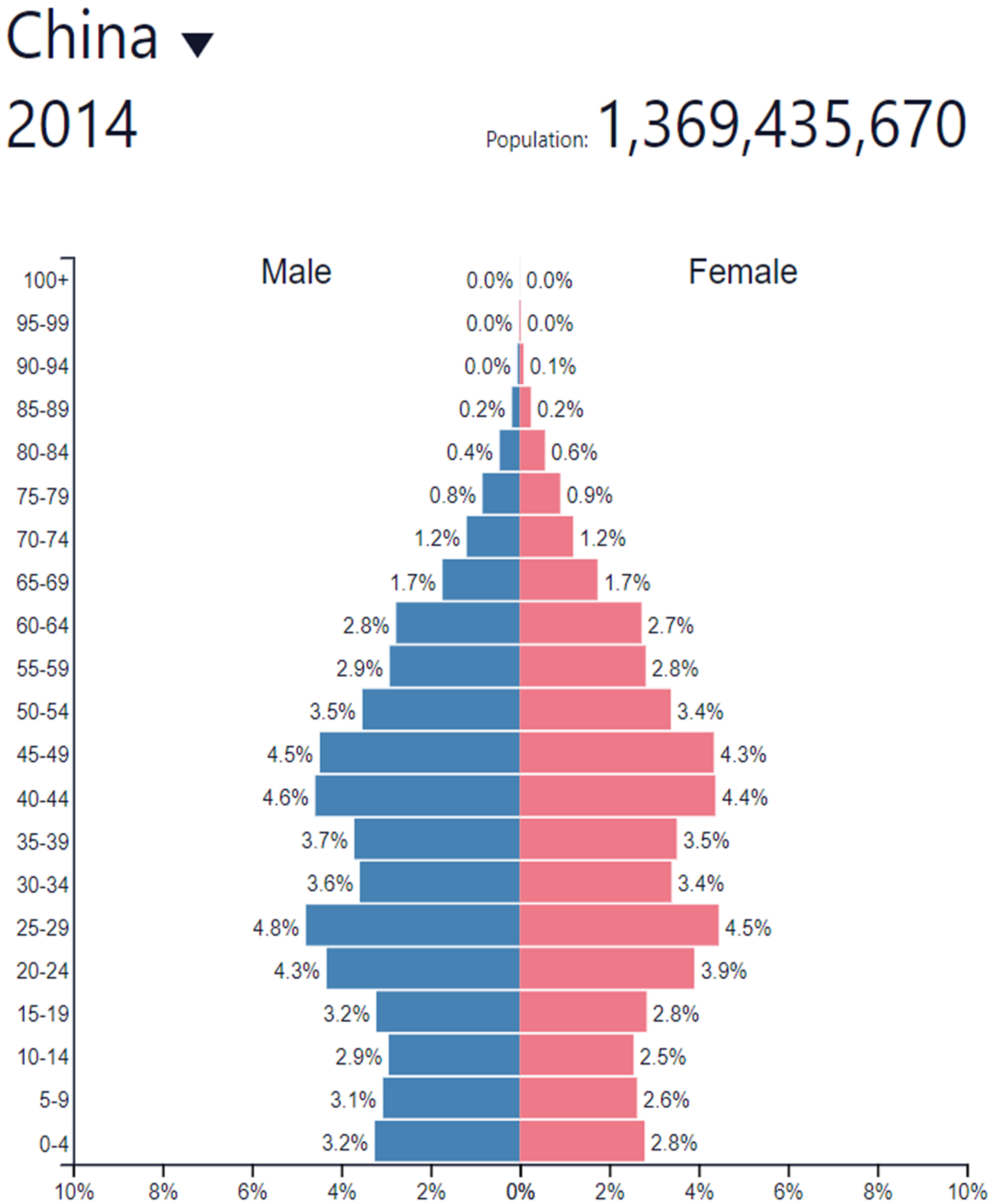
Table 1.Total and age-specific associations between sex and risk factors for stroke among population aged 40 and over using multivariable logistic regression analysis

	40+*	40-49		50-59		60-69		70+	
		OR (95%CI)†	*P value*	OR (95%CI)†	*P value*	OR (95%CI)†	*P value*	OR (95%CI)†	*P value*
Hypertension	0.87 (0.86-0.88)	1.01 (0.97-1.04)	0.9226	0.85 (0.82-0.87)	<0.0001	0.85 (0.83-0.87)	<0.0001	0.87 (0.85-0.89)	<0.0001
DM	0.88 (0.86-0.90)	1.05 (0.99-1.12)	0.1083	0.93 (0.90-0.98)	0.0025	0.84 (0.81-0.87)	<0.0001	0.84 (0.81-0.88)	<0.0001
Hyperlipidemia	1.15 (1.14-1.16)	1.04 (1.02-1.06)	0.0001	1.18 (1.15-1.20)	<0.0001	1.22 (1.19-1.25)	<0.0001	1.17 (1.14-1.20)	<0.0001
AF	0.70 (0.68-0.72)	0.54 (0.49-0.59)	<0.0001	0.62 (0.57-0.66)	<0.0001	0.75 (0.70-0.80)	<0.0001	0.81 (0.76-0.87)	<0.0001
Stroke	1.27 (1.23-1.32)	1.16 (1.00-1.34)	<0.0001	1.31 (1.21-1.42)	<0.0001	1.23 (1.16-1.30)	<0.0001	1.37 (1.28-1.45)	<0.0001
Physical inactivity	0.83 (0.82-0.84)	0.84 (0.82-0.86)	<0.0001	0.82 (0.80-0.84)	<0.0001	0.82 (0.80-0.84)	<0.0001	0.86 (0.83-0.88)	<0.0001
Overweight or obesity	0.88 (0.87-0.89)	1.09 (1.07-1.12)	<0.0001	0.84 (0.82-0.86)	<0.0001	0.78 (0.76-0.80)	<0.0001	0.81 (0.78-0.83)	<0.0001
Smoking	18.95 (18.55-19.37)	23.34 (22.31-24.42)	<0.0001	21.97 (21.11-22.86)	<0.0001	18.59 (17.84-17.38)	<0.0001	11.48 (10.94-12.05)	<0.0001

Note: *Adjusted for age, ethnicity, residential setting, region, and other variables in the model.
†Adjusted for ethnicity, residential setting, region, and other variables in the model. OR and 95% CI was determined using women as the reference for each risk factor. Of note, when stroke was the dependent variable, other risk factors are included in the multivariable regression model as control variables. Similarly, when hypertension was the dependent variable, other risk factors (except for stroke) are included in the multivariable regression model as control variables. For example, when we analyzed the association between sex and DM, in the multivariable model, we included these independent variables: age, sex, ethnicity, residential setting, region, AF, physical inactivity, hypertension, hyperlipidemia, smoking, overweight and obesity. Notably, the stroke did not include in these models. However, when we analyzed the association between sex and stroke, we included these independent variables: age, sex, ethnicity, residential setting, region, hypertension, AF, physical inactivity, DM, hyperlipidemia, smoking, overweight and obesity in the multivariable model.
Abbreviations: AF, atrial fibrillation; CI, confidence interval; DM, diabetes mellitus; OR, odds ratio.

Figure legend

Figure 1 Population pyramid of China 2014.



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