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Two-Year Changes in Proteinuria and the Risk of Stroke in the Chinese Population: A Prospective Cohort Study

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Background—Whether changes in proteinuria are associated with incident stroke in the general population is unclear. This study aimed to investigate the association between changes in proteinuria and incident stroke and its subtypes.

Methods and Results—The current study included 60 940 Chinese participants (mean age, 50.69 years) who were free of stroke at the time of surveys (2006–2007 and 2008–2009). Participants were divided into 4 categories according to 2-year changes in proteinuria: no proteinuria, remittent proteinuria, incident proteinuria, and persistent proteinuria. Cox proportional hazards models were used to calculate hazard ratios and their 95% CIs for stroke. After a median follow-up period of 6.92 years, 1769 individuals developed stroke. After adjustment for confounding factors, incident proteinuria and persistent proteinuria were associated with increased risk of stroke (hazard ratio, 1.46 [95% CI, 1.26–1.68] and hazard ratio, 1.71 [95% CI, 1.42–2.06], respectively) compared with no proteinuria, which were higher than proteinuria detected at one single point (hazard ratio, 1.25; 95% CI, 1.09–1.43). The effect size for risk of stroke subtypes including ischemic stroke and hemorrhagic stroke was similar.

Conclusions—Changes in proteinuria exposure, particularly persistent proteinuria, are more likely to reflect the risk of stroke, compared with proteinuria collected at a single time point in the general population. (***J Am Heart Assoc***. 2017;6:e006271. DOI: 10.1161/JAHA.117.006271.)

Key Words: change in proteinuria • cohort study • hemorrhage • ischemic stroke • proteinuria

P roteinuria is a major indicator of chronic kidney disease (CKD).[1] In 2012, a national survey reported that the prevalence of CKD was 10.8%, with ≈119.5 million adults 18 years or older diagnosed with CKD in China.[2] CKD and cardiovascular disease are major public health problems worldwide and often share the same pathophysiological mechanisms, including high blood pressure (BP), smoking, high cholesterol levels, and diabetes mellitus.[3] Furthermore, individuals with CKD have worse functional outcomes and an increased risk of cardiovascular disease and all-cause mortality, as well as progression to kidney failure.[4–7]

Several prospective studies have suggested that the presence of protein in urine is directly associated with stroke.[8–14] The VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) trial[9] and a Japanese trial[8] showed that proteinuria at baseline was a strong risk factor for stroke or cardiovascular events. The CRIC (Chronic Renal Insufficiency Cohort) study suggested that proteinuria and albuminuria are better predictors of stroke risk than estimated glomerular filtration rate in patients with CKD.[12] The China Stroke Primary Prevention Trial, which was conducted in 19 599 adults, also showed that baseline proteinuria measured by dipstick was an independent risk factor for first incident stroke and ischemic stroke.[10] However, an inherent limitation of previous studies is the reliance on a single time point by which to assess kidney damage and events using baseline proteinuria. This damage may have occurred several decades before the event and is thus likely to yield biased estimates of an association. Moreover, there has been no consideration of how proteinuria varies within individuals over time and the

Clinical Perspective

What Is New?

- Changes in proteinuria are more likely to reflect the risk of stroke, compared with proteinuria collected at a single time point in the general population.
- Participants with persistent proteinuria had the highest risk of developing stroke.
- The effect size of changes in proteinuria for risks of stroke subtypes including ischemic stroke and hemorrhagic stroke was similar.

What Are the Clinical Implications?

- Change in proteinuria is a practical and effective risk factor for incident stroke in a community population in China.
- Clinicians and public health practitioners should be aware that early detection and control of proteinuria may decrease the risk of stroke.

subsequent effect that this would have on changes in proteinuria (none, remittent, incident, and persistent) and the future risk of stroke. Therefore, the current study aimed to examine the prospective association between 2-year changes in proteinuria and incident stroke and subtypes in the Chinese population during a median of 6.92 years of follow-up.

Methods

Study Population

The Kailuan study[15] was a prospective cohort study that was conducted in the community of Kailuan in Tangshan. Tangshan is an industrial and modern city that is located in the central section of the circulating Bohai Sea Gulf region of China. From June 2006 to October 2007, a total of 101 510 participants (81 110 men and 20 400 women, aged 18–98 years) were recruited to participate in the Kailuan study. We excluded 26 149 participants who did not finish the 2008–2009 follow-up, 2047 participants with previous stroke before the 2008–2009 survey, and 12 374 participants without complete dipstick proteinuria data. Therefore, 60 940 participants who were free of stroke were included in the final analysis. We considered the 2008–2009 survey as the starting point and December 31, 2015, as the end point of the follow-up (Figure 1). The follow-up evaluations included biennial measurement of laboratory parameters and recording of adverse events. The study was approved by the ethics committees of Kailuan General Hospital, following the guidelines outlined by the Helsinki Declaration. All participants agreed to take part in the study and provided written informed consent.

Measurements of Proteinuria

At the baseline visit, dipstick urinalysis was performed on a fresh urine sample by physicians and visually read 1 minute after the dipstick test.[16] The urine test strip results were based on a color scale that quantified proteinuria as absent, trace, 1+, 2+, or 3+ proteinuria. Proteinuria was defined as trace or more protein at baseline or dipstick urinalysis at a follow-up visit. We also conducted sensitivity analyses in which proteinuria was defined as 1+ or more.

We defined 4 types of proteinuria according to changes in proteinuria from the baseline examination to the follow-up collection period. No proteinuria was defined as an absence of proteinuria during the baseline collection period and the follow-up collection period. Remittent proteinuria was defined as proteinuria that was present during the baseline collection period, but was not present at the follow-up collection period. Incident proteinuria was defined as proteinuria that was not present at baseline, but was present at the follow-up collection period. Persistent proteinuria was defined as proteinuria that was present during the baseline collection period and at the follow-up collection period.

Assessment of Potential Covariates

The demographic and clinical characteristics, including age, sex, alcohol use, personal monthly income, education, and history of disease were collected via questionnaires. Family per-member monthly income was categorized as < ¥600(US$ 77), from ¥600(US$ 77) to ¥799(US$ 102), or at least ¥800 (US$ 103). Educational attainment was categorized as illiteracy or primary, middle school, and high school or above. Physical activity was classified as ≥4 times per week and ≥20 minutes at a time, <80 minutes per week, or none. Smoking status and drinking status were classified as never, former, or current according to self-reported information.

Weight and height was measured and body mass index was calculated as weight (kg)/height (m)^2. Systolic BP and diastolic BP were measured 3 times with the participants in the seated position using a mercury sphygmomanometer, and the average of 3 readings was used in the analyses. Blood samples were collected from the antecubital vein after an overnight fast. All blood samples were tested using a Hitachi 747 auto-analyzer. Baseline estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[17] Hypertension was defined as any self-reported hypertension or use of antihypertensive drug, or BP ≥140/90 mm Hg. Dyslipidemia was defined as any self-reported history or use of lipid-lowering drugs, or serum triglyceride ≥1.69 mmol/L, low-density lipoprotein cholesterol ≥3.62 mmol/L, or high-density lipoprotein cholesterol ≤1.04 mmol/L. Diabetes mellitus
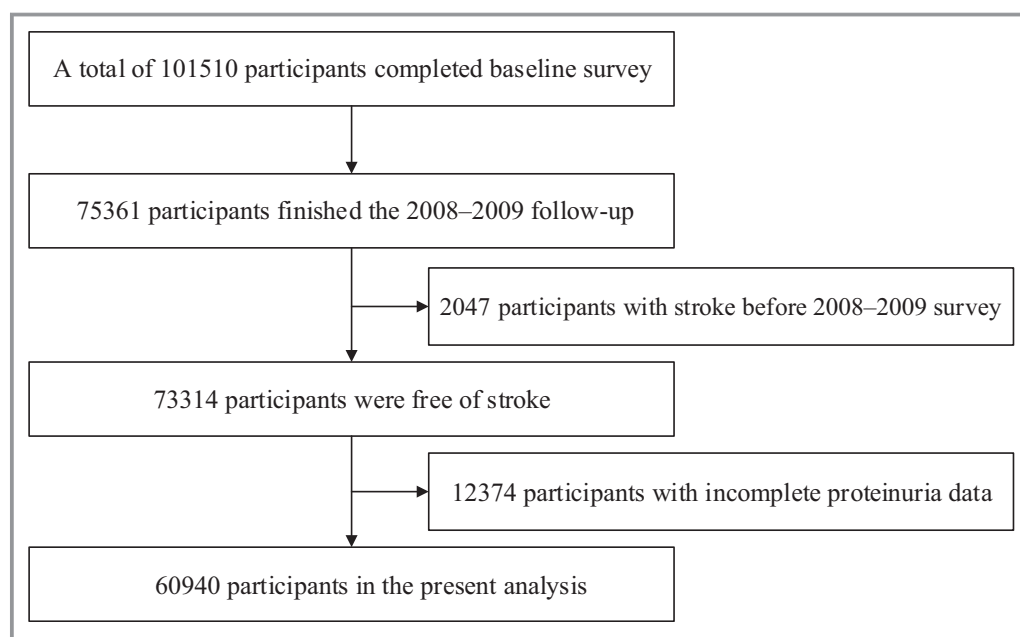
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│  A total of 101510 participants completed baseline survey    │
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│  75361 participants finished the 2008–2009 follow-up         │
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                            │       │ 2047 participants with stroke before      │
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│  73314 participants were free of stroke                      │
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                            │       │ 12374 participants with incomplete        │
                            │       │ proteinuria data                          │
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│  60940 participants in the present analysis                  │
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Figure 1. Study flowchart.

was defined as any self-reported diabetes mellitus or use of glucose-lowering drugs, or fasting blood glucose ≥7 mmol/L.

Follow-Up and Stroke Assessment

The primary outcome was the first occurrence of stroke, either the first nonfatal stroke event, or stroke death without a preceding nonfatal event. Participants were followed up by face-to-face interviews at every 2-year routine medical examination until December 31, 2015, or until the event of interest or death. For the participants without face-to-face follow-ups, outcome information was directly obtained by checking death certificates from provincial vital statistics offices, discharge summaries, and medical records. The outcome information was further confirmed by brain computed tomography or magnetic resonance imaging in medical records according to World Health Organization criteria[18] and classified into 3 types: cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage. The follow-up examinations were performed by trained physicians who were blinded to the baseline data. Considering the small sample size (n=44), we did not include the subarachnoid hemorrhage group in the subgroup analysis.

Statistical Analyses

Continuous variables are described as mean±SD and were compared by t test, Wilcoxon test, ANOVA, or the Kruskal–Wallis test. Categorical variables are described as percentages and were compared using chi-square test. Univariate

survival analysis was performed by the Kaplan–Meier method and log-rank test. Person-years were calculated from the date of when the 2008–2009 interview was conducted to the date when first stroke was detected, the date of death, or the date of participating in the last interview in this analysis, whichever came first.

Cox proportional hazards regression was used to estimate the risk of stroke by calculating hazard ratios (HRs) and 95% CIs. We fitted 3 multivariable Cox proportional hazards models. Model 1 was adjusted for age and sex in 2008. Model 2 was further adjusted for education level, drinking, smoking, physical activity, and body mass index in 2008. Model 3 was further adjusted for a history of hypertension, diabetes mellitus, or dyslipidemia; total cholesterol; triglycerides; low-density lipoprotein; high-density lipoprotein; systolic BP; diastolic BP; fasting blood glucose; and estimated glomerular filtration rate in 2008. To test the robustness of our findings, we conducted model 3 in participants excluding individuals with an estimated glomerular filtration rate <30 mL/min per 1.73 m^2 in 2008. Because 11 hospitals participated in the study, the hospital was treated as clusters in the Cox model and the sandwich estimators were used to account for the correlations and calculate the SE in the study. The proportional hazards assumption was tested by scaled Schoenfeld residuals; no appreciable violations were noted. All interactions were analyzed by multivariable Cox proportional hazards modeling.

In 12 374 participants with incomplete proteinuria data, 11 640 participants had 1 proteinuria data in 2006 or 2008. Considering that many individuals with incomplete proteinuria

Table 1. Characteristics of Participants According to Changes in Proteinuria From 2006 to 2008

Variable	Total	No Proteinuria	Remittent Proteinuria	Incident Proteinuria	Persistent Proteinuria	P Value
No. of participants	60 940	50 535	3339	5298	1768	
Men	47 292 (77.60)	38 897 (76.97)	2706 (81.04)	4232 (79.88)	1457 (82.41)	<0.0001
2006–2007 follow-up						
Age, y	50.69±12.08	50.40±12.00	51.82±12.33	51.68±12.37	53.80±12.20*	<0.0001
High school or above	13 836 (22.70)	11 893 (23.53)	613 (18.36)	1082 (20.42)	248 (14.03)*	<0.0001
Income ≥800 RMB(US$ 103)/mo	9495 (15.58)	8150 (16.13)	429 (12.85)	718 (13.55)	198 (11.20)	0.0621
Current smoker	22 193 (36.42)	18 460 (36.53)	1225 (36.69)	1917 (36.18)	591 (33.43)*	<0.0001
Current alcohol use	24 884 (40.83)	20 951 (41.46)	1293 (38.72)	2044 (38.58)	596 (33.71)*	0.0018
Active physical activity	10 060 (16.51)	8358 (16.54)	600 (17.97)	858 (16.19)	244 (13.80)*	<0.0001
Hypertension	24 300 (39.88)	18 816 (37.23)	1737 (52.02)	2577 (48.64)	1170 (66.18)*	<0.0001
Diabetes mellitus	5300 (8.70)	3685 (7.29)	510 (15.27)	654 (12.34)	451 (25.51)*	<0.0001
Dyslipidemia	21 452 (35.20)	17 276 (34.19)	1334 (39.95)	1987 (37.50)	855 (48.36)*	<0.0001
Body mass index, kg/m^2	25.08±3.49	24.98±3.46	25.33±3.60	25.48±3.56	26.21±3.82*	<0.0001
Systolic blood pressure, mm Hg	129.32±20.42	128.09±19.76	135.15±22.72	133.22±21.65	141.96±22.88*	<0.0001
Diastolic blood pressure, mm Hg	82.78±11.57	82.19±11.22	85.79±12.90	84.55±12.33	88.85±13.30*	<0.0001
Fasting blood glucose, mmol/L	5.44±1.62	5.35±1.46	5.88±2.04	5.66±1.997	6.44±2.73*	<0.0001
Total cholesterol, mmol/L	5.02±1.05	5.01±1.03	5.12±1.11	4.997±1.12	5.14±1.38	<0.0001
Triglycerides, mmol/L	1.63±1.36	1.59±1.32	1.78±1.47	1.76±1.45	2.16±1.71*	<0.0001
Low-density lipoprotein, mmol/L	2.36±0.91	2.36±0.88	2.40±0.98	2.39±1.07	2.34±1.20*	0.0002
High-density lipoprotein, mmol/L	1.53±0.40	1.52±0.39	1.54±0.43	1.54±0.40	1.57±0.44*	<0.0001
Estimated glomerular filtration rate, mL/min per 1.73 m^2	83.95±24.38	84.02±22.81	87.31±29.26	82.96±33.28	78.31±25.08*	
2008–2009 follow-up						
Age, y	52.84±12.22	52.55±12.14	53.92±12.44	53.91±12.55	55.97±12.38*	<0.0001
High school or above	14 827 (24.33)	12 664 (25.06)	646 (19.35)	1197 (22.59)	320 (18.10)	<0.0001
Current smoker	23 126 (37.95)	19 197 (37.99)	1324 (39.65)	1956 (36.92)	649 (36.71)*	0.0529
Current alcohol use	24 518 (40.23)	20 609 (40.78)	1308 (39.17)	1969 (37.16)	632 (35.75)*	<0.0001
Active physical activity	12 403 (20.35)	10 436 (20.65)	663 (19.86)	984 (18.57)	320 (18.10)	0.0003
Hypertension	27 677 (45.42)	21 589 (42.72)	1922 (57.56)	2894 (54.62)	1272 (71.95)*	<0.0001
Diabetes mellitus	6771 (11.11)	4768 (9.44)	570 (17.07)	892 (16.84)	541 (30.60)*	<0.0001
Dyslipidemia	22 875 (37.54)	18 456 (36.52)	1419 (42.50)	2092 (39.49)	908 (51.36)*	<0.0001
Body mass index, kg/m^2	24.98±3.45	24.90±3.41	25.14±3.57	25.30±3.55	25.86±3.76*	<0.0001
Systolic blood pressure, mm Hg	131.67±20.68	130.39±19.95	136.40±21.74	136.48±23.15	144.66±23.25*	<0.0001
Diastolic blood pressure, mm Hg	84.69±11.70	84.12±11.37	86.54±12.27	86.97±12.88	90.64±13.42*	<0.0001
Fasting blood glucose, mmol/L	5.67±1.82	5.58±1.67	5.96±2.01	6.04±2.28	6.73±3.02*	<0.0001
Total cholesterol, mmol/L	5.06±1.54	5.03±1.58	5.13±1.10	5.14±1.41	5.29±1.19*	<0.0001
Triglycerides, mmol/L,	1.66±1.85	1.62±1.80	1.76±1.60	1.78±2.24	2.12±2.40*	<0.0001
Low-density lipoprotein, mmol/L	2.60±1.16	2.58±1.19	2.65±0.86	2.74±1.07	2.72±0.92	<0.0001
High-density lipoprotein, mmol/L	1.53±0.56	1.52±0.51	1.57±0.90	1.53±0.72	1.52±0.52*	0.0247
Estimated glomerular filtration rate, mL/min per 1.73 m^2	87.81±21.99	88.53±21.77	87.39±22.84	84.04±21.68	79.24±24.35*	<0.0001

Continued

Table 1. Continued

Variable	Total	Change of Proteinuria				P Value
		No Proteinuria	Remittent Proteinuria	Incident Proteinuria	Persistent Proteinuria	
Total stroke	1769 (2.90)	1263 (2.50)	135 (4.04)	240 (4.53)	131 (7.41)*	<0.0001
Ischemic stroke	1492 (2.45)	1069 (2.12)	116 (3.47)	199 (3.76)	108 (6.11)*	<0.0001
Hemorrhagic stroke	283 (0.46)	195 (0.39)	22 (0.66)	40 (0.76)	26 (1.47)*	<0.0001

Values are number (percentage) or mean±SD.
*The difference with statistical significance (*P*<0.05) between remittent proteinuria group and persistent proteinuria group.

data both in 2006 and 2008 were excluded, which could have influenced the results. Therefore, we conducted 3 sensitivity analyses in participants with 1 or 2 measurements of proteinuria. First, all missing data of proteinuria in 2006 or 2008 were considered as no proteinuria. Second, all missing data of proteinuria in 2006 or 2008 were considered as presence of proteinuria. Finally, all missing data of proteinuria were considered as the same results as the other time measurements.

To compare the prediction ability for stroke risk between changes in proteinuria and baseline proteinuria, the area under receiver operating characteristic curve was used to give a quantitative assessment of the predictive ability.

Statistical analyses were performed using SAS 9.4 (SAS Institute; Cary, NC). All statistical tests were 2-sided and the significance level was set at 0.05.

Results

A total of 60 940 participants with available data of proteinuria (men, 77.60%) were analyzed in our study. The mean age of the remaining population was 50.69±12.08 years. We divided the participants into 4 categories according to changes in proteinuria from 2006 to 2008. The baseline characteristics in 2006 and 2008 of the 4 categories of participants are shown in Table 1. Compared with participants with no proteinuria, participants in the other groups had a higher proportion of men, lower educational levels, lower incomes, and a higher prevalence of hypertension, diabetes mellitus, oer dyslipidemia (all *P*<0.0001). Considering the clinical importance of remittent proteinuria, we also tested the differences of risk factors between the remittent proteinuria group and the persistent proteinuria group. In brief, participants in the remittent proteinuria group were younger and more educated, had more active physical activity, and had a lower prevalence of hypertension, diabetes mellitus, and dyslipidemia (Table 1).

After a mean follow-up period of 6.92 years, a total of 1769 stroke events were recorded, including 1492 participants with ischemic stroke, 283 with hemorrhagic stroke, and

44 with subarachnoid hemorrhage stroke. The incidence per 1000 person-years of total stroke ranged from 3.66 in the no proteinuria group to 11.23 in the persistent proteinuria group. Table 2 shows the adjusted HRs of incident stroke and subtypes associated with changes in proteinuria exposure. After adjustment for covariates, participants in the incident proteinuria and persistent proteinuria groups had 46% and 71% higher risks of developing stroke compared with participants in the no proteinuria group. The HRs were 1.46 (95% CI, 1.26−1.68) and 1.71 (95% CI, 1.42−2.06), respectively (all *P*<0.05). The same trends were found in the association between changes in proteinuria and stroke subtypes (ischemic stroke and hemorrhagic stroke). Sensitivity analysis yielded the same pattern of results (Tables 2 through 4).

Figure 2A through 2C show the Kaplan−Meier cumulative risk for stroke and subtypes within groups defined by changes in proteinuria. Participants in the persistent proteinuria group experienced a higher risk than participants in the other groups during the 6.92-year follow-up period for total stroke events (log-rank test, *P*<0.0001) (Figure 2A), ischemic stroke (log-rank test, *P*<0.0001) (Figure 2B), and hemorrhagic stroke (log-rank test, *P*<0.0001) (Figure 2C).

The associations between changes in proteinuria from 2006 to 2008 and incident stroke stratified by age and sex are shown in Table 5. After adjustment for potential confounders, the HRs for incident stroke for participants with persistent proteinuria were 3.03 (95% CI, 1.79−5.13) for women and 1.47 (95% CI, 1.19−1.82) for men, and 1.73 (95% CI, 1.32−2.28) for those younger than 60 years and 1.50 (1.13−1.98) for those 60 years and older compared with participants with no proteinuria. We also tested the interactions between changes in proteinuria and age or sex in relation to stroke and subtypes. There were significant interactions between changes in proteinuria and sex in relation to total stroke and ischemic stroke (*P*<0.05). No interaction was found between changes in proteinuria and age (*P*>0.05), which may have been attributable to the small sample size.

Table 2. Association Between Changes in Proteinuria From 2006 to 2008 and Incident Stroke

	Change of Proteinuria			
	No Proteinuria	Remittent Proteinuria	Incident Proteinuria	Persistent Proteinuria
All stroke types				
Case number	1263	135	240	131
Incidence rate, per 1000 person-y	3.66	5.92	6.79	11.23
Model 1	Reference	1.46 (1.22–1.75)	1.67 (1.45–1.92)	2.47 (2.05–2.99)
Model 2	Reference	1.44 (1.20–1.73)	1.61 (1.40–1.86)	2.32 (1.92–2.80)
Model 3	Reference	1.16 (0.97–1.39)	1.46 (1.26–1.68)	1.71 (1.42–2.06)
Sensitivity analysis*	Reference	1.16 (0.96–1.39)	1.46 (1.26–1.67)	1.69 (1.40–2.04)
Ischemic stroke				
Case number	1069	116	199	108
Incidence rate, per 1000 person-y	3.09	5.08	5.61	9.17
Model 1	Reference	1.48 (1.22–1.80)	1.64 (1.40–1.92)	2.40 (1.95–2.96)
Model 2	Reference	1.46 (1.20–1.77)	1.58 (1.35–1.85)	2.25 (1.82–2.77)
Model 3	Reference	1.17 (0.96–1.42)	1.41 (1.21–1.65)	1.62 (1.32–2.00)
Sensitivity analysis*	Reference	1.16 (0.95–1.41)	1.42 (1.21–1.65)	1.59 (1.29–1.96)
Hemorrhagic stroke				
Case number	195	22	40	26
Incidence rate, per 1000 person-y	0.56	0.95	1.11	2.15
Model 1	Reference	1.53 (0.98–2.40)	1.75 (1.23–2.49)	3.06 (1.98–4.72)
Model 2	Reference	1.52 (0.97–2.38)	1.72 (1.21–2.45)	2.94 (1.90–4.54)
Model 3	Reference	1.28 (0.82–2.00)	1.60 (1.13–2.26)	2.31 (1.51–3.53)
Sensitivity analysis*	Reference	1.28 (0.82–2.00)	1.56 (1.10–2.21)	2.36 (1.54–3.61)

Values are hazard ratios (95% CI). Model 1: adjusted for age and sex in 2008. Model 2: adjusted for age, sex, education, current smoker, current alcohol use, physical activity, and body mass index in 2008. Model 3: adjusted for variables in model 2 plus a history of hypertension, diabetes mellitus, or dyslipidemia; total cholesterol; triglycerides; low–density lipoprotein; high–density lipoprotein; systolic blood pressure; diastolic blood pressure; fasting blood glucose; and estimated glomerular filtration rate in 2008.
*Adjusted for model 3 and further excluded individuals with an estimated glomerular filtration rate <30 mL/min per 1.73 m^2 in 2008.

Table 6 shows the adjusted HRs of incident stroke and subtypes associated with baseline proteinuria exposure. In the fully adjusted model, participants with proteinuria at baseline had a 25% higher risk of developing stroke compared with participants with no proteinuria (HR, 1.25; 95% CI, 1.09–1.43). Similar patterns were found in ischemic stroke and hemorrhagic stroke.

The area under receiver operating characteristic curve values of changes in proteinuria and baseline proteinuria for risk of stroke were 0.56 (95% CI, 0.55–0.57) and 0.53 (95%

Table 3. The Association Between Changes in Proteinuria From 2006 to 2008 and Incident Stroke*

Outcomes	Hazard Ratio (95% CI)[†]			
	No Proteinuria	Remittent Proteinuria	Incident Proteinuria	Persistent Proteinuria
All stroke types	Reference	1.34 (1.02–1.76)	1.47 (1.27–1.69)	1.56 (1.20–2.02)
Ischemic stroke	Reference	1.32 (0.98–1.78)	1.33 (1.13–1.56)	1.54 (1.19–2.00)
Hemorrhagic stroke	Reference	1.34 (0.66–2.72)	1.49 (0.76–2.95)	2.03 (1.48–2.79)

*Proteinuria defined as ≥1+ protein.
[†]Adjusted for age; sex; education; current smoker; current alcohol use; physical activity; body mass index; history of hypertension, diabetes mellitus, or dyslipidemia; total cholesterol; triglycerides; low–density lipoprotein; high–density lipoprotein; systolic blood pressure; diastolic blood pressure; fasting blood glucose; and estimated glomerular filtration rate in 2008.

Table 4. Sensitivity Analysis in Participants With 1 or 2 Proteinuria Measurements

	Hazard Ratio (95% CI)*			
	No Proteinuria	Remittent Proteinuria	Incident Proteinuria	Persistent Proteinuria
All stroke types				
Model 1	Reference	1.11 (0.94–1.30)	1.41 (1.23–1.61)	1.71 (1.43–2.06)
Model 2	Reference	1.02 (0.87–1.20)	1.26 (1.13–1.42)	1.36 (1.16–1.60)
Model 3	Reference	1.16 (0.97–1.39)	1.46 (1.27–1.67)	1.36 (1.16–1.59)
Ischemic stroke				
Model 1	Reference	1.14 (0.96–1.36)	1.38 (1.19–1.60)	1.63 (1.34–2.00)
Model 2	Reference	1.02 (0.85–1.21)	1.25 (1.10–1.41)	1.37 (1.15–1.62)
Model 3	Reference	1.18 (0.97–1.43)	1.41 (1.21–1.65)	1.37 (1.16–1.63)
Hemorrhagic stroke				
Model 1	Reference	1.11 (0.74–1.64)	1.59 (1.15–2.21)	2.31 (1.52–3.51)
Model 2	Reference	1.14 (0.77–1.71)	1.32 (1.00–1.74)	1.66 (1.14–2.41)
Model 3	Reference	1.26 (0.81–1.97)	1.59 (1.13–2.23)	1.64 (1.14–2.37)

Model 1: all missing data of proteinuria in 2006 or 2008 were considered as no proteinuria. Model 2: all missing data of proteinuria in 2006 or 2008 were considered as presence of proteinuria. Model 3: all missing data of proteinuria in 2006 or 2008 were considered as the same results as the other measurements.
*Adjusted for age; sex; education; current smoker; current alcohol use; physical activity; body mass index; history of hypertension, diabetes mellitus, or dyslipidemia; total cholesterol; triglycerides; low-density lipoprotein; high-density lipoprotein; systolic blood pressure; diastolic blood pressure; fasting blood glucose; and estimated glomerular filtration rate in 2008.

CI, 0.52–0.54), respectively. These results showed that the changes of proteinuria were better than spot proteinuria in predicting the risk assessment of stroke.

Table 7 shows the comparison of demographic and other characteristics in 2006 of participants (n=60 940) and nonparticipants (n=12 374). In general, we found that nonparticipants were younger; were predominantly male; were less educated; had lower monthly incomes; had a lower proportion of current smokers, current alcohol use, and active physical activity; had a higher prevalence of hypertension and dyslipidemia; and had a slightly lower prevalence of diabetes mellitus.

Discussion

In our study, the presence of proteinuria as detected by urine dipstick screening independently predicted an increased risk for incident stroke during 6.92 years of follow-up. Moreover, we observed significant associations of changes in proteinuria and the incidence of stroke and subtypes in the Chinese population. This relationship persisted independently of other known major risk factors, including diabetes mellitus, hypertension, dyslipidemia, and obesity. Findings from the current study extend those from previous studies.[10–14,16] Our study shows that the presence of proteinuria is associated with a substantially higher risk of incident stroke compared with an absence of proteinuria when measured either at baseline or at follow-up visits.

Stroke accounts for 5 million deaths worldwide each year and is a leading cause of serious disability.[19] The stroke burden in China has increased during the past 30 years, and remains particularly high in rural areas. The recent NESS-China study, which was conducted in 155 urban and rural centers in 31 provinces in China, showed that the incidence of stroke was 345.1 per 100 000 person-years.[20] Therefore, the growing disease burden of stroke indicates that prevention is a necessary strategy, which, in turn, highlights the need for awareness regarding risk factors and warning signs.[21] Growing evidence has suggested an association between the presence of protein in the urine (proteinuria or albuminuria) and the risk of stroke.[10–14,22,23] The Honolulu Heart Program showed that proteinuria that was detected at urine dipstick screening independently predicted an increased risk for incident stroke over 27 years of follow-up.[22] A recent study from the China Stroke Primary Prevention Trial also found that baseline proteinuria as measured by dipstick was an independent risk factor for first incident stroke and ischemic stroke.[10] A meta-analysis of cohort studies or randomized controlled trials concluded that increasing albuminuria increased the risk of stroke.[23]

In accordance with the above-mentioned studies,[10–14,22,23] we found a significant association between baseline proteinuria and the risk of stroke. Patients with baseline proteinuria showed a 25% higher risk of reaching an end point in the follow-up. However, previous studies generally considered baseline proteinuria (a single point in time) as a risk predictor. The potential effect of a change in proteinuria over time was not well characterized in these studies. In the current study, 2-year changes of proteinuria were considered to be
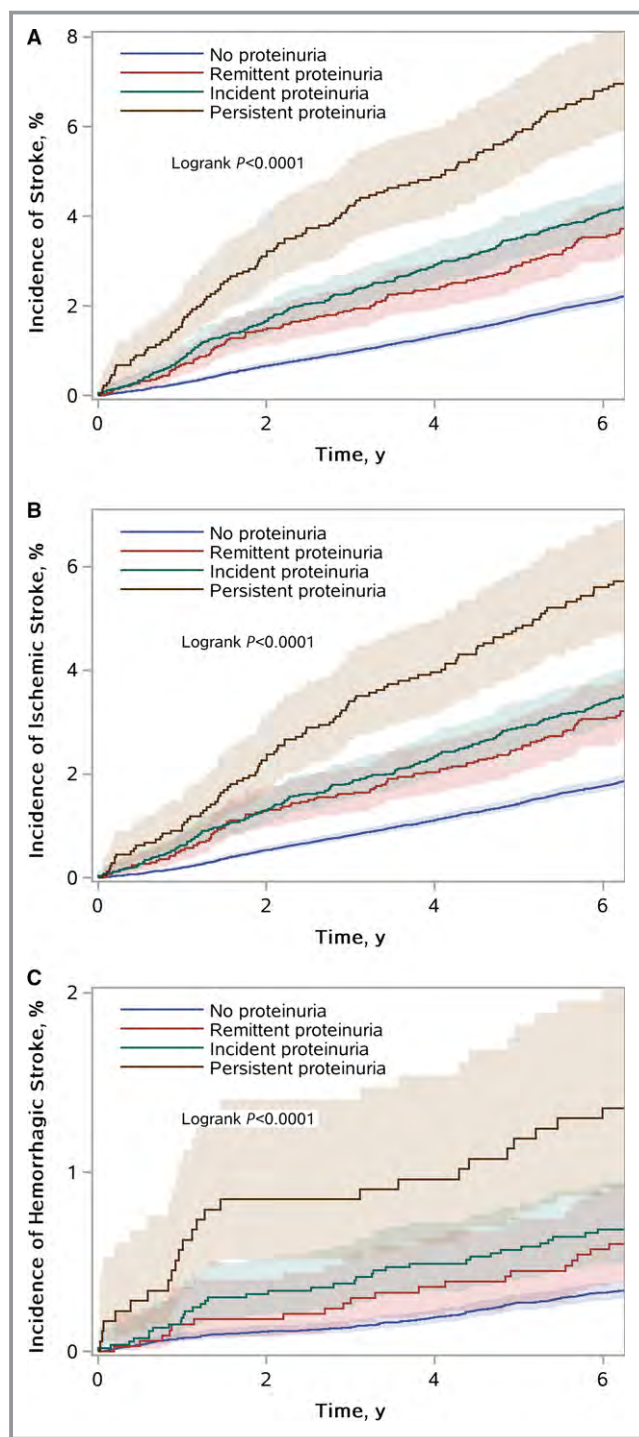
Figure 2. Kaplan–Meier curve of (A) all-type stroke incidence rate, (B) ischemic stroke incidence rate, and (C) hemorrhagic stroke incidence rate by changes in proteinuria.

associated with the risk of stroke. We also found that the risk factors including education level, active physical activity, hypertension, diabetes mellitus, and dyslipidemia were associated with remittent proteinuria. In terms of clinical significance, we could change the proteinuria status by controlling these risk factors, and, in turn, reduce the risk of stroke.

The current study is unique in that measurement of changes in proteinuria included 4 types (no, remittent, incident, and persistent proteinuria). Each of these types of proteinuria appeared to confer different risks of stroke, and the association between persistent proteinuria and incident stroke was the most significant. Patients with persistent proteinuria exposure showed a 71% higher risk of having stroke, which was higher than baseline proteinuria exposure. Moreover, the association between changes in proteinuria and the risk of stroke remained significant, even after excluding individuals with an estimated glomerular filtration rate of ≤ 30 mL/min per 1.73 m^2 from the analysis. Furthermore, our study investigated this association by distinguishing between ischemic and hemorrhagic stroke, as the patterns of results were consistent with total stroke. Interestingly, in subgroup analysis, the associations between changes in proteinuria and incident total stroke and ischemic stroke were more significant in women than in men. The reason for this finding is unclear. Further studies are required to investigate the effect of sex on the associations between changes in proteinuria and incident stroke. However, these associations showed no significance difference in subgroups stratified by age. Our findings taken together with previous studies suggest that not only is baseline proteinuria important, but a longitudinal change in proteinuria predicts a high risk that is compatible or beyond the baseline value. Therefore, monitoring longitudinal patterns of changes in proteinuria in clinical practice is important.

The pathophysiological mechanisms that mediate the link between proteinuria and stroke are unknown and require further investigation. There are several potential explanations for why the presence of proteinuria may be a risk factor for incident stroke. First, reduced kidney function as assessed by the presence of proteinuria is associated with inflammation, thromboembolism, endothelial dysfunction, and arterial stiffness/calcification, among other factors, all of which may contribute to the risk of stroke.[24–26] Second, participants with persistent proteinuria tend to have a higher prevalence of traditional risk factors for cardiovascular disease compared with participants without proteinuria. These risk factors include older age; a higher prevalence of hypertension, diabetes mellitus, and dyslipidemia; increased systolic and diastolic BP; higher fasting blood glucose levels; higher body mass index; and inactive physical activity. Third, proteinuria has been proposed to be associated with an increase in the albumin and fibrinogen transcapillary escape rate, which reflects widespread vascular damage.[27]

Strengths and Limitations

Our study has several strengths. This is the first prospective study to address the association between changes in

Table 5. The Association Between Changes in Proteinuria From 2006 to 2008 and Incident Stroke Stratified by Age and Sex

	Hazard Ratios and 95% CIs*				
	No Proteinuria	Remittent Proteinuria	Incident Proteinuria	Persistent Proteinuria	P for Interaction
Women					
All stroke types	Reference	1.23 (0.70–2.16)	2.12 (1.39–3.22)	3.03 (1.79–5.13)	0.0361
Ischemic stroke	Reference	1.24 (0.66–2.35)	2.49 (1.57–3.93)	3.53 (1.98–6.29)	0.0100
Hemorrhagic stroke	Reference	1.15 (0.34–3.95)	0.86 (0.26–2.92)	2.47 (0.77–7.97)	0.7730
Men					
All stroke types	Reference	1.15 (0.94–1.39)	1.33 (1.14–1.55)	1.47 (1.19–1.82)	
Ischemic stroke	Reference	1.15 (0.93–1.42)	1.27 (1.07–1.51)	1.39 (1.10–1.75)	
Hemorrhagic stroke	Reference	1.27 (0.78–2.07)	1.60 (1.10–2.33)	2.08 (1.28–3.37)	
Age <60 y					
All stroke types	Reference	1.36 (1.07–1.74)	1.33 (1.08–1.63)	1.73 (1.32–2.28)	0.0596
Ischemic stroke	Reference	1.39 (1.06–1.81)	1.29 (1.03–1.63)	1.64 (1.21–2.22)	0.0925
Hemorrhagic stroke	Reference	1.48 (0.84–2.62)	1.28 (0.77–2.14)	2.47 (1.37–4.45)	0.3776
Age ≥60 y					
All stroke types	Reference	0.97 (0.73–1.28)	1.48 (1.21–1.82)	1.50 (1.13–1.98)	
Ischemic stroke	Reference	0.96 (0.72–1.29)	1.46 (1.17–1.82)	1.48 (1.10–2.01)	
Hemorrhagic stroke	Reference	1.02 (0.48–2.15)	1.72 (1.04–2.86)	1.76 (0.89–3.49)	

*Adjusted for age; sex; current smoker; current alcohol use; physical activity; body mass index; a history of hypertension, diabetes mellitus, or dyslipidemia; total cholesterol; triglycerides; low-density lipoprotein; high-density lipoprotein; systolic blood pressure; diastolic blood pressure; fasting blood glucose; and estimated glomerular filtration rate in 2008.

proteinuria and the incidence of stroke in the general population. Furthermore, we distinguished between ischemic and hemorrhagic stroke. However, there are some inherent

Table 6. Association Between Baseline Proteinuria in 2006 and Incident Stroke

	Baseline Proteinuria	
	No Proteinuria	Proteinuria
All stroke types		
Model 3	Reference	1.25 (1.09–1.43)
Sensitivity analysis*	Reference	1.24 (1.08–1.43)
Ischemic stroke		
Model 3	Reference	1.23 (1.06–1.43)
Sensitivity analysis*	Reference	1.23 (1.06–1.43)
Hemorrhagic stroke		
Model 3	Reference	1.52 (1.09–2.11)
Sensitivity analysis*	Reference	1.50 (1.08–2.09)

Values are hazard ratios (95% CI). Model 3: adjusted for age; sex; level of education; smoking; current alcohol use; physical activity; body mass index at baseline; a history of hypertension, diabetes mellitus, or dyslipidemia; total cholesterol; triglycerides; low-density lipoprotein; high-density lipoprotein; systolic blood pressure; diastolic blood pressure; fasting blood glucose; and estimated glomerular filtration rate in 2006.
*Adjusted for model 3 and further excluded individuals with an estimated glomerular filtration rate <30 mL/min per 1.73 m² in 2006.

limitations. First, medications that modify urinary protein excretion (use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) were not included in the models as a potential disease-modifying therapy. Angiotensin-converting enzyme inhibitor and angiotensin receptor blocker agents decrease albuminuria in individuals with diabetes mellitus and hypertension[28] and decrease cardiovascular events in these patients.[29] Second, because all of the participants were recruited from Tangshan City, the cohort is not nationally representative. Therefore, our findings pertaining to changes in proteinuria and stroke are not generalizable to other parts of China. Third, the incomplete measurements of proteinuria are a weakness of the study. Our study may ultimately underestimate the effect of changes of proteinuria on the incidence of stroke. However, we conducted 3 sensitivity analyses in patients including 1 or 2 measurements of proteinuria and the results were similar with the primary analysis.

Conclusions

Our findings suggest that changes in proteinuria, particularly persistent proteinuria, compared with spot urinary protein collected at a single time point, is a more practical and effective risk factor for incident stroke in a community

Table 7. Comparison of Demographic and Other Characteristics in 2006 of Participants and Nonparticipants

Variable	Participants	Nonparticipants	P Value
No. of participants	60 940	12 374	
Age, y	50.69±12.08	48.88±12.53	<0.0001
Men	47 292 (77.60)	9993 (80.76)	<0.0001
High school or above	13 836 (22.70)	2120 (17.13)	<0.0001
Income ≥800 RMB(US$ 103)/mo	9495 (15.58)	1301 (10.51)	<0.0001
Current smoker	22 193 (36.42)	3160 (25.54)	<0.0001
Current alcohol use	24 884 (40.83)	3682 (29.76)	<0.0001
Active physical activity	10 060 (16.51)	1033 (8.35)	<0.0001
Hypertension	24 300 (39.88)	5886 (47.57)	<0.0001
Diabetes mellitus	5300 (8.70)	990 (8.00)	0.0118
Dyslipidemia	21 452 (35.20)	4539 (36.68)	0.0018
Body mass index, kg/m^2	25.08±3.49	25.02±3.40	0.0472
Systolic blood pressure, mm Hg	129.33±20.42	130.92±20.08	<0.0001
Diastolic blood pressure, mm Hg	82.78±11.57	84.03±11.35	<0.0001
Fasting blood glucose, mmol/L	5.44±1.62	5.43±1.52	0.0012
Total cholesterol, mmol/L	5.02±1.05	4.61±1.43	<0.0001
Triglycerides, mmol/L,	1.63±1.36	1.86±1.40	<0.0001
Low-density lipoprotein, mmol/L	2.36±0.91	2.31±0.99	<0.0001
High-density lipoprotein, mmol/L	1.53±0.40	1.59±0.39	<0.0001
Estimated glomerular filtration rate, mL/min per 1.73 m^2	83.95±24.38	80.08±29.68	<0.0001

Values are number (percentage) or mean±SD.

population in China. Clinicians and public health practitioners should be aware that early detection and control of proteinuria may decrease the risk of stroke.

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Disclosures

None.

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