Background and Purpose—Smoking is a major public health challenge and an important risk factor for cardiovascular diseases. No previous studies have evaluated the association among smoking, heart rate, and ischemic stroke in an Inner Mongolian population. We aim to evaluate the cumulative effect of smoking and heart rate on ischemic stroke incidence in this population.

Methods—A prospective cohort study from June 2003 through July 2012 was conducted among 2530 people ≥20 years of age from Inner Mongolia, China. We categorized the participants into 4 subgroups according to smoking status and heart rate. Cox proportional hazards models and receiver operating characteristic curves were used to evaluate the association among smoking, heart rate, and ischemic stroke.

Results—The multivariate-adjusted hazard ratios (95% confidence intervals) of ischemic stroke incidence for nonsmokers with heart rate ≥80 bpm, smokers with heart rate <80 bpm, and smokers with heart rate ≥80 bpm were 1.42 (0.62–3.28), 2.11 (1.06–4.23), and 2.86 (1.33–6.14), respectively, compared with nonsmokers with heart rate <80 bpm. The area under receiver operating characteristic curve (area under the curve) for a model containing smoking status and heart rate, along with conventional factors (area under the curve=0.755), was significantly (P=0.018) larger than the one containing only conventional factors (area under the curve=0.739).

Conclusions—Our study indicated that smoking was an independent risk factor of ischemic stroke, and smokers with faster heart rate had the highest risk of ischemic stroke among Inner Mongolians. These findings suggest that smoking status and heart rate may be valuable in predicting ischemic stroke incidence. (Stroke. 2013;44:00-00.)

Key Words: heart rate ■ ischemic stroke ■ Mongolian population ■ prospective cohort ■ smoking

Smoking, Heart Rate, and Ischemic Stroke
A Population-Based Prospective Cohort Study Among Inner Mongolians in China

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Materials and Methods

Study Participants
This prospective cohort study was conducted from June 2003 to July 2012 in Inner Mongolia, an autonomous region in north China. The methods for study participant recruitment and baseline data collection have been described elsewhere.15 Briefly, study participants ≥20 years of age were recruited from 32 villages in 2 adjacent townships located in the counties of Kezuohou Banner and Naiman Banner in Inner Mongolia. The majority of local residents are Mongolians who...
have lived there for many generations and maintain a traditional diet and lifestyle. A total of 3475 Mongolian people ≥20 years of age live in these villages. Among them, 889 people were excluded because they refused to participate or had cardiovascular diseases or endocrine diseases, including hyper/hypothyroidism, or were taking antihypertensive medication. Finally, a total of 2589 individuals were included in this study. Written informed consent was obtained for all study participants. This study was approved by the ethics committee at Soochow University in China.

Data Collection
Trained staff interviewed participants in Chinese using a standard questionnaire to obtain information on demographic characteristics, medical history, and lifestyle risk factors. Cigarette smoking was defined as having smoked ≥1 cigarette per day for ≥1 year. Three blood pressure measurements were taken for each participant while participants were seated using a mercury sphygmomanometer according to a standard protocol. The first and fifth Korotkoff sounds were recorded as systolic and diastolic blood pressure, respectively. The mean of these 3 blood pressure measurements was used for data analysis. Resting heart rates were measured by stethoscope at the apex of the heart and counted for a 60-second interval. Body weight and height were measured using standard methods, and body mass index was calculated as weight in kilograms divided by the square of height in meters (kg/m²).

Overnight fasting blood samples were obtained to measure total cholesterol, high-density lipoprotein cholesterol, and triglycerides. Plasma and serum samples were frozen at −80°C until laboratory testing. A modified hexokinase enzymatic method was applied to test plasma glucose levels. Total cholesterol, high-density lipoprotein cholesterol, and triglycerides were analyzed enzymatically using a Beckman Synchron CX5 Delta Clinical System (Beckman Coulter, Inc; Fullerton, CA) with commercial reagents. Low-density lipoprotein cholesterol levels were calculated using the Friedewald equation for participants who had <400 mg/dL triglycerides.

Follow-Up and Outcome Assessment
All participants were followed from June 2003 through July 2012. Ischemic stroke incidence during the follow-up period is the primary study outcome. Participants who did not have an ischemic stroke, who died from other causes, or who were lost to follow-up were defined as censored. If the participant was contacted and found to have had a stroke, the stroke incidence date was defined as end point date. Data were censored at the time of the contact if the participant was reached and was found not to have had a stroke and were censored at the day we contacted the participant last if he or she was lost to follow-up. For those who died from other causes, data were censored at the time of death date in the medical records. Four county hospitals with modern diagnostic facilities, including computed tomography and MRI, provide residents of the 32 villages with medical services. Since 2004, household surveys of all participants were conducted every 2 years to determine new ischemic stroke cases. Trained staff interviewed either the participants or their relatives, if participants were dead or unable to communicate, and completed a medical status questionnaire. If a participant reported that a stroke occurred during the period since the last survey, the staff reviewed hospital records, including outpatient or admission records, the discharge summary, and especially computed tomography or MRI scan results, to confirm. Stroke was defined as evidence of an acute disturbance of focal 24 hours and thought to be because of intracranial hemorrhage or ischemia. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria were used to classify ischemic stroke into the following subtypes: lacunar stroke, cardioembolic stroke, large-artery stroke, or unknown ischemic type. Participants who were diagnosed with ischemic stroke by head computed tomography or MRI scan at the hospital were considered to have the outcome of interest in this study. The exclusion criteria were as follows: (1) exclusively subarachnoid hemorrhage only, (2) intracerebral hemorrhage, (3) transient ischemic attack only, (4) and evidence from the medical history suggesting hospitalization was for a previous stroke.

Statistical Analysis
Heart rate was grouped comparing the upper tertile (≥80 bpm) to the bottom 2 tertiles (<80 bpm). Participants were categorized into 4 subgroups: nonsmokers with heart rate <80 bpm, smokers with heart rate <80 bpm, nonsmokers with heart rate ≥80 bpm, and smokers with heart rate ≥80 bpm. Conventional cardiovascular risk factors were compared across the 4 subgroups using ANOVA for continuous variables and χ² tests for categorical variables. The cumulative risk of events among the 4 subgroups was estimated using Kaplan–Meier curves and compared by log-rank test. We used locally weighted scatterplot smoothing curves to explore a nonlinear relationship between heart rate and cumulative incidence rate. In addition, we used Cox proportional hazards models to compute hazard ratios (HRs) of ischemic stroke across the 4 subgroups adjusting for important confounding factors, including age, sex, body mass index, drinking status, family history of cardiovascular disease, blood glucose, systolic blood pressure, diastolic blood pressure, and lipid levels. We set a multiplicative interaction term of smoking and heart rate in Cox proportional hazards model and tested its effect on ischemic stroke incidence, independent of smoking, heart rate, and other confounding factors. We also assessed the discriminatory value of smoking status/heart rate by computing the area under receiver operating characteristic curves (area under the curve) and comparing a model including only conventional risk factors with a model including smoking status and heart rate subgroup, in addition to conventional risk factors. All P values were 2-tailed, and a significance level of 0.05 was used. All statistical analyses were conducted using SAS statistical software (version 9.2) and R statistical software (version 2.15).

Results
As of July 31, 2012, we have followed participants for an average of 9.2 years, and a total of 23,292 person-years have been observed. Among 2589 participants, 6 were lost to follow-up, and the follow-up rate was 99.8%. Fifty-nine participants were excluded for missing key variables, and a total of 2530 people were included in the final analysis. Among 2530 people, a total of 76 patients with ischemic stroke were present during the follow-up period. The cumulative incidence rate was 2.9%, and the incidence density was 326 per 100,000 person-years.

Table 1 presents the baseline characteristics of participants by the 4 study subgroups. Conventional stroke risk factors, such as age, sex, body mass index, drinking status, family history of cardiovascular disease, blood pressure, blood glucose, and triglycerides, were significantly different among the 4 subgroups. Smokers in either heart rate group tended to be older, men, drinkers, and had lower body mass index. Smokers and nonsmokers with heart rate ≥80 bpm had higher family history of cardiovascular disease, systolic blood pressure, diastolic blood pressure, blood glucose, and triglycerides. Figure 1 depicts the relationship between heart rate and the ischemic stroke incidence rate. As expected, heart rate was positively associated with the cumulative incidence rate. The cumulative incidence rate of ischemic stroke gradually increased with higher heart rate.

During 10 years of follow-up, the cumulative incidence rate of ischemic stroke among nonsmokers with heart rate <80 bpm, nonsmokers with heart rate ≥80 bpm, smokers with heart rate <80 bpm, and smokers with heart rate ≥80 bpm was 1.41%, 1.98%, 3.97%, and 5.77%, respectively (P<0.001).
In Table 2, compared with nonsmokers with heart rate <80 bpm, smokers with heart rate ≥80 bpm/smokers were at a higher risk of ischemic stroke (HR [95% confidence interval], 2.66 [1.30–5.42]) in the age- and sex-adjusted model. After adjusting for other confounding factors, the HRs (95% confidence intervals [CIs]) of nonsmokers with heart rate ≥80 bpm, smokers with heart rate <80 bpm, and smokers with heart rate ≥80 bpm were 1.42 (0.62–3.28), 2.11 (1.06–4.23), and 2.86 (1.33–6.14), respectively, compared with the reference group. Smokers with heart rate ≥80 bpm were at a highest risk of ischemic stroke. We also analyzed the independent effects of smoking and heart rate on ischemic stroke incidence risk. The multivariable-adjusted HRs (95% CIs) of ischemic stroke for smoking and heart rate were 2.07 (1.21–3.53) and 0.73 (0.44–1.20), respectively. No significant interaction was detected between smoking and heart rate on ischemic stroke risk (P=0.92).

The area under the receiver operating characteristic curve for the model including only the conventional risk factors achieved reasonable discrimination with an area under the curve of 0.739. After adding smoking status and heart rate subgroup, the discriminatory value marginally improved by 0.016 (area under the curve=0.755; P=0.018; Figure 2).

### Discussion

In this population-based prospective cohort study among an Inner Mongolian population, smokers with heart rate <80 bpm and smokers with heart rate ≥80 bpm were at a significantly higher risk for ischemic stroke compared with nonsmokers with heart rate <80 bpm. Smokers with faster heart rate were at a highest risk in this population. Smoking was an independent risk factor for ischemic stroke in this study, whereas heart rate was not independently associated with ischemic stroke. Our study is the first to examine the cumulative effect of smoking and heart rate on ischemic stroke incidence in Inner Mongolians, an ethnic minority in China.

Several prospective cohorts have indicated that smoking is an important risk factor of ischemic stroke incidence, independent of hypertension, diabetes mellitus, and other conventional risk factors. The Strong Heart Study of 4549 American Indians showed that both current smokers and former smokers were at higher risk of ischemic stroke compared with nonsmokers. The HRs (95% CIs) were 2.38 (1.69–3.36) and 1.6 (1.14–2.25) for current and former smokers, respectively. Song and Cho reported that the stroke risk of sustained ex-smokers and never-smokers was lower (HR [95%CI], 0.66 [0.55–0.79]) among 475734 Korean men compared with smokers. In China, a multicenter prospective cohort study was conducted among the Han population in 7 large cities. They also found that cigarette smoking was a major determinant of ischemic stroke incidence in the Han population. There is evidence showing that smoking adversely affects various underlying risk factors, including hypertension, diabetes mellitus, and dyslipidemia. The association between smoking and ischemic stroke incidence is likely explained by the negative effects of smoking on these risk factors.
causes of stroke, including hypercoagulable state,26 changes in cerebral blood flow,27 atherosclerosis, and atrial fibrillation.28

Although few studies have focused on resting heart rate and ischemic stroke, a recent study indicated that resting heart rate has important prognostic implications for people who have survived stroke.13 Patients in the 2 highest quintiles of heart rate (77–82 bpm and >82 bpm) had as much as 70% higher risk for total mortality compared with those in the lowest quintile, and lower baseline heart rate was associated with better neurological outcomes. A potential mechanism for this finding may be that lower heart rate would induce vascular compensation and reduce stroke size.29 Although high heart rate alone is not an independent risk factor of ischemic stroke incidence, the coexistence of smoking and high heart rate is a notable issue in ischemic stroke prevention. The coexistence of smoking and high heart rate is a notable issue in ischemic stroke prevention. It might be more important for people with relatively high heart rate to avoid smoking to reduce ischemic stroke risk in our study population. Our study population is Inner Mongolians living in northern China. Their living environment and lifestyle are basically comparable with those of the other northern residents in China. Recent studies30–32 also reported a smoking proportion and heart rate level of Chinese northern populations similar to our study. Considering that incidence rate of ischemic stroke is relatively higher in northern China, our findings were at least valuable for the populations in northern China.

At present, patients with stroke still lack the ability to fully regenerate damaged brain tissue,33 often making functional recovery incomplete. Therefore, prevention is considered the most effective strategy. An overall healthy lifestyle, such as not smoking, eating a healthful diet, exercising regularly, drinking moderately, and controlling weight, may be effective in lowering stroke risk.

This study has several strengths that deserve mention. To our knowledge, it is the first study to examine the association among smoking, heart rate, and ischemic stroke in a minority population in China. The study participants were homogeneous regarding their genetic background and environmental exposures, the study data were collected with rigid quality control, and important covariables were measured and controlled in the analysis. In addition, our follow-up time is relatively long, which enabled us to get a less biased association between exposure variables and outcome events. However, there are also some limitations that should be mentioned. Packs of cigarettes per year and smoking duration were not included in this study, so the association between amount of cigarette smoking and ischemic stroke incidence could not be explored. We found that smoking status and heart rate were different between men and women. It is better to perform the analysis in stratifying participants by sex. Considering our sample size is not very large, we did not stratify participants by sex but adjusted sex as an important confounding variable in the multivariable analysis. Therefore, this finding on the association among smoking, heart rate, and ischemic stroke was independent of sex effect.

**Figure 2.** Area under the curve for the prediction of ischemic stroke incidence for baseline conventional risk factors and for the addition of smoking status/heart rate. Risk factors in the conventional model include age, sex, body mass index, drinking status, family history of cardiovascular disease, blood glucose, blood pressure, and lipids.

<table>
<thead>
<tr>
<th>Heart Rate争议 &lt;80 bpm</th>
<th>Cases</th>
<th>Person-Years</th>
<th>Age and Sex Adjusted Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>Multivariable Adjusted* Hazard Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate &lt;80 bpm/nonsmokers</td>
<td>12</td>
<td>7948</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Heart rate ≥80 bpm/nonsmokers</td>
<td>11</td>
<td>5227</td>
<td>1.44</td>
<td>0.64</td>
<td>3.28</td>
<td>1.42</td>
</tr>
<tr>
<td>Heart rate &lt;80 bpm/smokers</td>
<td>30</td>
<td>6878</td>
<td>1.66</td>
<td>0.84</td>
<td>3.28</td>
<td>2.11</td>
</tr>
<tr>
<td>Heart rate ≥80 bpm/smokers</td>
<td>21</td>
<td>3239</td>
<td>2.66</td>
<td>1.30</td>
<td>5.42</td>
<td>2.86</td>
</tr>
</tbody>
</table>

*Multivariable model adjusted for age, sex, body mass index, drinking status, family history of cardiovascular disease, blood glucose, systolic blood pressure, diastolic blood pressure, and lipids.
A recent system review also indicated that female smokers had a 25% higher risk of heart disease than male smokers,34 so we believed that female smokers would have at least a similar risk of ischemic stroke as male smokers. In addition, we did not further categorize smokers as former smokers and current smokers in this study. Whether smoking cessation would decrease hemorrhagic and ischemic stroke risk is still controversial in some studies.25,35,36 At baseline, ≈25% of the population from these villages did not participate, which may have introduced some selection bias. However, this bias is minimal because it is unlikely that participants decided not to participate because of their heart rate or smoking status.

Summary
In conclusion, we found that smoking was an independent risk factor for ischemic stroke, and smokers with faster heart rate had the highest risk of ischemic stroke among Inner Mongolians. These findings suggest that smoking status and heart rate may be valuable in predicting ischemic stroke incidence.

Sources of Funding
This study was supported by National Natural Science Foundation of China (grant No. 30972531) and a Project of the Priority Academic Program Development of Jiangsu Higher Education Institutions.

Disclosures
None.

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Stroke. published online July 23, 2013;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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