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

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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 ≥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

caused by intracranial hemorrhage or ischemia.[10] The investigators examined the medical records of participants reporting a diagnosis of stroke to check that they satisfied this definition. The diagnosis was also confirmed by computed tomography and magnetic resonance imaging scans. Detailed clinical information about stroke was based on the International Classification of Disease, 10th Revision, codes I60–I64.

DM2 was defined as fasting blood glucose ≥7.0 mmol/L, any use of antidiabetic medication, or self-reported history of DM2.[11] Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, any use of antihypertensive medication, or self-reported history of hypertension.[12]

Covariates

Age, sex, current employment status, marital status, level of education, cigarette smoking, alcohol consumption, physical activity, and family history of diseases including DM2, hypertension, and stroke were assessed using a standardized questionnaire. Employment status was categorized as manual, non-manual, unemployed, or retired. Education was categorized as below high school, high school, or above high school. Lifestyle variables included cigarette smoking, alcohol consumption, and physical activity level. Cigarette smoking was defined as having smoked at least 100 cigarettes in one's lifetime. Information was obtained on the amount and type of alcohol consumed during the previous year, and alcohol drinking was defined as consumption of ≥30 g of alcohol per week for ≥1 year. Regular leisure-time physical activity was defined as participation in moderate or vigorous activity for ≤30 min per day, ≥3 days a week. Each participant's height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) in light indoor clothing were

measured. Body mass index (BMI; in kg/m^2) was calculated; categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.0 kg/m^2), and overweight/obese (>24.0 kg/m^2).[13] Dyslipidemia was defined as use of any lipid-lowering medication or self-reported history of the condition.

Statistical analysis

Participants were divided into four groups in accordance with their smoking status and DM2: non-smokers with no DM2, smokers with no DM2, non-smokers with DM2, and smokers with DM2. Statistical analysis was performed using IBM SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA). The general characteristics of continuous variables were compared across the four subgroups using analysis of variance. The categorical variables were expressed as a percentage and the groups were compared using a chi-squared test. Logistic regression analysis was performed to estimate the probability of having a stroke and 95% confidence interval (CI) for each risk factor category stratified by DM2 and smoking, adjusting for age, sex, occupation, education, marital status, BMI, physical activity, drinking status, hypertension status, and family history of disease including DM2, hypertension, and stroke.

Biological interactions should be based on an additive scale rather than a multiplication scale.[14,15] Therefore, we used three measures to estimate biological interactions between DM2 and smoking: relative excess risk owing to interaction (RERI), attributable proportion (AP) owing to interaction, and synergy index (S). RERI is the excess risk attributed to interaction relative to the risk without exposure to diabetes and smoking. AP refers to the attributable proportion of disease caused by interaction in subjects with exposure to both variables. S is the excess risk from

exposure to both variables when there is a biological interaction relative to the risk from exposure to both variables without interaction. In the absence of additive interactions, RERI and AP are equal to 0.[14,16] In the current study, RERI >0, AP >0, and S >0 indicate statistical significance. A *p*-value <0.05 (two-tailed) was considered statistically significant.

Ethics approval and consent to participate

The study protocol was approved by the Xuzhou Center for Disease Control and Prevention. All participants provided written informed consent.

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 (χ^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 (χ^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 (χ^2 = 139.11, p <0.001). Individuals who smoked had a higher stroke incidence compared with non-smokers (3.36% *vs.* 1.96%; χ^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]

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

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

associated disability.

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

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

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

The pathophysiological mechanisms of hyperglycemia induce oxidative stress; promote formation of advanced glycosylation end products;[39,40] increase blood–brain barrier permeability and inflammatory responses;[41] lead to accumulation of reactive oxygen species/reactive nitrogen, inflammation, and mitochondrial dysfunction;[42] lead to cellular dysfunctions; damage vascular tissue; inhibit endogenous vascular protective factors; alter vascular homeostasis;[43] raise levels of reactive oxygen species and advanced glycation end products; decrease levels of mitochondrial superoxide dismutase;[40] and correlate with endothelial cell dysfunction and nitric oxide production.[44] All these actions contribute to accelerating the atherosclerotic process. Therefore, subjects with diabetes are more prone to develop stroke.

Cigarette smoking is associated with increased reactive oxygen species, oxidative stress, blood–brain barrier permeability, sympathetic activation and nitric oxide production, reduced cerebral blood flow and serum superoxide dismutase levels, attenuation of the vasodilation of cerebral arterioles, and induction of atherosclerosis and thrombosis.[45-48] Moreover, cigarette smoke elevates serum levels of advanced glycation end products and reduces soluble receptors for advanced glycation end products, resulting in the development of atherosclerosis and related stroke.[49-51] Smoking is therefore correlated with increased risk of stroke.

Collectively, diabetes and smoking induce oxidative stress and nitric oxide

production; increase reactive oxygen species, blood–brain barrier permeability, and the level of advanced glycation end products; and reduce cerebral blood flow and serum superoxide dismutase. Therefore, diabetic patients who smoke have a greater risk of stroke.

The strengths of the current study are that we used a community-based multistage sampling design, large sample size, and randomly selected participants. However, the study has several limitations. First, because of the cross-sectional design, we could not determine a causal relationship between DM2, smoking, and stroke. Second, we were unable to control for some important and well-known risk factors of stroke, such as heart rate[52] and cardiac causes.[6] Third, we did not measure fresh fruit consumption, [53] which is causally related to stroke.

Conclusion

The results of this cross-sectional study indicate subjects with diabetes who smoke are 3.5 times more likely to develop stroke than non-diabetics who do not smoke. Diabetes and smoking had a combined positive influence on stroke. Our results have important public health implications. Among Chinese adults, the current rate of smoking is as high as 28.3% [54] and DM2 prevalence is 11.6%.[55] Therefore, it is important for stroke prevention to reduce smoking and improve glycemic control in diabetic patients in China.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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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

be made freely available to external investigators upon request.

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

Reported variable	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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants 5	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/measurement	8*	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
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy 7-8	
		(*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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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 general is ability (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.

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

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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

- 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 ≥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

caused by intracranial hemorrhage or ischemia.[10] The investigators examined the medical records of participants reporting a diagnosis of stroke to check that they satisfied this definition. The diagnosis was also confirmed by computed tomography and magnetic resonance imaging scans. Detailed clinical information about stroke was based on the International Classification of Disease, 10th Revision, codes I60–I64.

DM2 was defined as fasting blood glucose ≥7.0 mmol/L, any use of antidiabetic medication, or self-reported history of DM2.[11] Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, any use of antihypertensive medication, or self-reported history of hypertension.[12]

Covariates

Age, sex, current employment status, marital status, level of education, cigarette smoking, alcohol consumption, physical activity, and family history of diseases including DM2, hypertension, and stroke were assessed using a standardized questionnaire. Employment status was categorized as manual, non-manual, unemployed, or retired. Education was categorized as below high school, high school, or above high school. Lifestyle variables included cigarette smoking, alcohol consumption, and physical activity level. Cigarette smoking was defined as having smoked at least 100 cigarettes in one's lifetime. Information was obtained on the amount and type of alcohol consumed during the previous year, and alcohol drinking was defined as consumption of ≥30 g of alcohol per week for ≥1 year. Regular leisure-time physical activity was defined as participation in moderate or vigorous activity for ≤30 min per day, ≥3 days a week. Each participant's height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) in light indoor clothing were

measured. Body mass index (BMI; in kg/m^2) was calculated; categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.0 kg/m^2), and overweight/obese (>24.0 kg/m^2).[13] Dyslipidemia was defined as use of any lipid-lowering medication or self-reported history of the condition.

Statistical analysis

Participants were divided into four groups in accordance with their smoking status and DM2: non-smokers with no DM2, smokers with no DM2, non-smokers with DM2, and smokers with DM2. Statistical analysis was performed using IBM SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA). The general characteristics of continuous variables were compared across the four subgroups using analysis of variance. The categorical variables were expressed as a percentage and the groups were compared using a chi-squared test. Logistic regression analysis was performed to estimate the probability of having a stroke and 95% confidence interval (CI) for each risk factor category stratified by DM2 and smoking, adjusting for age, sex, occupation, education, marital status, BMI, physical activity, drinking status, hypertension status, and family history of disease including DM2, hypertension, and stroke.

Biological interactions should be based on an additive scale rather than a multiplication scale.[14,15] Therefore, we used three measures to estimate biological interactions between DM2 and smoking: relative excess risk owing to interaction (RERI), attributable proportion (AP) owing to interaction, and synergy index (S). RERI is the excess risk attributed to interaction relative to the risk without exposure to diabetes and smoking. AP refers to the attributable proportion of disease caused by interaction in subjects with exposure to both variables. S is the excess risk from

exposure to both variables when there is a biological interaction relative to the risk from exposure to both variables without interaction. In the absence of additive interactions, RERI and AP are equal to 0.[14,16] In the current study, RERI >0, AP >0, and S >0 indicate statistical significance. A *p*-value <0.05 (two-tailed) was considered statistically significant.

Ethics approval and consent to participate

The study protocol was approved by Xuzhou Center for Disease Control and Prevention. The procedures followed were in accordance with the standards of the ethics committee of Xuzhou Center for Disease Control and Prevention and with the Declaration of Helsinki (1975, revised 2000). Written informed consent was obtained from all participants.

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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 (χ^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 (χ^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 (χ^2 = 139.11, p <0.001). Individuals who smoked had a higher stroke incidence compared with non-smokers (3.36% *vs.* 1.96%; χ^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

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). The risk of ischemic and haemorrhagic stroke were all increased by smoking after adjusting for confounders, the OR´s were 1.32(95% CI: 1.12–2.53) and 1.95(95% CI: 1.40–3.41),respectively.

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]

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

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

associated disability.

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

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

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

Papademetriou and colleagues reported that comparison with nonsmoking patients with no diabetes mellitus or hypertension, patients with diabetes mellitus and hypertension and smoking had a 3-fold increase in the prevalence of peripheral vascular disease and a 3.5-fold increase in cerebrovascular disease[39]. This evidence is strengthened by our results.

The pathophysiological mechanisms of hyperglycemia induce oxidative stress; promote formation of advanced glycosylation end products;[40,41]increase blood–brain barrier permeability and inflammatory responses;[42] lead to accumulation of reactive oxygen species/reactive nitrogen, inflammation, and mitochondrial dysfunction;[43] lead to cellular dysfunctions; damage vascular tissue; inhibit endogenous vascular protective factors; alter vascular homeostasis;[44] raise levels of reactive oxygen species and advanced glycation end products; decrease levels of mitochondrial superoxide dismutase;[41] and correlate with endothelial cell dysfunction and nitric oxide production.[45] All these actions contribute to accelerating the atherosclerotic process. Therefore, subjects with diabetes are more prone to develop stroke.

Cigarette smoking is associated with increased reactive oxygen species, oxidative stress, blood–brain barrier permeability, sympathetic activation and nitric oxide

production, reduced cerebral blood flow and serum superoxide dismutase levels, attenuation of the vasodilation of cerebral arterioles, and induction of atherosclerosis and thrombosis.[46-49] Moreover, cigarette smoke elevates serum levels of advanced glycation end products and reduces soluble receptors for advanced glycation end products, resulting in the development of atherosclerosis and related stroke.[50-52] Smoking is therefore correlated with increased risk of stroke.

Collectively, diabetes and smoking induce oxidative stress and nitric oxide production; increase reactive oxygen species, blood–brain barrier permeability, and the level of advanced glycation end products; and reduce cerebral blood flow and serum superoxide dismutase. Therefore, diabetic patients who smoke have a greater risk of stroke.

The strengths of the current study are that we used a community-based multistage sampling design, large sample size, and randomly selected participants. However, the study has several limitations. First, because of the cross-sectional design, we could not determine a causal relationship between DM2, smoking, and stroke. Second, we were unable to control for some important and well-known risk factors of stroke, such as heart rate[53] and cardiac causes.[6] Third, we did not measure fresh fruit consumption, [54] which is causally related to stroke. Fourth, the number of cigarettes smoking was recalled by participants, therefore, the risk of misclassification and recall bias with the definition of smoking could not be avoid.

Conclusion

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

results have important public health implications. Among Chinese adults, the current rate of smoking is as high as 28.3% [55] and DM2 prevalence is 11.6%.[56] Therefore, it is important for stroke prevention to reduce smoking and improve glycemic control in diabetic patients in China.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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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, XS, TL, CZ, XZ, and PL contributed to the discussion and reviewed/edited the manuscript. XZ 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 be made freely available to external investigators upon request.

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

Reported variable	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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants 5	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/measurement	8*	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
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy 7-8	
		(*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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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 general is ability (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

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

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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 ≥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 caused by intracranial hemorrhage or ischemia.[10] The investigators examined the medical records of participants reporting a diagnosis of stroke to check that they satisfied this definition. The diagnosis was also confirmed by computed tomography and magnetic resonance imaging scans. Detailed clinical information about stroke was based on the International Classification of Disease, 10th Revision, codes I60–I64.

DM2 was defined as fasting blood glucose ≥7.0 mmol/L, any use of antidiabetic medication, or self-reported history of DM2.[11] Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, any use of antihypertensive medication, or self-reported history of hypertension.[12]

Covariates

Age, sex, current employment status, marital status, level of education, cigarette smoking, alcohol consumption, physical activity, and family history of diseases including DM2, hypertension, and stroke were assessed using a standardized questionnaire. Employment status was categorized as manual, non-manual, unemployed, or retired. Education was categorized as below high school, high school, or above high school. Lifestyle variables included cigarette smoking, alcohol consumption, and physical activity level. Cigarette smoking was defined as having smoked at least 100 cigarettes in one's lifetime. Information was obtained on the amount and type of alcohol consumed during the previous year, and alcohol drinking was defined as consumption of ≥30 g of alcohol per week for ≥1 year. Regular leisure-time physical activity was defined as participation in moderate or vigorous activity for ≤30 min per day, ≥3 days a week. Each participant's height (to

the nearest 0.1 cm) and weight (to the nearest 0.1 kg) in light indoor clothing were measured. Body mass index (BMI; in kg/m^2) was calculated; categorized as underweight (<18.5 kg/m^2), normal weight (18.5−24.0 kg/m^2), and overweight/obese (>24.0 kg/m^2).[13] Dyslipidemia was defined as use of any lipid-lowering medication or self-reported history of the condition.

Statistical analysis

Participants were divided into four groups in accordance with their smoking status and DM2: non-smokers with no DM2, smokers with no DM2, non-smokers with DM2, and smokers with DM2. Statistical analysis was performed using IBM SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA). The general characteristics of continuous variables were compared across the four subgroups using analysis of variance. The categorical variables were expressed as a percentage and the groups were compared using a chi-squared test. Logistic regression analysis was performed to estimate the probability of having a stroke and 95% confidence interval (CI) for each risk factor category stratified by DM2 and smoking, adjusting for age, sex, occupation, education, marital status, BMI, physical activity, drinking status, hypertension status, and family history of disease including DM2, hypertension, and stroke.

Biological interactions should be based on an additive scale rather than a multiplication scale.[14,15] Therefore, we used three measures to estimate biological interactions between DM2 and smoking: relative excess risk owing to interaction (RERI), attributable proportion (AP) owing to interaction, and synergy index (S). RERI is the excess risk attributed to interaction relative to the risk without exposure to diabetes and smoking. AP refers to the attributable proportion of disease caused by

interaction in subjects with exposure to both variables. S is the excess risk from exposure to both variables when there is a biological interaction relative to the risk from exposure to both variables without interaction. In the absence of additive interactions, RERI and AP are equal to 0.[14,16] In the current study, RERI >0, AP >0, and S >0 indicate statistical significance. A *p*-value <0.05 (two-tailed) was considered statistically significant.

Ethics approval and consent to participate

The study protocol was approved by Xuzhou Center for Disease Control and Prevention. The procedures followed were in accordance with the standards of the ethics committee of Xuzhou Center for Disease Control and Prevention and with the Declaration of Helsinki (1975, revised 2000). Written informed consent was obtained from all participants.

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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 (χ^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 (χ^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 (χ^2 = 139.11, p <0.001). Individuals who smoked had a higher stroke incidence compared with non-smokers (3.36% *vs.* 1.96%; χ^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

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). The risk of ischemic and haemorrhagic stroke were all increased by smoking after adjusting for confounders, the OR´s were 1.32(95% CI: 1.12–2.53) and 1.95(95% CI: 1.40–3.41),respectively.

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]

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

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

associated disability.

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

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

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

Papademetriou and colleagues reported that comparison with nonsmoking patients with no diabetes mellitus or hypertension, patients with diabetes mellitus and hypertension and smoking had a 3-fold increase in the prevalence of peripheral vascular disease and a 3.5-fold increase in cerebrovascular disease[39]. This evidence is strengthened by our results.

The pathophysiological mechanisms of hyperglycemia induce oxidative stress; promote formation of advanced glycosylation end products;[40,41]increase blood–brain barrier permeability and inflammatory responses;[42] lead to accumulation of reactive oxygen species/reactive nitrogen, inflammation, and mitochondrial dysfunction;[43] lead to cellular dysfunctions; damage vascular tissue; inhibit endogenous vascular protective factors; alter vascular homeostasis;[44] raise levels of reactive oxygen species and advanced glycation end products; decrease levels of mitochondrial superoxide dismutase;[41] and correlate with endothelial cell dysfunction and nitric oxide production.[45] All these actions contribute to accelerating the atherosclerotic process. Therefore, subjects with diabetes are more prone to develop stroke.

Cigarette smoking is associated with increased reactive oxygen species, oxidative

stress, blood–brain barrier permeability, sympathetic activation and nitric oxide production, reduced cerebral blood flow and serum superoxide dismutase levels, attenuation of the vasodilation of cerebral arterioles, and induction of atherosclerosis and thrombosis.[46-49] Moreover, cigarette smoke elevates serum levels of advanced glycation end products and reduces soluble receptors for advanced glycation end products, resulting in the development of atherosclerosis and related stroke.[50-52] Smoking is therefore correlated with increased risk of stroke.

Collectively, diabetes and smoking induce oxidative stress and nitric oxide production; increase reactive oxygen species, blood–brain barrier permeability, and the level of advanced glycation end products; and reduce cerebral blood flow and serum superoxide dismutase. Therefore, diabetic patients who smoke have a greater risk of stroke.

The strengths of the current study are that we used a community-based multistage sampling design, large sample size, and randomly selected participants. However, the study has several limitations. First, because of the cross-sectional design, we could not determine a causal relationship between DM2, smoking, and stroke. Second, we were unable to control for some important and well-known risk factors of stroke, such as heart rate[53] and cardiac causes.[6] Third, we did not measure fresh fruit consumption, [54] which is causally related to stroke. Fourth, the number of cigarettes smoking was recalled by participants, therefore, the risk of misclassification and recall bias with the definition of smoking could not be avoid.

Conclusion

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

smoke. Diabetes and smoking had a combined positive influence on stroke. Our results have important public health implications. Among Chinese adults, the current rate of smoking is as high as 28.3% [55] and DM2 prevalence is 11.6%.[56] Therefore, it is important for stroke prevention to reduce smoking and improve glycemic control in diabetic patients in China.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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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, XS, TL, CZ, XZ, and PL contributed to the discussion and reviewed/edited the manuscript. XZ 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 be made freely available to external investigators upon request.

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

Reported variable	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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants 5	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/measurement	8*	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
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy 7-8	
		(*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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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 general is ability (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.

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

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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

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 in accordance with the population of each subdistrict/township from each region, with probability proportional to size sampling. In the second stage, five communities/villages were selected in accordance with 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 through use of a Kish selection table. Those who met either or both 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 ≥13,500 people were selected, assuming an estimation incidence of stroke of 2.0%,[9] with 90% power, α=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 examination and completed a structured questionnaire inquiring on 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 thought to be caused by intracranial hemorrhage or ischemia.[10] We examined the medical records of participants reporting a diagnosis of stroke to check that participants satisfied this definition. The diagnosis was also confirmed through computed tomography and magnetic resonance imaging scans. Detailed clinical information about stroke was based on the International Classification of Disease, 10th Revision, codes I60–I64.

DM2 was defined as fasting blood glucose ≥7.0 mmol/L, any use of antidiabetic medication, or self-reported history of DM2.[11] Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, any use of antihypertensive medication, or self-reported history of hypertension.[12]

Covariates

Age, sex, current employment status, marital status, level of education, cigarette smoking, alcohol consumption, physical activity, and family history of diseases, including DM2, hypertension, and stroke, were assessed using a standardized questionnaire. Employment status was categorized as manual, non-manual, unemployed, or retired. Education was categorized as below high school, high school, or above high school. Lifestyle variables included cigarette smoking, alcohol consumption, and physical activity level. Cigarette smoking was defined as having smoked at least 100 cigarettes in one's lifetime. Information was obtained on the amount and type of alcohol consumed during the previous year, and alcohol drinking was defined as consumption of ≥30 g per week for ≥1 year. Regular leisure-time physical activity was defined as participation in moderate or vigorous activity for ≤30 min per day, ≥3 days a week. Each participant's height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) in light indoor clothing were measured.

Body mass index (BMI; in kg/m^2) was calculated; categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.0 kg/m^2), or overweight/obese (>24.0 kg/m^2).[13] Dyslipidemia was defined as use of any lipid-lowering medication or self-reported history of the condition.

Statistical analysis

Participants were divided into four groups in accordance with their smoking status and DM2: non-smokers with no DM2, smokers with no DM2, non-smokers with DM2, and smokers with DM2. Statistical analysis was performed using IBM SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA). The general characteristics of continuous variables were compared across the four subgroups using analysis of variance. The categorical variables were expressed as a percentage and the groups were compared using a chi-squared test. Logistic regression analysis was performed to estimate the probability of having a stroke and 95% confidence interval (CI) for each risk factor category stratified by DM2 and smoking, adjusting for age, sex, occupation, education, marital status, BMI, physical activity, drinking status, hypertension status, and family history of disease, including DM2, hypertension, and stroke.

Biological interactions should be based on an additive scale rather than a multiplication scale.[14,15] We therefore used three measures to estimate biological interactions between DM2 and smoking: relative excess risk owing to interaction (RERI), attributable proportion (AP) owing to interaction, and synergy index (S). RERI is the excess risk attributed to interaction relative to the risk without exposure to diabetes and smoking. AP refers to the attributable proportion of disease caused by interaction in subjects with exposure to both variables. S is the excess risk from

exposure to both variables when there is a biological interaction relative to the risk from exposure to both variables without interaction. In the absence of additive interactions, RERI and AP equal 0.[14,16] In the current study, RERI >0, AP >0, and S >0 indicated statistical significance, set at p <0.05 (two-tailed).

Ethics approval and consent to participate

The study protocol was approved by Xuzhou Center for Disease Control and Prevention. The procedures followed were in accordance with the standards of the ethics committee of the Xuzhou Center for Disease Control and Prevention and with the Declaration of Helsinki (1975, revised 2000). Written informed consent was obtained from all participants.

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: 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 statistically significant difference between the two groups (χ^2 = 135.92, p <0.001). The proportion of smokers was 20.26% (8082/39,887), stroke participants who smoked was 32.24%,

and non-stroke participants who smoked was 19.98%; there was a statistically significant difference in smoking between stroke and non-stroke patients (χ^2 = 83.49, p <0.001).

Association of diabetes and smoking with stroke

The 5.50% incidence of stroke in subjects with DM2 exceeded the 2.06% incidence in those with no DM2 (χ^2 = 139.11, p <0.001). Individuals who smoked had a higher stroke incidence compared with non-smokers (3.36% *vs.* 1.96%; χ^2 = 83.49, p <0.001; see Table 2). Subjects 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 risks of ischemic and hemorrhagic stroke were increased by DM2, after adjusting for confounders; the ORs were 2.71 (95% CI: 1.72–4.49) and 1.82 (95% CI: 1.34–3.35), respectively. 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). The risks of ischemic and hemorrhagic stroke were increased by smoking, after adjusting for confounders; the ORs were 1.32 (95% CI: 1.12–2.53) and 1.95 (95% CI: 1.40–3.41), respectively.

Interaction between diabetes and smoking in 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 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

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

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

was associated with ischemic stroke (adjusted hazard ratio: 1.08, 95% CI: 1.07–1.09).[29] Moreover, a study of 4669 patients who had incurred a minor stroke revealed during a 3-month follow-up that stroke patients with diabetes experienced stroke recurrence and disability.[30] Therefore, effective glycemic control not only reduces the incidence of stroke but also can reduce stroke recurrence and associated disability.

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

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

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

One study reported that in comparison with nonsmoking patients with no diabetes mellitus or hypertension, patients with those conditions and who smoked had a threefold increase in prevalence of peripheral vascular disease and a 3.5-fold increase in cerebrovascular disease[39]. Our results reinforce such findings.

The pathophysiological mechanisms of hyperglycemia induce oxidative stress; promote formation of advanced glycosylation end products;[40,41] increase blood–brain barrier permeability and inflammatory responses;[42] lead to accumulation of reactive oxygen species/reactive nitrogen, inflammation, and mitochondrial dysfunction;[43] lead to cellular dysfunction; damage vascular tissue; inhibit endogenous vascular protective factors; alter vascular homeostasis;[44] raise levels of reactive oxygen species and advanced glycation end products; decrease

levels of mitochondrial superoxide dismutase;[41] and correlate with endothelial cell dysfunction and nitric oxide production.[45] All these actions contribute to accelerating the atherosclerotic process. Therefore, diabetic patients are more prone to incurring stroke.

Cigarette smoking is associated with increased reactive oxygen species, oxidative stress, blood–brain barrier permeability, sympathetic activation and nitric oxide production, reduced cerebral blood flow and serum superoxide dismutase levels, attenuation of the vasodilation of cerebral arterioles, and induction of atherosclerosis and thrombosis.[46-49] Moreover, cigarette smoke elevates serum levels of advanced glycation end products and reduces soluble receptors for those end products, resulting in development of atherosclerosis and related stroke.[50-52] Smoking is therefore correlated with increased risk of stroke.

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

The strengths of the current study are that we used a community-based multistage sampling design, large sample size, and randomly selected participants. However, the study has several limitations. First, because of the cross-sectional design, we could not determine a causal relationship between DM2, smoking, and stroke. Second, we were unable to control for some important and well-known risk factors of stroke, such as heart rate[53] and cardiac causes.[6] Third, we did not measure fresh fruit consumption, [54] which is causally negative related to stroke. Finally,

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

Conclusion

The results of this cross-sectional study indicate diabetic patients who smoke are 3.5 times more likely to develop stroke than non-diabetics who do not smoke. Diabetes and smoking had a combined positive correlation with stroke. These results have important public health implications. Among Chinese adults, the current rate of smoking is as high as 28.3% [55] and DM2 prevalence is 11.6%.[56] Therefore, it is important to implement stroke-prevention measures aimed at reducing smoking and improving glycemic control in diabetic patients in China.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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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, XS, TL, CZ, XZ, and PL contributed to the discussion and reviewed/edited the manuscript. XZ 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 be made freely available to external investigators upon request.

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

Reported variable	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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants 5	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/measurement	8*	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
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy 7-8	
		(*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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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 general is ability (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.