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ORIGINAL RESEARCH

Relationship Between Time-Dependent Proteinuria and Risk of Stroke in Population With Different Glucose Tolerance Status

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BACKGROUND: Proteinuria often changes and is known as a "time-dependent exposure." The effect of time-dependent proteinuria on the risk of future stroke remains unclear. Proteinuria is often detected in patients with diabetes mellitus. The present study was designed to evaluate the association between time-dependent proteinuria and the risk of stroke in a patient cohort with different glucose tolerance status.

METHODS AND RESULTS: A total of 82 938 participants, who were free of myocardial infarction or stroke and underwent fasting blood glucose and urinary protein measurements at baseline in the Kailuan study, were enrolled. Proteinuria was determined using urine dipstick tests at baseline and subsequent follow-ups. Time-dependent proteinuria was defined as the status of urine protein updated through the follow-up examinations, separately. Time-dependent Cox regression models were used to analyze the relationship between time-dependent proteinuria and the risk of stroke. During a median follow-up of 8.37 years, 2538 participants developed stroke. After adjusting for confounding factors, the hazard ratio (95% CI) for stroke in time-dependent proteinuria among all participants, and the normoglycemia, prediabetes, and diabetes mellitus populations were 1.68 (1.49–1.89), 1.73 (1.47–2.05), 2.15 (1.70–2.72), and 1.30 (1.03–1.65), respectively. There were interaction effects in patients with normoglycemia and prediabetes compared with those with diabetes mellitus. Findings were similar for ischemic and hemorrhagic strokes and were confirmed in sensitivity analyses.

CONCLUSIONS: Time-dependent proteinuria is an independent risk factor of stroke, especially in the normoglycemia and prediabetes populations.

Key Words: diabetes mellitus ■ prediabetes ■ stroke ■ time-dependent proteinuria

See Editorial by Alsanani and Shapiro

Stroke causes death and disability in adults worldwide,[1–3] and identifying and managing risk factors for stroke are essential and urgent for disease prevention. Urine protein dipstick testing is a common tool used to screen for proteinuria, which is an indicator of chronic kidney disease.[4] Several studies have suggested that proteinuria is linked to an increase in stroke events.[5–7] However, proteinuria is a changeable exposure, which may increase or decrease at different stages of monitoring[8] and, therefore, is termed "time dependent."[9] Time-dependent exposure exerts its short-term effects on outcomes,[9] which is defined as the effect of the interval between updates of exposure. Previous studies have generally examined urine protein at baseline or assessed the long-term effect of proteinuria on stroke. Few studies, however, have investigated time-dependent proteinuria and its relationship with stroke. Thus, the impact

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CLINICAL PERSPECTIVE

What Is New?

- This work focused on the short-term effect of proteinuria on stroke.
- We determined the predictive value of time-dependent proteinuria for stroke in diverse glucose tolerance status in a large prospective cohort study.

What Are the Clinical Implications?

- Time-dependent proteinuria was related to an increased risk of stroke among patients with normoglycemia and prediabetes compared with diabetes mellitus.
- Proteinuria monitoring is valuable for identifying individuals at higher risk for stroke among normoglycemia and prediabetes populations.
- Therapies targeted at intervention for proteinuria to prevent stroke warrant further investigation.

Nonstandard Abbreviations and Acronyms

CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
eGFR	Estimated Glomerular Filtration Rate
REGARDS	Reasons for Geographic and Racial Differences in Stroke

of time-dependent proteinuria on stroke risk remains unclear.

Prediabetes is an intermediated state between normal glucose tolerance and diabetes mellitus, which includes impaired fasting glucose or impaired glucose tolerance.[10] The American Diabetes Association defines prediabetes as a fasting plasma glucose concentration of 5.6 to 6.9 mmol/L.[11] Researchers have found that individuals with prediabetes demonstrated a high risk of hypertension, dyslipidemia, diabetes mellitus, and cerebrovascular disease such as stroke.[12,13] It has been established that diabetes mellitus is also an independent risk factor for stroke.[13] Studies have demonstrated that urine protein can be detected in patients with diabetes mellitus.[14] The association between time-dependent proteinuria and stroke in individuals with prediabetes or diabetes mellitus needs to be examined. Previous studies have reported that proteinuria has a long-term effect on stroke incidence in the populations with prediabetes and diabetes mellitus.[15] However, the relationship between time-dependent proteinuria and stroke risk has not been investigated in larger cohorts with diverse glucose levels.

Therefore, we conducted this study to investigate the effect of proteinuria, especially the effect of time-dependent proteinuria, on subsequent stroke among a large cohort of the Chinese population with different glucose levels.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Participants

The Kailuan study was a prospective cohort investigation involving 101 510 individuals aged 18–98 years in the Kailuan community in Tangshan, China. The design and characteristics of the Kailuan study have been described in detail previously.[16,17] For the present study, we excluded the following participants: 3669 with a history of myocardial infarction or stroke; 5476 without data regarding measured urinary protein; and 9427 who did not undergo urine dipstick testing in 2008, 2010, 2012, or 2014. Ultimately, 82 938 participants were included in this study (Figure 1). The characteristics of the participants and nonparticipants are summarized in Supplementary Material Table S1. All participants were provided with written informed consent, and the study was approved by the Ethics Committees of both Beijing Tiantan Hospital and Kailuan General Hospital and adhered to the principles of the Declaration of Helsinki.

Definition of Time-Dependent Proteinuria

A midstream morning urine sample was collected from each participant at the baseline examination (2005–2006) and at subsequent follow-ups, that is, first (2007–2008), second (2009–2010), third (2011–2012), and fourth (2012–2014). Samples from females were collected during the nonmenstrual period. Proteinuria was detected using automated dipstick urinalysis (H12-MA, DIRUI N-600), and test results were classified as none, trace, and 1+ through 4+. A number from 1 to 5 was used to describe each urine protein level from "none," "trace," "1+," "2+," and "≥3+" to reflect the severity of proteinuria. Proteinuria was defined dichotomously as negative (none, trace) or positive (1+ and above). Time-dependent proteinuria was defined as the status of urine protein updated through the follow-up examinations, separately.

Definition of Glucose Tolerance Status

According to criteria from the American Diabetes Association, prediabetes is defined as a fasting plasma glucose concentration of 5.6 to 6.9 mmol/L, and

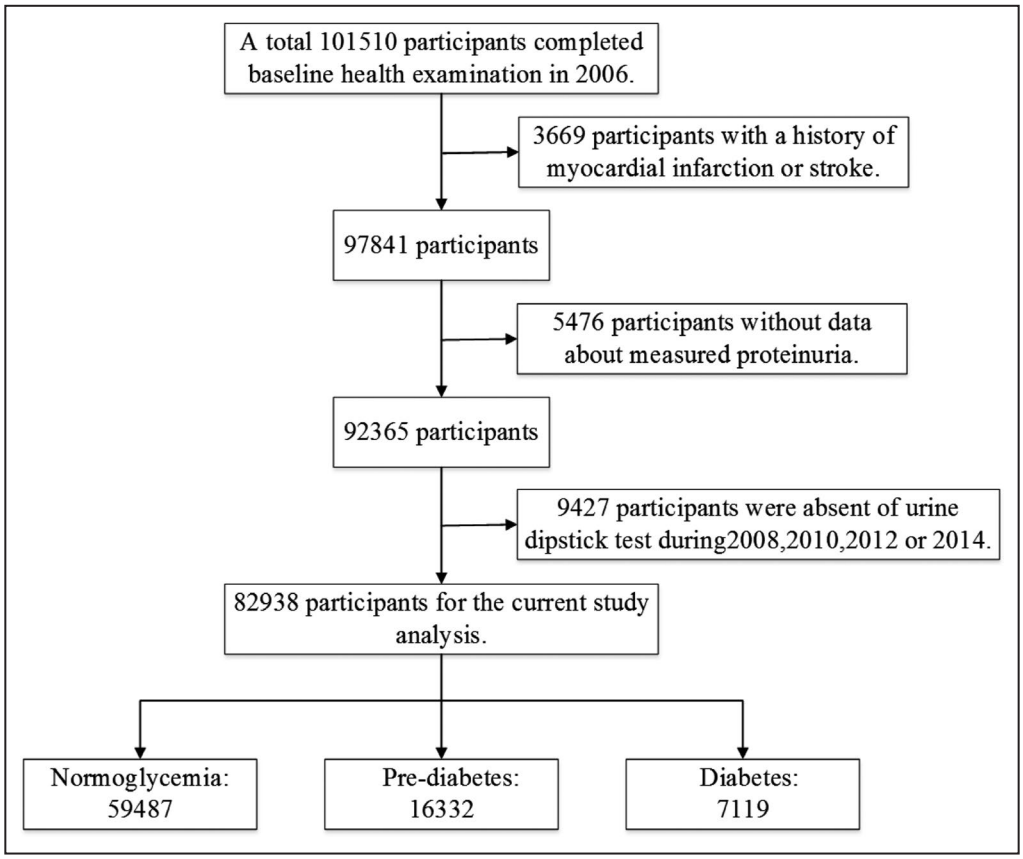

Figure 1. Flow chart of the study.

diabetes mellitus is defined as a fasting glucose level ≥7.0 mmol/L, or in those taking oral hypoglycemic agents or insulin, or having a history of diabetes mellitus.[11]

Potential Confounding Variables

Demographic information (eg, age, sex), behavioral risk factors (including smoking status and drinking), and clinical data (eg, a history of hypertension, dyslipidemia) were collected via standardized questionnaires.[15] Body mass index was calculated as weight (kg) divided by height in meters squared (m^2). Smoking and drinking status were classified as "never," "former," or "current." Hypertension was defined as taking antihypertensive agents, or a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or having a history of hypertension. Dyslipidemia was defined as triglyceride levels >1.7 mmol/L, total cholesterol >5.17 mmol/L, low-density lipoprotein cholesterol ≥3.37 mmol/L, or high-density lipoprotein cholesterol <1.04 mmol/L, taking lipid-lowering agents, or a history of dyslipidemia. Blood samples were stored in EDTA tubes after an overnight fast. Fasting blood glucose, triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and, serum creatinine were measured by an auto-analyzer (Hitachi 747; Hitachi, Tokyo, Japan) at the central laboratory of the Kailuan General Hospital. The estimated glomerular filtration rate (eGFR) was calculated by a modified 4-variable Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and adjusted for the Chinese population by multiplying a coefficient of 1.1.[18]

Follow-Up and Stroke Assessment

Participants underwent face-to-face follow-up by trained physicians who were blinded to the baseline information at every 2-year routine medical examination until December 31, 2015, or to the event of interest or death. The primary end point evaluated was the first occurrence of stroke, which is defined by the World Health Organization criteria[19] as an acute neurological deficit lasting >24 hours or leading to death.

Stroke diagnosis was additionally confirmed using brain computed tomography or magnetic resonance imaging and classified into 3 types: cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage. Considering the small sample size (n=65), in this study subarachnoid hemorrhage was excluded in the subgroup analyses. The criteria of diagnosis were consistent across all participating hospitals. All outcomes were validated by the Data Safety Monitoring Board and the Arbitration Committee for Clinical Outcomes.

Statistical Analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Continuous variables were expressed as mean±SD and were compared by ANOVA. Categorical variables were expressed as frequencies and percentages and were compared using the chi-square test. Time-dependent Cox proportional-hazards regression was used to assess associations between the stroke incidence and time-dependent proteinuria and calculated hazard ratios (HRs) and corresponding 95% CIs. Three models were used to adjust for all potential confounding systematically. The crude model was the unadjusted model. Model 1 was adjusted for age and sex. Model 2 was further adjusted for smoking status, drinking status, body mass index, hypertension, dyslipidemia, glucose tolerance status, and eGFR on the basis of Model 1. In the time-dependent analysis, the follow-up time for each participant was divided into different intervals. For each interval, a separate Cox regression analysis was performed using the specific result of urine protein at the beginning of the specific interval. Then, a weighted average of specific results was calculated across all the intervals. Finally, this weighted average of the series of short-term effects of urine protein on the stroke incidence is presented as a single HR.[9,20] To examine the potential effect of non-stroke-related death as a competing risk rather than a censoring event, which impeded the occurrence of stroke, a competing risk model (also known as the Fine and Gray model) was conducted. The Cox model with a sandwich covariance matrix was used as a random effect to account for the potential confounding effects of different hospitals, given that participants were from 11 hospitals. The cumulative risk of stroke in time-dependent proteinuria was estimated via a Kaplan-Meier method and compared by the Fine and Gray's test.

Additionally, we conducted interaction analyses to assess whether effect of time-dependent proteinuria on the risk of stroke differed among participants with different glucose tolerance status. Furthermore, sensitivity analyses were conducted to test the robustness of the findings. Because major fatal diseases, such as end-stage renal disease (eGFR <15 mL/min per 1.73 m^2), could affect proteinuria and future stroke risk, and glucose tolerance status would have changed during the follow-up period, the analyses were repeated, respectively, after excluding individuals with these conditions. All of our statistical tests were 2-sided, and differences with $P<0.05$ were considered to be statistically significant.

RESULTS

In this study, the mean (±SD) age of the population was 50.68±11.98 years, and 17 737 (21.39%) participants were female. The prevalence of prediabetes and diabetes mellitus was 19.69% (n=16 332) and 8.58% (n=7119). During a median follow-up of 8.37 years (interquartile range [IQR]: 7.91–8.75 years), 2538 (3.06%) participants developed stroke, of which 2047 were ischemic stroke, 495 were hemorrhagic stroke, and 65 were subarachnoid hemorrhage.

Participants were classified into different groups based on the urine protein monitoring result at baseline and follow-ups to describe the baseline characteristics (shown in Table 1). Proteinuria for one or more time group was defined as positive for urine protein in any of the tests, and the no proteinuria group was defined as negative in all the tests. Participants in whom proteinuria was detected once or more times were more likely to be men and older; have a higher body mass index, systolic blood pressure and diastolic

Table 1. Characteristics of the Study Population at Baseline

Variable	No Proteinuria (N=79766)	Proteinuria for One or More Times (N=3172)
Age, y, mean±SD	50.59±11.96	52.79±12.20*
Female, n (%)	17 109 (21.45)	628 (19.80)*
Current smoker, n (%)	26 722 (33.50)	950 (29.95)*
Current alcohol, n (%)	29 456 (36.93)	1041 (32.82)*
BMI, kg/m^2, mean±SD	25.03±3.45	26.00±3.74*
SBP, mm Hg, mean±SD	129.67±20.16	141.17±23.65*
DBP, mm Hg, mean±SD	83.11±11.50	88.77±13.56*
Hypertension, n (%)	33 024 (41.40)	2054 (64.75)*
Dyslipidemia, n (%)	27 446 (34.41)	1436 (45.27)*
Glucose tolerance status, n (%)		
Normal	57 692 (72.33)	1795 (56.59)*
Prediabetes	15 656 (19.63)	676 (21.31)
Diabetes mellitus	6418 (8.05)	701 (22.10)
FBG, mmol/L, mean±SD	5.40±1.56	6.24±2.56*
TC, mmol/L, mean±SD	4.94±1.13	5.12±1.35*
TG, mmol/L, mean±SD	1.66±1.37	2.06±1.69*
LDL-C, mmol/L, mean±SD	2.34±0.92	2.33±1.03
HDL-C, mmol/L, mean±SD	1.55±0.40	1.58±0.42*
eGFR (mL/min per 1.73 m^2), mean±SD	82.70±25.27	78.20±28.77*

Data are presented as N, n (%) or mean±SD. BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; and TG, triglyceride.

*There were significant differences between the no proteinuria group and the proteinuria for one or more times group ($P<0.05$).

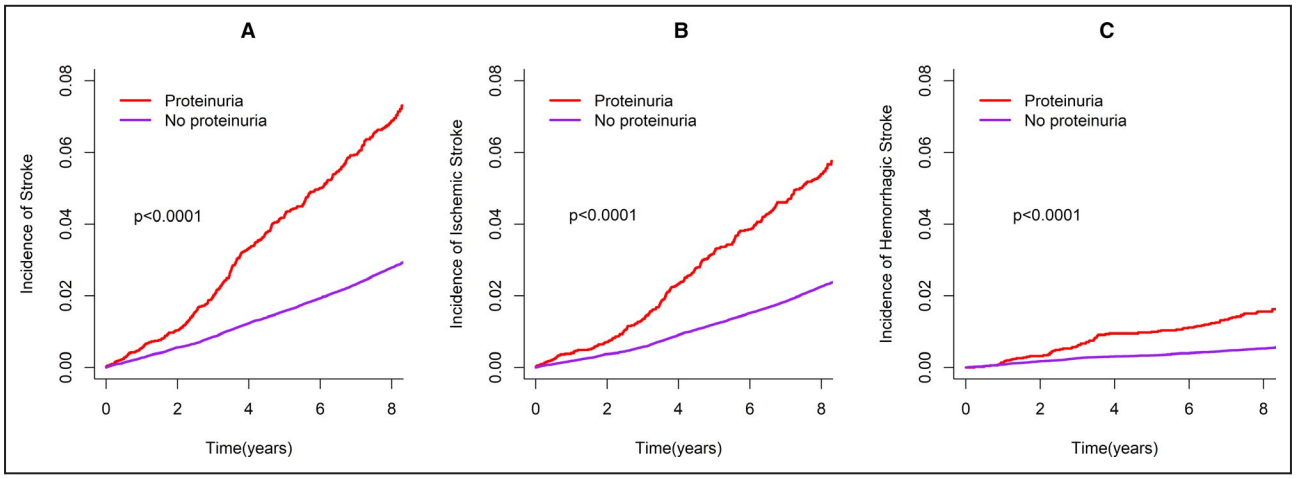

Figure 2. Cumulative incidence curves for all-type stroke (A), ischemic stroke (B), and hemorrhagic stroke (C) by time-dependent proteinuria.

blood pressure, and plasma concentrations of fasting blood glucose, total cholesterol, triglyceride, and high-density lipoprotein; prevalence of hypertension, prediabetes, diabetes mellitus, and dyslipidemia, and a lower prevalence of smoking and drinking; and have lower eGFR ($P<0.05$).

Cumulative incidence curves were obtained for all-type stroke and subtype stroke according to time-dependent proteinuria. Patients with time-dependent proteinuria demonstrated a higher risk for all-type (Figure 2A), ischemic (Figure 2B), and hemorrhagic (Figure 2C) stroke ($P<0.05$). The multivariate Cox regression model (Model 2) of the association between severity of proteinuria and stroke risk revealed that patients with each increase in proteinuria grades had 1.24 (95% CI, 1.18–1.30), 1.21 (95% CI, 1.14–1.27), and 1.37 (95% CI, 1.25–1.50) higher risks of all-type stroke, ischemic stroke, and hemorrhagic stroke, respectively. As the severity of proteinuria increased, the risk of stroke increased.

Next, we assessed the association of time-dependent proteinuria with the risk of stroke and the relationship between them in different glucose tolerance status subgroups (shown in Table 2). In the crude Cox regression model, time-dependent proteinuria was associated with the stroke incidence in all participants (HR, 2.36; 95% CI, 2.10–2.65), and in those with normoglycemia (HR, 2.25; 95% CI, 1.91–2.66), prediabetes (HR, 2.52; 95% CI, 1.99–3.20), and diabetes mellitus (HR, 1.51; 95% CI, 1.20–1.90). After adjusting for confounding factors, time-dependent proteinuria remained a predictor of stroke among all participants (HR, 1.68; 95% CI, 1.49–1.89), and those with normoglycemia (HR, 1.73; 95% CI, 1.47–2.05), prediabetes (HR, 2.15; 95% CI, 1.70–2.72), and diabetes mellitus (HR, 1.30; 95% CI, 1.03–1.65). In patients with time-dependent proteinuria, the risks of stroke were higher in the normoglycemia and prediabetes groups than in the diabetes mellitus group. Furthermore, we performed interaction analyses to assess the interaction between time-dependent proteinuria and glucose tolerance on the risks of stroke. Multivariable Cox models revealed that time-dependent proteinuria was significantly associated with an increased risk of stroke among patients with normoglycemia and prediabetes (P for interaction <0.01) compared with diabetes mellitus.

Similar results were observed for ischemic stroke and hemorrhagic stroke. However, there was no significant interaction between time-dependent proteinuria and glucose tolerance status on the occurrence of hemorrhagic stroke (P for interaction >0.05).

In the sensitivity analysis, after excluding participants with end-stage renal disease (shown in Table 2, sensitivity analysis 1) or altered glucose tolerance status (shown in Table 2, sensitivity analysis 2), similar results were observed. These sensitivity analyses confirmed the results (Table 2).

DISCUSSION

In this large prospective study, we investigated the relationship between time-dependent proteinuria and the incidence of stroke. We observed that time-dependent proteinuria was associated with an increased risk of stroke–both ischemic and hemorrhagic. Especially in the normoglycemia and prediabetes populations, time-dependent proteinuria significantly increased the risk of stroke. Our investigation was a prospective study to determine the predictive value of time-dependent proteinuria for stroke. Based on our results, clinicians need to focus on the effect of time-dependent proteinuria for stroke prevention, which is associated with the occurrence of stroke, especially in normoglycemia and prediabetes populations.

Table 2. Hazard Ratio (HR) for the Association Between Time-Dependent Proteinuria and Risk of Stroke Among All Participants, and Stratified Analysis in Subgroups With Different Glucose Tolerance Status Subgroups

	Total	Normoglycemia*	Prediabetes*	Diabetes Mellitus*
All-type stroke				
Crude model	2.36 (2.10–2.65)	2.25 (1.91–2.66)	2.52 (1.99–3.20)	1.51 (1.20–1.90)
Model 1	2.08 (1.85–2.34)	1.98 (1.68–2.34)	2.37 (1.87–3.00)	1.41 (1.12–1.78)
Model 2	1.68 (1.49–1.89)	1.73 (1.47–2.05)	2.15 (1.70–2.72)	1.30 (1.03–1.65)
P for interaction†		0.01	<0.01	Reference
Sensitivity analysis 1	1.68 (1.49–1.89)	1.73 (1.47–2.05)	2.16 (1.71–2.73)	1.30 (1.03–1.65)
P for interaction†		0.01	<0.01	Reference
Sensitivity analysis 2	1.61 (1.42–1.83)	1.67 (1.40–1.99)	2.19 (1.72–2.79)	1.20 (0.86–1.45)
P for interaction†		<0.01	<0.01	Reference
Ischemic stroke				
Crude model	2.26 (1.98–2.58)	2.11 (1.75–2.56)	2.44 (1.87–3.18)	1.45 (1.13–1.87)
Model 1	1.97 (1.72–2.24)	1.83 (1.51–2.21)	2.26 (1.73–2.95)	1.35 (1.05–1.74)
Model 2	1.57 (1.38–1.80)	1.61 (1.33–1.95)	2.06 (1.58–2.69)	1.26 (0.97–1.62)
P for interaction†		0.03	<0.01	Reference
Sensitivity analysis 1	1.58 (1.38–1.80)	1.61 (1.33–1.95)	2.07 (1.59–2.70)	1.26 (0.97–1.62)
P for interaction†		0.03	<0.01	Reference
Sensitivity analysis 2	1.52 (1.32–1.75)	1.56 (1.27–1.90)	2.15 (1.64–2.81)	1.08 (0.82–1.43)
P for interaction†		0.01	<0.01	Reference
Hemorrhagic stroke				
Crude model	2.79 (2.18–3.58)	2.59 (1.84–3.66)	2.80 (1.68–4.64)	2.35 (1.39–3.96)
Model 1	2.54 (1.99–3.26)	2.36 (1.67–3.34)	2.65 (1.60–4.39)	2.28 (1.35–3.87)
Model 2	2.13 (1.65–2.73)	2.03 (1.44–2.86)	2.37 (1.44–3.92)	2.10 (1.22–3.60)
P for interaction†		0.98	0.62	Reference
Sensitivity analysis 1	2.13 (1.65–2.73)	2.03 (1.44–2.87)	2.37 (1.43–3.91)	2.10 (1.22–3.61)
P for interaction†		0.98	0.62	Reference
Sensitivity analysis 2	1.96 (1.50–2.56)	1.89 (1.31–2.72)	2.21 (1.30–3.76)	1.77 (0.98–3.20)
P for interaction†		0.90	0.59	Reference

Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, smoking status, drinking status, body mass index, hypertension, dyslipidemia, glucose tolerance status, and estimated glomerular filtration rate. Sensitivity analysis 1: Adjusted for model 2 and further excluded individuals with end-stage renal disease (estimated glomerular filtration rate <15 mL/min per 1.73 m^2). Sensitivity analysis 2: Adjusted for model 2, further excluded individuals with changes of glucose tolerance status.

*Stratified analysis was conducted in different glucose tolerance status subgroups.

†Interaction effect analyses were performed to analyze the impact of different glucose tolerance status on the association of time-dependent proteinuria with risk of stroke via Cox regression analysis in model 2, sensitive analysis 1, and sensitive analysis 2. The diabetes mellitus group was treated as the reference.

Chronic kidney disease, which is defined as decreased eGFR or the presence of proteinuria, affects 8% to 16% of the population worldwide. With advances in research, we have gradually realized that chronic kidney disease contributes to the risk of stroke.[21] Previous studies have reported that urine protein is independently associated with stroke risk.[5,7,22] The REGARDS (Reasons for Geographic and Racial Differences in Stroke) study indicated that urinary albumin excretion was associated with a higher stroke risk in black patients.[22] A meta-analysis of 10 studies revealed that subjects with proteinuria had a higher risk for stroke compared with those without proteinuria.[5] Another study with a 27-year follow-up reported that proteinuria independently predicted an increased risk of stroke.[7] All of these studies had a common limitation, which was the assessment of proteinuria only once, and focused on the long-term effect of baseline proteinuria on long-term cardiovascular events. Because proteinuria is a changeable exposure, attention must to be devoted to its short-term effect. In our study, we measured urine protein in a short interval, which may provide a more accurate assessment of proteinuria, and assessed the short-term effect of proteinuria on cerebrovascular diseases. Similarly, our results indicated that the risk of stroke was increased in participants with time-dependent proteinuria compared with those without proteinuria. It is necessary for clinicians to strengthen monitoring of urinary protein, especially in a short interval, and devote attention to the short-term effect of proteinuria to prevent stroke.

Clinical proteinuria is an ominous development in subjects with diabetes mellitus and leads to decline in glomerular filtration and premature cardiovascular mortality.[23] Therefore, we analyzed the association between time-dependent proteinuria and stroke incidence in subgroups with diverse glucose tolerance status. Interestingly, the impact of time-dependent proteinuria on incident stroke or ischemic stroke was increased in the normoglycemia and prediabetes groups compared with the diabetes mellitus populations. To our knowledge, such findings have not been previously reported. However, there were no significant interactions between time-dependent proteinuria and hemorrhagic stroke among individuals with different glucose tolerance status. Therefore, identification and monitoring proteinuria in subjects with normoglycemia or prediabetes may provide an opportunity for improvement of modifiable lifestyle factors and medical intervention at an earlier stage to prevent the progression to stroke.

The pathophysiological mechanisms of stroke caused by proteinuria remain unclear; however, there are several potential explanations. Proteinuria is associated with inflammation and thromboembolism and reflects endothelial dysfunction, which all facilitate the progression of atherosclerosis.[21,24] Insulin resistance is also suggested to play an important role in the increased cardiovascular risk conferred by proteinuria.[25] Otherwise, patients with proteinuria tend to have higher risks of traditional cardiovascular diseases, such as diabetes mellitus or hypertension. Proteinuria may be a consideration of shared risk factors for cerebrovascular disease and not a direct cause of new strokes. Changes in urine protein may be an indicator of the severity of these stroke risk factors. Whether proteinuria is a potential therapeutic target for stroke requires further investigations to verify.

However, some limitations to the present study should be addressed. First, urinary albumin excretion can be measured by 24-hour urine albumin excretion, albumin-creatinine ratio, and dipstick test. Due to the practical circumstances and limited facilities, the dipstick test has been adopted as a common and convenient method and is suitable for large-scale screening. Second, participants in our study were exclusively an Asian population; therefore, further studies, including other ethnic groups, are needed to validate our findings. Third, the causes of proteinuria are variable, and patients with proteinuria would exhibit some abnormal results such as coagulation factors. Our study enrolled a large number of participants; as such, it is difficult to examine the reasons for proteinuria and draw definitive conclusions regarding abnormal results related to proteinuria. All of these limitations need to be addressed in our future studies.

In conclusion, we observed a relationship between time-dependent proteinuria and the risk of stroke. Time-dependent proteinuria was a more significant risk factor of stroke, especially in the normoglycemia and prediabetes populations. Our findings suggested that time-dependent proteinuria is an independent risk factor of stroke.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Characteristics of participants excluded from or included in the study.

Variable	Participants included (N=82938)	Participants excluded (N=14903)	P Value
Age in years, mean ±SD	50.68±11.98	56.18±14.65	< 0.01
Female, n (%)	17737(21.39)	2232(14.98)	< 0.01
Current smoker, n (%)	27672(33.36)	4665(31.30)	< 0.01
Current alcohol, n (%)	30497(36.77)	4903(32.90)	< 0.01
BMI, kg/m^2, mean ±SD	25.07±3.46	24.72±3.63	< 0.01
SBP, mmHg, mean ±SD	130.11±20.42	133.63±23.20	< 0.01
DBP, mmHg, mean ±SD	83.33±11.63	83.64±12.48	0.13
Hypertension, n (%)	35078(42.29)	6873(46.12)	< 0.01
Glucose tolerance status, n (%)			
normal	59487(71.72)	9699(65.08)	< 0.01
Pre-diabetes,	16332(19.69)	3566(23.93)	
Diabetes mellitus	7119(8.58)	1638(10.99)	
Dyslipidemia, n (%)	28882(34.82)	5517(37.02)	< 0.01
FBG, mmol/L, mean ±SD	5.43±1.62	5.68±1.91	< 0.01
TC, mmol/L, mean ±SD	4.95±1.14	4.93±1.18	0.02
TG, mmol/L, mean ±SD	1.68±1.38	1.64±1.31	0.20
LDL, mmol/L, mean ±SD	2.34±0.92	2.38±0.84	< 0.01
HDL, mmol/L, mean ±SD	1.55±0.40	1.54±0.40	< 0.01
eGFR (ml/min/1.73m^2), mean ±SD	82.53±25.43	80.71±27.63	< 0.01

Data are presented as N, n (%) or mean ±SD.

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; SD: standard deviation.