

Association of Persistent, Incident, and Remittent Proteinuria With Stroke Risk in Patients With Diabetes Mellitus or Prediabetes Mellitus

Anxin Wang, PhD;* Ruixuan Jiang, MD;* Zhaoping Su, MD; Jia Zhang, MD; Xingquan Zhao, MD; Shouling Wu, MD; Xiuhua Guo, PhD

Background—Proteinuria often changes dynamically, showing either regression or progression. The impact of changes in proteinuria on future stroke risk remains largely unknown. We hypothesized that changes in proteinuria would be associated with stroke risk in patients with diabetes mellitus and prediabetes mellitus.

Methods and Results—The study population included 17 380 participants with diabetes mellitus or prediabetes mellitus enrolled in a prospective Chinese cohort. From the baseline and 2-year dipstick screening results, participants were classified as having no proteinuria or remittent, incident, or persistent proteinuria. Reduction in proteinuria was calculated as the baseline minus 2-year proteinuria. Stroke outcomes were assessed in subsequent follow-ups. Data were analyzed using Cox proportional-hazards models. During a median follow-up of 6.9 years, we identified 751 patients with stroke. Stroke risk was increased for participants with persistent (hazard ratio [HR], 1.64; 95% confidence interval [CI], 1.18–2.30), incident (HR, 1.52; 95% CI, 1.22–1.89), and remittent (HR, 1.42; 95% CI, 1.01–2.02) proteinuria compared with those with no proteinuria. Persistent proteinuria was associated with a higher risk of stroke for participants with prediabetes mellitus (HR, 2.58; 95% CI, 1.58–4.22) compared with those with diabetes mellitus (HR, 1.35; 95% CI, 0.86–2.12 [*P* for interaction=0.0083]). Proteinuria reduction contributed to a decrease in stroke incidence (HR, 0.88; 95% CI, 0.81–0.95). The results were confirmed by sensitivity analyses.

Conclusions—Persistent, incident, and remittent proteinuria are independent indicators of stroke risk in both diabetic and prediabetic populations. (*J Am Heart Assoc.* 2017;6:e006178. DOI: 10.1161/JAHA.117.006178.)

Key Words: chronic kidney disease • diabetes mellitus • prediabetes mellitus • proteinuria • stroke

Stroke is a major cause of death and disability globally. Although traditional cardiovascular risk factors are well established, a better understanding of novel risk factors that contribute to stroke risk is important for stroke prevention. The urine dipstick is a widely used tool in clinical screening for proteinuria because of its easy accessibility and low cost.¹ Dipstick-positive proteinuria, a sign of chronic kidney disease, has emerged as a powerful and independent predictor of cardiovascular disease. Data suggest that baseline proteinuria confers a 50% to 92% greater risk of future stroke.²

However, proteinuria often changes dynamically, showing either regression or progression.³ Previous studies have examined proteinuria using only a single measurement.^{4–6} The value of multiple dipstick measurements for demonstrating changes in proteinuria and its relation to stroke outcomes has rarely been investigated. Thus, it is unclear whether changes in proteinuria also have an impact on stroke risk. Proteinuria is commonly detected in the diabetic population.⁷ Prediabetes mellitus is an intermediate hyperglycemic state between normoglycemia and diabetes

From the Department of Epidemiology and Health Statistics, School of Public Health (A.W., X.G.) and Department of Neurology, Beijing Tiantan Hospital (A.W., R.J., Z.S., J.Z., X.Z.), Capital Medical University, Beijing, China; China National Clinical Research Center for Neurological Diseases, Beijing, China (A.W., R.J., Z.S., J.Z., X.Z.); Center of Stroke, Beijing Institute for Brain Disorders, Beijing, China (A.W., R.J., Z.S., J.Z., X.Z.); Beijing Key Laboratory of Translational Medicine for Cerebrovascular Disease, Beijing, China (A.W., R.J., Z.S., J.Z., X.Z.); Beijing Municipal Key Laboratory of Clinical Epidemiology, Beijing, China (A.W., X.G.); Department of Cardiology, Kailuan Hospital, North China University of Science and Technology, Tangshan, China (S.W.).

*Dr Wang and Dr Jiang contributed equally to this work.

Correspondence to: Xiuhua Guo, PhD, Department of Epidemiology and Health Statistics, School of Public Health, Capital Medical University, No. 10 Xitoutiao, Youanmenwai, Fengtai District, Beijing 100069, China. E-mail: statguo@ccmu.edu.cn and Xingquan Zhao, MD, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, No. 6 Tiantanxili, Dongcheng District, Beijing 100050, China. E-mail: zxq@vip.163.com and Shouling Wu, MD, Department of Cardiology, Kailuan Hospital, North China University of Science and Technology, No. 57 Xinhua Road, Lubei District, Tangshan 063000, China. E-mail: drwusl@163.com

Received March 22, 2017; accepted August 14, 2017.

© 2017 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Clinical Perspective

What Is New?

- Persons with persistent, incident, or remittent proteinuria among diabetic and prediabetic populations are at increased risk of stroke compared with those without proteinuria.
- Persistent proteinuria confers a higher risk of stroke for patients with prediabetes mellitus compared with those with diabetes mellitus.
- Proteinuria reduction was associated with lower stroke incidence, independent of traditional cardiovascular risk factors.

What Are the Clinical Implications?

- Screenings for proteinuria change has added value in the identification of individuals at higher risk for stroke among diabetic and prediabetic populations.
- For patients with prediabetes mellitus with proteinuria, especially those with persistent proteinuria, interventions should be considered at an early stage in order to prevent disease progression and potentially reduce risk for stroke.
- Therapies targeted at proteinuria reduction for stroke prevention warrant further investigation.

mellitus that affects about a third of persons worldwide.⁸ These individuals also have a significantly increased risk of diabetes mellitus, chronic kidney disease, and cardiovascular disease, highlighting the public health impact of this disorder. The relationship between changes in proteinuria and stroke risk in this disease category has not been specifically examined.

Therefore, we conducted this study to assess the predictive value of proteinuria change for subsequent stroke outcomes in participants with diabetes mellitus or prediabetes mellitus. We also analyzed whether reduction in proteinuria would have a protective effect on stroke risk.

Methods

Study Population

The Kailuan Study is a prospective cohort study consisting of 101 510 individuals from the Kailuan Community in Tangshan, China. The study details have been previously reported.^{6,9–11} In brief, all participants aged 18 to 98 years at the first examination from June 2006 to October 2007 underwent face-to-face questionnaire interviews as well as clinical and laboratory examinations after obtaining written informed consent. Follow-ups occurred by means of biennial face-to-face examinations and annual comprehensive surveillance of medical records and death certificates. The study was conducted according to the Declaration of Helsinki and

approved by the ethics committees of the Kailuan General Hospital, Beijing Tiantan Hospital, and the participating hospitals.

Eligible patients for the present study were at least 18 years of age with a diagnosis of diabetes mellitus or prediabetes mellitus at the baseline survey and were free of stroke until the 2-year follow-up in 2008–2009. Diabetes mellitus was diagnosed if participants met the criteria of the American Diabetes Association for fasting glucose concentration ≥ 7 mmol/L, had any use of glucose-lowering drugs, or had self-reported diabetes mellitus. Prediabetes mellitus was defined as impaired fasting glucose of 5.6–6.9 mmol/L.¹² We first excluded 71 494 persons with normal glucose tolerance at baseline. Those with previous strokes by the 2-year survey, those who did not participate in the 2-year survey, and those with missing proteinuria data were further excluded. Therefore, 17 380 participants were available for the analysis (Figure 1).

Data Collection and Follow-Up

We collected morning urine samples both at baseline and at the 2-year survey. Automated dipstick urinalysis (H12-MA, DIRUI N-600) was used to measure urine protein. Women were analyzed during the nonmenstrual period. Urine protein was recorded as semiquantitative results of “none,” “trace,” “1+,” “2+,” or “ $\geq 3+$.”

Research doctors used questionnaires to obtain information on demographics, lifestyles, and medical histories at each survey. Standard protocols were used.⁶ Weight and height were measured, and body mass index was calculated as weight(kg)/height(m)². The average blood pressure (BP) from two separate readings was used for analysis. Blood samples were collected from the antecubital vein after an overnight fast. An autoanalyzer (Hitachi 747) was used for measuring blood variables. Hypertension was defined as any self-reported hypertension, any use of antihypertensive drugs, or a BP $\geq 140/90$ mm Hg. Dyslipidemia was defined as any self-reported history, use of lipid-lowering drugs, serum triglyceride ≥ 1.69 mmol/L, low-density lipoprotein cholesterol ≥ 3.62 mmol/L, or high-density lipoprotein cholesterol ≤ 1.04 mmol/L.

Trained physicians who were blinded to the baseline information performed face-to-face follow-ups every 2 years. Outcome events occurring after the 2-year survey were identified until December 31, 2015. The primary outcome was stroke (either nonfatal or fatal), defined by the World Health Organization criteria,¹³ as an acute neurological deficit lasting >24 hours or leading to death. Stroke diagnosis was additionally confirmed by brain computed tomography or magnetic resonance imaging scans. We classified stroke into 3 types: ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. The diagnostic criteria were

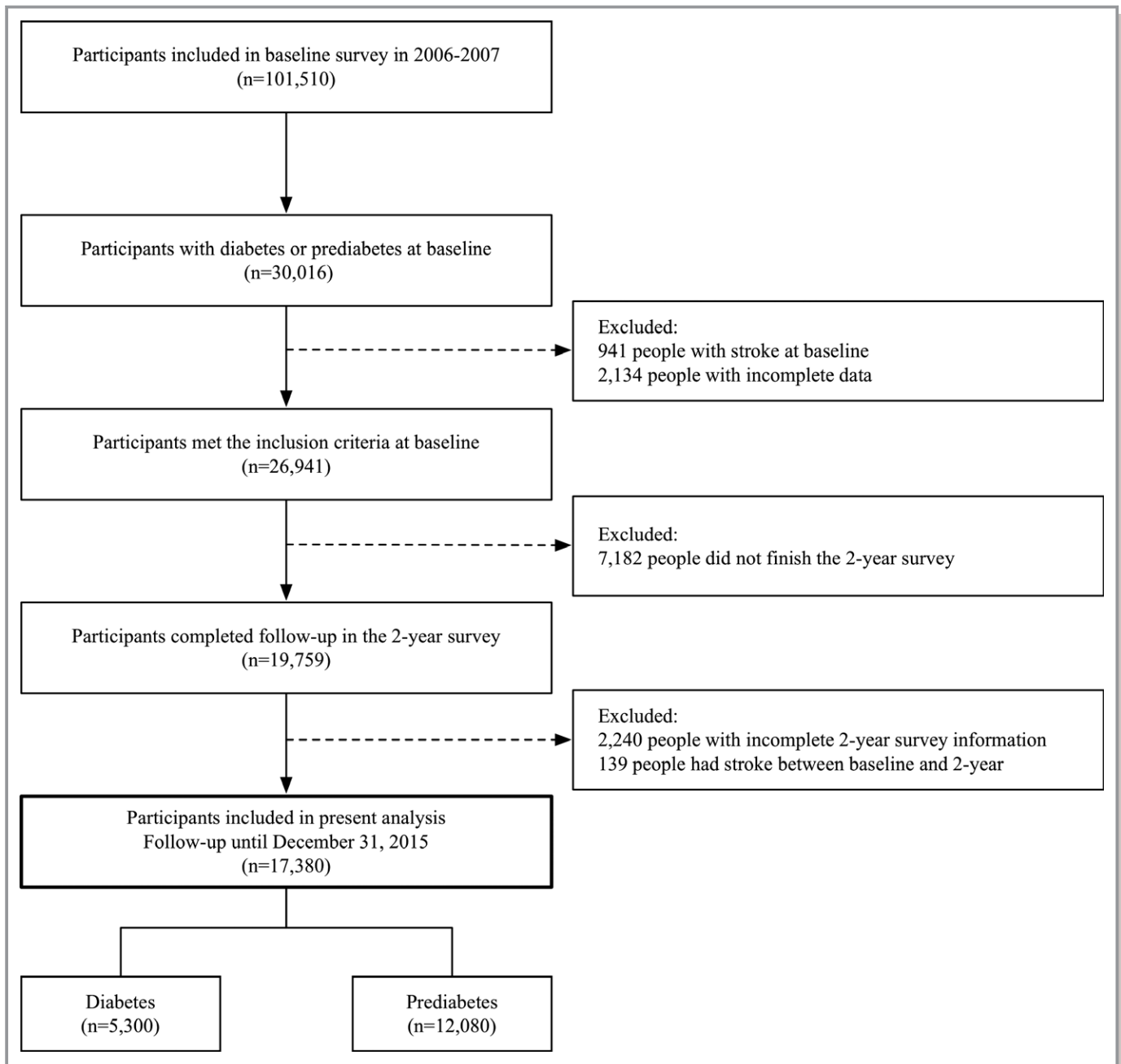


Figure 1. Study flowchart.

consistent across all participating hospitals, and all stroke outcomes were validated by the Data Safety Monitoring Board and the Arbitration Committee for Clinical Outcomes.

Statistical Analyses

For the main analyses, we defined dipstick results of $\geq 1+$ as positive for proteinuria. Based on the changes in proteinuria status from baseline to the 2-year follow-up, we classified the participants into 4 subgroups: no proteinuria (negative at both screens), remittent proteinuria (baseline positive and 2-year

negative), incident proteinuria (baseline negative and 2-year positive), and persistent proteinuria (positive at both screenings). Data from the baseline survey were used for selected covariates (listed in Table 1). Continuous variables were described as mean \pm SD and were compared across the 4 subgroups using ANOVA. Categorical variables were described as counts (percentages) and were compared using chi-square test or Fisher exact test.

Incidence rates of stroke were calculated per 1000 person-years of follow-up. Cox proportional-hazards regression was used to calculate the hazard ratio (HR) and 95%

Table 1. Characteristics at Baseline Survey by Changes in Proteinuria

Characteristics	Total	Changes in Proteinuria				P Value
		No Proteinuria	Remittent Proteinuria	Incident Proteinuria	Persistent Proteinuria	
No. of participants	17 380	14 961 (86.1)	459 (2.6)	1560 (9.0)	400 (2.3)	
Age, y	52.6±10.9	52.3±10.8	53.3±11.0	54.1±11.2	55.8±10.8	<0.0001
Sex, male, No. (%)	14 416 (83.0)	12 380 (82.8)	375 (81.7)	1328 (85.1)	333 (83.3)	0.1025
Current smoker, No. (%)	6646 (38.2)	5780 (38.6)	183 (39.9)	560 (35.9)	123 (30.8)	0.0022
Current alcohol, No. (%)	7471 (43.0)	6570 (43.9)	195 (42.5)	573 (36.7)	133 (33.3)	<0.0001
Active physical activity, No. (%)	3191 (18.4)	2789 (18.6)	107 (23.3)	234 (15.0)	61 (15.3)	<0.0001
Hypertension, No. (%)	8834 (50.3)	7252 (48.5)	308 (67.1)	963 (61.7)	311 (77.8)	<0.0001
Prediabetes mellitus, No. (%)	12 080 (69.5)	10 773 (72.0)	258 (56.2)	897 (57.5)	152 (38.0)	<0.0001
Diabetes mellitus, No. (%)	5300 (30.5)	4188 (28.0)	201 (43.8)	663 (42.5)	248 (62.0)	<0.0001
Dyslipidemia, No. (%)	7648 (44.0)	6405 (42.8)	228 (49.7)	769 (49.3)	246 (61.5)	<0.0001
Body mass index, kg/m ²	25.9±3.4	25.8±3.4	26.4±3.6	26.2±3.4	27.0±4.1	<0.0001
Systolic blood pressure, mm Hg	134.4±20.9	133.3±20.5	142.6±24.2	139.6±21.8	147.3±21.0	<0.0001
Diastolic blood pressure, mm Hg	85.2±11.7	84.6±11.5	89.6±14.0	87.2±12.5	91.0±12.7	<0.0001
Fasting blood glucose, mmol/L	7.0±2.3	6.9±2.1	7.7±2.7	7.7±2.8	8.7±3.2	<0.0001
Total cholesterol, mmol/L	5.2±1.1	5.2±1.1	5.3±1.2	5.2±1.2	5.4±1.8	<0.0001
Triglycerides, mmol/L	1.9±1.7	1.9±1.6	2.2±1.9	2.1±1.7	2.8±2.2	<0.0001
Low-density lipoprotein, mmol/L	2.5±0.9	2.5±0.9	2.6±1.0	2.5±1.2	2.4±1.4	0.0017
High-density lipoprotein, mmol/L	1.5±0.4	1.5±0.4	1.5±0.4	1.6±0.4	1.6±0.5	<0.0001
Creatinine, μmol/L	89.9±32.3	89.2±31.2	88.0±27.3	95.2±40.5	99.4±38.8	<0.0001
All-type stroke, No. (%)	751 (4.3)	562 (3.8)	34 (7.4)	113 (7.2)	42 (10.5)	<0.0001
Ischemic stroke	646 (3.7)	488 (3.3)	31 (6.8)	90 (5.8)	37 (9.3)	<0.0001
Intracerebral hemorrhage	110 (0.6)	79 (0.5)	3 (0.7)	23 (1.5)	5 (1.3)	0.0002
Subarachnoid hemorrhage	14 (0.1)	10 (0.1)	0 (0.0)	3 (0.2)	1 (0.3)	0.1519

confidence interval (CI) for stroke outcomes based on changes in proteinuria, using participants with no proteinuria as the reference group. To calculate proteinuria reduction from baseline to the 2-year follow-up, a number from 0 to 4 was first designated for each proteinuria level from “none” to “≥3+.” Then, proteinuria reduction was calculated as baseline proteinuria minus 2-year proteinuria using the assigned number. For example, if a participant went from “1+” (designated as 2) at baseline to “none” (designated as 0) at the 2-year follow-up, then the value of proteinuria reduction would be 2 (2-0). Variables with a $P<0.2$ in the univariate analysis and the well-established predictors of the outcomes were selected as adjustment covariates in the multivariable analyses. Three multivariable models were applied to adjust for confounding covariates including age, sex, current smoking status, current alcohol intake, physical activity, body mass index, history of hypertension, diabetes mellitus, dyslipidemia, total cholesterol, systolic BP, diastolic BP, fasting blood glucose, and creatinine. Variables including age, body mass index, total cholesterol, systolic BP, diastolic BP, fasting blood

glucose, and creatinine were adjusted as continuous variables in the Cox models. We used these models with a sandwich covariance matrix as a random effect to account for the potential confounding effect of the 11 different hospitals in the study. In the analysis of stroke risk per degree decrease in proteinuria, baseline proteinuria was adjusted in addition to the above models. Participants contributed person-time of follow-up from the date of return of the 2-year survey questionnaire to either the date of stroke onset, death, or end of follow-up. We did not include subarachnoid hemorrhage ($n=14$) in the analysis because of the small sample size. The cumulative risk of stroke among the 4 subgroups of proteinuria change was estimated using the Kaplan–Meier method and compared by the log-rank test. To address the different effects of diabetes mellitus status (diabetes mellitus and prediabetes mellitus), we performed separate analyses dichotomizing the cohort into 2 groups, those with diabetes mellitus and those with prediabetes mellitus.

Sensitivity analyses were also performed. First, to look at the effect of misclassifying trace as “none,” we redefined the

proteinuria-positive dipstick result with trace or more (trace+) proteinuria, and we regrouped the participants accordingly for no proteinuria (reference group), remittent proteinuria, incident proteinuria, and persistent proteinuria. Second, to minimize the misclassification of participants with diabetes mellitus, we excluded those who were diagnosed with diabetes mellitus by fasting glucose ≥ 7 mmol/L at the baseline survey but had normal glucose levels at the 2-year survey.

We used SAS version 9.4 (SAS Institute) for all analyses. All reported *P* values were based on 2-sided tests of significance, and *P*<0.05 was deemed statistically significant.

Results

Our study population included 5300 participants with diabetes mellitus and 12 080 participants with prediabetes mellitus with a mean age of 52.6 ± 10.9 . Characteristics of the subgroups at the baseline survey are shown in Table 1. Proteinuria was positive in 10.8% of participants with prediabetes mellitus and 21.0% of participants with diabetes mellitus. Regarding changes in proteinuria, 86.1% of participants had no proteinuria, while 2.6% had remittent

proteinuria, 9.0% had incident proteinuria, and 2.3% had persistent proteinuria. Differences in age, body mass index, BP, cholesterol concentration, creatinine level, and concomitant morbidities (hypertension, diabetes mellitus, or dyslipidemia) were found between proteinuria change groups (*P*<0.05). No significant differences in sex were observed between groups.

During a median follow-up of 6.9 years, we identified 751 patients with an incidence of stroke. The incidence stroke rate was 5.55 events per 1000 person-years for patients with no proteinuria, 11.12 for those with remittent proteinuria, 11.04 for those with incident proteinuria, and 16.37 for those with persistent proteinuria. Compared with patients without proteinuria, HRs for stroke were 1.42 (95% CI, 1.01–2.02) for remittent proteinuria, 1.52 (95% CI, 1.22–1.89) for incident proteinuria, and 1.64 (95% CI, 1.18–2.30) for persistent proteinuria. This result was attenuated but still significant after full adjustment. Similar findings were observed for ischemic strokes. The results for intracerebral hemorrhage were statistically insignificant except for the incident proteinuria group (HR, 2.25; 95% CI, 1.35–3.73), possibly because of the limited number of observed outcomes. In addition, we examined the effect of proteinuria reduction

Table 2. Stroke Incidence Rate and Hazard Ratios for Stroke Risk by Changes in Proteinuria

	Changes in Proteinuria				Per Degree Decrease*
	No Proteinuria	Remittent Proteinuria	Incident Proteinuria	Persistent Proteinuria	
All-type stroke					
Case No.	562	34	113	42	
Incidence rate, per 1000 person-y	5.55	11.12	11.04	16.37	
Model 1	Reference	1.93 (1.36–2.73)	1.79 (1.43–2.22)	2.48 (1.79–3.43)	0.83 (0.76–0.89)
Model 2	Reference	1.88 (1.33–2.66)	1.76 (1.41–2.19)	2.39 (1.72–3.31)	0.83 (0.77–0.90)
Model 3	Reference	1.42 (1.01–2.02)	1.52 (1.22–1.89)	1.64 (1.18–2.30)	0.88 (0.81–0.95)
Ischemic stroke					
Case No.	488	31	90	37	
Incidence rate, per 1000 person-y	4.80	10.12	8.71	14.33	
Model 1	Reference	2.00 (1.39–2.88)	1.64 (1.29–2.09)	2.51 (1.77–3.55)	0.84 (0.77–0.92)
Model 2	Reference	1.93 (1.34–2.79)	1.60 (1.26–2.05)	2.39 (1.68–3.38)	0.85 (0.78–0.93)
Model 3	Reference	1.45 (1.01–2.10)	1.37 (1.07–1.75)	1.61 (1.13–2.31)	0.90 (0.82–0.98)
Intracerebral hemorrhage					
Case No.	79	3	23	5	
Incidence rate, per 1000 person-y	0.77	0.95	2.18	1.83	
Model 1	Reference	1.20 (0.38–3.80)	2.53 (1.53–4.18)	2.09 (0.83–5.29)	0.75 (0.62–0.90)
Model 2	Reference	1.22 (0.39–3.88)	2.57 (1.55–4.25)	2.14 (0.84–5.42)	0.74 (0.61–0.90)
Model 3	Reference	0.93 (0.29–2.98)	2.25 (1.35–3.73)	1.58 (0.62–4.05)	0.78 (0.64–0.94)

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, current smoker, current alcohol, physical activity, and body mass index. Model 3: adjusted for variables in model 2 plus history of hypertension, diabetes mellitus, dyslipidemia, total cholesterol, systolic blood pressure, diastolic blood pressure, fasting blood glucose, and creatinine.

*Adjusted for proteinuria at baseline survey in addition to models 1, 2, and 3, respectively.

during the 2-year interval on the assessment of stroke risk. Notably, each degree of proteinuria decline was associated with a significant 12% reduction of stroke risk (HR, 0.88; 95% CI, 0.81–0.95), independent of age, sex, and potential risk factors. Findings were consistent for stroke subtypes, with a 10% decrease (HR, 0.90; 95% CI, 0.82–0.98) for ischemic stroke and a 22% decrease (HR, 0.78; 95% CI, 0.64–0.94) for intracerebral hemorrhage (Table 2). We also generated cumulative incidence curves for the incidence of stroke. The time to incidence of stroke differed significantly among the proteinuria change subgroups (overall log-rank test, $P < 0.0001$). Compared with participants without proteinuria, the cumulative incidence rate of all types of stroke (Figure 2A) and ischemic stroke (Figure 2B) for participants with remittent, incident, and persistent proteinuria were higher. The cumulative incidence rate of intracerebral hemorrhage was also higher for participants with incident proteinuria (Figure 2C).

Diabetes mellitus status showed a significant interaction with persistent proteinuria. When dichotomizing participants into those with diabetes mellitus or prediabetes mellitus, the results demonstrated a significantly higher magnitude of stroke risk in participants with prediabetes mellitus with persistent proteinuria (HR, 2.58; 95% CI, 1.58–4.22) than in participants with diabetes mellitus with persistent proteinuria (HR, 1.35; 95% CI, 0.86–2.12 [P for interaction=0.0083]) (Table 3). Proteinuria reduction resulted in a similar decreased risk of stroke both for participants with diabetes mellitus (HR, 0.84; 95% CI, 0.75–0.95) and those with prediabetes mellitus (HR, 0.89; 95% CI, 0.80–0.99 [P for interaction=0.6984]). Although some of the analyses yielded wide CIs, this was likely because of limited stroke incidences in separate groups.

To explore the robustness of the results, sensitivity analyses were performed. First, we explored the effect of misclassifying trace+ proteinuria to none. By reclassifying participants to the 4 proteinuria groups using trace+ as proteinuria-positive, the effect of incident trace+ proteinuria (HR, 1.42; 95% CI, 1.14–1.76) or persistent trace+ proteinuria

(HR, 1.62; 95% CI, 1.25–2.10) on stroke risks did not essentially change. When we repeated the analyses after excluding participants with normal glucose levels at the 2-year survey to minimize the misclassification of diabetes mellitus, the results were similar. These sensitivity analyses confirm the results of the main analysis.

Discussion

In this study, we found that remittent, incident, and persistent proteinuria of $\geq 1+$ was independently associated with increased stroke risk. In addition, persistent proteinuria confers a higher risk of stroke for patients with prediabetes mellitus compared with those with diabetes mellitus.

Individuals with chronic kidney disease are 5 to 10 times more likely to die of cardiovascular diseases than they are to progress to end-stage kidney disease.^{7,14,15} Proteinuria has acted as a multiplier of cardiovascular risk and mortality across all stages of kidney disease.^{5,16} Previous studies have reported that baseline proteinuria is associated with a higher stroke risk.^{2,4,17} By contrast, the association between changes in proteinuria and stroke outcomes has rarely been studied. Post hoc analysis of randomized clinical trials among patients with hypertension and/or diabetes mellitus showed that the reduction of proteinuria was associated with reduced risk of cardiovascular events.^{18–20} A meta-analysis of these pharmacological trials reported that a 10% proteinuria reduction corresponded to a 29% reduction of stroke.²¹ It has been postulated that treatment aimed at reducing proteinuria could result in additional benefits beyond those achieved with BP or glucose lowering alone. Similarly, our results showed that each degree of proteinuria decline in the first 2 years was associated with a significant 12% reduction of future stroke risk. This reinforces the concept that stroke risk is reduced when proteinuria is diminished, independent of traditional cardiovascular risk factors.

Notably, although proteinuria reduction was associated with a decrease in stroke risk, individuals with remittent $\geq 1+$

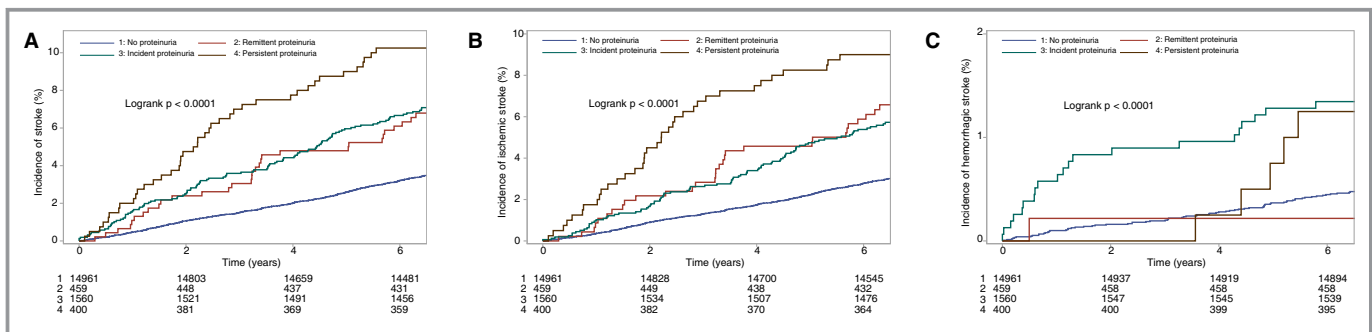


Figure 2. Cumulative incidence curve of (A) all-type stroke incidence rate, (B) ischemic stroke incidence rate, and (C) intracerebral hemorrhage incidence rate by changes in proteinuria.

Table 3. Association of Proteinuria Change From Baseline to 2 Years and Stroke Risk in Patients With Diabetes Mellitus and Prediabetes Mellitus

	Changes in Proteinuria*				Per Degree Decrease [†]
	No Proteinuria	Remittent Proteinuria	Incident Proteinuria	Persistent Proteinuria	
Prediabetes mellitus					
All-type stroke	Reference	1.24 (0.69–2.21)	1.62 (1.17–2.23)	2.58 (1.58–4.22) [‡]	0.84 (0.75–0.95)
Ischemic stroke	Reference	1.21 (0.64–2.29)	1.57 (1.11–2.23)	2.58 (1.50–4.42) [§]	0.84 (0.74–0.95)
Intracerebral hemorrhage	Reference	1.17 (0.28–4.85)	1.59 (0.71–3.52)	3.28 (1.12–9.63)	0.85 (0.64–1.12)
Diabetes mellitus					
All-type stroke	Reference	1.57 (1.01–2.45)	1.42 (1.05–1.93)	1.35 (0.86–2.12)	0.89 (0.80–0.99)
Ischemic Stroke	Reference	1.62 (1.03–2.56)	1.22 (0.87–1.71)	1.35 (0.84–2.16)	0.94 (0.83–1.05)
Intracerebral hemorrhage	Reference	0.70 (0.09–5.18)	2.86 (1.43–5.70)	0.56 (0.07–4.21)	0.70 (0.54–0.90)

*Adjusted for age, sex, current smoker, current alcohol, physical activity, and body mass index, history of hypertension, dyslipidemia, total cholesterol, systolic blood pressure, diastolic blood pressure, and creatinine (model 3).

[†]Adjusted for proteinuria at baseline survey in addition to model 3; no significant interaction was detected for diabetes mellitus status and per degree decrease of proteinuria change (all *P* for interaction >0.05).

[‡]Diabetes mellitus status showed significant interaction terms with persistent proteinuria (*P* for interaction=0.0083).

[§]Diabetes mellitus status showed significant interaction terms with persistent proteinuria (*P* for interaction=0.0167).

proteinuria were still at higher risk for future stroke compared with those without proteinuria in our cohort. Stroke risk was also increased for patients with incident and persistent trace+ proteinuria. However, participants with remittent trace+ proteinuria did not have a significantly higher future stroke risk than those without proteinuria. One possibility is that nonpathological causes can result in transient reversible trace+ proteinuria of no consequence. In contrast, remittent $\geq 1+$ levels of proteinuria are more likely to signify renal structural damage, which also reflects the susceptibility of cerebral arteries.²² Previous studies have shown that stroke risk rises with degree of proteinuria, suggesting a possible dose-response association.^{4,23} A retrospective analysis of 2 trials found that an increase in proteinuria by $\geq 100\%$ is associated with a 30% increase in cardiovascular events and 54% increase in cardiovascular death. Additionally, shifts toward greater deteriorations in proteinuria were associated with increased cardiovascular events.²⁴ Another study reported a stepwise increased cardiovascular risk for transient proteinuria and persistent proteinuria as measured by means of urine dipsticks.²⁵ Our findings are consistent with these results, as stroke incidence was increased in participants with incident or remittent $\geq 1+$ proteinuria compared with those without proteinuria, and it was highest in the group with persistent proteinuria.

In addition, we examined the association between proteinuria change and stroke risk stratified for the presence of diabetes mellitus or prediabetes mellitus. Our findings extended these relationships to the prediabetic population, showing that participants with prediabetes mellitus with incident or persistent proteinuria also had higher stroke risks than those without proteinuria. Interestingly, the risk of stroke

was more profound for participants with prediabetes mellitus with persistent proteinuria compared with the participants with diabetes mellitus. These findings have not been previously reported. A substantial burden of chronic kidney disease exists in those individuals with prediabetes mellitus. Campaigns to promote awareness of both kidney damage and stroke risk at this early disease stage may be beneficial.²⁶ For participants with prediabetes with proteinuria, especially those with persistent proteinuria, lifestyle modification and intervention should be considered to prevent progression as well as complications of diabetes mellitus, renal dysfunction, and stroke.

Annual screenings of proteinuria are suggested for diabetic and prediabetic populations.²⁷ Despite the wide availability and ease of use in the clinical setting, few studies have used urine dipsticks to screen changes in proteinuria and assess their value in the prediction of stroke. Assessing proteinuria using the simple dipstick test could be a convenient way to reflect an individual's systematic vasculature permeability and susceptibility to target organ damage.²⁸ Our results suggest that repeating the dipstick screening at 2-year intervals for detection of proteinuria change has added value in the identification of individuals at higher risk for stroke, especially for those who have incident and persistent proteinuria. These findings are potentially clinically important since dipstick measuring is easy and relatively inexpensive compared with other methods for stratifying stroke risk and monitoring the effectiveness of preventive measures among diabetic and prediabetic populations.

The mechanisms linking proteinuria to stroke risk remain obscure. The Steno hypothesis suggests that proteinuria not only reflects localized renal damage but is also an

independent marker of systemic vascular endothelial dysfunction or microvascular disease.²⁹ Proteinuria is associated with several inflammatory and thrombogenic factors, which play important roles in the development of atherosclerosis and stroke.^{5,23} Insulin resistance is also suggested to play an important role in the increased cardiovascular risk conferred by proteinuria.³⁰ Otherwise, proteinuria is associated with a high prevalence of traditional cardiovascular risk factors, such as hypertension and diabetes mellitus. Proteinuria may be a sign of shared risk factors for vascular disease rather than a direct cause of new strokes. Changes in urine protein over time may be an indicator of the severity of stroke risk factors. In diabetic and prediabetic populations, proteinuria may largely reflect diabetes mellitus control. In addition, patients with renal damage frequently receive fewer prevention approaches for stroke.⁵

Study Strengths and Limitations

The strengths of our study include the prospective design, use of a large cohort, long follow-up period, and use of changes in proteinuria to estimate the risk of stroke. However, our results should be interpreted in the context of some limitations. First, participants in our analysis were from a Chinese population and had either diabetes mellitus or prediabetes mellitus. Thus, our findings cannot be directly generalized to other populations and will need confirmation from other studies. Second, there are limitations of using a dipstick test. The dipstick method could overlook proteinuria.¹ A timed 24-hour urine collection or albumin:creatinine ratio might be more precise in measuring proteinuria, although the dipstick method has a cost advantage.³¹

Conclusions

Persistent, incident, and remittent proteinuria as detected by the serial urine dipstick method independently predicted future stroke risk in diabetic and prediabetic populations. Therapies targeted at proteinuria reduction for stroke prevention warrant further investigation.

Acknowledgments

We thank all enrolled participants and their relatives.

Sources of Funding

This work is supported by the Beijing Health System Medical High Level Academic Leader Plan (No. 2014-2-010), the Beijing Municipal Administration of Hospitals' Ascent Plan (No. DFL20150501), and the Beijing Municipal Science &

Technology Commission (Z161100002616008). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the article.

Disclosures

None.

References

- White SL, Yu R, Craig JC, Polkinghorne KR, Atkins RC, Chadban SJ. Diagnostic accuracy of urine dipsticks for detection of albuminuria in the general community. *Am J Kidney Dis*. 2011;58:19–28.
- Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Impact of microalbuminuria on incident stroke: a meta-analysis. *Stroke*. 2010;41:2625–2631.
- Brantsma AH, Bakker SJ, de Zeeuw D, de Jong PE, Gansevoort RT, Group PS. Extended prognostic value of urinary albumin excretion for cardiovascular events. *J Am Soc Nephrol*. 2008;19:1785–1791.
- Ninomiya T, Perkovic V, Verdon C, Barzi F, Cass A, Gallagher M, Jardine M, Anderson C, Chalmers J, Craig JC, Huxley R. Proteinuria and stroke: a meta-analysis of cohort studies. *Am J Kidney Dis*. 2009;53:417–425.
- Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, Matsushita K, Wen CP. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet*. 2013;382:339–352.
- Li Z, Wang A, Cai J, Gao X, Zhou Y, Luo Y, Wu S, Zhao X. Impact of proteinuria and glomerular filtration rate on risk of ischaemic and intracerebral hemorrhagic stroke: a result from the Kailuan study. *Eur J Neurol*. 2015;22:355–360.
- Global Burden of Metabolic Risk Factors for Chronic Diseases C. Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: a comparative risk assessment. *Lancet Diabetes Endocrinol*. 2014;2:634–647.
- Warren B, Pankow JS, Matsushita K, Punjabi NM, Daya NR, Grams M, Woodward M, Selvin E. Comparative prognostic performance of definitions of prediabetes: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. *Lancet Diabetes Endocrinol*. 2017;5:34–42.
- Wang A, Li Z, Zhou Y, Wang C, Luo Y, Liu X, Guo X, Wu S, Zhao X. Hypertriglyceridemic waist phenotype and risk of cardiovascular diseases in China: results from the Kailuan study. *Int J Cardiol*. 2014;174:106–109.
- Zhang Q, Zhou Y, Gao X, Wang C, Zhang S, Wang A, Li N, Bian L, Wu J, Jia Q, Wu S, Zhao X. Ideal cardiovascular health metrics and the risks of ischemic and intracerebral hemorrhagic stroke. *Stroke*. 2013;44:2451–2456.
- Wu S, Li Y, Jin C, Yang P, Li D, Li H, Shen C. Intra-individual variability of high-sensitivity C-reactive protein in Chinese general population. *Int J Cardiol*. 2012;157:75–79.
- American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2005;28(suppl 1):S37–S42.
- Stroke—1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. *Stroke*. 1989;20:1407–1431.
- Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, Jafar T, Jassal SK, Landman GW, Muntner P, Roderick P, Sairenchi T, Schottker B, Shankar A, Shlipak M, Tonelli M, Townsend J, van Zuilen A, Yamagishi K, Yamashita K, Gansevoort R, Sarnak M, Warnock DG, Woodward M, Arnlov J, Consortium CKDP. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol*. 2015;3:514–525.
- Thompson S, James M, Wiebe N, Hemmelgarn B, Manns B, Klarenbach S, Tonelli M; Alberta Kidney Disease N. Cause of death in patients with reduced kidney function. *J Am Soc Nephrol*. 2015;26:2504–2511.
- Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. *Lancet*. 2017;389:1238–1252.
- Zhang C, Wang X, He M, Qin X, Tang G, Xu X, Wang Y, Huo Y, Cai Y, Fu J, Zhao G, Dong Q, Xu X, Wang B, Hou FF. Proteinuria is an independent risk factor for first incident stroke in adults under treatment for hypertension in China. *J Am Heart Assoc*. 2015;4:e002639. DOI: 10.1161/JAHA.115.002639.
- Group AS, Gerstein HC, Miller ME, Genuth S, Ismail-Beigi F, Buse JB, Goff DC Jr, Probstfield JL, Cushman WC, Ginsberg HN, Bigger JT, Grimm RH Jr, Byington RP, Rosenberg YD, Friedewald WT. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med*. 2011;364:818–828.

19. Tonkin A, Hunt D, Voysey M, Kesaniemi A, Hamer A, Waites J, Mahar L, Mann S, Glasziou P, Forder P, Simes J, Keech AC; Investigators FS. Effects of fenofibrate on cardiovascular events in patients with diabetes, with and without prior cardiovascular disease: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Am Heart J*. 2012;163:508–514.
20. Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B, Snapinn SM, Wan Y, Lyle PA. Does albuminuria predict cardiovascular outcomes on treatment with losartan versus atenolol in patients with diabetes, hypertension, and left ventricular hypertrophy? The LIFE study. *Diabetes Care*. 2006;29:595–600.
21. Savarese G, Dei Cas A, Rosano G, D'Amore C, Musella F, Mosca S, Reiner MF, Marchioli R, Trimarco B, Perrone-Filardi P. Reduction of albumin urinary excretion is associated with reduced cardiovascular events in hypertensive and/or diabetic patients. A meta-regression analysis of 32 randomized trials. *Int J Cardiol*. 2014;172:403–410.
22. Cao JJ, Barzilay JJ, Peterson D, Manolio TA, Psaty BM, Kuller L, Wexler J, Bleyer AJ, Cushman M. The association of microalbuminuria with clinical cardiovascular disease and subclinical atherosclerosis in the elderly: the Cardiovascular Health Study. *Atherosclerosis*. 2006;187:372–377.
23. Masson P, Webster AC, Hong M, Turner R, Lindley RL, Craig JC. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2015;30:1162–1169.
24. Schmieder RE, Mann JF, Schumacher H, Gao P, Mancia G, Weber MA, McQueen M, Koon T, Yusuf S; Investigators O. Changes in albuminuria predict mortality and morbidity in patients with vascular disease. *J Am Soc Nephrol*. 2011;22:1353–1364.
25. Madison JR, Spies C, Schatz IJ, Masaki K, Chen R, Yano K, Curb JD. Proteinuria and risk for stroke and coronary heart disease during 27 years of follow-up: the Honolulu Heart Program. *Arch Intern Med*. 2006;166:884–889.
26. Vassalotti JA, Li S, Chen SC, Collins AJ. Screening populations at increased risk of CKD: the kidney early evaluation program (KEEP) and the public health problem. *Am J Kidney Dis*. 2009;53:S107–S114.
27. American Diabetes Association. 8. Cardiovascular disease and risk management. *Diabetes Care*. 2016;39(suppl 1):S60–S71.
28. Eckardt KU, Coresh J, Devuyst O, Johnson RJ, Kottgen A, Levey AS, Levin A. Evolving importance of kidney disease: from subspecialty to global health burden. *Lancet*. 2013;382:158–169.
29. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage. The steno hypothesis. *Diabetologia*. 1989;32:219–226.
30. De Cosmo S, Minenna A, Ludovico O, Mastroianno S, Di Giorgio A, Pirro L, Trischitta V. Increased urinary albumin excretion, insulin resistance, and related cardiovascular risk factors in patients with type 2 diabetes: evidence of a sex-specific association. *Diabetes Care*. 2005;28:910–915.
31. Levin A, Stevens PE. Summary of KDIGO 2012 CKD guideline: behind the scenes, need for guidance, and a framework for moving forward. *Kidney Int*. 2014;85:49–61.



Association of Persistent, Incident, and Remittent Proteinuria With Stroke Risk in Patients With Diabetes Mellitus or Prediabetes Mellitus

Anxin Wang, Ruixuan Jiang, Zhaoping Su, Jia Zhang, Xingquan Zhao, Shouling Wu and Xiuhua Guo

J Am Heart Assoc. 2017;6:e006178; originally published October 12, 2017;
doi: 10.1161/JAHA.117.006178

The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://jaha.ahajournals.org/content/6/10/e006178>