

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Interaction of diabetes and smoking on stroke: A population-based cross-sectional survey in China

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017706
Article Type:	Research
Date Submitted by the Author:	12-May-2017
Complete List of Authors:	Lou, Heqing Dong, Zongmei Zhang, Pan Shao, Xiaoping Li, Ting Zhao, Chunyan Zhang, Xunbao Lou, Peian
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	STROKE MEDICINE, DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY

SCHOLARONE™
Manuscripts

Peer Review Only

1
2
3 **Interaction of diabetes and smoking on stroke: A population-based cross-sectional**
4 **survey in China**

5
6 **Heqing Lou¹, Zongmei Dong², Pan Zhang², Xiaoping Shao,¹ Ting Li², Chunyan Zhao¹,**
7 **Xunbao Zhang^{*1}, Peian Lou^{*1,2}**

8
9
10
11
12 1. The School of Public Health, Xuzhou Medical University, Xuzhou, China

13
14 2. Department of Non-communicable Disease Control, Xuzhou Center for Disease
15 Control and Prevention, The School of Public Health, Xuzhou Medical University,
16 Xuzhou, China

17
18
19
20
21 ***Corresponding authors:**

22 Xunbao Zhang, 209 Tongshan Road, Xuzhou City, Jiangsu Province, China

23 Phone: +86 516-83262018; Fax: +86 516-82702478; E-mail: 437335090@qq.com

24
25
26
27 Peian Lou, 142 West Erhuan Road, Xuzhou City, Jiangsu Province, China

28 Phone: +86 516-85956785; Fax: +86 516-89596797; E-mail: lpa82835415@126.com

29
30
31
32 Manuscript category: Research article

33
34 **Keywords:** type 2 diabetes mellitus; smoking; interaction; stroke

Abstract

Objectives: Diabetes and smoking are known independent risk factors for stroke, but their interaction with relation to stroke is less clear. We aimed to explore the interaction and its influence on stroke in Chinese adults.

Design: Cross-sectional study.

Setting: Community-based investigation in Xuzhou, China.

Participants: A total of 39,887 Chinese adults who fulfilled the inclusion criteria were included.

Methods: Participants were selected using a multi-stage stratified cluster method, and completed self-reported questionnaires on stroke and smoking. Type 2 diabetes mellitus (DM2) was assessed by fasting blood glucose or use of antidiabetic medication. Interaction, relative excess risk owing to interaction (RERI), the attributable proportion (AP), and the synergy index (S) were evaluated using a logistic regression model.

Results: After adjustment for age, gender, marital status, educational level, occupation, physical activity, body mass index, hypertension, stroke family history, alcohol use, and blood lipids, the relationships between DM2 and stroke, and between smoking and stroke, were still significant: odds ratios (OR) were 2.75 (95% confidence interval [CI]: 2.03–3.73) and 1.70 (95% CI: 1.38–2.10), respectively. In subjects with DM2 who smoked, the RERI, AP, and S values (and 95% CIs) were 1.80 (1.24–3.83), 0.52 (0.37–0.73), and 1.50 (1.18–1.84), respectively.

Conclusions: The results suggest there are additive interactions between DM2 and smoking and that these affect stroke in Chinese adults.

Article summary: Strengths and limitations of this study

- This study describes the status of stroke, and how it relates with diabetes and smoking, in people in Xuzhou, China.
- Stroke was found to be related to diabetes and smoking.
- People with diabetes and who smoke were found to have a higher risk of stroke.
- The large sample was a strength of this study.
- The cross-sectional design was a study limitation.

INTRODUCTION

Stroke is an ongoing global health problem. In 2015, there were 6 326.2 thousand deaths from stroke worldwide. It was also the second most common cause of premature mortality and secondary disability.¹ The 2015 Report on Chinese Stroke Prevention indicates stroke as the leading cause of death in China, with incidence increasing by 8.7% every year.² Stroke rates in China are higher than those in Western countries and other Asian countries.^{3,4} Moreover, the number of stroke patients is likely to increase because of lifestyle, demographic changes, and inadequate control of major risk factors for stroke in China.² Therefore, it is important to identify and prevent these risk factors.

The major risk factors for stroke are hypertension, diabetes mellitus, hypercholesterolemia, smoking, physical inactivity, obesity, and a family history of stroke.⁵⁻⁸ More than 90% of the global burden of stroke in 2013 was attributable to the combined effect of all modifiable risk factors.⁸ Although these risk factors play a role in the development of stroke, the disease results from the interaction between genetic and environmental factors. The more risk factors a person has, the more likely they are to incur a stroke.⁷

There is also little understanding of the combined effect of multiple factors on stroke. To our knowledge, while prevalence of smoking and diabetes are very high in China, there are no studies on the interaction of diabetes and smoking on stroke in Chinese adults. Therefore, the primary aim of this cross-sectional study was to examine the interaction of type 2 diabetes mellitus (DM2) and smoking on stroke in Chinese adults. A secondary aim was to assess the associations between DM2 and stroke, and between smoking and stroke.

MATERIALS AND METHODS

Study design and recruitment criteria

This population-based, cross-sectional survey was conducted in Xuzhou City, Jiangsu Province, China, from February to June 2013. The sample was selected with probability proportional to size from all 11 regions in Xuzhou. In the first stage, five subdistricts/townships in urban/rural areas were selected from each region. In the second stage, five communities/villages were selected from each subdistrict/township. In the final stage, one person ≥ 18 years old and who had lived in his or her current residence for ≥ 5 years was selected from each household using a Kish selection table. Participants who met one of the following criteria were excluded: (1) previous diagnosis of neuropathy, psychosis, or unclear speech or (2) member of the floating population or temporary residents. A total of $\geq 13,500$ people were selected, assuming an estimation incidence of stroke of 2.0%,⁹ with 90% power, α level of 0.05, and allowing for a dropout rate of 15%. Trained interviewers interviewed participants face-to-face on the day of the participants' regular medical appointments. All participants underwent 12-h overnight fasting and blood sampling to test basic fasting plasma glucose. After blood sampling, each received a health check and completed a structured questionnaire covering demographic information, medical history, medication history, and smoking, alcohol consumption, and exercise habits.

Key measurements

Stroke was assessed using subjects' self-reported responses, and defined as an acute disturbance of focal areas in the brain lasting for ≥ 24 h and that was thought to be

1
2
3 caused by intracranial hemorrhage or ischemia.¹⁰ The investigators examined the
4
5 medical records of participants reporting a diagnosis of stroke to check that they
6
7 satisfied this definition. The diagnosis was also confirmed by computed tomography
8
9 and magnetic resonance imaging scans. Detailed clinical information about stroke
10
11 was based on the International Classification of Disease, 10th Revision, codes
12
13 I60–I64.
14
15

16
17 DM2 was defined as fasting blood glucose ≥ 7.0 mmol/L, any use of antidiabetic
18
19 medication, or self-reported history of DM2.¹¹ Hypertension was defined as systolic
20
21 blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, any use of
22
23 antihypertensive medication, or self-reported history of hypertension.¹²
24
25

26 **Covariates**

27
28 Age, sex, current employment status, marital status, level of education,
29
30 cigarette smoking, alcohol consumption, physical activity, and family history of
31
32 diseases including DM2, hypertension, and stroke were assessed using a
33
34 standardized questionnaire. Employment status was categorized as manual,
35
36 non-manual, unemployed, or retired. Education was categorized as below high
37
38 school, high school, or above high school. Lifestyle variables included cigarette
39
40 smoking, alcohol consumption, and physical activity level. Cigarette smoking was
41
42 defined as having smoked at least 100 cigarettes in one's lifetime. Information was
43
44 obtained on the amount and type of alcohol consumed during the previous year, and
45
46 alcohol drinking was defined as consumption of ≥ 30 g of alcohol per week for ≥ 1
47
48 year. Regular leisure-time physical activity was defined as participation in moderate
49
50 or vigorous activity for ≤ 30 min per day, ≥ 3 days a week. Each participant's height (to
51
52 the nearest 0.1 cm) and weight (to the nearest 0.1 kg) in light indoor clothing were
53
54
55
56
57
58
59
60

1
2
3 measured. Body mass index (BMI; in kg/m²) was calculated; categorized as
4
5 underweight (<18.5 kg/m²), normal weight (18.5–24.0 kg/m²), and overweight/obese
6
7 (>24.0 kg/m²).¹³ Dyslipidemia was defined as use of any lipid-lowering medication or
8
9 self-reported history of the condition.
10

11 **Statistical analysis**

12
13
14 Participants were divided into four groups in accordance with their smoking
15
16 status and DM2: non-smokers with no DM2, smokers with no DM2, non-smokers
17
18 with DM2, and smokers with DM2. Statistical analysis was performed using IBM SPSS
19
20 for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA). The general characteristics of
21
22 continuous variables were compared across the four subgroups using analysis of
23
24 variance. The categorical variables were expressed as a percentage and the groups
25
26 were compared using a chi-squared test. Logistic regression analysis was performed
27
28 to estimate the probability of having a stroke and 95% confidence interval (CI) for
29
30 each risk factor category stratified by DM2 and smoking, adjusting for age, sex,
31
32 occupation, education, marital status, BMI, physical activity, drinking status,
33
34 hypertension status, and family history of disease including DM2, hypertension, and
35
36 stroke.
37
38
39
40

41
42 Biological interactions should be based on an additive scale rather than a
43
44 multiplication scale.^{14,15} Therefore, we used three measures to estimate biological
45
46 interactions between DM2 and smoking: relative excess risk owing to interaction
47
48 (RERI), attributable proportion (AP) owing to interaction, and synergy index (S). RERI
49
50 is the excess risk attributed to interaction relative to the risk without exposure to
51
52 diabetes and smoking. AP refers to the attributable proportion of disease caused by
53
54 interaction in subjects with exposure to both variables. S is the excess risk from
55
56
57
58
59
60

1
2
3 exposure to both variables when there is a biological interaction relative to the risk
4
5 from exposure to both variables without interaction. In the absence of additive
6
7 interactions, RERI and AP are equal to 0.^{14,16} In the current study, RERI >0, AP >0, and
8
9 S >0 indicate statistical significance. A *p*-value <0.05 (two-tailed) was considered
10
11 statistically significant.
12
13
14
15

16 17 **Ethics approval and consent to participate**

18
19 The study protocol was approved by the Xuzhou Center for Disease Control and
20
21 Prevention. All participants provided written informed consent.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

RESULTS

General characteristics of participants

Of the 41,658 individuals initially sampled, 1253 did not respond to the smoking question or complete the blood glucose tests, and 518 did not meet our study criteria. A final total of 39,887 adults (19,178 men and 20,709 women) with complete data were included in the analysis (response rate of 95.7%). Table 1 shows the characteristics of the study population. The proportion of participants with DM2 was 7.00% (2783/39,887), of stroke subjects with DM2 was 16.67%, and of non-stroke subjects with DM2 was only 6.75%; there was a significant statistical difference between the two groups ($\chi^2 = 135.92$, $p < 0.001$). The proportion of smokers was 20.26% (8082/39,887), the proportion of stroke participants who smoked was 32.24%, and the proportion of non-stroke participants who smoked was 19.98%; there was a significant statistical difference in smoking between stroke and non-stroke patients ($\chi^2 = 83.49$, $p < 0.001$).

Association of diabetes and smoking with stroke

The 5.50% incidence of stroke in subjects with DM2 was higher than the 2.06% incidence in subjects with no DM2 ($\chi^2 = 139.11$, $p < 0.001$). Individuals who smoked had a higher stroke incidence compared with non-smokers (3.36% vs. 1.96%; $\chi^2 = 83.49$, $p < 0.001$; see Table 2). Individuals with DM2 had a significantly increased risk of stroke compared with those with no DM2 (OR: 2.65, 95% CI: 1.70–4.41, $p < 0.001$) after adjusting for confounders (see Table 3). Smokers had a significantly increased risk of stroke compared with non-smokers (OR: 1.83, 95% CI: 1.59–2.14, $p < 0.001$) after adjusting for confounders (see Table 3).

Interaction between diabetes and smoking with relation to stroke

Individuals who only had DM2 or only smoked had a significantly increased risk of stroke compared with those who did not have DM2 and did not smoke (OR: 2.00, 95% CI: 1.56–2.56; OR: 1.65, 95% CI: 1.36–2.00; respectively; all $p < 0.001$) after adjusting for confounders. Table 3 shows the results from the multiple logistic regression models. The incidence of stroke was greatest in those who had DM2 and smoked (OR: 3.45, 95% CI: 2.30–5.16, $p < 0.001$), after adjusting for confounders.

Sensitivity analysis

There was a strong additive interaction between DM2 and smoking (RERI: 1.80, 95% CI: 1.24–2.14; AP: 0.52, 95% CI: 0.37–0.73; and S: 1.50, 95% CI: 1.18–1.84, respectively.); 52% of occurring stroke was attributed to the interaction between DM2 and smoking (Table 4).

DISCUSSION

There were two main findings in this study. First, there was an interaction of DM2 and smoking with relation to the incidence of stroke. Second, DM2 and smoking were found to be significantly associated with increased risk of stroke in Chinese adults, independent of potential confounders such as age, sex, occupation, education, marital status, BMI, physical activity, drinking status, hypertension status, and family history of diseases including diabetes, hypertension, or stroke.

The proportion of participants with DM2 in this study was 19.67%, which is lower than that reported in the China National Stroke Registry Study (27.0%),¹⁷ lower than that reported in a comparison of risk factors for ischemic stroke in Chinese versus Caucasian individuals (25.0%),¹⁸ and higher than that reported in a study of the Chinese National Health Insurance program (3.8%)¹⁹ and a review of stroke in China (4–15%).²⁰ Our results are also inconsistent with figures for diabetes in stroke patients reported for other countries.^{21,22} This discrepancy may be because of differences in study design, sampling size, region, diabetes diagnosis, and the clinical features of stroke, but could also be a result of ethnic group differences, as many studies have shown that different ethnic groups have different stroke incidence rates.²³

Numerous epidemiologic studies, including cross-sectional studies and prospective cohort studies, have demonstrated associations between diabetes and stroke.^{22,24-27} A population-based study of 173,979 discharged patients admitted with hemorrhagic stroke was conducted in Spain from 2003 to 2012. The authors reported a positive association between diabetes and stroke (incidence rate ratio: 1.38, 95% CI: 1.35–1.40 for men; incidence rate ratio: 1.31, 95% CI: 1.29–1.34 for women).²²

1
2
3 Folsom et al. reported that the relative risk (RR) of ischemic stroke was 2.22 (95% CI:
4 1.5–3.2) for individuals with diabetes after adjustment for other stroke risk factors in
5 a 6–8-year follow-up.²⁴ Iso et al.²⁵ reported that the association between
6 non-embolic ischemic stroke and diabetes was particularly strong among
7 non-hypertensive subjects with higher subscapular skinfold thickness values: the
8 multivariate RR was 4.9 (95% CI: 2.5–9.5) in a 17-year prospective cohort study of
9 10,582 Japanese individuals (4287 men and 6295 women) aged 40–69 years. A
10 systematic review and meta-analysis of 64 cohort studies with 775,385 individuals
11 showed that diabetes is consistently associated with increased risk of stroke; the
12 pooled maximum-adjusted RR of stroke associated with diabetes was 2.28 (95% CI:
13 1.93–2.69) for women and 1.83 (1.60–2.08) for men.²⁶ Liao et al. have also reported
14 that diabetic patients have an increased risk of stroke (adjusted hazard ratio: 1.75,
15 95% CI: 1.64–1.86) compared with those without diabetes; associations between
16 diabetes and stroke risk were significant for both sexes and all age groups.²⁷ Our
17 findings also demonstrate an association between diabetes and stroke.

18
19 Robson et al.²⁸ confirmed that poor blood sugar control increases the risk of
20 stroke. One prospective cohort study of 467,508 men and women aged 30–79 years
21 with no history of diabetes or stroke showed that each 1-mmol/L (18-mg/dL) higher
22 than usual increase of random plasma glucose level above 5.9 mmol/L (106 mg/dL)
23 was associated with ischemic stroke (adjusted hazard ratio: 1.08, 95% CI:
24 1.07–1.09).²⁹ Moreover, a study of 4669 patients who had had a minor stroke
25 revealed that stroke patients with diabetes experienced stroke recurrence and
26 disability during a 3-month follow-up.³⁰ Therefore, effective glycemic control not
27 only reduces the incidence of stroke but also can reduce stroke recurrence and

1
2
3 associated disability.

4
5 Stroke patients tend to contain a higher proportion of smokers than non-stroke
6
7 patients. Wang et al. reported that 48% of stroke patients smoked.³¹ Tsai et al.¹⁸
8
9 reported a figure of 38% and we found that 32.24% of stroke patients smoked.
10
11 Although these proportions differ, they are all quite high. This discrepancy may
12
13 reflect a bias in the reporting of smoking status among study participants.
14
15

16
17 Many studies have shown that smoking is a strong risk factor for development
18
19 of stroke.³²⁻³⁴ The British Regional Heart Study, which included 7735 men aged 40–59
20
21 years, showed that after full adjustment for other risk factors, current smokers had a
22
23 nearly fourfold RR of stroke compared with never-smokers (RR: 3.7, 95% CI: 2.0–6.9).
24
25 Ex-cigarette smokers showed lower risk than current smokers but showed excess risk
26
27 compared with never-smokers (RR: 1.7, 95% CI: 0.9–3.3, $p = 0.11$).³³ During a mean
28
29 follow-up of 8.5 years, the risk for all strokes significantly increased (RR: 0.9–3.3, 95%
30
31 CI: 1.4–24) and increased for ischemic strokes (RR: 4.8, 95% CI: 1.2–20) among
32
33 cigarette-smoking women with a cigarette-smoking spouse compared with those
34
35 with a non-smoking spouse after adjusting for other cardiovascular risk factors.³⁴
36
37 However, a systematic review and meta-analysis of 81 cohorts in Asia, including
38
39 3,980,359 individuals and 42,401 strokes, showed smoking does not contribute to
40
41 the risk of stroke.³⁵ The proportion of Chinese stroke patients who smoke is higher
42
43 than that of Caucasians.¹⁸ One systematic review and meta-analysis of 15 cohort
44
45 studies and 178 case-control studies found smoking was an independent risk factor
46
47 for stroke (pooled RRs: 1.27, 95% CI: 1.21–1.35) in the Chinese population.⁷
48
49 Individuals who smoke more are more likely to have strokes.^{36,37} A meta-analysis
50
51 that included 16,886 men and 18,539 women without known diabetes revealed
52
53
54
55
56
57
58
59
60

1
2
3 hemoglobin A1c was 0.10% (95% CI: 0.08–0.12, 1.1 mmol/mol [0.9–1.3]) higher in
4
5 current smokers and 0.03% (95% CI: 0.01–0.05, 0.3 mmol/mol [0.1–0.5]) higher in
6
7 ex-smokers than in never-smokers.³⁸ Therefore, our findings support previous
8
9 evidence smoking is associated with stroke in Chinese populations.⁴
10

11
12 The pathophysiological mechanisms of hyperglycemia induce oxidative stress;
13
14 promote formation of advanced glycosylation end products;^{39,40} increase
15
16 blood–brain barrier permeability and inflammatory responses;⁴¹ lead to
17
18 accumulation of reactive oxygen species/reactive nitrogen, inflammation, and
19
20 mitochondrial dysfunction;⁴² lead to cellular dysfunctions; damage vascular tissue;
21
22 inhibit endogenous vascular protective factors; alter vascular homeostasis;⁴³ raise
23
24 levels of reactive oxygen species and advanced glycation end products; decrease
25
26 levels of mitochondrial superoxide dismutase;⁴⁰ and correlate with endothelial cell
27
28 dysfunction and nitric oxide production.⁴⁴ All these actions contribute to accelerating
29
30 the atherosclerotic process. Therefore, subjects with diabetes are more prone to
31
32 develop stroke.
33
34
35

36
37 Cigarette smoking is associated with increased reactive oxygen species, oxidative
38
39 stress, blood–brain barrier permeability, sympathetic activation and nitric oxide
40
41 production, reduced cerebral blood flow and serum superoxide dismutase levels,
42
43 attenuation of the vasodilation of cerebral arterioles, and induction of
44
45 atherosclerosis and thrombosis.⁴⁵⁻⁴⁸ Moreover, cigarette smoke elevates serum
46
47 levels of advanced glycation end products and reduces soluble receptors for
48
49 advanced glycation end products, resulting in the development of atherosclerosis
50
51 and related stroke.⁴⁹⁻⁵¹ Smoking is therefore correlated with increased risk of stroke.
52
53
54

55
56 Collectively, diabetes and smoking induce oxidative stress and nitric oxide
57

1
2
3 production; increase reactive oxygen species, blood–brain barrier permeability, and
4
5 the level of advanced glycation end products; and reduce cerebral blood flow and
6
7 serum superoxide dismutase. Therefore, diabetic patients who smoke have a greater
8
9 risk of stroke.
10

11
12 The strengths of the current study are that we used a community-based
13
14 multistage sampling design, large sample size, and randomly selected participants.
15
16 However, the study has several limitations. First, because of the cross-sectional
17
18 design, we could not determine a causal relationship between DM2, smoking, and
19
20 stroke. Second, we were unable to control for some important and well-known risk
21
22 factors of stroke, such as heart rate⁵² and cardiac causes.⁶ Third, we did not measure
23
24 fresh fruit consumption,⁵³ which is causally related to stroke.
25
26

27 28 **Conclusion**

29
30 The results of this cross-sectional study indicate subjects with diabetes who
31
32 smoke are 3.5 times more likely to develop stroke than non-diabetics who do not
33
34 smoke. Diabetes and smoking had a combined positive influence on stroke. Our
35
36 results have important public health implications. Among Chinese adults, the current
37
38 rate of smoking is as high as 28.3%⁵⁴ and DM2 prevalence is 11.6%.⁵⁵ Therefore, it is
39
40 important for stroke prevention to reduce smoking and improve glycemic control in
41
42 diabetic patients in China.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

COMPETING INTERESTS

The authors declare that they have no competing interests.

Acknowledgments

We thank all the participants involved in the survey. We also thank the Regional Centers for Disease Control and Prevention as well as clinics in Xuzhou for their collaboration.

Funding

This research was funded by the Preventive Medicine research projects of Jiangsu Province Health Department in 2015 (Y2015010) and the Science and Technology projects of Xuzhou City in 2015 (KC15SM046). The researchers were independent from the funders. The study funders had no influence on the study design, data collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Duality of interest

The authors declare there is no duality of interest associated with this manuscript.

Authors' contributions

HL wrote/edited the manuscript and created tables. ZD, PZ, XH, PC, TL, CQ, CH, XH, and PL contributed to the discussion and reviewed/edited the manuscript. XH conceptualized the study. PL is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. All authors read and approved the final manuscript.

Availability of data and materials

All data relevant to the given manuscript have been stored in a separate file that can

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

be made freely available to external investigators upon request.

For peer review only

References

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1459-1544.
2. Stroke Control Project Committee of National Health and Family Planning Commission of the People's Republic of China. Report on the Chinese Stroke Prevention (2015) 1st ed. Beijing: China Pecking Union Medical College Press, 2015.
3. Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, et al. Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013;381(9882):1987-2015.
4. Hata J, Kiyohara Y. Epidemiology of Stroke and Coronary Artery Disease in Asia. *Circ J*. 2013; 77(8):1923-32.
5. Mi T, Sun S, Du Y, Guo S, Cong L, Cao M, et al. Differences in the distribution of risk factors for stroke among the high-risk population in urban and rural areas of Eastern China. *Brain Behav*. 2016;6(5):e00461.
6. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*. 2010;376(9735):112-23.
7. Wang J, Wen X, Li W, Li X, Wang Y, Lu W. Risk Factors for Stroke in the Chinese Population: A Systematic Review and Meta-Analysis. *J Stroke Cerebrovasc Dis*. 2016; pii: S1052-3057(16)30599-7.
8. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol*. 2016;15(9):913-24.
9. Zhang P, Jiao S, Zhou Y, Li G, Shi Y, Li H, et al. Studies on prevalence and control of several common chronic diseases among Beijing adults in 2005. *Chin J Epidemiol*, 2007;28(7):625-630.
10. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association.

- 1
2
3 Stroke 2013; 44:2064-89.
- 4 11. Chinese Diabetes Society. Chinese guidelines for the prevention and treatment of
5 type 2 diabetes mellitus (2010 Edition). Chinese Journal of Diabetes, 2012;20(1):
6 1-36.
- 7
8
9 12. China hypertension prevention guidelines revision committee. Guidelines for
10 prevention and treatment of hypertension in China[2010 Edition]. Chinese Journal
11 of hypertension, 2011;19(8):701-743.
- 12
13
14 13. Zhou BF. Predictive values of body mass index and waist circumference for risk
15 factors of certain related diseases in Chinese adults--study on optimal cut-off
16 points of body mass index and waist circumference in Chinese adults. Biomed
17 Environ Sci 2002;15, 83-96.
- 18
19
20 14. Hosmer DW, Lemeshow S . Confidence interval estimation of interaction.
21 Epidemiology 1992; 3(5):452-456.
- 22
23
24 15. Knol MJ, van der Tweel I, Grobbee DE, Numans ME, Geerlings MI. Estimating
25 interaction on an additive scale between continuous determinants in a logistic
26 regression model. Int J Epidemiol. 2007;36(5):1111-8.
- 27
28
29 16. Knol MJ, VanderWeele TJ, Groenwold RH, Klungel OH, Rovers MM, Grobbee
30 DE. Estimating measures of interaction on an additive scale for preventive
31 exposures. Eur J Epidemiol 2011; 26(6):433–438.
- 32
33
34 17. Pan Y, Wang Y, Li H, Gaisano HY, Wang Y, He Y. Association of Diabetes and
35 Prognosis of Minor Stroke and Its Subtypes: A Prospective Observational Study.
36 PLoS One. 2016;11(4):e0153178.
- 37
38
39 18. Tsai CF, Anderson N, Thomas B, Sudlow CL. Risk factors for ischemic stroke
40 and its subtypes in Chinese vs. Caucasians: Systematic review and meta-analysis.
41 Int J Stroke. 2015;10(4):485-93.
- 42
43
44 19. Guo Y, Wang H, Tao T, Tian Y, Wang Y, Chen Y, et al. Determinants and Time
45 Trends for Ischaemic and Haemorrhagic Stroke in a Large Chinese Population.
46 PLoS ONE 2016; 11(9):e0163171.
- 47
48 20. Shi FL, Hart RG, Sherman DG, Tegeler CH. Stroke in the People's Republic of
49 China. Stroke. 1989;20(11):1581-5.
- 50
51 21. Chang T, Gajasinghe S, Arambepola C. Prevalence of Stroke and Its Risk Factors
52 in Urban Sri Lanka Population-Based Study. Stroke. 2015;46(10):2965-8.
- 53
54
55 22. Muñoz-Rivas N, Méndez-Bailón M, Hernández-Barrera V, de Miguel-Yanes JM,
- 56
57
58
59
60

- 1
2
3 Jimenez-Garcia R, Esteban-Hernández J, et al. Type 2 Diabetes and
4 Hemorrhagic Stroke: A Population-Based Study in Spain from 2003 to 2012. *J*
5 *Stroke Cerebrovasc Dis.* 2016;25(6):1431-43.
6
7
8 23. Tsai CF, Thomas B, Sudlow CL. Epidemiology of stroke and its subtypes in
9 Chinese vs white populations. *Neurology.* 2013;81(3):264-72.
10
11 24. Folsom AR, Rasmussen ML, Chambless LE, Howard G, Cooper LS, Schmidt MI,
12 et al. Prospective associations of fasting insulin, body fat distribution, and diabetes
13 with risk of ischemic stroke. The Atherosclerosis Risk in Communities (ARIC)
14 Study Investigators. *Diabetes Care.* 1999;22(7):1077-83
15
16 25. Iso H, Imano H, Kitamura A, Sato S, Naito Y, Tanigawa T, et al. Type 2 diabetes
17 and risk of non-embolic ischaemic stroke in Japanese men and women.
18 *Diabetologia.* 2004;47(12):2137-44.
19
20 26. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in
21 women compared with men: a systematic review and meta-analysis of 64 cohorts,
22 including 775 385 individuals and 12 539 strokes. *Lancet.*
23 2014;383(9933):1973-80.
24
25 27. Liao CC, Shih CC, Yeh CC, Chang YC, Hu CJ, Lin JG, et al. Impact of Diabetes
26 on Stroke Risk and Outcomes: Two Nationwide Retrospective Cohort Studies.
27 *Medicine (Baltimore).* 2015;94(52):e2282.
28
29 28. Robson R, Lacey AS, Luzio SD, Van Woerden H, Heaven ML, Wani M, et al.
30 HbA1c measurement and relationship to incident stroke. *Diab Med.*
31 2016;33:459–62.
32
33 29. Bragg F, Li L, Bennett D, Guo Y, Lewington S, Bian Z, et al. Association of
34 Random Plasma Glucose Levels With the Risk for Cardiovascular Disease Among
35 Chinese Adults Without Known Diabetes. *JAMA Cardiol.* 2016;1(7):813-823.
36
37 30. Wu L, Wang A, Wang X, Zhao X, Wang C, Liu L, et al. Factors for short-term
38 outcomes in patients with a minor stroke: results from China National Stroke
39 Registry. *BMC Neurol.* 2015;15:253.
40
41 31. Wang W, Jiang B, Sun H, Ru X, Sun D, Wang L, et al. Prevalence, Incidence and
42 Mortality of Stroke in China: Results from a Nationwide Population-Based Survey
43 of 480,687 Adults. *Circulation.* 2017;135(8):759-771.
44
45 32. Wolf PA, D'Agostino RB, Kannel WB, Bonita R, Belanger AJ. Cigarette smoking
46 as risk factor for stroke the framingham study. *JAMA.* 1988;259(7):1025-9.
47
48 33. Wannamethee SG, Shaper AG, Whincup PH, Walker M. Smoking cessation and
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 the risk of stroke in middle-aged men. *J AMA*. 1995;274(2):155-60.
- 4 34. Qureshi AI, Suri MF, Kirmani JF, Divani AA. Cigarette smoking among spouses:
5 another risk factor for stroke in women. *Stroke*, 2005;36(9):e74-6.
- 6
7 35. Peters SA, Huxley RR, Woodward M. Smoking as a Risk Factor for Stroke in
8 Women Compared With Men A Systematic Review and Meta-analysis of 81
9 Cohorts, Including 3 980 359 Individuals and 42 401 Strokes. *Stroke*.
10 2013;44(10):2821-8.
- 11
12 36. Shah RS, Cole JW. Smoking and stroke: the more you smoke the more you stroke.
13 *Expert Rev Cardiovasc Ther*. 2010;8:917–932. doi: 10.1586/erc.10.56.
- 14
15 37. Chang S, Kim H, Kim V, Lee K, Jeong H, Lee JH, et al. Association Between
16 Smoking and Physician-Diagnosed Stroke and Myocardial Infarction in Male
17 Adults in Korea. *Int J Environ Res Public Health*. 2016;13(2):158.
- 18
19 38. Soulimane S, Simon D, Herman WH, Lange C, Lee CM, Colagiuri S, et al.
20 HbA1c, fasting and 2 h plasma glucose in current, ex- and never-smokers: a
21 meta-analysis. *Diabetologia*. 2014;57(1):30-9.
- 22
23 39. Aronson D, Rayfield EJ. How hyperglycemia promotes atherosclerosis: molecular
24 mechanisms. *Cardiovasc Diabetol*. 2002;1:1.
- 25
26 40. Rehni AK, Nautiyal N, Perez-Pinzon MA, Dave KR. Hyperglycemia /
27 hypoglycemia-induced mitochondrial dysfunction and cerebral ischemic damage in
28 diabetics. *Metab Brain Dis*. 2015;30(2):437-47.
- 29
30 41. Shukla V, Shakya AK, Perez-Pinzon MA, Dave KR. Cerebral ischemic damage in
31 diabetes: an inflammatory perspective. *J Neuroinflammation*. 2017;14(1):21.
- 32
33 42. Zhang Z, Yan J, Shi H. Hyperglycemia as a Risk Factor of Ischemic Stroke. *J*
34 *Drug Metab Toxicol*. 2013;4(4). pii: 153.
- 35
36 43. Kitada M, Zhang Z, Mima A, King GL. Molecular mechanisms of diabetic
37 vascular complications. *J Diabetes Investig*. 2010;1(3):77-89.
- 38
39 44. Kemeny SF, Figueroa DS, Clyne AM. Hypo- and Hyperglycemia Impair
40 Endothelial Cell Actin Alignment and Nitric Oxide Synthase Activation in
41 Response to Shear Stress. *PLoS ONE*, 2013;8(6): e66176.
- 42
43 45. Iida M, Iida H, Dohi S, Takenaka M, Fujiwara H. Mechanisms underlying
44 cerebrovascular effects of cigarette smoking in rats in vivo. *Stroke*,
45 1998;29(8):1656-65.
- 46
47 46. Barua RS, Ambrose JA, Srivastava S, DeVoe MC, Eales-Reynolds LJ. Reactive
48 oxygen species are involved in smoking-induced dysfunction of nitric oxide
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 biosynthesis and upregulation of endothelial nitric oxide synthase: an in vitro
4 demonstration in human coronary artery endothelial cells. *Circulation*
5 2003;107(18):2342–2347.
6
7
8 47. Benowitz NL. Cigarette smoking and cardiovascular disease: pathophysiology and
9 implications for treatment. *Prog Cardiovasc Dis.*, 2003;46(1):91–111.
10
11 48. Chen S, Wu P, Zhou L, Shen Y, Li Y, Song H. Relationship between increase of
12 serum homocysteine caused by smoking and oxidative damage in elderly patients
13 with cardiovascular disease. *Int J Clin Exp Med.* 2015;8(3):4446-54.
14
15 49. Prasad K, Dhar I, Caspar-Bell G. Role of Advanced Glycation End Products and
16 Its Receptors in the Pathogenesis of Cigarette Smoke-Induced Cardiovascular
17 Disease. *Int J Angiol.* 2015;24(2):75-80.
18
19 50. Ottum MS, Mistry AM. Advanced glycation end products: modifiable
20 environmental factors profoundly mediate insulin resistance. *J Clin Biochem Nutr.*
21 2015;57(1):1-12.
22
23 51. Biswas SK, Mudi SR, Mollah FH, Bierhaus A, Arslan MI. Serum soluble receptor
24 for advanced glycation end products (sRAGE) is independently associated with
25 cigarette smoking in non-diabetic healthy subjects. *Vasc Dis Res.* 2013;
26 10(4):380-2.
27
28 52. Zhong C, Zhong X, Xu T, Peng H, Li H, Zhang M, et al. Combined effects of
29 hypertension and heart rate on the risk of stroke and coronary heart disease: a
30 population-based prospective cohort study among Inner Mongolians in China.
31 *Hypertens Res.* 2015;38(12):883-8.
32
33 53. Du H, Li L, Bennett D, Guo Y, Key TJ, Bian Z, et al. Fresh Fruit Consumption
34 and Major Cardiovascular Disease in China. *N Engl J Med.* 2016; 374(14):
35 1332–1343.
36
37 54. Ding L, Xu Y, Wang LM, Jiang Y, Zhang M, Li YC, et al. Smoking and Its
38 Relation to Metabolic Status among Chinese Adults: Analysis of a Nationwide
39 Survey. *Biomed Environ Sci.* 2016;29(9):619-627.
40
41 55. Xu Y, Wang L, He J, Bi Y, Li M, Wang T, et al. Prevalence and Control of
42 Diabetes in Chinese Adults. *JAMA.* 2013;310(9):948-59.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1 General characteristics of diabetes and smoking in the study population (n = 39,887)

<i>Reported variable</i>	Non-smoking /non-DM2	Smoking /non-DM2	Non-smoking /DM2	Smoking /DM2	P
Total	29568	7536	2237	546	
Gender(man)	11087	6890	726	475	<0.01
Age(years)	46.93±17.13	49.64±15.97	61.52±12.71	59.03±11.95	<0.01
Marred (living with partners)	24290	6622	1844	506	<0.01
Below high school	21906	5757	1832	409	
high school	4684	1235	263	94	<0.01
Above high school	2978	544	142	43	
Manual	20702	5538	1382	326	
Non-manual	3664	909	145	59	<0.01
Retired	2277	589	563	124	
Unemployed	2925	500	147	37	
alcohol use	1832	4061	156	284	<0.01
Regular exercise	5943	1519	580	172	
Family history of					
Hypertension	2007	740	218	56	<0.01
Family history of DM2	350	128	120	26	<0.01
Family history of stroke	574	209	32	13	
Hypertension	6339	2004	759	255	
BMI(≥24kg/m ²)	12532	3536	1382	335	<0.01
Dyslipidemia	3602	1134	456	137	<0.01

Table 2 Associations between smoking, diabetes, and stroke

Variables		Stroke	Non-stroke	OR (95%CI)	P
Smoking	No	622	31183	1.83 (1.59-2.14)	<0.01
	Yes	296	7786		
DM2	No	765	36339	2.65 (1.70-4.41)	<0.01
	Yes	153	2630		

Adjusted for age, sex, education, marriage status, employment, family history of diabetes, family history of hypertension, family history of stroke, alcohol consumption, physical activity, hypertension, diabetes or smoking, body mass index, and lipids.

Table 3 Odds ratios (ORs) for the association between smoking and stroke by diabetes among participants

Smoking	Diabetes	No stroke	Stroke	OR (95%CI)	P
No	No	29056	512	1	
	Yes	2127	110	2.00 (1.56-2.56)	<0.01
Yes	No	7283	253	1.65 (1.36-2.00)	<0.01
	Yes	503	43	3.45 (2.30-5.16)	<0.01

Adjusted for age, sex, education, marriage status, employment, family history of diabetes, family history of hypertension, family history of stroke, alcohol consumption, physical activity, hypertension, body mass index, and lipids.

Table 4 Measures for estimating biological interaction between smoking and diabetes for prevalence of stroke in participants

Measures of biological interaction	Estimate (95% CI)
RERI	1.80(1.24—3.84)
AP	0.52(0.37—0.73)
S	1.50(1.18—1.84)

Reference group is no smoking with non-diabetes.
Adjusted for age, sex, education, marriage status, employment, family history of diabetes, family history of hypertension, family history of stroke, alcohol consumption, physical activity, hypertension, body mass index, and lipids.

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	6-7
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Data sources/measurement	8*	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Bias	9	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Study size	10	Describe any efforts to address potential sources of bias	5
Quantitative variables	11	Explain how the study size was arrived at	7-8
		Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
		(a) Describe all statistical methods, including those used to control for confounding	
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
Statistical methods	12	(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	7-8
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Interaction of diabetes and smoking on stroke: A population-based cross-sectional survey in China

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017706.R1
Article Type:	Research
Date Submitted by the Author:	03-Nov-2017
Complete List of Authors:	Lou, Heqing; The School of Public Health, Xuzhou Medical University, Xuzhou, China Dong, Zongmei; The School of Public Health, Xuzhou Medical University, Xuzhou, China; Xuzhou Center for Disease Control and Prevention, Xuzhou, China Zhang, Pan; Xuzhou Center for Disease Control and Prevention, Xuzhou, China, Department of Non-communicable Disease Control Shao, Xiaoping ; The School of Public Health, Xuzhou Medical University, Xuzhou, China Li, Ting; Xuzhou Center for Disease Control and Prevention, Xuzhou, China Zhao, Chunyan; The School of Public Health, Xuzhou Medical University, Xuzhou, China Zhang, Xunbao; The School of Public Health, Xuzhou Medical University, Xuzhou, China Lou, Peian; Xuzhou Center for Disease Control and Prevention, Xuzhou, China, Department of Non-communicable Disease Control; The School of Public Health, Xuzhou Medical University, Xuzhou, China
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	STROKE MEDICINE, DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY

SCHOLARONE™
Manuscripts

1
2
3 **Interaction of diabetes and smoking on stroke: A population-based cross-sectional**
4 **survey in China**
5

6 **Heqing Lou¹, Zongmei Dong^{1,2}, Pan Zhang², Xiaoping Shao,¹ Ting Li², Chunyan Zhao¹,**
7 **Xunbao Zhang^{*1}, Peian Lou^{*1,2}**
8
9

10
11
12 1. The School of Public Health, Xuzhou Medical University, Xuzhou, China

13
14 2. Department of Non-communicable Disease Control, Xuzhou Center for Disease
15 Control and Prevention, Xuzhou, China
16

17
18
19 ***Corresponding authors:**

20 Xunbao Zhang, 209 Tongshan Road, Xuzhou City, Jiangsu Province, China

21 Phone: +86 516-83262018; Fax: +86 516-82702478; E-mail: 437335090@qq.com
22
23

24
25
26 Peian Lou, 142 West Erhuan Road, Xuzhou City, Jiangsu Province, China

27 Phone: +86 516-85956785; Fax: +86 516-89596797; E-mail: lpa82835415@126.com
28
29

30
31 Manuscript category: Research article

32
33 **Keywords:** type 2 diabetes mellitus; smoking; interaction; stroke
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abstract

Objectives: Diabetes and smoking are known independent risk factors for stroke, but their interaction with relation to stroke is less clear. We aimed to explore the interaction and its influence on stroke in Chinese adults.

Design: Cross-sectional study.

Setting: Community-based investigation in Xuzhou, China.

Participants: A total of 39,887 Chinese adults who fulfilled the inclusion criteria were included.

Methods: Participants were selected using a multi-stage stratified cluster method, and completed self-reported questionnaires on stroke and smoking. Type 2 diabetes mellitus (DM2) was assessed by fasting blood glucose or use of antidiabetic medication. Interaction, relative excess risk owing to interaction (RERI), the attributable proportion (AP), and the synergy index (S) were evaluated using a logistic regression model.

Results: After adjustment for age, gender, marital status, educational level, occupation, physical activity, body mass index, hypertension, stroke family history, alcohol use, and blood lipids, the relationships between DM2 and stroke, and between smoking and stroke, were still significant: odds ratios (OR) were 2.75 (95% confidence interval [CI]: 2.03–3.73) and 1.70 (95% CI: 1.38–2.10), respectively. In subjects with DM2 who smoked, the RERI, AP, and S values (and 95% CIs) were 1.80 (1.24–3.83), 0.52 (0.37–0.73), and 1.50 (1.18–1.84), respectively.

Conclusions: The results suggest there are additive interactions between DM2 and smoking and that these affect stroke in Chinese adults.

Article summary: Strengths and limitations of this study

- The strengths of this study were that participants of a large sample were randomly selected from the general population of Xuzhou, and many confounding risk factors were adjusted for.
- Owing to the cross-sectional design, we could not determine a causal combined relationship between diabetes, smoking and stroke.
- We were not able to control for some important and well-known risk factors of diabetes—for example, heart rate and cardiac causes..
- We did not measure fresh fruit consumption, which is causally related to stroke.

INTRODUCTION

Stroke is an ongoing global health problem. In 2015, there were 6 326.2 thousand deaths from stroke worldwide. It was also the second most common cause of premature mortality and secondary disability.¹ The 2015 Report on Chinese Stroke Prevention indicates stroke as the leading cause of death in China, with incidence increasing by 8.7% every year.² Stroke rates in China are higher than those in Western countries and other Asian countries.^{3,4} Moreover, the number of stroke patients is likely to increase because of lifestyle, demographic changes, and inadequate control of major risk factors for stroke in China.² Therefore, it is important to identify and prevent these risk factors.

The major risk factors for stroke are hypertension, diabetes mellitus, hypercholesterolemia, smoking, physical inactivity, obesity, and a family history of stroke.⁵⁻⁸ More than 90% of the global burden of stroke in 2013 was attributable to the combined effect of all modifiable risk factors.⁸ Although these risk factors play a role in the development of stroke, the disease results from the interaction between genetic and environmental factors. The more risk factors a person has, the more likely they are to incur a stroke.⁷

People with comorbid diabetes and smoking might represent a subgroup with high risk of developing stroke. However, there are a few studies on the interaction of diabetes and smoking on stroke. Therefore, the primary aim of this cross-sectional study was to examine the interaction of type 2 diabetes mellitus (DM2) and smoking on stroke in Chinese adults. A secondary aim was to assess the associations between DM2 and stroke, and between smoking and stroke.

MATERIALS AND METHODS

Study design and recruitment criteria

This population-based, cross-sectional survey was conducted in Xuzhou City, Jiangsu Province, China, from February to June 2013. The sample was selected with two-stage probability proportional to size from all 11 regions in Xuzhou. In the first stage, five subdistricts/townships in urban/rural areas were selected from each region with probability proportional to size sampling. In the second stage, five communities/villages were selected from each subdistrict/township with probability proportional to size sampling. In the final stage, one person ≥ 18 years old and who had lived in his or her current residence for ≥ 5 years was selected from each household using a Kish selection table. Participants who met one of the following criteria were excluded: (1) previous diagnosis of neuropathy, psychosis, or unclear speech or (2) member of the floating population or temporary residents. A total of $\geq 13,500$ people were selected, assuming an estimation incidence of stroke of 2.0%,⁹ with 90% power, α level of 0.05, and allowing for a dropout rate of 15%. Trained interviewers interviewed participants face-to-face on the day of the participants' regular medical appointments. All participants underwent 12-h overnight fasting and blood sampling to test basic fasting plasma glucose. After blood sampling, each received a health check and completed a structured questionnaire covering demographic information, medical history, medication history, and smoking, alcohol consumption, and exercise habits.

Key measurements

Stroke was assessed using subjects' self-reported responses, and defined as an acute disturbance of focal areas in the brain lasting for ≥ 24 h and that was thought to be

1
2
3 caused by intracranial hemorrhage or ischemia.¹⁰ The investigators examined the
4
5 medical records of participants reporting a diagnosis of stroke to check that they
6
7 satisfied this definition. The diagnosis was also confirmed by computed tomography
8
9 and magnetic resonance imaging scans. Detailed clinical information about stroke
10
11 was based on the International Classification of Disease, 10th Revision, codes
12
13 I60–I64.
14
15

16
17 DM2 was defined as fasting blood glucose ≥ 7.0 mmol/L, any use of antidiabetic
18
19 medication, or self-reported history of DM2.¹¹ Hypertension was defined as systolic
20
21 blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, any use of
22
23 antihypertensive medication, or self-reported history of hypertension.¹²
24
25

26 **Covariates**

27
28 Age, sex, current employment status, marital status, level of education,
29
30 cigarette smoking, alcohol consumption, physical activity, and family history of
31
32 diseases including DM2, hypertension, and stroke were assessed using a
33
34 standardized questionnaire. Employment status was categorized as manual,
35
36 non-manual, unemployed, or retired. Education was categorized as below high
37
38 school, high school, or above high school. Lifestyle variables included cigarette
39
40 smoking, alcohol consumption, and physical activity level. Cigarette smoking was
41
42 defined as having smoked at least 100 cigarettes in one's lifetime. Information was
43
44 obtained on the amount and type of alcohol consumed during the previous year, and
45
46 alcohol drinking was defined as consumption of ≥ 30 g of alcohol per week for ≥ 1
47
48 year. Regular leisure-time physical activity was defined as participation in moderate
49
50 or vigorous activity for ≤ 30 min per day, ≥ 3 days a week. Each participant's height (to
51
52 the nearest 0.1 cm) and weight (to the nearest 0.1 kg) in light indoor clothing were
53
54
55
56
57

1
2
3 measured. Body mass index (BMI; in kg/m^2) was calculated; categorized as
4
5 underweight ($<18.5 \text{ kg}/\text{m}^2$), normal weight ($18.5\text{--}24.0 \text{ kg}/\text{m}^2$), and overweight/obese
6
7 ($>24.0 \text{ kg}/\text{m}^2$).¹³ Dyslipidemia was defined as use of any lipid-lowering medication or
8
9 self-reported history of the condition.
10

11 **Statistical analysis**

12
13
14 Participants were divided into four groups in accordance with their smoking
15
16 status and DM2: non-smokers with no DM2, smokers with no DM2, non-smokers
17
18 with DM2, and smokers with DM2. Statistical analysis was performed using IBM SPSS
19
20 for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA). The general characteristics of
21
22 continuous variables were compared across the four subgroups using analysis of
23
24 variance. The categorical variables were expressed as a percentage and the groups
25
26 were compared using a chi-squared test. Logistic regression analysis was performed
27
28 to estimate the probability of having a stroke and 95% confidence interval (CI) for
29
30 each risk factor category stratified by DM2 and smoking, adjusting for age, sex,
31
32 occupation, education, marital status, BMI, physical activity, drinking status,
33
34 hypertension status, and family history of disease including DM2, hypertension, and
35
36 stroke.
37
38
39
40

41
42 Biological interactions should be based on an additive scale rather than a
43
44 multiplication scale.^{14,15} Therefore, we used three measures to estimate biological
45
46 interactions between DM2 and smoking: relative excess risk owing to interaction
47
48 (RERI), attributable proportion (AP) owing to interaction, and synergy index (S). RERI
49
50 is the excess risk attributed to interaction relative to the risk without exposure to
51
52 diabetes and smoking. AP refers to the attributable proportion of disease caused by
53
54 interaction in subjects with exposure to both variables. S is the excess risk from
55
56
57
58
59
60

1
2
3 exposure to both variables when there is a biological interaction relative to the risk
4
5 from exposure to both variables without interaction. In the absence of additive
6
7 interactions, RERI and AP are equal to 0.^{14,16} In the current study, RERI >0, AP >0, and
8
9 S >0 indicate statistical significance. A *p*-value <0.05 (two-tailed) was considered
10
11 statistically significant.
12
13

14 15 16 17 **Ethics approval and consent to participate**

18
19 The study protocol was approved by Xuzhou Center for Disease Control and
20
21 Prevention. The procedures followed were in accordance with the standards of the
22
23 ethics committee of Xuzhou Center for Disease Control and Prevention and with the
24
25 Declaration of Helsinki (1975, revised 2000). Written informed consent was obtained
26
27 from all participants.
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

RESULTS

General characteristics of participants

Of the 41,658 individuals initially sampled, 1253 did not respond to the smoking question or complete the blood glucose tests, and 518 did not meet our study criteria. A final total of 39,887 adults (19,178 men and 20,709 women) with complete data were included in the analysis (response rate of 95.7%). Table 1 shows the characteristics of the study population. The proportion of participants with DM2 was 7.00% (2783/39,887), of stroke subjects with DM2 was 16.67%, and of non-stroke subjects with DM2 was only 6.75%; there was a significant statistical difference between the two groups ($\chi^2 = 135.92, p < 0.001$). The proportion of smokers was 20.26% (8082/39,887), the proportion of stroke participants who smoked was 32.24%, and the proportion of non-stroke participants who smoked was 19.98%; there was a significant statistical difference in smoking between stroke and non-stroke patients ($\chi^2 = 83.49, p < 0.001$).

Association of diabetes and smoking with stroke

The 5.50% incidence of stroke in subjects with DM2 was higher than the 2.06% incidence in subjects with no DM2 ($\chi^2 = 139.11, p < 0.001$). Individuals who smoked had a higher stroke incidence compared with non-smokers (3.36% vs. 1.96%; $\chi^2 = 83.49, p < 0.001$; see Table 2). Individuals with DM2 had a significantly increased risk of stroke compared with those with no DM2 (OR: 2.65, 95% CI: 1.70–4.41, $p < 0.001$) after adjusting for confounders (see Table 3). The risk of ischemic and haemorrhagic stroke were all increased by DM2 after adjusting for confounders, the OR's were 2.71 (95% CI: 1.72–4.49) and 1.82 (95% CI: 1.34–3.35), respectively. Smokers had a

1
2
3 significantly increased risk of stroke compared with non-smokers (OR: 1.83, 95% CI:
4
5 1.59–2.14, $p < 0.001$) after adjusting for confounders (see Table 3). The risk of
6
7 ischemic and haemorrhagic stroke were all increased by smoking after adjusting for
8
9 confounders, the OR's were 1.32(95% CI: 1.12–2.53) and 1.95(95% CI:
10
11 1.40–3.41), respectively.
12
13
14
15

16 **Interaction between diabetes and smoking with relation to stroke**

17
18 Individuals who only had DM2 or only smoked had a significantly increased risk of
19
20 stroke compared with those who did not have DM2 and did not smoke (OR: 2.00,
21
22 95% CI: 1.56–2.56; OR: 1.65, 95% CI: 1.36–2.00; respectively; all $p < 0.001$) after
23
24 adjusting for confounders. Table 3 shows the results from the multiple logistic
25
26 regression models. The incidence of stroke was greatest in those who had DM2 and
27
28 smoked (OR: 3.45, 95% CI: 2.30–5.16, $p < 0.001$), after adjusting for confounders.
29
30
31

32 **Sensitivity analysis**

33
34 There was a strong additive interaction between DM2 and smoking (RERI: 1.80, 95%
35
36 CI: 1.24–2.14; AP: 0.52, 95% CI: 0.37–0.73; and S: 1.50, 95% CI: 1.18–1.84,
37
38 respectively.); 52% of occurring stroke was attributed to the interaction between
39
40 DM2 and smoking (Table 4).
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

DISCUSSION

There were two main findings in this study. First, there was an interaction of DM2 and smoking with relation to the incidence of stroke. Second, DM2 and smoking were found to be significantly associated with increased risk of stroke in Chinese adults, independent of potential confounders such as age, sex, occupation, education, marital status, BMI, physical activity, drinking status, hypertension status, and family history of diseases including diabetes, hypertension, or stroke.

The proportion of participants with DM2 in this study was 19.67%, which is lower than that reported in the China National Stroke Registry Study (27.0%),¹⁷ lower than that reported in a comparison of risk factors for ischemic stroke in Chinese versus Caucasian individuals (25.0%),¹⁸ and higher than that reported in a study of the Chinese National Health Insurance program (3.8%)¹⁹ and a review of stroke in China (4–15%).²⁰ Our results are also inconsistent with figures for diabetes in stroke patients reported for other countries.^{21,22} This discrepancy may be because of differences in study design, sampling size, region, diabetes diagnosis, and the clinical features of stroke, but could also be a result of ethnic group differences, as many studies have shown that different ethnic groups have different stroke incidence rates.²³

Numerous epidemiologic studies, including cross-sectional studies and prospective cohort studies, have demonstrated associations between diabetes and stroke.^{22,24-27} A population-based study of 173,979 discharged patients admitted with hemorrhagic stroke was conducted in Spain from 2003 to 2012. The authors reported a positive association between diabetes and stroke (incidence rate ratio: 1.38, 95% CI: 1.35–1.40 for men; incidence rate ratio: 1.31, 95% CI: 1.29–1.34 for women).²²

1
2
3 Folsom et al. reported that the relative risk (RR) of ischemic stroke was 2.22 (95% CI:
4 1.5–3.2) for individuals with diabetes after adjustment for other stroke risk factors in
5 a 6–8-year follow-up.²⁴ Iso et al.²⁵ reported that the association between
6 non-embolic ischemic stroke and diabetes was particularly strong among
7 non-hypertensive subjects with higher subscapular skinfold thickness values: the
8 multivariate RR was 4.9 (95% CI: 2.5–9.5) in a 17-year prospective cohort study of
9 10,582 Japanese individuals (4287 men and 6295 women) aged 40–69 years. A
10 systematic review and meta-analysis of 64 cohort studies with 775,385 individuals
11 showed that diabetes is consistently associated with increased risk of stroke; the
12 pooled maximum-adjusted RR of stroke associated with diabetes was 2.28 (95% CI:
13 1.93–2.69) for women and 1.83 (1.60–2.08) for men.²⁶ Liao et al. have also reported
14 that diabetic patients have an increased risk of stroke (adjusted hazard ratio: 1.75,
15 95% CI: 1.64–1.86) compared with those without diabetes; associations between
16 diabetes and stroke risk were significant for both sexes and all age groups.²⁷ Our
17 findings also demonstrate an association between diabetes and stroke.

18
19 Robson et al.²⁸ confirmed that poor blood sugar control increases the risk of
20 stroke. One prospective cohort study of 467,508 men and women aged 30–79 years
21 with no history of diabetes or stroke showed that each 1-mmol/L (18-mg/dL) higher
22 than usual increase of random plasma glucose level above 5.9 mmol/L (106 mg/dL)
23 was associated with ischemic stroke (adjusted hazard ratio: 1.08, 95% CI:
24 1.07–1.09).²⁹ Moreover, a study of 4669 patients who had had a minor stroke
25 revealed that stroke patients with diabetes experienced stroke recurrence and
26 disability during a 3-month follow-up.³⁰ Therefore, effective glycemic control not
27 only reduces the incidence of stroke but also can reduce stroke recurrence and

1
2
3 associated disability.
4

5 Stroke patients tend to contain a higher proportion of smokers than non-stroke
6
7 patients. Wang et al. reported that 48% of stroke patients smoked.³¹ Tsai et al.¹⁸
8
9 reported a figure of 38% and we found that 32.24% of stroke patients smoked.
10
11 Although these proportions differ, they are all quite high. This discrepancy may
12
13 reflect a bias in the reporting of smoking status among study participants.
14
15

16 Many studies have shown that smoking is a strong risk factor for development
17
18 of stroke.³²⁻³⁴ The British Regional Heart Study, which included 7735 men aged 40–59
19
20 years, showed that after full adjustment for other risk factors, current smokers had a
21
22 nearly fourfold RR of stroke compared with never-smokers (RR: 3.7, 95% CI: 2.0–6.9).
23
24 Ex-cigarette smokers showed lower risk than current smokers but showed excess risk
25
26 compared with never-smokers (RR: 1.7, 95% CI: 0.9–3.3, $p = 0.11$).³³ During a mean
27
28 follow-up of 8.5 years, the risk for all strokes significantly increased (RR: 0.9–3.3, 95%
29
30 CI: 1.4–24) and increased for ischemic strokes (RR: 4.8, 95% CI: 1.2–20) among
31
32 cigarette-smoking women with a cigarette-smoking spouse compared with those
33
34 with a non-smoking spouse after adjusting for other cardiovascular risk factors.³⁴
35
36 However, a systematic review and meta-analysis of 81 cohorts in Asia, including
37
38 3,980,359 individuals and 42,401 strokes, showed smoking does not contribute to
39
40 the risk of stroke.³⁵ The proportion of Chinese stroke patients who smoke is higher
41
42 than that of Caucasians.¹⁸ One systematic review and meta-analysis of 15 cohort
43
44 studies and 178 case-control studies found smoking was an independent risk factor
45
46 for stroke (pooled RRs: 1.27, 95% CI: 1.21–1.35) in the Chinese population.⁷
47
48 Individuals who smoke more are more likely to have strokes.^{36,37} A meta-analysis
49
50 that included 16,886 men and 18,539 women without known diabetes revealed
51
52
53
54
55
56
57
58
59
60

1
2
3 hemoglobin A1c was 0.10% (95% CI: 0.08–0.12, 1.1 mmol/mol [0.9–1.3]) higher in
4
5 current smokers and 0.03% (95% CI: 0.01–0.05, 0.3 mmol/mol [0.1–0.5]) higher in
6
7 ex-smokers than in never-smokers.³⁸ Therefore, our findings support previous
8
9 evidence smoking is associated with stroke in Chinese populations.⁴ However, the
10
11 present study only wanted to observe the interaction of smoking and diabetes on
12
13 stroke, the cigarette smokers were not categorized as current, former and never
14
15 smokers. Therefore, when compared our results with others should be carefully.

16
17
18 Papademetriou and colleagues reported that comparison with nonsmoking
19
20 patients with no diabetes mellitus or hypertension, patients with diabetes mellitus
21
22 and hypertension and smoking had a 3-fold increase in the prevalence of peripheral
23
24 vascular disease and a 3.5-fold increase in cerebrovascular disease^[39]. This evidence
25
26 is strengthened by our results.
27
28

29
30 The pathophysiological mechanisms of hyperglycemia induce oxidative stress;
31
32 promote formation of advanced glycosylation end products;^{40,41} increase blood–brain
33
34 barrier permeability and inflammatory responses;⁴² lead to accumulation of reactive
35
36 oxygen species/reactive nitrogen, inflammation, and mitochondrial dysfunction;⁴³
37
38 lead to cellular dysfunctions; damage vascular tissue; inhibit endogenous vascular
39
40 protective factors; alter vascular homeostasis;⁴⁴ raise levels of reactive oxygen
41
42 species and advanced glycation end products; decrease levels of mitochondrial
43
44 superoxide dismutase;⁴¹ and correlate with endothelial cell dysfunction and nitric
45
46 oxide production.⁴⁵ All these actions contribute to accelerating the atherosclerotic
47
48 process. Therefore, subjects with diabetes are more prone to develop stroke.
49
50
51

52
53 Cigarette smoking is associated with increased reactive oxygen species, oxidative
54
55 stress, blood–brain barrier permeability, sympathetic activation and nitric oxide
56
57

1
2
3 production, reduced cerebral blood flow and serum superoxide dismutase levels,
4
5 attenuation of the vasodilation of cerebral arterioles, and induction of
6
7 atherosclerosis and thrombosis.⁴⁶⁻⁴⁹ Moreover, cigarette smoke elevates serum
8
9 levels of advanced glycation end products and reduces soluble receptors for
10
11 advanced glycation end products, resulting in the development of atherosclerosis
12
13 and related stroke.⁵⁰⁻⁵² Smoking is therefore correlated with increased risk of stroke.
14
15

16
17 Collectively, diabetes and smoking induce oxidative stress and nitric oxide
18
19 production; increase reactive oxygen species, blood–brain barrier permeability, and
20
21 the level of advanced glycation end products; and reduce cerebral blood flow and
22
23 serum superoxide dismutase. Therefore, diabetic patients who smoke have a greater
24
25 risk of stroke.
26
27

28
29 The strengths of the current study are that we used a community-based
30
31 multistage sampling design, large sample size, and randomly selected participants.
32
33 However, the study has several limitations. First, because of the cross-sectional
34
35 design, we could not determine a causal relationship between DM2, smoking, and
36
37 stroke. Second, we were unable to control for some important and well-known risk
38
39 factors of stroke, such as heart rate⁵³ and cardiac causes.⁶ Third, we did not measure
40
41 fresh fruit consumption,⁵⁴ which is causally related to stroke. Fourth, the number of
42
43 cigarettes smoking was recalled by participants, therefore, the risk of
44
45 misclassification and recall bias with the definition of smoking could not be avoid.
46
47
48

49 **Conclusion**

50
51 The results of this cross-sectional study indicate subjects with diabetes who
52
53 smoke are 3.5 times more likely to develop stroke than non-diabetics who do not
54
55 smoke. Diabetes and smoking had a combined positive influence on stroke. Our
56
57

1
2
3 results have important public health implications. Among Chinese adults, the current
4
5 rate of smoking is as high as 28.3%⁵⁵ and DM2 prevalence is 11.6%.⁵⁶ Therefore, it is
6
7 important for stroke prevention to reduce smoking and improve glycemc control in
8
9 diabetic patients in China.
10

11 12 **COMPETING INTERESTS**

13
14
15 The authors declare that they have no competing interests.
16

17 **Acknowledgments**

18
19 We thank all the participants involved in the survey. We also thank the Regional
20
21 Centers for Disease Control and Prevention as well as clinics in Xuzhou for their
22
23 collaboration.
24

25 **Funding**

26
27
28 This research was funded by the Preventive Medicine research projects of Jiangsu
29
30 Province Health Department in 2015 (Y2015010) and the Science and Technology
31
32 projects of Xuzhou City in 2015 (KC15SM046). The researchers were independent
33
34 from the funders. The study funders had no influence on the study design, data
35
36 collection, analysis, interpretation of data, writing of the report, or decision to
37
38 submit the article for publication.
39
40
41

42 **Duality of interest**

43
44 The authors declare there is no duality of interest associated with this manuscript.
45

46 **Authors' contributions**

47
48 HL wrote/edited the manuscript and created tables. ZD, PZ, XS, TL, CZ, XZ, and PL
49
50 contributed to the discussion and reviewed/edited the manuscript. XZ
51
52 conceptualized the study. PL is the guarantor of this work and, as such, had full
53
54 access to all data in the study and takes responsibility for the integrity of the data
55
56
57

1
2
3 and accuracy of the data analysis. All authors read and approved the final
4
5 manuscript.

6
7 **Availability of data and materials**

8
9 All data relevant to the given manuscript have been stored in a separate file that can
10
11 be made freely available to external investigators upon request.
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

References

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1459-1544.
2. Stroke Control Project Committee of National Health and Family Planning Commission of the People's Republic of China. Report on the Chinese Stroke Prevention (2015) 1st ed. Beijing: China Pecking Union Medical College Press, 2015.
3. Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, et al. Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013;381(9882):1987-2015.
4. Hata J, Kiyohara Y. Epidemiology of Stroke and Coronary Artery Disease in Asia. *Circ J*. 2013; 77(8):1923-32.
5. Mi T, Sun S, Du Y, Guo S, Cong L, Cao M, et al. Differences in the distribution of risk factors for stroke among the high-risk population in urban and rural areas of Eastern China. *Brain Behav*. 2016;6(5):e00461.
6. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*. 2010;376(9735):112-23.
7. Wang J, Wen X, Li W, Li X, Wang Y, Lu W. Risk Factors for Stroke in the Chinese Population: A Systematic Review and Meta-Analysis. *J Stroke Cerebrovasc Dis*. 2016; pii: S1052-3057(16)30599-7.
8. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol*. 2016;15(9):913-24.
9. Zhang P, Jiao S, Zhou Y, Li G, Shi Y, Li H, et al. Studies on prevalence and control of several common chronic diseases among Beijing adults in 2005. *Chin J Epidemiol*, 2007;28(7):625-630.
10. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association.

- 1
2
3 Stroke 2013; 44:2064-89.
- 4 11. Chinese Diabetes Society. Chinese guidelines for the prevention and treatment of
5 type 2 diabetes mellitus (2010 Edition). Chinese Journal of Diabetes, 2012;20(1):
6 1-36.
- 7
8 12. China hypertension prevention guidelines revision committee. Guidelines for
9 prevention and treatment of hypertension in China[2010 Edition]. Chinese Journal
10 of hypertension, 2011;19(8):701-743.
- 11
12 13. Zhou BF. Predictive values of body mass index and waist circumference for risk
13 factors of certain related diseases in Chinese adults--study on optimal cut-off
14 points of body mass index and waist circumference in Chinese adults. Biomed
15 Environ Sci 2002;15, 83-96.
- 16
17 14. Hosmer DW, Lemeshow S . Confidence interval estimation of interaction.
18 Epidemiology 1992; 3(5):452-456.
- 19
20 15. Knol MJ, van der Tweel I, Grobbee DE, Numans ME, Geerlings MI. Estimating
21 interaction on an additive scale between continuous determinants in a logistic
22 regression model. Int J Epidemiol. 2007;36(5):1111-8.
- 23
24 16. Knol MJ, VanderWeele TJ, Groenwold RH, Klungel OH, Rovers MM, Grobbee
25 DE. Estimating measures of interaction on an additive scale for preventive
26 exposures. Eur J Epidemiol 2011; 26(6):433–438.
- 27
28 17. Pan Y, Wang Y, Li H, Gaisano HY, Wang Y, He Y. Association of Diabetes and
29 Prognosis of Minor Stroke and Its Subtypes: A Prospective Observational Study.
30 PLoS One. 2016;11(4):e0153178.
- 31
32 18. Tsai CF, Anderson N, Thomas B, Sudlow CL. Risk factors for ischemic stroke
33 and its subtypes in Chinese vs. Caucasians: Systematic review and meta-analysis.
34 Int J Stroke. 2015;10(4):485-93.
- 35
36 19. Guo Y, Wang H, Tao T, Tian Y, Wang Y, Chen Y, et al. Determinants and Time
37 Trends for Ischaemic and Haemorrhagic Stroke in a Large Chinese Population.
38 PLoS ONE 2016; 11(9):e0163171.
- 39
40 20. Shi FL, Hart RG, Sherman DG, Tegeler CH. Stroke in the People's Republic of
41 China. Stroke. 1989;20(11):1581-5.
- 42
43 21. Chang T, Gajasinghe S, Arambepola C. Prevalence of Stroke and Its Risk Factors
44 in Urban Sri Lanka Population-Based Study. Stroke. 2015;46(10):2965-8.
- 45
46 22. Muñoz-Rivas N, Méndez-Bailón M, Hernández-Barrera V, de Miguel-Yanes JM,
47
48
49
50
51
52
53
54
55
56

- 1
2
3 Jimenez-Garcia R, Esteban-Hernández J, et al. Type 2 Diabetes and
4 Hemorrhagic Stroke: A Population-Based Study in Spain from 2003 to 2012. *J*
5 *Stroke Cerebrovasc Dis.* 2016;25(6):1431-43.
6
7
8 23. Tsai CF, Thomas B, Sudlow CL. Epidemiology of stroke and its subtypes in
9 Chinese vs white populations. *Neurology.* 2013;81(3):264-72.
10
11 24. Folsom AR, Rasmussen ML, Chambless LE, Howard G, Cooper LS, Schmidt MI,
12 et al. Prospective associations of fasting insulin, body fat distribution, and diabetes
13 with risk of ischemic stroke. The Atherosclerosis Risk in Communities (ARIC)
14 Study Investigators. *Diabetes Care.* 1999;22(7):1077-83
15
16 25. Iso H, Imano H, Kitamura A, Sato S, Naito Y, Tanigawa T, et al. Type 2 diabetes
17 and risk of non-embolic ischaemic stroke in Japanese men and women.
18 *Diabetologia.* 2004;47(12):2137-44.
19
20 26. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in
21 women compared with men: a systematic review and meta-analysis of 64 cohorts,
22 including 775 385 individuals and 12 539 strokes. *Lancet.*
23 2014;383(9933):1973-80.
24
25 27. Liao CC, Shih CC, Yeh CC, Chang YC, Hu CJ, Lin JG, et al. Impact of Diabetes
26 on Stroke Risk and Outcomes: Two Nationwide Retrospective Cohort Studies.
27 *Medicine (Baltimore).* 2015;94(52):e2282.
28
29 28. Robson R, Lacey AS, Luzio SD, Van Woerden H, Heaven ML, Wani M, et al.
30 HbA1c measurement and relationship to incident stroke. *Diab Med.*
31 2016;33:459–62.
32
33 29. Bragg F, Li L, Bennett D, Guo Y, Lewington S, Bian Z, et al. Association of
34 Random Plasma Glucose Levels With the Risk for Cardiovascular Disease Among
35 Chinese Adults Without Known Diabetes. *JAMA Cardiol.* 2016;1(7):813-823.
36
37 30. Wu L, Wang A, Wang X, Zhao X, Wang C, Liu L, et al. Factors for short-term
38 outcomes in patients with a minor stroke: results from China National Stroke
39 Registry. *BMC Neurol.* 2015;15:253.
40
41 31. Wang W, Jiang B, Sun H, Ru X, Sun D, Wang L, et al. Prevalence, Incidence and
42 Mortality of Stroke in China: Results from a Nationwide Population-Based Survey
43 of 480,687 Adults. *Circulation.* 2017;135(8):759-771.
44
45 32. Wolf PA, D'Agostino RB, Kannel WB, Bonita R, Belanger AJ. Cigarette smoking
46 as risk factor for stroke the framingham study. *JAMA.* 1988;259(7):1025-9.
47
48 33. Wannamethee SG, Shaper AG, Whincup PH, Walker M. Smoking cessation and
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 the risk of stroke in middle-aged men. *JAMA*. 1995;274(2):155-60.
- 4 34. Qureshi AI, Suri MF, Kirmani JF, Divani AA. Cigarette smoking among spouses:
5 another risk factor for stroke in women. *Stroke*, 2005;36(9):e74-6.
- 6
7 35. Peters SA, Huxley RR, Woodward M. Smoking as a Risk Factor for Stroke in
8 Women Compared With Men A Systematic Review and Meta-analysis of 81
9 Cohorts, Including 3 980 359 Individuals and 42 401 Strokes. *Stroke*.
10 2013;44(10):2821-8.
- 11
12 36. Shah RS, Cole JW. Smoking and stroke: the more you smoke the more you stroke.
13 *Expert Rev Cardiovasc Ther*. 2010;8:917–932. doi: 10.1586/erc.10.56.
- 14
15 37. Chang S, Kim H, Kim V, Lee K, Jeong H, Lee JH, et al. Association Between
16 Smoking and Physician-Diagnosed Stroke and Myocardial Infarction in Male
17 Adults in Korea. *Int J Environ Res Public Health*. 2016;13(2):158.
- 18
19 38. Soulimane S, Simon D, Herman WH, Lange C, Lee CM, Colagiuri S, et al.
20 HbA1c, fasting and 2 h plasma glucose in current, ex- and never-smokers: a
21 meta-analysis. *Diabetologia*. 2014;57(1):30-9.
- 22
23 39. Papademetriou V, Narayan P, Rubins H, Collins D, Robins S. Influence of risk factors
24 on peripheral and cerebrovascular disease in men with coronary artery disease,
25 low high-density lipoprotein cholesterol levels, and desirable low-density
26 lipoprotein cholesterol levels. HIT Investigators. Department of Veterans Affairs
27 HDL Intervention Trial. *Am Heart J*. 1998;136(4 Pt 1):734-40.
- 28
29 40. Aronson D, Rayfield EJ. How hyperglycemia promotes atherosclerosis: molecular
30 mechanisms. *Cardiovasc Diabetol*. 2002;1:1.
- 31
32 41. Rehni AK, Nautiyal N, Perez-Pinzon MA, Dave KR. Hyperglycemia /
33 hypoglycemia-induced mitochondrial dysfunction and cerebral ischemic damage in
34 diabetics. *Metab Brain Dis*. 2015;30(2):437-47.
- 35
36 42. Shukla V, Shakya AK, Perez-Pinzon MA, Dave KR. Cerebral ischemic damage in
37 diabetes: an inflammatory perspective. *J Neuroinflammation*. 2017;14(1):21.
- 38
39 43. Zhang Z, Yan J, Shi H. Hyperglycemia as a Risk Factor of Ischemic Stroke. *J*
40 *Drug Metab Toxicol*. 2013;4(4). pii: 153.
- 41
42 44. Kitada M, Zhang Z, Mima A, King GL. Molecular mechanisms of diabetic
43 vascular complications. *J Diabetes Investig*. 2010;1(3):77-89.
- 44
45 45. Kemeny SF, Figueroa DS, Clyne AM. Hypo- and Hyperglycemia Impair
46 Endothelial Cell Actin Alignment and Nitric Oxide Synthase Activation in

- 1
2
3 Response to Shear Stress. PLoS ONE, 2013;8(6): e66176.
- 4 46. Iida M, Iida H, Dohi S, Takenaka M, Fujiwara H. Mechanisms underlying
5 cerebrovascular effects of cigarette smoking in rats in vivo. Stroke,
6 1998;29(8):1656-65.
- 7
8 47. Barua RS, Ambrose JA, Srivastava S, DeVoe MC, Eales-Reynolds LJ. Reactive
9 oxygen species are involved in smoking-induced dysfunction of nitric oxide
10 biosynthesis and upregulation of endothelial nitric oxide synthase: an in vitro
11 demonstration in human coronary artery endothelial cells. Circulation
12 2003;107(18):2342–2347.
- 13
14 48. Benowitz NL. Cigarette smoking and cardiovascular disease: pathophysiology and
15 implications for treatment. Prog Cardiovasc Dis., 2003;46(1):91–111.
- 16
17 49. Chen S, Wu P, Zhou L, Shen Y, Li Y, Song H. Relationship between increase of
18 serum homocysteine caused by smoking and oxidative damage in elderly patients
19 with cardiovascular disease. Int J Clin Exp Med. 2015;8(3):4446-54.
- 20
21 50. Prasad K, Dhar I, Caspar-Bell G. Role of Advanced Glycation End Products and
22 Its Receptors in the Pathogenesis of Cigarette Smoke-Induced Cardiovascular
23 Disease. Int J Angiol. 2015;24(2):75-80.
- 24
25 51. Ottum MS, Mistry AM. Advanced glycation end products: modifiable
26 environmental factors profoundly mediate insulin resistance. J Clin Biochem Nutr.
27 2015;57(1):1-12.
- 28
29 52. Biswas SK, Mudi SR, Mollah FH, Bierhaus A, Arslan MI. Serum soluble receptor
30 for advanced glycation end products (sRAGE) is independently associated with
31 cigarette smoking in non-diabetic healthy subjects. Vasc Dis Res. 2013;
32 10(4):380-2.
- 33
34 53. Zhong C, Zhong X, Xu T, Peng H, Li H, Zhang M, et al. Combined effects of
35 hypertension and heart rate on the risk of stroke and coronary heart disease: a
36 population-based prospective cohort study among Inner Mongolians in China.
37 Hypertens Res. 2015;38(12):883-8.
- 38
39 54. Du H, Li L, Bennett D, Guo Y, Key TJ, Bian Z, et al. Fresh Fruit Consumption
40 and Major Cardiovascular Disease in China. N Engl J Med. 2016; 374(14):
41 1332–1343.
- 42
43 55. Ding L, Xu Y, Wang LM, Jiang Y, Zhang M, Li YC, et al. Smoking and Its
44 Relation to Metabolic Status among Chinese Adults: Analysis of a Nationwide
45 Survey. Biomed Environ Sci. 2016;29(9):619-627.
- 46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

56.. Xu Y, Wang L, He J, Bi Y, Li M, Wang T, et mal. Prevalence and Control of Diabetes in Chinese Adults. JAMA. 2013;310(9):948-59.

For peer review only

Table 1 General characteristics of diabetes and smoking in the study population (n = 39,887)

<i>Reported variable</i>	Non-smoking /non-DM2	Smoking /non-DM2	Non-smoking /DM2	Smoking /DM2	P
Total	29568	7536	2237	546	
Gender(man)	11087(37.50%)	6890(91.43%)	726(32.45%)	475(87.00%)	<0.01
Age(years)	46.93±17.13	49.64±15.97	61.52±12.71	59.03±11.95	<0.01
Married (living with partners)	24290(82.15%)	6622(87.87%)	1844(82.43%)	506(92.67%)	<0.01
Below high school	21906(74.09%)	5757(76.39%)	1832(81.90%)	409(74.91%)	
high school	4684(15.84%)	1235(16.39%)	263(11.76%)	94(17.22%)	<0.01
Above high school	2978(10.07%)	544(7.22%)	142(6.34%)	43(7.87%)	
Manual	20702(70.01%)	5538(73.49%)	1382(61.78%)	326(59.71%)	
Non-manual	3664(12.39%)	909(12.06%)	145(6.48%)	59(10.80%)	<0.01
Retired	2277(7.70%)	589(7.82%)	563(25.17%)	124(22.71%)	
Unemployed	2925(9.89%)	500(6.63%)	147(6.57%)	37(6.78%)	
alcohol use	1832(6.20%)	4061(53.89%)	156(6.97%)	284(52.01%)	<0.01
Regular exercise	5943(20.10%)	1519(20.16%)	580(25.93%)	172(31.50%)	
Family history of Hypertension	2007(6.79%)	740(9.82%)	218(9.75%)	56(10.26%)	<0.01
Family history of DM2	350(1.18%)	128(1.70%)	120(5.36%)	26(4.76%)	<0.01
Family history of stroke	574(1.94%)	209(2.77%)	32(1.43%)	13(2.38%)	
Hypertension	6339(21.44%)	2004(26.59%)	759(33.93%)	255(46.70%)	
BMI(≥24kg/m ²)	12532(42.38%)	3536(46.92%)	1382(61.78%)	335(65.02%)	<0.01
Dyslipidemia	3602(12.18%)	1134(15.05%)	456(20.38%)	137(25.09%)	<0.01

Table 2 Associations between smoking, diabetes, and stroke

Variables	Stroke	Non-stroke	Unadjusted OR(95%CI)	Adjusted OR (95%CI)	P	
Smoking	No	622(67.76%)	31183(80.02%)	1.91 (1.63-2.31)	1.83 (1.59-2.14)	<0.01
	Yes	296(32.24%)	7786(19.98%)			
DM2	No	765(83.33%)	36339(93.25%)	2.76 (1.77-4.68)	2.65 (1.70-4.41)	<0.01
	Yes	153(16.67%)	2630(6.75%)			

Adjusted for age, sex, education, marriage status, employment, family history of diabetes, family history of hypertension, family history of stroke, alcohol consumption, physical activity, hypertension, diabetes or smoking, body mass index, and lipids.

Table 3 Odds ratios (ORs) for the association between smoking and stroke by diabetes among participants

Smoking	Diabetes	No stroke	Stroke	Unadjusted OR(95%CI)	Adjusted OR (95%CI)	P
No	No	29056	512	1	1	
	Yes	2127	110	2.93(1.73-3.15)	2.00 (1.56-2.56)	<0.01
Yes	No	7283	253	1.97(1.54-2.37)	1.65 (1.36-2.00)	<0.01
	Yes	503	43	4.85(2.65-6.21)	3.45 (2.30-5.16)	<0.01

Adjusted for age, sex, education, marriage status, employment, family history of diabetes, family history of hypertension, family history of stroke, alcohol consumption, physical activity, hypertension, body mass index, and lipids.

Table 4 Measures for estimating biological interaction between smoking and diabetes for prevalence of stroke in participants

Measures of biological interaction	Estimate (95% CI)
RERI	1.80(1.24—3.84)
AP	0.52(0.37—0.73)
S	1.50(1.18—1.84)

Reference group is no smoking with non-diabetes.

Adjusted for age, sex, education, marriage status, employment, family history of diabetes, family history of hypertension, family history of stroke, alcohol consumption, physical activity, hypertension, body mass index, and lipids.

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	6-7
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Data sources/measurement	8*	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Bias	9	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Study size	10	Describe any efforts to address potential sources of bias	5
Quantitative variables	11	Explain how the study size was arrived at	7-8
		Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
		(a) Describe all statistical methods, including those used to control for confounding	
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
Statistical methods	12	(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	7-8
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Interaction of diabetes and smoking on stroke: A population-based cross-sectional survey in China

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017706.R2
Article Type:	Research
Date Submitted by the Author:	08-Dec-2017
Complete List of Authors:	Lou, Heqing; The School of Public Health, Xuzhou Medical University, Xuzhou, China Dong, Zongmei; The School of Public Health, Xuzhou Medical University, Xuzhou, China; Xuzhou Center for Disease Control and Prevention, Xuzhou, China Zhang, Pan; Xuzhou Center for Disease Control and Prevention, Xuzhou, China, Department of Non-communicable Disease Control Shao, Xiaoping ; The School of Public Health, Xuzhou Medical University, Xuzhou, China Li, Ting; Xuzhou Center for Disease Control and Prevention, Xuzhou, China Zhao, Chunyan; The School of Public Health, Xuzhou Medical University, Xuzhou, China Zhang, Xunbao; The School of Public Health, Xuzhou Medical University, Xuzhou, China Lou, Peian; Xuzhou Center for Disease Control and Prevention, Xuzhou, China, Department of Non-communicable Disease Control; The School of Public Health, Xuzhou Medical University, Xuzhou, China
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	STROKE MEDICINE, DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY

SCHOLARONE™
Manuscripts

1
2
3 **Interaction of diabetes and smoking on stroke: A population-based cross-sectional**
4 **survey in China**
5

6 **Heqing Lou¹, Zongmei Dong^{1,2}, Pan Zhang², Xiaoping Shao,¹ Ting Li², Chunyan Zhao¹,**
7 **Xunbao Zhang^{*1}, Peian Lou^{*1,2}**
8
9

10
11
12 1. The School of Public Health, Xuzhou Medical University, Xuzhou, China

13
14 2. Department of Non-communicable Disease Control, Xuzhou Center for Disease
15 Control and Prevention, Xuzhou, China
16

17
18
19 ***Corresponding authors:**

20 Xunbao Zhang, 209 Tongshan Road, Xuzhou City, Jiangsu Province, China

21 Phone: +86 516-83262018; Fax: +86 516-82702478; E-mail: 437335090@qq.com
22
23

24
25
26 Peian Lou, 142 West Erhuan Road, Xuzhou City, Jiangsu Province, China

27 Phone: +86 516-85956785; Fax: +86 516-89596797; E-mail: lpa82835415@126.com
28
29

30
31 Manuscript category: Research article

32
33 **Keywords:** type 2 diabetes mellitus; smoking; interaction; stroke
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abstract

Objectives: Diabetes and smoking are known independent risk factors for stroke, but their interaction with relation to stroke is less clear. We aimed to explore the interaction and its influence on stroke in Chinese adults.

Design: Cross-sectional study.

Setting: Community-based investigation in Xuzhou, China.

Participants: A total of 39,887 Chinese adults who fulfilled the inclusion criteria were included.

Methods: Participants were selected using a multi-stage stratified cluster method, and completed self-reported questionnaires on stroke and smoking. Type 2 diabetes mellitus (DM2) was assessed by fasting blood glucose or use of antidiabetic medication. Interaction, relative excess risk owing to interaction (RERI), the attributable proportion (AP), and the synergy index (S) were evaluated using a logistic regression model.

Results: After adjustment for age, gender, marital status, educational level, occupation, physical activity, body mass index, hypertension, stroke family history, alcohol use, and blood lipids, the relationships between DM2 and stroke, and between smoking and stroke, were still significant: odds ratios (OR) were 2.75 (95% confidence interval [CI]: 2.03–3.73) and 1.70 (95% CI: 1.38–2.10), respectively. In subjects with DM2 who smoked, the RERI, AP, and S values (and 95% CIs) were 1.80 (1.24–3.83), 0.52 (0.37–0.73), and 1.50 (1.18–1.84), respectively.

Conclusions: The results suggest there are additive interactions between DM2 and smoking and that these affect stroke in Chinese adults.

Article summary: Strengths and limitations of this study

- The strengths of this study were that participants of a large sample were randomly selected from the general population of Xuzhou, and many confounding risk factors were adjusted for.
- Owing to the cross-sectional design, we could not determine a causal combined relationship between diabetes, smoking and stroke.
- We were not able to control for some important and well-known risk factors of diabetes—for example, heart rate and cardiac causes..
- We did not measure fresh fruit consumption, which is causally related to stroke.

INTRODUCTION

Stroke is an ongoing global health problem. In 2015, there were 6 326.2 thousand deaths from stroke worldwide. It was also the second most common cause of premature mortality and secondary disability.¹ The 2015 Report on Chinese Stroke Prevention indicates stroke as the leading cause of death in China, with incidence increasing by 8.7% every year.² Stroke rates in China are higher than those in Western countries and other Asian countries.^{3,4} Moreover, the number of stroke patients is likely to increase because of lifestyle, demographic changes, and inadequate control of major risk factors for stroke in China.² Therefore, it is important to identify and prevent these risk factors.

The major risk factors for stroke are hypertension, diabetes mellitus, hypercholesterolemia, smoking, physical inactivity, obesity, and a family history of stroke.⁵⁻⁸ More than 90% of the global burden of stroke in 2013 was attributable to the combined effect of all modifiable risk factors.⁸ Although these risk factors play a role in the development of stroke, the disease results from the interaction between genetic and environmental factors. The more risk factors a person has, the more likely they are to incur a stroke.⁷

People with comorbid diabetes and smoking might represent a subgroup with high risk of developing stroke. However, there are a few studies on the interaction of diabetes and smoking on stroke. Therefore, the primary aim of this cross-sectional study was to examine the interaction of type 2 diabetes mellitus (DM2) and smoking on stroke in Chinese adults. A secondary aim was to assess the associations between DM2 and stroke, and between smoking and stroke.

MATERIALS AND METHODS

Study design and recruitment criteria

This population-based, cross-sectional survey was conducted in Xuzhou City, Jiangsu Province, China, from February to June 2013. The sample was selected with two-stage probability proportional to size from all 11 regions in Xuzhou. In the first stage, five subdistricts/townships in urban/rural areas were selected according to the population of each subdistrict/township from each region with probability proportional to size sampling. In the second stage, five communities/villages were selected according to the population of each community/village from each subdistrict/township with probability proportional to size sampling. In the final stage, one person ≥ 18 years old and who had lived in his or her current residence for ≥ 5 years was selected from each household using a Kish selection table. Participants who met one of the following criteria were excluded: (1) previous diagnosis of neuropathy, psychosis, or unclear speech or (2) member of the floating population or temporary residents. A total of $\geq 13,500$ people were selected, assuming an estimation incidence of stroke of 2.0%,⁹ with 90% power, α level of 0.05, and allowing for a dropout rate of 15%. Trained interviewers interviewed participants face-to-face on the day of the participants' regular medical appointments. All participants underwent 12-h overnight fasting and blood sampling to test basic fasting plasma glucose. After blood sampling, each received a health check and completed a structured questionnaire covering demographic information, medical history, medication history, and smoking, alcohol consumption, and exercise habits.

Key measurements

Stroke was assessed using subjects' self-reported responses, and defined as an acute

1
2
3 disturbance of focal areas in the brain lasting for ≥ 24 h and that was thought to be
4
5 caused by intracranial hemorrhage or ischemia.¹⁰ The investigators examined the
6
7 medical records of participants reporting a diagnosis of stroke to check that they
8
9 satisfied this definition. The diagnosis was also confirmed by computed tomography
10
11 and magnetic resonance imaging scans. Detailed clinical information about stroke
12
13 was based on the International Classification of Disease, 10th Revision, codes
14
15 I60–I64.
16
17

18
19 DM2 was defined as fasting blood glucose ≥ 7.0 mmol/L, any use of antidiabetic
20
21 medication, or self-reported history of DM2.¹¹ Hypertension was defined as systolic
22
23 blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, any use of
24
25 antihypertensive medication, or self-reported history of hypertension.¹²
26
27

28 **Covariates**

29
30 Age, sex, current employment status, marital status, level of education,
31
32 cigarette smoking, alcohol consumption, physical activity, and family history of
33
34 diseases including DM2, hypertension, and stroke were assessed using a
35
36 standardized questionnaire. Employment status was categorized as manual,
37
38 non-manual, unemployed, or retired. Education was categorized as below high
39
40 school, high school, or above high school. Lifestyle variables included cigarette
41
42 smoking, alcohol consumption, and physical activity level. Cigarette smoking was
43
44 defined as having smoked at least 100 cigarettes in one's lifetime. Information was
45
46 obtained on the amount and type of alcohol consumed during the previous year, and
47
48 alcohol drinking was defined as consumption of ≥ 30 g of alcohol per week for ≥ 1
49
50 year. Regular leisure-time physical activity was defined as participation in moderate
51
52 or vigorous activity for ≤ 30 min per day, ≥ 3 days a week. Each participant's height (to
53
54
55
56
57

1
2
3 the nearest 0.1 cm) and weight (to the nearest 0.1 kg) in light indoor clothing were
4
5 measured. Body mass index (BMI; in kg/m^2) was calculated; categorized as
6
7 underweight ($<18.5 \text{ kg}/\text{m}^2$), normal weight ($18.5\text{--}24.0 \text{ kg}/\text{m}^2$), and overweight/obese
8
9 ($>24.0 \text{ kg}/\text{m}^2$).¹³ Dyslipidemia was defined as use of any lipid-lowering medication or
10
11 self-reported history of the condition.
12
13

14 **Statistical analysis**

15
16 Participants were divided into four groups in accordance with their smoking
17
18 status and DM2: non-smokers with no DM2, smokers with no DM2, non-smokers
19
20 with DM2, and smokers with DM2. Statistical analysis was performed using IBM SPSS
21
22 for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA). The general characteristics of
23
24 continuous variables were compared across the four subgroups using analysis of
25
26 variance. The categorical variables were expressed as a percentage and the groups
27
28 were compared using a chi-squared test. Logistic regression analysis was performed
29
30 to estimate the probability of having a stroke and 95% confidence interval (CI) for
31
32 each risk factor category stratified by DM2 and smoking, adjusting for age, sex,
33
34 occupation, education, marital status, BMI, physical activity, drinking status,
35
36 hypertension status, and family history of disease including DM2, hypertension, and
37
38 stroke.
39
40
41
42
43

44 Biological interactions should be based on an additive scale rather than a
45
46 multiplication scale.^{14,15} Therefore, we used three measures to estimate biological
47
48 interactions between DM2 and smoking: relative excess risk owing to interaction
49
50 (RERI), attributable proportion (AP) owing to interaction, and synergy index (S). RERI
51
52 is the excess risk attributed to interaction relative to the risk without exposure to
53
54 diabetes and smoking. AP refers to the attributable proportion of disease caused by
55
56
57
58
59
60

1
2
3 interaction in subjects with exposure to both variables. S is the excess risk from
4
5 exposure to both variables when there is a biological interaction relative to the risk
6
7 from exposure to both variables without interaction. In the absence of additive
8
9 interactions, RERI and AP are equal to 0.^{14,16} In the current study, RERI >0, AP >0, and
10
11 $S >0$ indicate statistical significance. A p -value <0.05 (two-tailed) was considered
12
13 statistically significant.
14
15

16 17 18 19 **Ethics approval and consent to participate**

20
21 The study protocol was approved by Xuzhou Center for Disease Control and
22
23 Prevention. The procedures followed were in accordance with the standards of the
24
25 ethics committee of Xuzhou Center for Disease Control and Prevention and with the
26
27 Declaration of Helsinki (1975, revised 2000). Written informed consent was obtained
28
29 from all participants.
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

RESULTS

General characteristics of participants

Of the 41,658 individuals initially sampled, 1253 did not respond to the smoking question or complete the blood glucose tests, and 518 did not meet our study criteria. A final total of 39,887 adults (19,178 men and 20,709 women) with complete data were included in the analysis (response rate of 95.7%). Table 1 shows the characteristics of the study population. The proportion of participants with DM2 was 7.00% (2783/39,887), of stroke subjects with DM2 was 16.67%, and of non-stroke subjects with DM2 was only 6.75%; there was a significant statistical difference between the two groups ($\chi^2 = 135.92$, $p < 0.001$). The proportion of smokers was 20.26% (8082/39,887), the proportion of stroke participants who smoked was 32.24%, and the proportion of non-stroke participants who smoked was 19.98%; there was a significant statistical difference in smoking between stroke and non-stroke patients ($\chi^2 = 83.49$, $p < 0.001$).

Association of diabetes and smoking with stroke

The 5.50% incidence of stroke in subjects with DM2 was higher than the 2.06% incidence in subjects with no DM2 ($\chi^2 = 139.11$, $p < 0.001$). Individuals who smoked had a higher stroke incidence compared with non-smokers (3.36% vs. 1.96%; $\chi^2 = 83.49$, $p < 0.001$; see Table 2). Individuals with DM2 had a significantly increased risk of stroke compared with those with no DM2 (OR: 2.65, 95% CI: 1.70–4.41, $p < 0.001$) after adjusting for confounders (see Table 3). The risk of ischemic and haemorrhagic stroke were all increased by DM2 after adjusting for confounders, the OR's were 2.71 (95% CI: 1.72–4.49) and 1.82 (95% CI: 1.34–3.35), respectively. Smokers had a

1
2
3 significantly increased risk of stroke compared with non-smokers (OR: 1.83, 95% CI:
4
5 1.59–2.14, $p < 0.001$) after adjusting for confounders (see Table 3). The risk of
6
7 ischemic and haemorrhagic stroke were all increased by smoking after adjusting for
8
9 confounders, the OR's were 1.32(95% CI: 1.12–2.53) and 1.95(95% CI:
10
11 1.40–3.41), respectively.
12
13
14
15

16 **Interaction between diabetes and smoking with relation to stroke**

17
18 Individuals who only had DM2 or only smoked had a significantly increased risk of
19
20 stroke compared with those who did not have DM2 and did not smoke (OR: 2.00,
21
22 95% CI: 1.56–2.56; OR: 1.65, 95% CI: 1.36–2.00; respectively; all $p < 0.001$) after
23
24 adjusting for confounders. Table 3 shows the results from the multiple logistic
25
26 regression models. The incidence of stroke was greatest in those who had DM2 and
27
28 smoked (OR: 3.45, 95% CI: 2.30–5.16, $p < 0.001$), after adjusting for confounders.
29
30
31

32 **Sensitivity analysis**

33
34 There was a strong additive interaction between DM2 and smoking (RERI: 1.80, 95%
35
36 CI: 1.24–2.14; AP: 0.52, 95% CI: 0.37–0.73; and S: 1.50, 95% CI: 1.18–1.84,
37
38 respectively.); 52% of occurring stroke was attributed to the interaction between
39
40 DM2 and smoking (Table 4).
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

DISCUSSION

There were two main findings in this study. First, there was an interaction of DM2 and smoking with relation to the incidence of stroke. Second, DM2 and smoking were found to be significantly associated with increased risk of stroke in Chinese adults, independent of potential confounders such as age, sex, occupation, education, marital status, BMI, physical activity, drinking status, hypertension status, and family history of diseases including diabetes, hypertension, or stroke.

The proportion of participants with DM2 in this study was 19.67%, which is lower than that reported in the China National Stroke Registry Study (27.0%),¹⁷ lower than that reported in a comparison of risk factors for ischemic stroke in Chinese versus Caucasian individuals (25.0%),¹⁸ and higher than that reported in a study of the Chinese National Health Insurance program (3.8%)¹⁹ and a review of stroke in China (4–15%).²⁰ Our results are also inconsistent with figures for diabetes in stroke patients reported for other countries.^{21,22} This discrepancy may be because of differences in study design, sampling size, region, diabetes diagnosis, and the clinical features of stroke, but could also be a result of ethnic group differences, as many studies have shown that different ethnic groups have different stroke incidence rates.²³

Numerous epidemiologic studies, including cross-sectional studies and prospective cohort studies, have demonstrated associations between diabetes and stroke.^{22,24-27} A population-based study of 173,979 discharged patients admitted with hemorrhagic stroke was conducted in Spain from 2003 to 2012. The authors reported a positive association between diabetes and stroke (incidence rate ratio: 1.38, 95% CI: 1.35–1.40 for men; incidence rate ratio: 1.31, 95% CI: 1.29–1.34 for women).²²

1
2
3 Folsom et al. reported that the relative risk (RR) of ischemic stroke was 2.22 (95% CI:
4 1.5–3.2) for individuals with diabetes after adjustment for other stroke risk factors in
5 a 6–8-year follow-up.²⁴ Iso et al.²⁵ reported that the association between
6 non-embolic ischemic stroke and diabetes was particularly strong among
7 non-hypertensive subjects with higher subscapular skinfold thickness values: the
8 multivariate RR was 4.9 (95% CI: 2.5–9.5) in a 17-year prospective cohort study of
9 10,582 Japanese individuals (4287 men and 6295 women) aged 40–69 years. A
10 systematic review and meta-analysis of 64 cohort studies with 775,385 individuals
11 showed that diabetes is consistently associated with increased risk of stroke; the
12 pooled maximum-adjusted RR of stroke associated with diabetes was 2.28 (95% CI:
13 1.93–2.69) for women and 1.83 (1.60–2.08) for men.²⁶ Liao et al. have also reported
14 that diabetic patients have an increased risk of stroke (adjusted hazard ratio: 1.75,
15 95% CI: 1.64–1.86) compared with those without diabetes; associations between
16 diabetes and stroke risk were significant for both sexes and all age groups.²⁷ Our
17 findings also demonstrate an association between diabetes and stroke.

18
19 Robson et al.²⁸ confirmed that poor blood sugar control increases the risk of
20 stroke. One prospective cohort study of 467,508 men and women aged 30–79 years
21 with no history of diabetes or stroke showed that each 1-mmol/L (18-mg/dL) higher
22 than usual increase of random plasma glucose level above 5.9 mmol/L (106 mg/dL)
23 was associated with ischemic stroke (adjusted hazard ratio: 1.08, 95% CI:
24 1.07–1.09).²⁹ Moreover, a study of 4669 patients who had had a minor stroke
25 revealed that stroke patients with diabetes experienced stroke recurrence and
26 disability during a 3-month follow-up.³⁰ Therefore, effective glycemic control not
27 only reduces the incidence of stroke but also can reduce stroke recurrence and

1
2
3 associated disability.

4
5 Stroke patients tend to contain a higher proportion of smokers than non-stroke
6
7 patients. Wang et al. reported that 48% of stroke patients smoked.³¹ Tsai et al.¹⁸
8
9 reported a figure of 38% and we found that 32.24% of stroke patients smoked.
10
11 Although these proportions differ, they are all quite high. This discrepancy may
12
13 reflect a bias in the reporting of smoking status among study participants.
14
15

16
17 Many studies have shown that smoking is a strong risk factor for development
18
19 of stroke.³²⁻³⁴ The British Regional Heart Study, which included 7735 men aged 40–59
20
21 years, showed that after full adjustment for other risk factors, current smokers had a
22
23 nearly fourfold RR of stroke compared with never-smokers (RR: 3.7, 95% CI: 2.0–6.9).
24
25 Ex-cigarette smokers showed lower risk than current smokers but showed excess risk
26
27 compared with never-smokers (RR: 1.7, 95% CI: 0.9–3.3, $p = 0.11$).³³ During a mean
28
29 follow-up of 8.5 years, the risk for all strokes significantly increased (RR: 0.9–3.3, 95%
30
31 CI: 1.4–24) and increased for ischemic strokes (RR: 4.8, 95% CI: 1.2–20) among
32
33 cigarette-smoking women with a cigarette-smoking spouse compared with those
34
35 with a non-smoking spouse after adjusting for other cardiovascular risk factors.³⁴
36
37 However, a systematic review and meta-analysis of 81 cohorts in Asia, including
38
39 3,980,359 individuals and 42,401 strokes, showed smoking does not contribute to
40
41 the risk of stroke.³⁵ The proportion of Chinese stroke patients who smoke is higher
42
43 than that of Caucasians.¹⁸ One systematic review and meta-analysis of 15 cohort
44
45 studies and 178 case-control studies found smoking was an independent risk factor
46
47 for stroke (pooled RRs: 1.27, 95% CI: 1.21–1.35) in the Chinese population.⁷
48
49 Individuals who smoke more are more likely to have strokes.^{36,37} A meta-analysis
50
51 that included 16,886 men and 18,539 women without known diabetes revealed
52
53
54
55
56
57
58
59
60

1
2
3 hemoglobin A1c was 0.10% (95% CI: 0.08–0.12, 1.1 mmol/mol [0.9–1.3]) higher in
4
5 current smokers and 0.03% (95% CI: 0.01–0.05, 0.3 mmol/mol [0.1–0.5]) higher in
6
7 ex-smokers than in never-smokers.³⁸ Therefore, our findings support previous
8
9 evidence smoking is associated with stroke in Chinese populations.⁴ However, the
10
11 present study only wanted to observe the interaction of smoking and diabetes on
12
13 stroke, the cigarette smokers were not categorized as current, former and never
14
15 smokers. Therefore, when compared the association between smoking and stroke of
16
17 our study with that of others should be carefully.

20
21 Papademetriou and colleagues reported that comparison with nonsmoking
22
23 patients with no diabetes mellitus or hypertension, patients with diabetes mellitus
24
25 and hypertension and smoking had a 3-fold increase in the prevalence of peripheral
26
27 vascular disease and a 3.5-fold increase in cerebrovascular disease^[39]. This evidence
28
29 is strengthened by our results.

31
32 The pathophysiological mechanisms of hyperglycemia induce oxidative stress;
33
34 promote formation of advanced glycosylation end products;^{40,41} increase blood–brain
35
36 barrier permeability and inflammatory responses;⁴² lead to accumulation of reactive
37
38 oxygen species/reactive nitrogen, inflammation, and mitochondrial dysfunction;⁴³
39
40 lead to cellular dysfunctions; damage vascular tissue; inhibit endogenous vascular
41
42 protective factors; alter vascular homeostasis;⁴⁴ raise levels of reactive oxygen
43
44 species and advanced glycation end products; decrease levels of mitochondrial
45
46 superoxide dismutase;⁴¹ and correlate with endothelial cell dysfunction and nitric
47
48 oxide production.⁴⁵ All these actions contribute to accelerating the atherosclerotic
49
50 process. Therefore, subjects with diabetes are more prone to develop stroke.
51
52
53

54
55 Cigarette smoking is associated with increased reactive oxygen species, oxidative
56

1
2
3 stress, blood–brain barrier permeability, sympathetic activation and nitric oxide
4
5 production, reduced cerebral blood flow and serum superoxide dismutase levels,
6
7 attenuation of the vasodilation of cerebral arterioles, and induction of
8
9 atherosclerosis and thrombosis.⁴⁶⁻⁴⁹ Moreover, cigarette smoke elevates serum
10
11 levels of advanced glycation end products and reduces soluble receptors for
12
13 advanced glycation end products, resulting in the development of atherosclerosis
14
15 and related stroke.⁵⁰⁻⁵² Smoking is therefore correlated with increased risk of stroke.

16
17
18 Collectively, diabetes and smoking induce oxidative stress and nitric oxide
19
20 production; increase reactive oxygen species, blood–brain barrier permeability, and
21
22 the level of advanced glycation end products; and reduce cerebral blood flow and
23
24 serum superoxide dismutase. Therefore, diabetic patients who smoke have a greater
25
26 risk of stroke.
27
28

29
30 The strengths of the current study are that we used a community-based
31
32 multistage sampling design, large sample size, and randomly selected participants.
33
34 However, the study has several limitations. First, because of the cross-sectional
35
36 design, we could not determine a causal relationship between DM2, smoking, and
37
38 stroke. Second, we were unable to control for some important and well-known risk
39
40 factors of stroke, such as heart rate⁵³ and cardiac causes.⁶ Third, we did not measure
41
42 fresh fruit consumption,⁵⁴ which is causally related to stroke. Fourth, the number of
43
44 cigarettes smoking was recalled by participants, therefore, the risk of
45
46 misclassification and recall bias with the definition of smoking could not be avoid.
47
48
49

50 51 **Conclusion**

52
53 The results of this cross-sectional study indicate subjects with diabetes who
54
55 smoke are 3.5 times more likely to develop stroke than non-diabetics who do not
56
57

1
2
3 smoke. Diabetes and smoking had a combined positive influence on stroke. Our
4
5 results have important public health implications. Among Chinese adults, the current
6
7 rate of smoking is as high as 28.3%⁵⁵ and DM2 prevalence is 11.6%.⁵⁶ Therefore, it is
8
9 important for stroke prevention to reduce smoking and improve glycemc control in
10
11 diabetic patients in China.
12
13

14 15 **COMPETING INTERESTS**

16
17 The authors declare that they have no competing interests.
18

19 **Acknowledgments**

20
21 We thank all the participants involved in the survey. We also thank the Regional
22
23 Centers for Disease Control and Prevention as well as clinics in Xuzhou for their
24
25 collaboration.
26
27

28 **Funding**

29
30 This research was funded by the Preventive Medicine research projects of Jiangsu
31
32 Province Health Department in 2015 (Y2015010) and the Science and Technology
33
34 projects of Xuzhou City in 2015 (KC15SM046). The researchers were independent
35
36 from the funders. The study funders had no influence on the study design, data
37
38 collection, analysis, interpretation of data, writing of the report, or decision to
39
40 submit the article for publication.
41
42
43

44 **Duality of interest**

45
46 The authors declare there is no duality of interest associated with this manuscript.
47

48 **Authors' contributions**

49
50 HL wrote/edited the manuscript and created tables. ZD, PZ, XS, TL, CZ, XZ, and PL
51
52 contributed to the discussion and reviewed/edited the manuscript. XZ
53
54 conceptualized the study. PL is the guarantor of this work and, as such, had full
55
56

1
2
3 access to all data in the study and takes responsibility for the integrity of the data
4
5 and accuracy of the data analysis. All authors read and approved the final
6
7 manuscript.
8

9
10 **Availability of data and materials**

11
12 All data relevant to the given manuscript have been stored in a separate file that can
13
14 be made freely available to external investigators upon request.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1459-1544.
2. Stroke Control Project Committee of National Health and Family Planning Commission of the People's Republic of China. Report on the Chinese Stroke Prevention (2015) 1st ed. Beijing: China Pecking Union Medical College Press, 2015.
3. Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, et al. Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013;381(9882):1987-2015.
4. Hata J, Kiyohara Y. Epidemiology of Stroke and Coronary Artery Disease in Asia. *Circ J*. 2013; 77(8):1923-32.
5. Mi T, Sun S, Du Y, Guo S, Cong L, Cao M, et al. Differences in the distribution of risk factors for stroke among the high-risk population in urban and rural areas of Eastern China. *Brain Behav*. 2016;6(5):e00461.
6. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*. 2010;376(9735):112-23.
7. Wang J, Wen X, Li W, Li X, Wang Y, Lu W. Risk Factors for Stroke in the Chinese Population: A Systematic Review and Meta-Analysis. *J Stroke Cerebrovasc Dis*. 2016; pii: S1052-3057(16)30599-7.
8. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol*. 2016;15(9):913-24.
9. Zhang P, Jiao S, Zhou Y, Li G, Shi Y, Li H, et al. Studies on prevalence and control of several common chronic diseases among Beijing adults in 2005. *Chin J Epidemiol*, 2007;28(7):625-630.
10. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare

- professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; 44:2064-89.
11. Chinese Diabetes Society. Chinese guidelines for the prevention and treatment of type 2 diabetes mellitus (2010 Edition). *Chinese Journal of Diabetes*, 2012;20(1): 1-36.
 12. China hypertension prevention guidelines revision committee. Guidelines for prevention and treatment of hypertension in China[2010 Edition]. *Chinese Journal of hypertension*,2011;19(8):701-743.
 13. Zhou BF. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults--study on optimal cut-off points of body mass index and waist circumference in Chinese adults. *Biomed Environ Sci* 2002;15, 83-96.
 14. Hosmer DW, Lemeshow S . Confidence interval estimation of interaction. *Epidemiology* 1992; 3(5):452-456.
 15. Knol MJ, van der Tweel I, Grobbee DE, Numans ME, Geerlings MI. Estimating interaction on an additive scale between continuous determinants in a logistic regression model. *Int J Epidemiol*. 2007;36(5):1111-8.
 16. Knol MJ, VanderWeele TJ, Groenwold RH, Klungel OH, Rovers MM, Grobbee DE. Estimating measures of interaction on an additive scale for preventive exposures. *Eur J Epidemiol* 2011; 26(6):433-438.
 17. Pan Y, Wang Y, Li H, Gaisano HY, Wang Y, He Y. Association of Diabetes and Prognosis of Minor Stroke and Its Subtypes: A Prospective Observational Study. *PLoS One*. 2016;11(4):e0153178.
 18. Tsai CF, Anderson N, Thomas B, Sudlow CL. Risk factors for ischemic stroke and its subtypes in Chinese vs. Caucasians: Systematic review and meta-analysis. *Int J Stroke*. 2015;10(4):485-93.
 19. Guo Y, Wang H, Tao T, Tian Y, Wang Y, Chen Y, et al. Determinants and Time Trends for Ischaemic and Haemorrhagic Stroke in a Large Chinese Population. *PLoS ONE* 2016; 11(9):e0163171.
 20. Shi FL, Hart RG, Sherman DG, Tegeler CH. Stroke in the People's Republic of China. *Stroke*. 1989;20(11):1581-5.
 21. Chang T, Gajasinghe S, Arambepola C. Prevalence of Stroke and Its Risk Factors in Urban Sri Lanka Population-Based Study. *Stroke*. 2015;46(10):2965-8.

- 1
2
3 22. Muñoz-Rivas N, Méndez-Bailón M, Hernández-Barrera V, de Miguel-Yanes JM,
4 Jimenez-Garcia R, Esteban-Hernández J, et al. Type 2 Diabetes and
5 Hemorrhagic Stroke: A Population-Based Study in Spain from 2003 to 2012. *J*
6 *Stroke Cerebrovasc Dis.* 2016;25(6):1431-43.
7
8
9 23. Tsai CF, Thomas B, Sudlow CL. Epidemiology of stroke and its subtypes in
10 Chinese vs white populations. *Neurology.* 2013;81(3):264-72.
11
12 24. Folsom AR, Rasmussen ML, Chambless LE, Howard G, Cooper LS, Schmidt MI,
13 et al. Prospective associations of fasting insulin, body fat distribution, and diabetes
14 with risk of ischemic stroke. The Atherosclerosis Risk in Communities (ARIC)
15 Study Investigators. *Diabetes Care.* 1999;22(7):1077-83
16
17 25. Iso H, Imano H, Kitamura A, Sato S, Naito Y, Tanigawa T, et al. Type 2 diabetes
18 and risk of non-embolic ischaemic stroke in Japanese men and women.
19 *Diabetologia.* 2004;47(12):2137-44.
20
21 26. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in
22 women compared with men: a systematic review and meta-analysis of 64 cohorts,
23 including 775 385 individuals and 12 539 strokes. *Lancet.*
24 2014;383(9933):1973-80.
25
26 27. Liao CC, Shih CC, Yeh CC, Chang YC, Hu CJ, Lin JG, et al. Impact of Diabetes
27 on Stroke Risk and Outcomes: Two Nationwide Retrospective Cohort Studies.
28 *Medicine (Baltimore).* 2015;94(52):e2282.
29
30 28. Robson R, Lacey AS, Luzio SD, Van Woerden H, Heaven ML, Wani M, et al.
31 HbA1c measurement and relationship to incident stroke. *Diab Med.*
32 2016;33:459-62.
33
34 29. Bragg F, Li L, Bennett D, Guo Y, Lewington S, Bian Z, et al. Association of
35 Random Plasma Glucose Levels With the Risk for Cardiovascular Disease Among
36 Chinese Adults Without Known Diabetes. *JAMA Cardiol.* 2016;1(7):813-823.
37
38 30. Wu L, Wang A, Wang X, Zhao X, Wang C, Liu L, et al. Factors for short-term
39 outcomes in patients with a minor stroke: results from China National Stroke
40 Registry. *BMC Neurol.* 2015;15:253.
41
42 31. Wang W, Jiang B, Sun H, Ru X, Sun D, Wang L, et al. Prevalence, Incidence and
43 Mortality of Stroke in China: Results from a Nationwide Population-Based Survey
44 of 480,687 Adults. *Circulation.* 2017;135(8):759-771.
45
46 32 Wolf PA, D'Agostino RB, Kannel WB, Bonita R, Belanger AJ. Cigarette smoking
47 as risk factor for stroke the framingham study. *JAMA.* 1988;259(7):1025-9.
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 33. Wannamethee SG, Shaper AG, Whincup PH, Walker M. Smoking cessation and
4 the risk of stroke in middle-aged men. *JAMA*. 1995;274(2):155-60.
5
6 34. Qureshi AI, Suri MF, Kirmani JF, Divani AA. Cigarette smoking among spouses:
7 another risk factor for stroke in women. *Stroke*, 2005;36(9):e74-6.
8
9 35. Peters SA, Huxley RR, Woodward M. Smoking as a Risk Factor for Stroke in
10 Women Compared With Men A Systematic Review and Meta-analysis of 81
11 Cohorts, Including 3 980 359 Individuals and 42 401 Strokes. *Stroke*.
12 2013;44(10):2821-8.
13
14 36. Shah RS, Cole JW. Smoking and stroke: the more you smoke the more you stroke.
15 *Expert Rev Cardiovasc Ther*. 2010;8:917-932. doi: 10.1586/erc.10.56.
16
17 37. Chang S, Kim H, Kim V, Lee K, Jeong H, Lee JH, et al. Association Between
18 Smoking and Physician-Diagnosed Stroke and Myocardial Infarction in Male
19 Adults in Korea. *Int J Environ Res Public Health*. 2016;13(2):158.
20
21 38. Soulimane S, Simon D, Herman WH, Lange C, Lee CM, Colagiuri S, et al.
22 HbA1c, fasting and 2 h plasma glucose in current, ex- and never-smokers: a
23 meta-analysis. *Diabetologia*. 2014;57(1):30-9.
24
25 39. Papademetriou V, Narayan P, Rubins H, Collins D, Robins S. Influence of risk factors
26 on peripheral and cerebrovascular disease in men with coronary artery disease,
27 low high-density lipoprotein cholesterol levels, and desirable low-density
28 lipoprotein cholesterol levels. HIT Investigators. Department of Veterans Affairs
29 HDL Intervention Trial. *Am Heart J*. 1998;136(4 Pt 1):734-40.
30
31 40. Aronson D, Rayfield EJ. How hyperglycemia promotes atherosclerosis: molecular
32 mechanisms. *Cardiovasc Diabetol*. 2002;1:1.
33
34 41. Rehni AK, Nautiyal N, Perez-Pinzon MA, Dave KR. Hyperglycemia /
35 hypoglycemia-induced mitochondrial dysfunction and cerebral ischemic damage in
36 diabetics. *Metab Brain Dis*. 2015;30(2):437-47.
37
38 42. Shukla V, Shakya AK, Perez-Pinzon MA, Dave KR. Cerebral ischemic damage in
39 diabetes: an inflammatory perspective. *J Neuroinflammation*. 2017;14(1):21.
40
41 43. Zhang Z, Yan J, Shi H. Hyperglycemia as a Risk Factor of Ischemic Stroke. *J*
42 *Drug Metab Toxicol*. 2013;4(4). pii: 153.
43
44 44. Kitada M, Zhang Z, Mima A, King GL. Molecular mechanisms of diabetic
45 vascular complications. *J Diabetes Investig*. 2010;1(3):77-89.
46
47 45. Kemeny SF, Figueroa DS, Clyne AM. Hypo- and Hyperglycemia Impair
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 Endothelial Cell Actin Alignment and Nitric Oxide Synthase Activation in
4 Response to Shear Stress. PLoS ONE, 2013;8(6): e66176.
5
6 46. Iida M, Iida H, Dohi S, Takenaka M, Fujiwara H. Mechanisms underlying
7 cerebrovascular effects of cigarette smoking in rats in vivo. Stroke,
8 1998;29(8):1656-65.
9
10 47. Barua RS, Ambrose JA, Srivastava S, DeVoe MC, Eales-Reynolds LJ. Reactive
11 oxygen species are involved in smoking-induced dysfunction of nitric oxide
12 biosynthesis and upregulation of endothelial nitric oxide synthase: an in vitro
13 demonstration in human coronary artery endothelial cells. Circulation
14 2003;107(18):2342–2347.
15
16 48. Benowitz NL. Cigarette smoking and cardiovascular disease: pathophysiology and
17 implications for treatment. Prog Cardiovasc Dis., 2003;46(1):91–111.
18
19 49. Chen S, Wu P, Zhou L, Shen Y, Li Y, Song H. Relationship between increase of
20 serum homocysteine caused by smoking and oxidative damage in elderly patients
21 with cardiovascular disease. Int J Clin Exp Med. 2015;8(3):4446-54.
22
23 50. Prasad K, Dhar I, Caspar-Bell G. Role of Advanced Glycation End Products and
24 Its Receptors in the Pathogenesis of Cigarette Smoke-Induced Cardiovascular
25 Disease. Int J Angiol. 2015;24(2):75-80.
26
27 51. Ottum MS, Mistry AM. Advanced glycation end products: modifiable
28 environmental factors profoundly mediate insulin resistance. J Clin Biochem Nutr.
29 2015;57(1):1-12.
30
31 52. Biswas SK, Mudi SR, Mollah FH, Bierhaus A, Arslan MI. Serum soluble receptor
32 for advanced glycation end products (sRAGE) is independently associated with
33 cigarette smoking in non-diabetic healthy subjects. Vasc Dis Res. 2013;
34 10(4):380-2.
35
36 53. Zhong C, Zhong X, Xu T, Peng H, Li H, Zhang M, et al. Combined effects of
37 hypertension and heart rate on the risk of stroke and coronary heart disease: a
38 population-based prospective cohort study among Inner Mongolians in China.
39 Hypertens Res. 2015;38(12):883-8.
40
41 54. Du H, Li L, Bennett D, Guo Y, Key TJ, Bian Z, et al. Fresh Fruit Consumption
42 and Major Cardiovascular Disease in China. N Engl J Med. 2016; 374(14):
43 1332–1343.
44
45 55. Ding L, Xu Y, Wang LM, Jiang Y, Zhang M, Li YC, et al. Smoking and Its
46 Relation to Metabolic Status among Chinese Adults: Analysis of a Nationwide
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Survey. *Biomed Environ Sci*. 2016;29(9):619-627.
56.. Xu Y, Wang L, He J, Bi Y, Li M, Wang T, et mal. Prevalence and Control of
Diabetes in Chinese Adults. *JAMA*. 2013;310(9):948-59.

For peer review only

Table 1 General characteristics of diabetes and smoking in the study population (n = 39,887)

<i>Reported variable</i>	Non-smoking /non-DM2	Smoking /non-DM2	Non-smoking /DM2	Smoking /DM2	P
Total	29568	7536	2237	546	
Gender(man)	11087(37.50%)	6890(91.43%)	726(32.45%)	475(87.00%)	<0.01
Age(years)	46.93±17.13	49.64±15.97	61.52±12.71	59.03±11.95	<0.01
Marred (living with partners)	24290(82.15%)	6622(87.87%)	1844(82.43%)	506(92.67%)	<0.01
Below high school	21906(74.09%)	5757(76.39%)	1832(81.90%)	409(74.91%)	
high school	4684(15.84%)	1235(16.39%)	263(11.76%)	94(17.22%)	<0.01
Above high school	2978(10.07%)	544(7.22%)	142(6.34%)	43(7.87%)	
Manual	20702(70.01%)	5538(73.49%)	1382(61.78%)	326(59.71%)	
Non-manual	3664(12.39%)	909(12.06%)	145(6.48%)	59(10.80%)	<0.01
Retired	2277(7.70%)	589(7.82%)	563(25.17%)	124(22.71%)	
Unemployed	2925(9.89%)	500(6.63%)	147(6.57%)	37(6.78%)	
alcohol use	1832(6.20%)	4061(53.89%)	156(6.97%)	284(52.01%)	<0.01
Regular exercise	5943(20.10%)	1519(20.16%)	580(25.93%)	172(31.50%)	
Family history of Hypertension	2007(6.79%)	740(9.82%)	218(9.75%)	56(10.26%)	<0.01
Family history of DM2	350(1.18%)	128(1.70%)	120(5.36%)	26(4.76%)	<0.01
Family history of stroke	574(1.94%)	209(2.77%)	32(1.43%)	13(2.38%)	
Hypertension	6339(21.44%)	2004(26.59%)	759(33.93%)	255(46.70%)	
BMI(≥24kg/m ²)	12532(42.38%)	3536(46.92%)	1382(61.78%)	335(65.02%)	<0.01
Dyslipidemia	3602(12.18%)	1134(15.05%)	456(20.38%)	137(25.09%)	<0.01

Table 2 Associations between smoking, diabetes, and stroke

Variables	Stroke	Non-stroke	Unadjusted OR(95%CI)	Adjusted OR (95%CI)	P	
Smoking	No	622(67.76%)	31183(80.02%)	1.91 (1.63-2.31)	1.83 (1.59-2.14)	<0.01
	Yes	296(32.24%)	7786(19.98%)			
DM2	No	765(83.33%)	36339(93.25%)	2.76 (1.77-4.68)	2.65 (1.70-4.41)	<0.01
	Yes	153(16.67%)	2630(6.75%)			

Adjusted for age, sex, education, marriage status, employment, family history of diabetes, family history of hypertension, family history of stroke, alcohol consumption, physical activity, hypertension, diabetes or smoking, body mass index, and lipids.

Table 3 Odds ratios (ORs) for the association between smoking and stroke by diabetes among participants

Smoking	Diabetes	No stroke	Stroke	Unadjusted OR(95%CI)	Adjusted OR (95%CI)	P
No	No	29056	512	1	1	
	Yes	2127	110	2.93(1.73-3.15)	2.00 (1.56-2.56)	<0.01
Yes	No	7283	253	1.97(1.54-2.37)	1.65 (1.36-2.00)	<0.01
	Yes	503	43	4.85(2.65-6.21)	3.45 (2.30-5.16)	<0.01

Adjusted for age, sex, education, marriage status, employment, family history of diabetes, family history of hypertension, family history of stroke, alcohol consumption, physical activity, hypertension, body mass index, and lipids.

Table 4 Measures for estimating biological interaction between smoking and diabetes for prevalence of stroke in participants

Measures of biological interaction	Estimate (95% CI)
RERI	1.80(1.24—3.84)
AP	0.52(0.37—0.73)
S	1.50(1.18—1.84)

Reference group is no smoking with non-diabetes.

Adjusted for age, sex, education, marriage status, employment, family history of diabetes, family history of hypertension, family history of stroke, alcohol consumption, physical activity, hypertension, body mass index, and lipids.

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	6-7
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Data sources/measurement	8*	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Bias	9	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Study size	10	Describe any efforts to address potential sources of bias	5
Quantitative variables	11	Explain how the study size was arrived at	7-8
		Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
		(a) Describe all statistical methods, including those used to control for confounding	
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
Statistical methods	12	(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	7-8
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Interaction of diabetes and smoking on stroke: A population-based cross-sectional survey in China

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017706.R3
Article Type:	Research
Date Submitted by the Author:	23-Jan-2018
Complete List of Authors:	Lou, Heqing; The School of Public Health, Xuzhou Medical University, Xuzhou, China Dong, Zongmei; The School of Public Health, Xuzhou Medical University, Xuzhou, China; Xuzhou Center for Disease Control and Prevention, Xuzhou, China Zhang, Pan; Xuzhou Center for Disease Control and Prevention, Xuzhou, China, Department of Non-communicable Disease Control Shao, Xiaoping ; The School of Public Health, Xuzhou Medical University, Xuzhou, China Li, Ting; Xuzhou Center for Disease Control and Prevention, Xuzhou, China Zhao, Chunyan; The School of Public Health, Xuzhou Medical University, Xuzhou, China Zhang, Xunbao; The School of Public Health, Xuzhou Medical University, Xuzhou, China Lou, Peian; Xuzhou Center for Disease Control and Prevention, Xuzhou, China, Department of Non-communicable Disease Control; The School of Public Health, Xuzhou Medical University, Xuzhou, China
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	STROKE MEDICINE, DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY

SCHOLARONE™
Manuscripts

1
2
3 **Interaction of diabetes and smoking on stroke: A population-based cross-sectional**
4 **survey in China**
5

6 **Heqing Lou¹, Zongmei Dong^{1,2}, Pan Zhang², Xiaoping Shao,¹ Ting Li², Chunyan Zhao¹,**
7 **Xunbao Zhang^{*1}, Peian Lou^{*1,2}**
8
9

10
11
12 1. The School of Public Health, Xuzhou Medical University, Xuzhou, China

13
14 2. Department of Non-communicable Disease Control, Xuzhou Center for Disease
15 Control and Prevention, Xuzhou, China
16

17
18
19 ***Corresponding authors:**

20 Xunbao Zhang, 209 Tongshan Road, Xuzhou City, Jiangsu Province, China

21 Phone: +86 516-83262018; Fax: +86 516-82702478; E-mail: 437335090@qq.com
22
23

24
25
26 Peian Lou, 142 West Erhuan Road, Xuzhou City, Jiangsu Province, China

27 Phone: +86 516-85956785; Fax: +86 516-89596797; E-mail: lpa82835415@126.com
28
29

30
31 Manuscript category: Research article

32
33 **Keywords:** type 2 diabetes mellitus; smoking; interaction; stroke
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abstract

Objectives: Diabetes and smoking are known independent risk factors for stroke; however, their interaction concerning stroke is less clear. We aimed to explore such interaction and its influence on stroke in Chinese adults.

Design: Cross-sectional study.

Setting: Community-based investigation in Xuzhou, China.

Participants: A total of 39,887 Chinese adults who fulfilled the inclusion criteria were included.

Methods: Participants were selected using a multi-stage stratified cluster method, and completed self-reported questionnaires on stroke and smoking. Type 2 diabetes mellitus (DM2) was assessed by fasting blood glucose or use of antidiabetic medication. Interaction, relative excess risk owing to interaction (RERI), attributable proportion (AP), and synergy index (S) were evaluated using a logistic regression model.

Results: After adjustment for age, sex, marital status, educational level, occupation, physical activity, body mass index, hypertension, family history of stroke, alcohol use, and blood lipids, the relationships between DM2 and stroke, and between smoking and stroke, were still significant: odds ratios were 2.75 (95% confidence interval [CI]: 2.03–3.73) and 1.70 (95% CI: 1.38–2.10), respectively. In subjects with DM2 who smoked, the RERI, AP, and S values (and 95% CIs) were 1.80 (1.24–3.83), 0.52 (0.37–0.73), and 1.50 (1.18–1.84), respectively.

Conclusions: The results suggest there are additive interactions between DM2 and smoking and that these affect stroke in Chinese adults.

Article Summary: Strengths and limitations of this study

- The strengths of this study were that a large sample population was randomly selected from the general population of Xuzhou and many confounding risk factors were adjusted for.
- Owing to the cross-sectional design, we could not determine a causal combined relationship among diabetes, smoking and stroke.
- We were not able to control for some important and well-known risk factors of diabetes, such as heart rate and cardiovascular causes.
- We did not measure fresh fruit consumption, which is causally related to stroke.

INTRODUCTION

Stroke is an ongoing global health problem. In 2016, there were 5.53 million from stroke worldwide. Stroke was also the second most common cause of premature mortality and secondary disability.¹ The 2015 Report on Chinese Stroke Prevention indicates stroke as the leading cause of death in China, with incidence increasing by 8.7% per annum.² Stroke rates in China are higher than those in Western and other Asian countries.^{3,4} Moreover, the number of stroke patients in China is likely to increase because of lifestyles, demographic changes, and inadequate control of major risk factors for stroke.² It is therefore important to identify and prevent these risk factors.

The major risk factors for stroke are hypertension, diabetes mellitus, hypercholesterolemia, smoking, physical inactivity, obesity, and a family history of stroke.⁵⁻⁸ Although these play a role in the development of stroke, its formation is not entirely caused by a single risk factor. The more risk factors a person has, the greater the likelihood of incurring a stroke.⁷ In fact, >90% of the global burden of stroke in 2013 was attributable to the combined effect of all modifiable risk factors.⁸

People with comorbid diabetes and smoking may represent a subgroup with high risk of developing stroke; however, few studies have examined the interaction of diabetes and smoking with regard to stroke. The primary aim of this cross-sectional study was to examine the interaction of type 2 diabetes mellitus (DM2) and smoking on stroke in Chinese adults. A secondary aim was to evaluate the associations between DM2 and stroke, and between smoking and stroke.

MATERIALS AND METHODS

Study design and recruitment criteria

1
2
3 This population-based, cross-sectional survey was conducted in Xuzhou City,
4
5 Jiangsu Province, China, from February to June 2013. The sample was selected
6
7 with two-stage probability proportional to size, from all 11 regions in Xuzhou. In
8
9 the first stage, five subdistricts/townships in urban/rural areas were selected in
10
11 accordance with the population of each subdistrict/township from each region,
12
13 with probability proportional to size sampling. In the second stage, five
14
15 communities/villages were selected in accordance with the population of each
16
17 community/village from each subdistrict/township with probability proportional
18
19 to size sampling. In the final stage, one person ≥ 18 years old and who had lived
20
21 in his or her current residence for ≥ 5 years was selected from each household
22
23 through use of a Kish selection table. Those who met either or both of the
24
25 following criteria were excluded: (1) previous diagnosis of neuropathy, psychosis,
26
27 or unclear speech or (2) member of the floating population or temporary
28
29 residents. A total of $\geq 13,500$ people were selected, assuming an estimation
30
31 incidence of stroke of 2.0%,⁹ with 90% power, $\alpha=0.05$, and allowing for a
32
33 dropout rate of 15%. Trained interviewers interviewed participants face-to-face
34
35 on the day of the participants' regular medical appointments. All participants
36
37 underwent 12-h overnight fasting and blood sampling to test basic fasting
38
39 plasma glucose. After blood sampling, each received a health examination and
40
41 completed a structured questionnaire inquiring on demographic information,
42
43 medical history, medication history, and smoking, alcohol consumption, and
44
45 exercise habits.
46
47
48
49
50
51

52 53 **Key measurements**

54
55 Stroke was assessed using subjects' self-reported responses, and defined as an acute
56
57

1
2
3 disturbance of focal areas in the brain lasting for ≥ 24 h and thought to be caused by
4
5 intracranial hemorrhage or ischemia.¹⁰ We examined the medical records of
6
7 participants reporting a diagnosis of stroke to check that participants satisfied this
8
9 definition. The diagnosis was also confirmed through computed tomography and
10
11 magnetic resonance imaging scans. Detailed clinical information about stroke was
12
13 based on the International Classification of Disease, 10th Revision, codes I60–I64.
14
15 DM2 was defined as fasting blood glucose ≥ 7.0 mmol/L, any use of antidiabetic
16
17 medication, or self-reported history of DM2.¹¹ Hypertension was defined as systolic
18
19 blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, any use of
20
21 antihypertensive medication, or self-reported history of hypertension.¹²
22
23
24
25

26 **Covariates**

27
28 Age, sex, current employment status, marital status, level of education,
29
30 cigarette smoking, alcohol consumption, physical activity, and family history of
31
32 diseases, including DM2, hypertension, and stroke, were assessed using a
33
34 standardized questionnaire. Employment status was categorized as manual,
35
36 non-manual, unemployed, or retired. Education was categorized as below high
37
38 school, high school, or above high school. Lifestyle variables included cigarette
39
40 smoking, alcohol consumption, and physical activity level. Cigarette smoking was
41
42 defined as having smoked at least 100 cigarettes in one's lifetime. Information was
43
44 obtained on the amount and type of alcohol consumed during the previous year, and
45
46 alcohol drinking was defined as consumption of ≥ 30 g per week for ≥ 1 year. Regular
47
48 leisure-time physical activity was defined as participation in moderate or vigorous
49
50 activity for ≤ 30 min per day, ≥ 3 days a week. Each participant's height (to the nearest
51
52 0.1 cm) and weight (to the nearest 0.1 kg) in light indoor clothing were measured.
53
54
55
56
57

1
2
3 Body mass index (BMI; in kg/m²) was calculated; categorized as underweight (<18.5
4 kg/m²), normal weight (18.5–24.0 kg/m²), or overweight/obese (>24.0 kg/m²).¹³

5
6
7 Dyslipidemia was defined as use of any lipid-lowering medication or self-reported
8 history of the condition.
9

10 11 12 **Statistical analysis**

13
14 Participants were divided into four groups in accordance with their smoking
15 status and DM2: non-smokers with no DM2, smokers with no DM2, non-smokers
16 with DM2, and smokers with DM2. Statistical analysis was performed using IBM SPSS
17 for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA). The general characteristics of
18 continuous variables were compared across the four subgroups using analysis of
19 variance. The categorical variables were expressed as a percentage and the groups
20 were compared using a chi-squared test. Logistic regression analysis was performed
21 to estimate the probability of having a stroke and 95% confidence interval (CI) for
22 each risk factor category stratified by DM2 and smoking, adjusting for age, sex,
23 occupation, education, marital status, BMI, physical activity, drinking status,
24 hypertension status, and family history of disease, including DM2, hypertension, and
25 stroke.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

41 Biological interactions should be based on an additive scale rather than a
42 multiplication scale.^{14,15} We therefore used three measures to estimate biological
43 interactions between DM2 and smoking: relative excess risk owing to interaction
44 (RERI), attributable proportion (AP) owing to interaction, and synergy index (S). RERI
45 is the excess risk attributed to interaction relative to the risk without exposure to
46 diabetes and smoking. AP refers to the attributable proportion of disease caused by
47 interaction in subjects with exposure to both variables. S is the excess risk from
48
49
50
51
52
53
54
55
56
57

1
2
3 exposure to both variables when there is a biological interaction relative to the risk
4
5 from exposure to both variables without interaction. In the absence of additive
6
7 interactions, RERI and AP equal 0.^{14,16} In the current study, RERI >0, AP >0, and S >0
8
9 indicated statistical significance, set at $p < 0.05$ (two-tailed).
10
11
12
13

14 **Ethics approval and consent to participate**

15
16
17 The study protocol was approved by Xuzhou Center for Disease Control and
18
19 Prevention. The procedures followed were in accordance with the standards of the
20
21 ethics committee of the Xuzhou Center for Disease Control and Prevention and with
22
23 the Declaration of Helsinki (1975, revised 2000). Written informed consent was
24
25 obtained from all participants.
26
27
28
29
30
31

32 **RESULTS**

33 **General characteristics of participants**

34
35
36 Of the 41,658 individuals initially sampled, 1253 did not respond to the smoking
37
38 question or complete the blood glucose tests, and 518 did not meet our study
39
40 criteria. A final total of 39,887 adults (19,178 men and 20,709 women) with
41
42 complete data were included in the analysis (response rate: 95.7%). Table 1 shows
43
44 the characteristics of the study population. The proportion of participants with DM2
45
46 was 7.00% (2783/39,887), of stroke subjects with DM2 was 16.67%, and of
47
48 non-stroke subjects with DM2 was only 6.75%; there was a statistically significant
49
50 difference between the two groups ($\chi^2 = 135.92$, $p < 0.001$). The proportion of
51
52 smokers was 20.26% (8082/39,887), stroke participants who smoked was 32.24%,
53
54
55
56
57
58
59
60

1
2
3 and non-stroke participants who smoked was 19.98%; there was a statistically
4
5 significant difference in smoking between stroke and non-stroke patients ($\chi^2 = 83.49$,
6
7 $p < 0.001$).

10 **Association of diabetes and smoking with stroke**

11
12
13 The 5.50% incidence of stroke in subjects with DM2 exceeded the 2.06% incidence
14
15 in those with no DM2 ($\chi^2 = 139.11$, $p < 0.001$). Individuals who smoked had a higher
16
17 stroke incidence compared with non-smokers (3.36% vs. 1.96%; $\chi^2 = 83.49$, $p < 0.001$;
18
19 see Table 2). Subjects with DM2 had a significantly increased risk of stroke compared
20
21 with those with no DM2 (OR: 2.65, 95% CI: 1.70–4.41, $p < 0.001$), after adjusting for
22
23 confounders (see Table 3). The risks of ischemic and hemorrhagic stroke were
24
25 increased by DM2, after adjusting for confounders; the ORs were 2.71 (95% CI:
26
27 1.72–4.49) and 1.82 (95% CI: 1.34–3.35), respectively. Smokers had a significantly
28
29 increased risk of stroke compared with non-smokers (OR: 1.83, 95% CI: 1.59–2.14, p
30
31 < 0.001), after adjusting for confounders (see Table 3). The risks of ischemic and
32
33 hemorrhagic stroke were increased by smoking, after adjusting for confounders; the
34
35 ORs were 1.32 (95% CI: 1.12–2.53) and 1.95 (95% CI: 1.40–3.41), respectively.

42 **Interaction between diabetes and smoking in relation to stroke**

43
44
45 Individuals who only had DM2 or only smoked had a significantly increased risk of
46
47 stroke compared with those who did not have DM2 and did not smoke (OR: 2.00, 95%
48
49 CI: 1.56–2.56; OR: 1.65, 95% CI: 1.36–2.00; respectively; all $p < 0.001$), after adjusting
50
51 for confounders. Table 3 shows the results from the multiple logistic regression
52
53 models. The incidence of stroke was greatest in those who had DM2 and smoked
54
55 (OR: 3.45, 95% CI: 2.30–5.16, $p < 0.001$), after adjusting for confounders.

Sensitivity analysis

There was a strong additive interaction between DM2 and smoking (RERI: 1.80, 95% CI: 1.24–2.14; AP: 0.52, 95% CI: 0.37–0.73; and S: 1.50, 95% CI: 1.18–1.84, respectively); 52% of stroke occurrence was attributed to the interaction between DM2 and smoking (Table 4).

DISCUSSION

There were two main findings in this study. First, there was an interaction of DM2 and smoking with relation to the incidence of stroke. Second, DM2 and smoking were found to be significantly associated with increased risk of stroke in Chinese adults, independent of potential confounders such as age, sex, occupation, education, marital status, BMI, physical activity, drinking status, hypertension status, and family history of diseases including diabetes, hypertension, or stroke.

The proportion of participants with DM2 in this study was 19.67%, which is lower than that reported in the China National Stroke Registry Study (27.0%),¹⁷ lower than that reported in a comparison of risk factors for ischemic stroke in Chinese versus Caucasian individuals (25.0%),¹⁸ and higher than that reported in a study of the Chinese National Health Insurance program (3.8%)¹⁹ and a review of stroke in China (4%–15%).²⁰ The present results are also inconsistent with figures for diabetes in stroke patients reported for other countries.^{21,22} This discrepancy may be due to differences in study design, sampling size, region, diabetes diagnosis, and the clinical features of stroke, but could also be a result of ethnic group differences, as many studies have shown that stroke incidence rates differ among ethnic groups.²³

Numerous epidemiologic studies, including cross-sectional studies and

1
2
3 prospective cohort studies, have demonstrated associations between diabetes and
4
5 stroke.^{22,24-27} A population-based study of 173,979 discharged patients admitted with
6
7 hemorrhagic stroke was conducted in Spain from 2003 to 2012. The authors of that
8
9 study reported a positive association between diabetes and stroke (incidence rate
10
11 ratio: 1.38, 95% CI: 1.35–1.40 for men; incidence rate ratio: 1.31, 95% CI: 1.29–1.34
12
13 for women).²² Folsom et al. reported that the relative risk (RR) of ischemic stroke was
14
15 2.22 (95% CI: 1.5–3.2) for individuals with diabetes after adjustment for other stroke
16
17 risk factors in a 6–8-year follow-up.²⁴ Iso et al.²⁵ reported that the association
18
19 between non-embolic ischemic stroke and diabetes was particularly strong among
20
21 non-hypertensive subjects with higher subscapular skinfold thickness values; the
22
23 multivariate RR was 4.9 (95% CI: 2.5–9.5) in a 17-year prospective cohort study of
24
25 10,582 Japanese individuals (4287 men and 6295 women) aged 40–69 years. A
26
27 systematic review and meta-analysis of 64 cohort studies with 775,385 individuals
28
29 showed that diabetes is consistently associated with increased risk of stroke; the
30
31 pooled maximum-adjusted RR of stroke associated with diabetes was 2.28 (95% CI:
32
33 1.93–2.69) for women and 1.83 (95% CI: 1.60–2.08) for men.²⁶ Liao et al. also
34
35 reported that diabetic patients have an increased risk of stroke (adjusted hazard ratio:
36
37 1.75, 95% CI: 1.64–1.86) compared with those without diabetes; associations
38
39 between diabetes and stroke risk were significant for both sexes and all age groups.²⁷
40
41 The present findings also demonstrated an association between diabetes and stroke.
42
43
44
45
46
47

48
49 Robson et al.²⁸ confirmed that poor blood sugar control increases the risk of
50
51 stroke. One prospective cohort study of 467,508 men and women aged 30–79 years
52
53 with no history of diabetes or stroke showed that each 1-mmol/L (18-mg/dL) higher
54
55 than usual increase of random plasma glucose level above 5.9 mmol/L (106 mg/dL)
56
57

1
2
3 was associated with ischemic stroke (adjusted hazard ratio: 1.08, 95% CI:
4
5 1.07–1.09).²⁹ Moreover, a study of 4669 patients who had incurred a minor stroke
6
7 revealed during a 3-month follow-up that stroke patients with diabetes experienced
8
9 stroke recurrence and disability.³⁰ Therefore, effective glycemic control not only
10
11 reduces the incidence of stroke but also can reduce stroke recurrence and associated
12
13 disability.
14
15

16
17 A higher proportion of stroke than non-stroke patients tend to be smokers.
18
19 Indeed, Wang et al. reported that 48% of stroke patients smoked.³¹ Tsai et al.¹⁸
20
21 reported a figure of 38% and our results showed 32.24%. Although the proportions
22
23 differ, they are all quite high. The discrepancy may reflect a bias in the reporting of
24
25 smoking status among study participants.
26
27

28
29 Many studies have shown that smoking is a strong risk factor for development
30
31 of stroke.³²⁻³⁴ The British Regional Heart Study, which included 7735 men aged 40–59
32
33 years, showed that after full adjustment for other risk factors, current smokers had a
34
35 nearly fourfold RR of stroke compared with never-smokers (RR: 3.7, 95% CI: 2.0–6.9).
36
37 Ex-cigarette smokers showed lower risk than current smokers, but showed excess
38
39 risk compared with never-smokers (RR: 1.7, 95% CI: 0.9–3.3, $p = 0.11$).³³ During a
40
41 mean follow-up of 8.5 years, the risk for all forms of stroke significantly increased
42
43 (RR: 0.9–3.3, 95% CI: 1.4–24) and increased for ischemic strokes (RR: 4.8, 95% CI:
44
45 1.2–20) among cigarette-smoking women with a cigarette-smoking spouse
46
47 compared with those with a non-smoking spouse and after adjusting for other
48
49 cardiovascular risk factors.³⁴ However, a systematic review and meta-analysis of 81
50
51 cohorts in Asia, including 3,980,359 individuals and 42,401 strokes, showed smoking
52
53 did not contribute to the risk of stroke.³⁵ The proportion of Chinese stroke patients
54
55
56
57
58
59
60

1
2
3 who smoke is higher than that of Caucasians.¹⁸ One systematic review and
4
5 meta-analysis of 15 cohort studies and 178 case-control studies found smoking was
6
7 an independent risk factor for stroke (pooled RRs: 1.27, 95% CI: 1.21–1.35) in a
8
9 Chinese population.⁷ More frequent smokers are more likely to incur a stroke.^{36,37} A
10
11 meta-analysis that included 16,886 men and 18,539 women without known diabetes
12
13 revealed hemoglobin A1c was 0.10% (95% CI: 0.08–0.12, 1.1 mmol/mol [0.9–1.3])
14
15 higher in current smokers and 0.03% (95% CI: 0.01–0.05, 0.3 mmol/mol [0.1–0.5])
16
17 higher in ex-smokers than in never-smokers.³⁸ Therefore, our findings support
18
19 previous evidence smoking is associated with stroke in Chinese populations.⁴
20
21 However, the present study only wanted to observe the interaction of smoking and
22
23 diabetes on stroke, the cigarette smokers were not categorized as current, former
24
25 and never smokers. Therefore, when compared the association between smoking
26
27 and stroke of our study with that of others should be carefully.

28
29
30
31
32
33 One study reported that in comparison with nonsmoking patients with no
34
35 diabetes mellitus or hypertension, patients with those conditions and who smoked
36
37 had a threefold increase in prevalence of peripheral vascular disease and a 3.5-fold
38
39 increase in cerebrovascular disease^[39]. Our results reinforce such findings.

40
41
42 The pathophysiological mechanisms of hyperglycemia induce oxidative stress;
43
44 promote formation of advanced glycosylation end products;^{40,41} increase
45
46 blood–brain barrier permeability and inflammatory responses;⁴² lead to
47
48 accumulation of reactive oxygen species/reactive nitrogen, inflammation, and
49
50 mitochondrial dysfunction;⁴³ lead to cellular dysfunction; damage vascular tissue;
51
52 inhibit endogenous vascular protective factors; alter vascular homeostasis;⁴⁴ raise
53
54 levels of reactive oxygen species and advanced glycation end products; decrease
55
56

1
2
3 levels of mitochondrial superoxide dismutase;⁴¹ and correlate with endothelial cell
4
5 dysfunction and nitric oxide production.⁴⁵ All these actions contribute to accelerating
6
7 the atherosclerotic process. Therefore, diabetic patients are more prone to incurring
8
9 stroke.

10
11 Cigarette smoking is associated with increased reactive oxygen species, oxidative
12
13 stress, blood–brain barrier permeability, sympathetic activation and nitric oxide
14
15 production, reduced cerebral blood flow and serum superoxide dismutase levels,
16
17 attenuation of the vasodilation of cerebral arterioles, and induction of
18
19 atherosclerosis and thrombosis.⁴⁶⁻⁴⁹ Moreover, cigarette smoke elevates serum
20
21 levels of advanced glycation end products and reduces soluble receptors for those
22
23 end products, resulting in development of atherosclerosis and related stroke.⁵⁰⁻⁵²
24
25 Smoking is therefore correlated with increased risk of stroke.
26
27
28
29

30 Collectively, diabetes and smoking induce oxidative stress and nitric oxide
31
32 production; increase reactive oxygen species, blood–brain barrier permeability, and
33
34 the level of advanced glycation end products; and reduce cerebral blood flow and
35
36 serum superoxide dismutase. Therefore, diabetic patients who smoke also have a
37
38 greater risk of stroke.
39
40

41 The strengths of the current study are that we used a community-based
42
43 multistage sampling design, large sample size, and randomly selected participants.
44
45 However, the study has several limitations. First, because of the cross-sectional
46
47 design, we could not determine a causal relationship between DM2, smoking, and
48
49 stroke. Second, we were unable to control for some important and well-known risk
50
51 factors of stroke, such as heart rate⁵³ and cardiac causes.⁶ Third, we did not measure
52
53 fresh fruit consumption,⁵⁴ which is causally negative related to stroke. Finally,
54
55
56
57

1
2
3 patients self-reported their cigarette smoking status; therefore, the risk of
4
5 misclassification and recall bias with the definition of smoking could not be avoid.
6

7 **Conclusion**

8
9 The results of this cross-sectional study indicate diabetic patients who smoke are
10
11 3.5 times more likely to develop stroke than non-diabetics who do not smoke.
12
13 Diabetes and smoking had a combined positive correlation with stroke. These results
14
15 have important public health implications. Among Chinese adults, the current rate of
16
17 smoking is as high as 28.3%⁵⁵ and DM2 prevalence is 11.6%.⁵⁶ Therefore, it is
18
19 important to implement stroke-prevention measures aimed at reducing smoking and
20
21 improving glycemic control in diabetic patients in China.
22
23
24
25

26 **COMPETING INTERESTS**

27
28 The authors declare that they have no competing interests.
29

30 **Acknowledgments**

31
32 We thank all the participants involved in the survey. We also thank the Regional
33
34 Centers for Disease Control and Prevention as well as clinics in Xuzhou for their
35
36 collaboration.
37
38
39

40 **Funding**

41
42 This research was funded by the Preventive Medicine research projects of Jiangsu
43
44 Province Health Department in 2015 (Y2015010) and the Science and Technology
45
46 projects of Xuzhou City in 2015 (KC15SM046). The researchers were independent
47
48 from the funders. The study funders had no influence on the study design, data
49
50 collection, analysis, interpretation of data, writing of the report, or decision to
51
52 submit the article for publication.
53
54
55

56 **Duality of interest**

1
2
3 The authors declare there is no duality of interest associated with this manuscript.

4 **Authors' contributions**

5
6 HL wrote/edited the manuscript and created tables. ZD, PZ, XS, TL, CZ, XZ, and PL

7
8 contributed to the discussion and reviewed/edited the manuscript. XZ

9
10 conceptualized the study. PL is the guarantor of this work and, as such, had full

11
12 access to all data in the study and takes responsibility for the integrity of the data

13
14 and accuracy of the data analysis. All authors read and approved the final

15
16 manuscript.

17
18 **Availability of data and materials**

19
20 All data relevant to the given manuscript have been stored in a separate file that can

21
22 be made freely available to external investigators upon request.

References

1. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390(10100):1151-1210.
2. Stroke Control Project Committee of National Health and Family Planning Commission of the People's Republic of China. Report on the Chinese Stroke Prevention (2015) 1st ed. Beijing: China Pecking Union Medical College Press, 2015.
3. Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, et al. Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013;381(9882):1987-2015.
4. Hata J, Kiyohara Y. Epidemiology of Stroke and Coronary Artery Disease in Asia. *Circ J*. 2013; 77(8):1923-32.
5. Mi T, Sun S, Du Y, Guo S, Cong L, Cao M, et al. Differences in the distribution of risk factors for stroke among the high-risk population in urban and rural areas of Eastern China. *Brain Behav*. 2016;6(5):e00461.
6. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*. 2010;376(9735):112-23.
7. Wang J, Wen X, Li W, Li X, Wang Y, Lu W. Risk Factors for Stroke in the Chinese Population: A Systematic Review and Meta-Analysis. *J Stroke Cerebrovasc Dis*. 2016; pii: S1052-3057(16)30599-7.
8. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol*. 2016;15(9):913-24.
9. Zhang P, Jiao S, Zhou Y, Li G, Shi Y, Li H, et al. Studies on prevalence and control of several common chronic diseases among Beijing adults in 2005. *Chin J Epidemiol*, 2007;28(7):625-630.
10. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; 44:2064-89.

11. Chinese Diabetes Society. Chinese guidelines for the prevention and treatment of type 2 diabetes mellitus (2010 Edition). *Chinese Journal of Diabetes*, 2012;20(1): 1-36.
12. China hypertension prevention guidelines revision committee. Guidelines for prevention and treatment of hypertension in China[2010 Edition]. *Chinese Journal of hypertension*,2011;19(8):701-743.
13. Zhou BF. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults--study on optimal cut-off points of body mass index and waist circumference in Chinese adults. *Biomed Environ Sci* 2002;15, 83-96.
14. Hosmer DW, Lemeshow S . Confidence interval estimation of interaction. *Epidemiology* 1992; 3(5):452-456.
15. Knol MJ, van der Tweel I, Grobbee DE, Numans ME, Geerlings MI. Estimating interaction on an additive scale between continuous determinants in a logistic regression model. *Int J Epidemiol*. 2007;36(5):1111-8.
16. Knol MJ, VanderWeele TJ, Groenwold RH, Klungel OH, Rovers MM, Grobbee DE. Estimating measures of interaction on an additive scale for preventive exposures. *Eur J Epidemiol* 2011; 26(6):433–438.
17. Pan Y, Wang Y, Li H, Gaisano HY, Wang Y, He Y. Association of Diabetes and Prognosis of Minor Stroke and Its Subtypes: A Prospective Observational Study. *PLoS One*. 2016;11(4):e0153178.
18. Tsai CF, Anderson N, Thomas B, Sudlow CL. Risk factors for ischemic stroke and its subtypes in Chinese vs. Caucasians: Systematic review and meta-analysis. *Int J Stroke*. 2015;10(4):485-93.
19. Guo Y, Wang H, Tao T, Tian Y, Wang Y, Chen Y, et al. Determinants and Time Trends for Ischaemic and Haemorrhagic Stroke in a Large Chinese Population. *PLoS ONE* 2016; 11(9):e0163171.
20. Shi FL, Hart RG, Sherman DG, Tegeler CH. Stroke in the People's Republic of China. *Stroke*. 1989;20(11):1581-5.
21. Chang T, Gajasinghe S, Arambepola C. Prevalence of Stroke and Its Risk Factors in Urban Sri Lanka Population-Based Study. *Stroke*. 2015;46(10):2965-8.
22. Muñoz-Rivas N, Méndez-Bailón M, Hernández-Barrera V, de Miguel-Yanes JM, Jimenez-Garcia R, Esteban-Hernández J, et al. Type 2 Diabetes and

- 1
2
3 Hemorrhagic Stroke: A Population-Based Study in Spain from 2003 to 2012. *J*
4 *Stroke Cerebrovasc Dis.* 2016;25(6):1431-43.
5
6 23. Tsai CF, Thomas B, Sudlow CL. Epidemiology of stroke and its subtypes in
7 Chinese vs white populations. *Neurology.* 2013;81(3):264-72.
8
9 24. Folsom AR, Rasmussen ML, Chambless LE, Howard G, Cooper LS, Schmidt MI,
10 et al. Prospective associations of fasting insulin, body fat distribution, and diabetes
11 with risk of ischemic stroke. The Atherosclerosis Risk in Communities (ARIC)
12 Study Investigators. *Diabetes Care.* 1999;22(7):1077-83
13
14 25. Iso H, Imano H, Kitamura A, Sato S, Naito Y, Tanigawa T, et al. Type 2 diabetes
15 and risk of non-embolic ischaemic stroke in Japanese men and women.
16 *Diabetologia.* 2004;47(12):2137-44.
17
18 26. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in
19 women compared with men: a systematic review and meta-analysis of 64 cohorts,
20 including 775 385 individuals and 12 539 strokes. *Lancet.*
21 2014;383(9933):1973-80.
22
23 27. Liao CC, Shih CC, Yeh CC, Chang YC, Hu CJ, Lin JG, et al. Impact of Diabetes
24 on Stroke Risk and Outcomes: Two Nationwide Retrospective Cohort Studies.
25 *Medicine (Baltimore).* 2015;94(52):e2282.
26
27 28. Robson R, Lacey AS, Luzio SD, Van Woerden H, Heaven ML, Wani M, et al.
28 HbA1c measurement and relationship to incident stroke. *Diab Med.*
29 2016;33:459–62.
30
31 29. Bragg F, Li L, Bennett D, Guo Y, Lewington S, Bian Z, et al. Association of
32 Random Plasma Glucose Levels With the Risk for Cardiovascular Disease Among
33 Chinese Adults Without Known Diabetes. *JAMA Cardiol.* 2016;1(7):813-823.
34
35 30. Wu L, Wang A, Wang X, Zhao X, Wang C, Liu L, et al. Factors for short-term
36 outcomes in patients with a minor stroke: results from China National Stroke
37 Registry. *BMC Neurol.* 2015;15:253.
38
39 31. Wang W, Jiang B, Sun H, Ru X, Sun D, Wang L, et al. Prevalence, Incidence and
40 Mortality of Stroke in China: Results from a Nationwide Population-Based Survey
41 of 480,687 Adults. *Circulation.* 2017;135(8):759-771.
42
43 32 Wolf PA, D'Agostino RB, Kannel WB, Bonita R, Belanger AJ. Cigarette smoking
44 as risk factor for stroke the framingham study. *JAMA.* 1988;259(7):1025-9.
45
46 33. Wannamethee SG, Shaper AG, Whincup PH, Walker M. Smoking cessation and
47 the risk of stroke in middle-aged men. *JAMA.* 1995;274(2):155-60.
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 34. Qureshi AI, Suri MF, Kirmani JF, Divani AA. Cigarette smoking among spouses:
4 another risk factor for stroke in women. *Stroke*, 2005;36(9):e74-6.
5
6 35. Peters SA, Huxley RR, Woodward M. Smoking as a Risk Factor for Stroke in
7 Women Compared With Men A Systematic Review and Meta-analysis of 81
8 Cohorts, Including 3 980 359 Individuals and 42 401 Strokes. *Stroke*.
9 2013;44(10):2821-8.
10
11 36. Shah RS, Cole JW. Smoking and stroke: the more you smoke the more you stroke.
12 *Expert Rev Cardiovasc Ther*. 2010;8:917–932. doi: 10.1586/erc.10.56.
13
14 37. Chang S, Kim H, Kim V, Lee K, Jeong H, Lee JH, et al. Association Between
15 Smoking and Physician-Diagnosed Stroke and Myocardial Infarction in Male
16 Adults in Korea. *Int J Environ Res Public Health*. 2016;13(2):158.
17
18 38. Soulimane S, Simon D, Herman WH, Lange C, Lee CM, Colagiuri S, et al.
19 HbA1c, fasting and 2 h plasma glucose in current, ex- and never-smokers: a
20 meta-analysis. *Diabetologia*. 2014;57(1):30-9.
21
22 39. Papademetriou V, Narayan P, Rubins H, Collins D, Robins S. Influence of risk factors
23 on peripheral and cerebrovascular disease in men with coronary artery disease,
24 low high-density lipoprotein cholesterol levels, and desirable low-density
25 lipoprotein cholesterol levels. HIT Investigators. Department of Veterans Affairs
26 HDL Intervention Trial. *Am Heart J*. 1998;136(4 Pt 1):734-40.
27
28 40. Aronson D, Rayfield EJ. How hyperglycemia promotes atherosclerosis: molecular
29 mechanisms. *Cardiovasc Diabetol*. 2002;1:1.
30
31 41. Rehni AK, Nautiyal N, Perez-Pinzon MA, Dave KR. Hyperglycemia /
32 hypoglycemia-induced mitochondrial dysfunction and cerebral ischemic damage in
33 diabetics. *Metab Brain Dis*. 2015;30(2):437-47.
34
35 42. Shukla V, Shakya AK, Perez-Pinzon MA, Dave KR. Cerebral ischemic damage in
36 diabetes: an inflammatory perspective. *J Neuroinflammation*. 2017;14(1):21.
37
38 43. Zhang Z, Yan J, Shi H. Hyperglycemia as a Risk Factor of Ischemic Stroke. *J*
39 *Drug Metab Toxicol*. 2013;4(4). pii: 153.
40
41 44. Kitada M, Zhang Z, Mima A, King GL. Molecular mechanisms of diabetic
42 vascular complications. *J Diabetes Investig*. 2010;1(3):77-89.
43
44 45. Kemeny SF, Figueroa DS, Clyne AM. Hypo- and Hyperglycemia Impair
45 Endothelial Cell Actin Alignment and Nitric Oxide Synthase Activation in
46 Response to Shear Stress. *PLoS ONE*, 2013;8(6): e66176.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 46. Iida M, Iida H, Dohi S, Takenaka M, Fujiwara H. Mechanisms underlying
4 cerebrovascular effects of cigarette smoking in rats in vivo. *Stroke*,
5 1998;29(8):1656-65.
6
7
8 47. Barua RS, Ambrose JA, Srivastava S, DeVoe MC, Eales-Reynolds LJ. Reactive
9 oxygen species are involved in smoking-induced dysfunction of nitric oxide
10 biosynthesis and upregulation of endothelial nitric oxide synthase: an in vitro
11 demonstration in human coronary artery endothelial cells. *Circulation*
12 2003;107(18):2342–2347.
13
14
15 48. Benowitz NL. Cigarette smoking and cardiovascular disease: pathophysiology and
16 implications for treatment. *Prog Cardiovasc Dis.*, 2003;46(1):91–111.
17
18 49. Chen S, Wu P, Zhou L, Shen Y, Li Y, Song H. Relationship between increase of
19 serum homocysteine caused by smoking and oxidative damage in elderly patients
20 with cardiovascular disease. *Int J Clin Exp Med.* 2015;8(3):4446-54.
21
22
23 50. Prasad K, Dhar I, Caspar-Bell G. Role of Advanced Glycation End Products and
24 Its Receptors in the Pathogenesis of Cigarette Smoke-Induced Cardiovascular
25 Disease. *Int J Angiol.* 2015;24(2):75-80.
26
27
28 51. Ottum MS, Mistry AM. Advanced glycation end products: modifiable
29 environmental factors profoundly mediate insulin resistance. *J Clin Biochem Nutr.*
30 2015;57(1):1-12.
31
32
33 52. Biswas SK, Mudi SR, Mollah FH, Bierhaus A, Arslan MI. Serum soluble receptor
34 for advanced glycation end products (sRAGE) is independently associated with
35 cigarette smoking in non-diabetic healthy subjects. *Vasc Dis Res.* 2013;
36 10(4):380-2.
37
38
39 53. Zhong C, Zhong X, Xu T, Peng H, Li H, Zhang M, et al. Combined effects of
40 hypertension and heart rate on the risk of stroke and coronary heart disease: a
41 population-based prospective cohort study among Inner Mongolians in China.
42 *Hypertens Res.* 2015;38(12):883-8.
43
44
45 54. Du H, Li L, Bennett D, Guo Y, Key TJ, Bian Z, et al. Fresh Fruit Consumption
46 and Major Cardiovascular Disease in China. *N Engl J Med.* 2016; 374(14):
47 1332–1343.
48
49
50 55. Ding L, Xu Y, Wang LM, Jiang Y, Zhang M, Li YC, et al. Smoking and Its
51 Relation to Metabolic Status among Chinese Adults: Analysis of a Nationwide
52 Survey. *Biomed Environ Sci.* 2016;29(9):619-627.
53
54
55 56.. Xu Y, Wang L, He J, Bi Y, Li M, Wang T, et mal. Prevalence and Control of
56
57
58
59

1
2
3 Diabetes in Chinese Adults. JAMA. 2013;310(9):948-59.
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Table 1 General characteristics of diabetes and smoking in the study population (n = 39,887)

<i>Reported variable</i>	Non-smoking /non-DM2	Smoking /non-DM2	Non-smoking /DM2	Smoking /DM2	P
Total	29568	7536	2237	546	
Gender(man)	11087(37.50%)	6890(91.43%)	726(32.45%)	475(87.00%)	<0.01
Age(years)	46.93±17.13	49.64±15.97	61.52±12.71	59.03±11.95	<0.01
Marred (living with partners)	24290(82.15%)	6622(87.87%)	1844(82.43%)	506(92.67%)	<0.01
Below high school	21906(74.09%)	5757(76.39%)	1832(81.90%)	409(74.91%)	
high school	4684(15.84%)	1235(16.39%)	263(11.76%)	94(17.22%)	<0.01
Above high school	2978(10.07%)	544(7.22%)	142(6.34%)	43(7.87%)	
Manual	20702(70.01%)	5538(73.49%)	1382(61.78%)	326(59.71%)	
Non-manual	3664(12.39%)	909(12.06%)	145(6.48%)	59(10.80%)	<0.01
Retired	2277(7.70%)	589(7.82%)	563(25.17%)	124(22.71%)	
Unemployed	2925(9.89%)	500(6.63%)	147(6.57%)	37(6.78%)	
alcohol use	1832(6.20%)	4061(53.89%)	156(6.97%)	284(52.01%)	<0.01
Regular exercise	5943(20.10%)	1519(20.16%)	580(25.93%)	172(31.50%)	
Family history of Hypertension	2007(6.79%)	740(9.82%)	218(9.75%)	56(10.26%)	<0.01
Family history of DM2	350(1.18%)	128(1.70%)	120(5.36%)	26(4.76%)	<0.01
Family history of stroke	574(1.94%)	209(2.77%)	32(1.43%)	13(2.38%)	
Hypertension	6339(21.44%)	2004(26.59%)	759(33.93%)	255(46.70%)	
BMI(≥24kg/m ²)	12532(42.38%)	3536(46.92%)	1382(61.78%)	335(65.02%)	<0.01
Dyslipidemia	3602(12.18%)	1134(15.05%)	456(20.38%)	137(25.09%)	<0.01

Table 2 Associations between smoking, diabetes, and stroke

Variables	Stroke	Non-stroke	Unadjusted OR(95%CI)	Adjusted OR (95%CI)	P	
Smoking	No	622(67.76%)	31183(80.02%)	1.91 (1.63-2.31)	1.83 (1.59-2.14)	<0.01
	Yes	296(32.24%)	7786(19.98%)			
DM2	No	765(83.33%)	36339(93.25%)	2.76 (1.77-4.68)	2.65 (1.70-4.41)	<0.01
	Yes	153(16.67%)	2630(6.75%)			

Adjusted for age, sex, education, marriage status, employment, family history of diabetes, family history of hypertension, family history of stroke, alcohol consumption, physical activity, hypertension, diabetes or smoking, body mass index, and lipids.

Table 3 Odds ratios (ORs) for the association between smoking and stroke by diabetes among participants

Smoking	Diabetes	No stroke	Stroke	Unadjusted OR(95%CI)	Adjusted OR (95%CI)	P
No	No	29056	512	1	1	
	Yes	2127	110	2.93(1.73-3.15)	2.00 (1.56-2.56)	<0.01
Yes	No	7283	253	1.97(1.54-2.37)	1.65 (1.36-2.00)	<0.01
	Yes	503	43	4.85(2.65-6.21)	3.45 (2.30-5.16)	<0.01

Adjusted for age, sex, education, marriage status, employment, family history of diabetes, family history of hypertension, family history of stroke, alcohol consumption, physical activity, hypertension, body mass index, and lipids.

Table 4 Measures for estimating biological interaction between smoking and diabetes for prevalence of stroke in participants

Measures of biological interaction	Estimate (95% CI)
RERI	1.80(1.24–3.84)
AP	0.52(0.37–0.73)
S	1.50(1.18–1.84)

Reference group is no smoking with non-diabetes.
Adjusted for age, sex, education, marriage status, employment, family history of diabetes, family history of hypertension, family history of stroke, alcohol consumption, physical activity, hypertension, body mass index, and lipids.

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	6-7
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Data sources/measurement	8*	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Bias	9	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Study size	10	Describe any efforts to address potential sources of bias	5
Quantitative variables	11	Explain how the study size was arrived at	7-8
		Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
		(a) Describe all statistical methods, including those used to control for confounding	
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
Statistical methods	12	(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	7-8
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.