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Cerebral Stroke: Its Prevalence, Risk Factors and Associated Ocular Diseases. The Beijing Eye Study.

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Abstract

Objective: To assess the prevalence of cerebral stroke in the general population of Beijing and its association with systemic risk factors and ocular diseases.

Setting: The population-based Beijing Eye Study was conducted in a rural and an urban region of Greater Beijing.

Participants: With an eligibility criterion of an age of 50+ years and living in the study regions, 3468 subjects (78.8%) out of 4403 eligible individuals participated.

Primary and secondary outcome measures: The study participants underwent a detailed systemic and ophthalmological examination and an interview in which the occurrence of a previous stroke was assessed.

Results: A previous stroke was reported by 235 individuals (7.33%;95% confidence interval [CI]:6.43,8.24). The prevalence of previous stroke increased from 2.0% (95%CI:0.9,3.1) in the age group of 50 to <55 years to 21.9% (95%CI:16.4,27.4) in the age group of 80+ years. In multivariate regression analysis, a higher prevalence of previous stroke was correlated (Nagelkerke R^2:0.16) with the systemic parameters of older age (*P*<0.001; odds ratio [OR]:1.07;95%CI:1.05,1.09), male gender (*P*=0.006;OR:0.59;95%CI:0.40,0.86), lower quality of life score (*P*<0.001;OR:1.44;95%CI:1.24,1.67) and higher prevalence of diabetes mellitus (*P*=0.04;OR:1.57;95%CI:1.02,2.41) and arterial hypertension (*P*<0.001;OR:2.22;95%CI:1.43,3.43), and with the ocular parameter of a higher stage of diabetic retinopathy (*P*<0.0011;OR:1.67;95%CI:1.20,1.33) (or alternatively, presence of diabetic retinopathy (*P*<0.001;OR: 3.97;95%CI:1.87,8.43). Lower amount of physical activity showed a marginal association with a higher prevalence of previous stroke (*P*=0.09;OR:0.94;95%CI:0.88,1.01).

Conclusions: In this North Chinese population aged 50+ years, the prevalence of a previous stroke was 7.33% (95%CI:6.43,8.24). Besides known systemic risk factors of older age, male gender and higher prevalence of diabetes and arterial hypertension, presence and stage of diabetic retinopathy were additional risk factors. Previous stroke prevalence increased for each step increase in the stage of diabetic retinopathy by a factor of 1.67 (95%CI:1.20,1.33), and for the presence of diabetic retinopathy by a factor of 3.97 (95%CI:1.87,8.43).

Article Summary

Strengths and limitations of this study:

- In this North Chinese population aged 50+ years, the prevalence of a previous stroke was 7.33% (95%CI:6.43,8.24).
- Besides known systemic risk factors of older age, male gender and a higher prevalence of diabetes mellitus and arterial hypertension, the presence and stage of diabetic retinopathy were additional risk factors.
- The prevalence of previous stroke increased for each increase in the stage of diabetic retinopathy by a factor of 1.67 (95%CI:1.20,1.33), and for the presence of diabetic retinopathy by a factor of 3.97 (95%CI:1.87,8.43).
- Limitations of our study were that the data on the prevalence of a previous self-reported stroke depended on the information provided by the study participants in the face-to-face interviews, and that patients who had died as a sequel of a previous stroke were not included into the study. The results of our study are therefore valid primarily only for stroke survivors.
- Another limitation was intracerebral hemorrhage was not differentiated from ischemic stroke.

Introduction

Cerebral stroke as one of the main contributors of the global burden of disease has caused 116 million or 4.8% of all DALYs (Disability-Adjusted Life Years) and 14.5 million or 1.8% of all YLDs (Years Lived with Disability) worldwide in the year 2013.[1-4] In particular China has witnessed a marked increase in the importance of stroke in the spectrum of diseases causing YLLs. While in 1990, lower respiratory infections or preterm birth complications were the leading causes of YLLs in almost half of the provinces of China (16 out of 33), cerebrovascular disease were the leading cause in 27 of the 33 provinces in 2013.[5,6] Since the eye and the brain share the same arterial blood supply through the inner carotid artery and since the retina and optic nerve as former outgrowth of the anterior end of the embryological neural groove are of neuro-ectodermal origin, a major cerebral disease such as a stroke may be associated with ocular diseases, in particular disorders of the optic nerve and retina. Since comprehensive population-based studies on associations between stroke and eye have been scare so far and have not been conducted for the population of China, we investigated the prevalence of cerebral stroke and its relationships between systemic factors and ocular diseases in a Chinese population.

Methods

The Beijing Eye Study 2011 is a population-based study which was conducted in a rural region and an urban region of Greater Beijing. The Medical Ethics Committee of the Beijing Tongren Hospital approved the study design, and all study participants gave an informed consent. The eligibility criteria for inclusion into the study were an age of 50+ years and living in the study regions. Out of 4403 eligible individuals, 3468 subjects (1963 (56.6%) women) participated (response rate: 78.8%). The mean age was 64.6 ± 9.8 years (median 64 years; range: 50–93 years). There were 1633 (47.1%) individuals (943 (57.7%) women) coming from the rural region, with the remaining 1835 (52.9%) study participants (1020 (55.6%) women) living in the urban region. The study design has been described in detail previously.[7,8]

All study participants underwent a structured interview by trained research technicians.

The interview included more than 200 standardized questions on demographic parameters, the socioeconomic background, the diet and alcohol consumption, smoking habits, known major systemic diseases and current systemic medical therapies. Using the mini–mental state examination (MMSE) scale, we assessed the cognitive function. Fasting blood samples were collected for measurement of blood lipids, glucose, glycosylated hemoglobin HbA1c and serum creatinine. The blood pressure was measured with the participant sitting for at least 5 min. We also measured body height and weight and the circumference of the waist and hip.

Arterial hypertension was defined as a systolic blood pressure ≥160 mm Hg and/or a diastolic blood pressure ≥95 mm Hg, and/or self-reported current treatment for arterial hypertension with antihypertensive medication. Diabetes mellitus was characterized by a blood glucose concentration ≥7.0 mmol/L, an HbA1c value ≥6%, by a self-reported history of physician diagnosis of diabetes mellitus, or by a history of drug treatment for diabetes (insulin or oral hypoglycemic agents). Depressive symptoms were evaluated using a Chinese depression scale adapted from the Zung self-rated depression scale.[9] The prevalence of previous stroke was examined in the interview by standardized questions on whether a previous cerebral stroke had occurred with typical symptoms such as sudden-onset face weakness, arm drift, abnormal speech, hemiplegia, or numbness for at least 24 hours, when such a stroke had occurred and whether it had been treated.

The ophthalmological examination consisted of automatic refractometry (Auto Refractometer AR-610; Nidek Co., Ltd, Tokyo, Japan), measurement of presenting visual acuity, uncorrected visual acuity and best-corrected visual acuity, tonometry, slit lamp based biomicroscopy of the anterior and posterior segment of the eyes, and photography of the cornea and lens (Neitz CT-R camera; Neitz Instruments Co., Tokyo, Japan) and of the macula and optic disc (fundus camera; Type CR6-45MM; Canon Inc., Tokyo, Japan) in medical mydriasis. Using the photographs, we measured the dimensions of the optic disc, optic cup and parapapillary alpha, beta and gamma zones. The optic nerve head and macula were additionally examined by spectral-domain optical coherence tomography (OCT) using the enhanced depth imaging modality (Spectralis; Heidelberg Engineering, Heidelberg, Germany). We determined the thickness of the peripapillary retinal nerve fiber layer, of the retina in the foveal region and of the subfoveal choroid. Applying optical low-coherence reflectometry

(Lenstar 900 Optical Biometer; Haag-Streit, Koeniz, Switzerland), we measured ocular biometric parameters such as the anterior corneal curvature, central corneal thickness, anterior chamber depth, lens thickness and axial length. The degree of cataract was determined using the lens photographs. The degree of nuclear opacities was assessed in 6 grades using the grading system of the Age-Related Eye Disease Study.[10] In addition, retro-illuminated photographs of the lens were obtained (Neitz CT-R camera; Neitz Instruments Co., Tokyo, Japan), and the percentage of the areas with cortical and posterior subcapsular lens opacities was measured using a grid. The standard to diagnose a nuclear cataract was a nuclear cataract grade of 4 or more, the standard to diagnose a posterior subcapsular cataract was an amount of posterior subcapsular opacities of 0.01 or more, and the standard to diagnose a cortical cataract was an amount of cortical opacities of 0.05 or more. The degree of fundus tessellation defined as the visibility of the large choroidal vessels was assessed on the fundus photographs of the macula and of the optic disc as described in detail previously.[8] It was graded using a scale which ranged from “0” for “no tessellation” to ”3” for “marked tessellation”. Diabetic retinopathy was assessed on the fundus photographs using the Early Treatment of Diabetic Retinopathy Study (ETDRS) criteria. The minimum criterion for diagnosis of diabetic retinopathy was the presence of at least one microaneurysm. The diagnosis for each individual was based on the grading of the individual´s eye with the highest stage of diabetic retinopathy. We differentiated between the mild non-proliferative stage, the moderate non-proliferative stage, the advanced non-proliferative stage, and the proliferative stage of diabetic retinopathy. Glaucomatous optic neuropathy was defined using the criteria of the International Society of Geographic and Epidemiological Ophthalmology ISGEO.[11] Pseudoexfoliation was assessed by an experienced ophthalmologist during the slit lamp assisted biomicroscopy of the anterior segment after pupillary dilation. The diagnosis of pseudoexfoliation was definite, if the lens surface showed a central whitish coating with a diameter of little less than the normal pupillary diameter, or if the periphery of the lens surface showed a whitish coating which was anteriorly bordered by a darker ring-like region on the lens surface. The assessment of pseudoexfoliation was performed only in phakic eyes. For the diagnosis of age-related macular degeneration, the International ARM (Age-related Maculopathy Epidemiological Study Group) Grading system was used. The subjective

symptoms of dry eye were evaluated using a questionnaire composed of three questions: “Do your eyes ever feel dry?”; “Do you ever feel a gritty or sandy sensation in your eyes?”; and “Do your eyes ever have a burning sensation?” Possible answers to the questions were none (0), less than once a month (1), once or twice a week (2), at least once every day (3), all the time (4). The presence of dry eye symptoms was defined as having one or more symptoms at least once every day (3 and 4). A quantitative grading score of subjective dry eye symptoms was obtained by summarizing the answers to the different questions (0–12).[12]

Statistical analysis was performed using a commercially available statistical software package (SPSS for Windows, version 22.0, IBM-SPSS, Chicago, IL, USA). As a first step, we examined the mean value of the main outcome parameter, i.e. the prevalence of stroke (presented as mean and 95% confidence intervals (CI)) and assessed differences between the stroke group and the non-stroke group in age and gender. As second step, we performed a binary regression analysis with the prevalence of stroke as dependent parameter after adjusting for age and gender. As a third step, we conducted an extended multivariate binary analysis which included as independent parameters all those systemic variables which were correlated (P<0.10) with the stroke prevalence in the previous analysis. We then dropped all those parameters which were no longer significantly associated with the stroke prevalence. We first started with the systemic independent parameters, such as age and blood pressure. We calculated the odds ratio (OR) and its 95% CIs. All P-values were two-sided and considered statistically significant, if the values were less than 0.05.

Patient and Public Involvement statement: Patients were not involved in this study

Results

Out of 3468 study participants, 3205 (92.4%) individuals participated in the interview with available information on previous stroke and underwent the systemic and ophthalmologic examination. The participating group as compared to the group of individuals without available information on previous stroke or without systemic and ocular examination was significantly younger (64.4 ± 9.7 years (median: 63 years; range: 50 – 93 years) versus 67.1 ± 11.1 years; P<0.001) and came significantly more often from the urban region than from the

rural area (rural / urban region of habitation: 1439 / 1766 versus 194 / 69; *P*<0.001), while the differences in gender (men / women: 1386 / 1819 versus 119 / 144; *P*=0.56), axial length (23.3 ± 1.1 mm versus 23.2 ± 1.9 mm; *P*=0.31) and refractive error (-0.22 ± 2.12 diopters versus -0.31 ± 2.17 diopters; *P*=0.59) were not statistically significant.

A previous stroke was reported by 235 individuals (235 / 3205 or 7.33% [95%CI: 6.43, 8.24]). Among the 235 patients, 192 individuals were on oral medication for the prophylaxis of a recurrence of the stroke. The stroke had taken place 7.5 ± 5.7 years ago (median: 7 years; range: 1 month to 26 years).

In the stroke group as compared with the non-stroke group (control group), age was significantly older (71.1 ± 9.2 years versus 63.9 ± 9.5 years; *P*<0.001) and had a higher proportion of men than women (men / women: 128 / 107 versus 1258 / 1712; *P*<0.001) (Fig. 1). The prevalence of a previous stroke increased from 2.0% (95%CI: 0.9, 3.1) in the age group of 50 to <55 years, to 6.9% (95%CI: 4.5, 9.2) in the age group of 65 to <70 years and to 21.9% (95%CI: 16.4, 27.4) in the age group of 80+ years (Table 1).

Since many systemic and ocular parameters were age-related, we performed in a next step of the statistical examination a binary regression analysis with the prevalence of stroke as the dependent parameter and other systemic and ocular parameters as single independent variables, with adjusting for age and gender (Table 2). In that analysis, a higher prevalence of stroke was associated with the systemic parameters of higher body mass index (*P*=0.03), lower frequency of alcohol consumption (*P*=0.001), lower number of days with vigorous physical activities (*P*=0.05) or moderately intensive physical activities (*P*=0.01) and higher number of hours spent with sitting per day (*P*=0.04), lower life quality score (*P*<0.001), higher depression score (*P*<0.001), higher blood concentration of glucose (*P*=0.01) and glycosylated hemoglobin HbA1c (*P*=0.008), and higher prevalence of diabetes mellitus (*P*<0.001) and arterial hypertension (*P*<0.001); and with the ocular parameters of thicker central corneal thickness (*P*=0.09), lower foveal thickness (*P*=0.04), higher incidence of localized retinal nerve fiber layer defects (*P*=0.06), dry eye feeling (*P*=0.08), and higher prevalence of keratoconus (≥49 diopters) (*P*=0.02), nuclear cataract (*P*=0.06) and diabetic retinopathy (*P*<0.001) (Table 2).

In a third step of the statistical analysis, we performed a multivariate analysis with the

prevalence of previous stroke as the dependent variable and as independent variables all those systemic parameters for which the *P*-value in the previous analysis was <0.10 (Table 2). We then dropped the parameters of the prevalence of keratoconus (*P*=1.00), foveal thickness (*P*=0.48), number of days with moderate physical activities (*P*=0.86), blood concentration of HbA1c (*P*=0.63), number of hour spent with sitting per day (*P*=0.61), blood concentration of glucose (*P*=0.30), central corneal thickness (*P*=0.40), dry eye (*P*=0.31), body mass index (*P*=0.81), alcohol consumption (*P*=0.23), incidence of localized retinal nerve fiber layer defects (*P*=0.78), number of days with intensive physical activities (*P*=0.39), and depression index (*P*=0.12). In the final model, a higher prevalence of previous stroke was correlated (Nagelkerke R^2: 0.16) with older age (*P*<0.001), male gender (*P*=0.006), lower quality of life score (*P*<0.001), higher prevalence of diabetes mellitus (*P*=0.04) and arterial hypertension (*P*<0.001), lower prevalence of nuclear cataract (*P*=0.01), and higher stage of diabetic retinopathy (*P*<0.001) (Table 3).

If the parameter of staging of diabetic retinopathy was replaced by the presence of diabetic retinopathy, the latter was associated with previous stroke (*P*<0.001; OR: 3.97; 95%CI: 1.87, 8.43). If we added cardiovascular disease to the list of independent parameters, it was significantly (*P*=0.004; OR: 1.89; 95%CI: 1.23, 2.90), while diabetes mellitus was no longer significantly associated (*P*=0.17). If we added the parameter of physical activity (number of days with moderate physical activities) to the model, it showed a marginal association with a lower prevalence of previous stroke (*P*=0.09; OR: 0.94; 95%CI: 0.88, 1.01). When we added other parameters in a step by step manner, body mass index (*P*=0.45), body height (*P*=0.30), blood concentration of high-density lipoproteins (*P*=0.59), low-density lipoproteins (*P*=0.32), triglycerides (*P*=0.28), cholesterol (*P*=0.49), creatinine (*P*=0.71) and C-reactive protein (*P*=0.96), prevalence of localized retinal nerve fiber layer defects (*P*=0.72) or the mean thickness of the retinal nerve fiber layer (*P*=0.43) were not significantly associated with the prevalence of stroke.

Discussion

In our population-based study on a population aged 50+ years in Greater Beijing, the

prevalence of a previous stroke was 7.33% (95%CI:6.43,8.24). Besides the systemic risk factors of older age, male gender, a higher prevalence of arterial hypertension and a higher prevalence of diabetes mellitus or of cardiovascular disease, the presence and a higher stage of diabetic retinopathy were main factors for a higher prevalence of a previous stroke. The prevalence of a previous stroke increased for each increase in the stage of diabetic retinopathy (with altogether 4 stages) by a factor of 1.67 (95%CI: 1.20, 1.33), and for the presence of diabetic retinopathy by a factor of 3.97 (95%CI: 1.87, 8.43). Lower degree of physical activity showed a marginal association with a higher prevalence of previous stroke (*P*=0.09).

The findings obtained in our study agree with the results of previous investigations. In a review of studies conducted since 1990 in Chinese populations, Tsai and colleagues reported on an age-standardized annual first-ever stroke incidence of 205-584 per 100,000 in Chinese for the age group of 45-74 years.[13] Li and colleagues performing a population-based stroke surveillance on more than 14,000 residents in Tianjin, China from 1992 to 2012, reported on an increase in the age-standardized incidence for both intracerebral hemorrhage (37.8 per 100,000 person-years in 1992-1998, 46.5 in 1999-2005, and 76.5 in 2006-2012) and for ischemic stroke (83.9 in 1992-1998, 135.3 in 1999-2005, and 238.0 in 2006-2012).[14] The age-standardized incidence of first-ever stroke increased annually by 4.9% for intracerebral hemorrhage and by 7.3% for ischemic stroke. In a similar study, Ning and associates found that the age-standardized incidence of first-ever stroke per 100 000 person-years increased significantly, from 122 in the years 1992 to 1999, to 216 in 2000 to 2007, and to 471.8 in 2008 to 2015.[15] The greatest increases were observed in adults aged 55 to 64 years. In the China National Stroke Screening Survey as reported by Guan and coworkers, the adjusted stroke prevalence in 2014 was 2.06% in adults aged 40 years and older.[16] The incidence of first-ever stroke in adults aged 40-74 years increased from 189/100,000 individuals in 2002 to 379/100,000 in 2013-an overall annual increase of 8.3%.

The systemic factors associated with the prevalence of a previous Stroke in our study population were similar to those reported in previous investigations: older age, male gender and a higher prevalence of diabetes mellitus and arterial hypertension. In the China National Stroke Screening Survey, the largest contributor as risk factor was arterial hypertension

(population-attributable risk 53.2%), followed by family history, dyslipidemia, atrial fibrillation, diabetes, physical inactivity, smoking, and overweight/obesity.[16] As in our study, the review by Kyu and colleagues revealed that individuals with a higher level of physical activity had a lower risk of ischemic stroke.[17] Interestingly, self-reported alcohol consumption was not significantly associated with the prevalence of previous stroke in our study population.

The interesting finding in our study is that, after adjusting for other systemic risk factors, the presence of diabetic of diabetic retinopathy increased the likelihood of a previous stroke by a factor of 3.97, and in a parallel manner, that an increase by one step in the stage of diabetic retinopathy increased the probability of a previous stroke by a factor of 1.67. In previous studies by Cheung et al. and by Petitti and colleagues a similar association was described..[18,19] In a population-based, prospective cohort study of 1617 middle-aged persons with diabetes, Cheung found that after a mean follow-up of 7.8 years diabetic retinopathy was associated with an increased risk of ischemic stroke (hazard rate ratio, 2.34; 95% CI, 1.13 to 4.86), after adjusting for systemic parameters such as age, gender, race, arterial blood pressure, duration and therapy of diabetes, blood lipid concentrations and levels and cigarette smoking status.[18] In an earlier study, Petitti and associates found in a nested case-control study, that the estimated relative risk of stroke in diabetic subjects with retinopathy was 4.0 (95%CI: 1.0 , 14.5) after adjustment for systemic risk factors.[19] The reason for this association may be that diabetic retinopathy as a microangiopathy indicates a wide-spread vascular disorder.

When discussing the results of our study, its limitations have to be taken into account. First, the data on the prevalence of a previous self-reported stroke depended on the information provided by the study participants in the face-to-face interviews. Second, patients who had died as a sequel of a previous stroke were not included into the study. The results of our study are therefore valid primarily only for stroke survivors. Third, due to regional differences in China, findings obtained in our study may not completely be transferable to South China or pother world regions.[20] Fourth, we did not differentiate between intracerebral hemorrhage and ischemic stroke.[21] Fifth, we did not assess the role of atrial fibrillation as risk factor for stroke in our study. Fifth, the study population with an age of 50+ years had experienced major societal changes and economic developments in China

during their lifetime. This elderly generation may differ from the young generations in China and from populations in other countries.

In conclusion, in this North Chinese population aged 50+ years, the prevalence of a previous stroke was 7.33% (95%CI:6.43,8.24). Besides known systemic risk factors of older age, male gender and a higher prevalence of diabetes mellitus and arterial hypertension, the presence and stage of diabetic retinopathy were additional risk factors. The prevalence of previous stroke increased for each increase in the stage of diabetic retinopathy by a factor of 1.67 (95%CI:1.20,1.33), and for the presence of diabetic retinopathy by a factor of 3.97 (95%CI:1.87,8.43). Diabetic subjects with retinopathy appear to be a group at particularly high risk of ischemic stroke. Development of preventive interventions may focus on this group.

A. contributor ship statement: Design and conception: Ya Xing Wang, Wen Bin Wei, Liang Xu , Jost B. Jonas; Statistical analysis: Ya Xing Wang, Jost B. Jonas; Writing of the manuscript: Jost B. Jonas; Editing and final approval of the manuscript: Ya Xing Wang, Wen Bin Wei, Liang Xu , Jost B. Jonas;

B. competing interests: None

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D. Data sharing statement: There are no additional data available.

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Table 1

Prevalence (Mean and 95% Confidence Interval) of previous stroke in the Beijing Eye Study

Age Group (Years)	Men		Women		Total	
	n	Prevalence	n	Prevalence	n	Prevalence
50 to <55	250	2.5% (0.5, 4.3)	363	1.7% (0.3, 3.0)	613	2.0% (0.9, 3.1)
55 to <60	237	3.0% (0.8, 5.1)	366	3.0% (1.3, 4.8)	603	3.0% (1.6, 4.4)
60 to <65	196	7.7% (3.9, 11.4)	282	6.7% (3.8, 9.7)	478	7.1% (4.8, 9.4)
65 to <70	168	8.3% (4.1, 12.6)	270	5.9% (3.1, 8.8)	438	6.9% (4.5, 9.2)
70 to <75	247	10.9% (7.0, 14.9)	256	8.6% (5.1, 12.1)	503	9.7% (7.1, 12.3)
75 to <80	169	16.6 (10.9, 22.2)	182	8.8% (4.6, 12.9)	351	12.5% (9.1, 16.0)
80+	119	18.1, 34.1)	100	17.0% (9.5, 24.5)	219	21.9% (16.4, 27.4)

Table 2

Associations between the prevalence of cerebral stroke and systemic and ocular parameters after adjusting for age and gender in the Beijing Eye Study 2011

Parameter	*P*-Value	Odds Ratio	95% Confidence Interval
Systemic Parameters			
Rural / Urban Region of Habitation	0.11	1.29	0.95, 1.75
Body Mass Index (kg/m^2)	0.03	1.04	1.001, 1.08
Level of Education (1-5)	0.64	1.04	0.92, 1.18
Self-Reported Income	0.73	0.99	0.93, 1.05
Cognitive Score	0.77	1.00	0.96, 1.03
Alcohol Consumption Frequency	0.001	0.85	0.77, 0.94
Smoking Never / Former/ Current	0.19	0.87	0.71, 1.07
Smoking Never / Ever	0.98	1.00	0.72, 1.38
Smoking Package Years	0.38	1.00	1.00, 1.01
Physical Activity			
“How Many Days Do you Walk?”	0.51	0.98	0.92, 1.04
“How Many Days Do You Do Vigorously Intensive Sport or Activities?”	0.05	0.81	0.66, 1.00
“How Many Days Do You Do Moderately Intensive Sport or Activities?”	0.01	0.94	0.89, 0.99
“How Many Hours Do You Sit Per Day?”	0.04	1.06	1.004, 1.12
Quality of Life			
Summed Score	<0.001	1.44	1.31, 1.59

Mobility: I have no / some problems in walking about / I am confined to bed	<0.001	2.79	2.01, 3.86
Self-Care: I have I have no / some problems in washing or dressing myself / I am unable to wash or dress myself	<0.001	3.33	2.33, 4.75
Usual Activities (e.g. Work, study, housework, family or leisure activities): I am able to wash or dress myself / I have some problems with performing my usual activities / I am unable to perform my usual activities	<0.001	3.27	2.36, 4.53
Pain/Discomfort:	0.001	1.62	1.22, 2.14
Anxiety/Depression: I am not / moderately / extremely anxious or depressed	<0.001	2.07	1.45, 2.95
Depression Score	<0.001	1.06	1.04, 1.08
Blood Concentration of:			
Glucose (mmol/L)	0.01	1.11	1.02, 1.21
Glycosylated hemoglobin HbA1c	0.008	1.18	1.04, 1.33
High-Density Lipoproteins (mmol/L)	0.11	0.70	0.45, 1.09
Low-Density Lipoproteins (mmol/L)	0.28	0.90	0.74, 1.09
Triglycerides (mmol/L)	0.95	1.01	0.86, 1.17
Cholesterol (mmol/L)	0.18	0.88	0.74, 1.06
C-reactive Protein	0.47	1.01	0.98, 1.04
Diabetes Mellitus, Prevalence	<0.001	1.86	1.32, 2.61
Systolic Blood Pressure (mmHg)	0.14	1.01	1.00,1.02
Diastolic Blood Pressure (mmHg)	0.82	1.00	0.99, 1.01
Mean Blood Pressure (mmHg)	0.40	1.00	0.99, 1.01

Arterial Hypertension	<0.001	2.42	1.76, 3.34
Estimated Cerebrospinal Fluid Pressure (mm Hg)	0.17	1.03	0.99, 1.09
Creatinine (mmol/L)	0.67	1.00	0.99, 1.02
Estimated Glomerular Filtration Rate (GFR) (mL/min / 1·73 m²) (MDRD Formula)	0.79	1.00	0.99, 1.01
Estimated Glomerular Filtration Rate (mL/min / 1·73 m²) (CKDE Formula)	0.79	1.00	0.98, 1.01
Ocular Parameters			
Refractive Error (Diopters)	0.47	0.98	0.92, 1.04
Axial Length (mm)	0.70	0.98	0.86, 1.11
Anterior Corneal Curvature Radius (mm)	0.16	0.66	0.37, 1.18
Central Corneal Thickness (µm)	0.09	1.004	0.999, 1.008
Anterior Chamber Depth (mm)	0.92	1.01	0.79, 1.29
Lens Thickness (mm)	0.14	1.41	0.89, 2.22
Intraocular Pressure mmHg)	0.66	1.01	0.96, 1.06
Retinal Nerve Fiber Layer Thickness (µm)	0.62	1.00	0.99, 1.01
Localized Defects of the Retinal Nerve Fiber Layer, Prevalence	0.42	1.18	0.79, 1.77
Localized Defects of the Retinal Nerve Fiber Layer, 10-Year Incidence	0.06	1.83	0.98, 3.42
Subfoveal Choroidal Thickness (µm)	0.83	1.00	1.00, 1.00
Fundus Tessellation	0.66	1.02	0.92, 1.13
Macular Retinal Thickness (µm)	0.04	0.994	0.989, 1.000
Optic Disc Size (mm^2)	0.69	1.09	0.71, 1.70
Neuroretinal Rim Area (mm^2)	0.52	1.15	0.75, 1.77

Dry Eye, Yes or No	0.80	1.04	0.79, 1.36
Dry Eye, Number of Days	0.08	1.04	0.995, 1.10
Keratoconus (Anterior Corneal Curvature refractive Power ≥48 Diopters)	0.27	2.04	0.58, 7.18
Keratoconus (Anterior Corneal Curvature refractive Power ≥49 Diopters)	0.02	8.00	1.31, 48.9
Pseudoexfoliation Syndrome	0.49	0.82	0.47, 1.43
Nuclear Cataract	0.06	0.72	0.51, 1.02
Cortical Cataract	0.87	0.97	0.66, 1.43
Subcapsular Posterior Cataract	0.34	1.29	0.77, 2.16
Glaucoma, Prevalence, Total	0.61	0.87	0.52, 1.47
Open-Angle Glaucoma	0.26	0.63	0.28, 1.40
Primary Angle-Closure Glaucoma	0.36	0.57	0.17, 1.89
Age-Related Macular Degeneration, Prevalence, Total	0.60	0.92	0.68, 1.25
Age-Related Macular Degeneration, Early Stage	0.29	0.75	0.44, 1.28
Age-Related Macular Degeneration, Intermediate Stage	0.75	0.95	0.67, 1.34
Age-Related Macular Degeneration, Late Stage	0.11	2.26	0.84, 6.06
Diabetic Retinopathy, Prevalence	<0.001	1.63	1.27, 2.08
Diabetic Retinopathy, Score	<0.001	4.75	2.67, 8.46
Retinal Vein Occlusion, Total	0.18	1.55	0.82, 2.93
Branch Retinal Vein Occlusion	0.65	1.25	0.48, 3.29
Myopic Retinopathy	0.77	1.20	0.36, 4.03

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Table 3

Associations (multivariate analysis) between the prevalence of cerebral stroke and systemic and ocular parameters in the Beijing Eye Study 2011

Parameter	*P*-Value	Odds Ratio (OR)	95% Confidence Interval of OR
Age (Years)	<0.001	1.07	1.05, 1.09
Gender (Men / Women)	0.006	0.59	0.40, 0.86
Quality of Life Score	<0.001	1.44	1.24, 1.67
Prevalence of Diabetes Mellitus	0.04	1.57	1.02, 2.41
Stage of Diabetic Retinopathy	0.002	1.67	1.20, 2.33
Prevalence of Arterial Hypertension	<0.001	2.22	1.43, 3.43
Prevalence of Nuclear Cataract	0.01	0.58	0.38, 0.89

Fig. 1

Graph showing the distribution of the prevalence of a previous stroke stratified by age and gender in the Beijing Eye Study

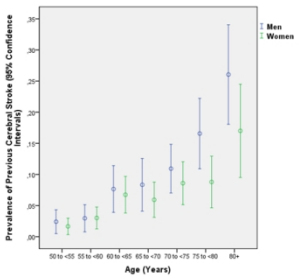

Fig. 1: Graph showing the distribution of the prevalence of a previous stroke stratified by age and gender in the Beijing Eye Study

323x199mm (120 x 120 DPI)

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Prevalence, Risk Factors and Associated Ocular Diseases of Cerebral Stroke: The Population-based Beijing Eye Study

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Abstract

Objective: To assess the prevalence of cerebral stroke in the general population of Beijing and its association with systemic risk factors and ocular diseases.

Setting: The population-based Beijing Eye Study was conducted in a rural and an urban region of Greater Beijing.

Participants: With an eligibility criterion of an age of 50+ years and living in the study regions, 3468 subjects (78.8%) out of 4403 eligible individuals participated.

Primary and secondary outcome measures: The study participants underwent a detailed systemic and ophthalmological examination and an interview in which the occurrence of a previous stroke was assessed.

Results: A previous stroke was reported by 235 individuals (7.33%;95% confidence interval [CI]:6.43,8.24). The prevalence of previous stroke increased from 2.0% (95%CI:0.9,3.1) in the age group of 50 to <55 years to 21.9% (95%CI:16.4,27.4) in the age group of 80+ years. In multivariable regression analysis, a higher prevalence of previous stroke was correlated (Nagelkerke R^2:0.20) with the systemic parameters of older age (P<0.001; odds ratio [OR]:1.06;95%CI:1.04,1.08), male gender (P<0.001;OR:0.54;95%CI:0.40,0.74), lower quality of life score (P<0.001;OR:1.39;95%CI:1.25,1.55), higher prevalence of arterial hypertension (P<0.001;OR:2.86;95%CI:2.05,3.98), and cardiovascular disease (P<0.001;OR:1.8554;95%CI:1.34,2.56), and with the ocular parameter of a higher prevalence of diabetic retinopathy (P<0.001;OR:4.41;95%CI:2.38,8.18) (or alternatively, with a higher stage of diabetic retinopathy (P<0.001;OR:1.64;95%CI:1.26,2.14).

Conclusions: In this North Chinese population aged 50+ years, the prevalence of a previous stroke was 7.33% (95%CI:6.43,8.24). After adjusting for systemic risk factors of older age, male gender and higher prevalence of arterial hypertension and cardiovascular disease, higher prevalence of previous stroke was significantly correlated with a higher prevalence presence and stage of diabetic retinopathy. Previous stroke prevalence increased for each step increase in the stage of diabetic retinopathy by an odds ratio of 1.64 (95%CI:1.26,2.14), and for the presence of diabetic retinopathy by an odds ratio of 4.41 (95%CI:2.38,8.18).

Article Summary

Strengths and limitations of this study:

- Limitation: Data on the prevalence of a previous stroke depended on self-reported information; patients who had died as a sequel of a previous stroke were not included into the study; the results of our study are therefore valid primarily only for stroke survivors.
- Limitation: Intracerebral hemorrhage was not differentiated from ischemic stroke.
- Limitation: Cross-sectional analysis
- Strength: Population-based study design
- Strength: Large number of parameters including ophthalmological variables assessed

Introduction

Cerebral stroke as one of the main contributors of the global burden of disease has caused 116 million or 4.8% of all DALYs (Disability-Adjusted Life Years) and 14.5 million or 1.8% of all YLDs (Years Lived with Disability) worldwide in the year 2013.[1-4] In particular China has witnessed a marked increase in the importance of stroke in the spectrum of diseases causing DALYS and years of life lost (YLLs). While in 1990, lower respiratory infections or preterm birth complications were the leading causes of YLLs in almost half of the provinces of China (16 out of 33), cerebrovascular disease were the leading cause in 27 of the 33 provinces in 2013.[5,6] Since the eye and brain share the same arterial blood supply through the inner carotid artery and since the retina and optic nerve as former outgrowth of the anterior end of the embryological neural groove are of neuro-ectodermal origin, a major cerebral disease such as stroke may be associated with ocular diseases, in particular disorders of the optic nerve and retina. Since comprehensive population-based studies on associations between stroke and ocular parameters have been scare so far and have not been conducted for the population of China, we investigated the prevalence of cerebral stroke and its potential associations with ocular diseases, after adjusting for systemic factors, in a population-based study performed in China.

Methods

The Beijing Eye Study 2011 is a population-based study which was conducted in a rural region and an urban area of Greater Beijing. The Medical Ethics Committee of the Beijing Tongren Hospital approved the study design, and all study participants gave an informed consent. The eligibility criteria for inclusion into the study were an age of 50+ years and living in the study regions. Out of 4403 eligible individuals, 3468 subjects (1963 (56.6%) women) participated (response rate: 78.8%). The mean age was 64.6 ± 9.8 years (median 64 years; range: 50–93 years). There were 1633 (47.1%) individuals (943 (57.7%) women) coming from the rural region, with the remaining 1835 (52.9%) study participants (1020 (55.6%) women) living in the urban region. The study design has been described in detail previously.[7,8]

All study participants underwent a structured interview by trained research technicians. The interview included more than 200 standardized questions on demographic parameters, socioeconomic background, diet and alcohol consumption, smoking habits, known major systemic diseases and current systemic medical therapies. Using the mini–mental state examination (MMSE) scale, we assessed the cognitive function. Fasting blood samples were collected for measurement of blood lipids, glucose, glycosylated hemoglobin HbA1c and serum creatinine. The blood pressure was measured with the participant sitting for at least 5 min. We also measured body height and weight and the circumference of the waist and hip.

Arterial hypertension was defined by a systolic blood pressure ≥160 mm Hg and/or a diastolic blood pressure ≥95 mm Hg, and/or self-reported current treatment for arterial hypertension with antihypertensive medication. Diabetes mellitus was characterized by a blood glucose concentration ≥7.0 mmol/L, an HbA1c value ≥6%, by a self-reported history of physician diagnosis of diabetes mellitus, or by a history of drug treatment for diabetes (insulin or oral hypoglycemic agents). Depressive symptoms were evaluated using a Chinese depression scale adapted from the Zung self-rated depression scale.[9] The prevalence of previous stroke was examined in the interview by standardized questions on whether a previous cerebral stroke had occurred with typical symptoms such as sudden-onset face weakness, arm drift, abnormal speech hemiplegia, or numbness for at least 24 hours, when such a stroke had occurred, and whether it had been treated.

The ophthalmological examination consisted of automatic refractometry (Auto Refractometer AR-610; Nidek Co., Ltd, Tokyo, Japan), measurement of presenting visual acuity, uncorrected visual acuity and best-corrected visual acuity, tonometry, slit lamp based biomicroscopy of the anterior and posterior segment of the eyes, and photography of the cornea and lens (Neitz CT-R camera; Neitz Instruments Co., Tokyo, Japan) and of the macula and optic disc (fundus camera; Type CR6-45MM; Canon Inc., Tokyo, Japan) in medical mydriasis. Using the photographs, we measured the dimensions of the optic disc, optic cup and parapapillary alpha, beta and gamma zones. The optic nerve head and macula were additionally examined by spectral-domain optical coherence tomography (OCT) using the enhanced depth imaging modality (Spectralis; Heidelberg Engineering, Heidelberg, Germany).

We determined the thickness of the peripapillary retinal nerve fiber layer, of the retina in the foveal region and of the subfoveal choroid. Applying optical low-coherence reflectometry (Lenstar 900 Optical Biometer; Haag-Streit, Koeniz, Switzerland), we measured ocular biometric parameters such as the anterior corneal curvature, central corneal thickness, anterior chamber depth, lens thickness and axial length. The degree of cataract was determined using the lens photographs. The degree of nuclear opacities was assessed in 6 grades using the grading system of the Age-Related Eye Disease Study.[10] In addition, retro-illuminated photographs of the lens were obtained (Neitz CT-R camera; Neitz Instruments Co., Tokyo, Japan), and the percentage of the areas with cortical and posterior subcapsular lens opacities was measured using a grid. The standard to diagnose a nuclear cataract was a nuclear cataract grade of 4 or more, the standard to diagnose a posterior subcapsular cataract was an amount of posterior subcapsular opacities of 0.01 or more, and the standard to diagnose a cortical cataract was an amount of cortical opacities of 0.05 or more. The degree of fundus tessellation defined as the visibility of the large choroidal vessels was assessed on the fundus photographs of the macula and of the optic disc as described in detail previously.[8] It was graded using a scale which ranged from “0” for “no tessellation” to ”3” for “marked tessellation”. Diabetic retinopathy was assessed on the fundus photographs using the Early Treatment of Diabetic Retinopathy Study (ETDRS) criteria. The minimum criterion for diagnosis of diabetic retinopathy was the presence of at least one microaneurysm. The diagnosis for each individual was based on the grading of the individual´s eye with the highest stage of diabetic retinopathy. We differentiated between the mild non-proliferative stage, the moderate non-proliferative stage, the advanced non-proliferative stage, and the proliferative stage of diabetic retinopathy. Glaucomatous optic neuropathy was defined using the criteria of the International Society of Geographic and Epidemiological Ophthalmology ISGEO.[11] Pseudoexfoliation was assessed by an experienced ophthalmologist during the slit lamp assisted biomicroscopy of the anterior segment after pupillary dilation. The diagnosis of pseudoexfoliation was definite, if the lens surface showed a central whitish coating with a diameter of little less than the normal pupillary diameter, or if the periphery of the lens surface showed a whitish coating which was anteriorly bordered by a darker ring-like region on the lens surface. The assessment of

pseudoexfoliation was performed only in phakic eyes. For the diagnosis of age-related macular degeneration, the International ARM (Age-related Maculopathy Epidemiological Study Group) Grading system was used. The subjective symptoms of dry eye were evaluated using a questionnaire composed of three questions: “Do your eyes ever feel dry?”; “Do you ever feel a gritty or sandy sensation in your eyes?”; and “Do your eyes ever have a burning sensation?” Possible answers to the questions were none (0), less than once a month (1), once or twice a week (2), at least once every day (3), all the time (4). The presence of dry eye symptoms was defined as having one or more symptoms at least once every day (3 and 4). A quantitative grading score of subjective dry eye symptoms was obtained by summarizing the answers to the different questions (0–12).[12]

The statistical analysis was performed using a commercially available statistical software package (SPSS for Windows, version 25.0, IBM-SPSS, Chicago, IL, USA). As a first step, we assessed the prevalence of previous stroke (expressed as binary parameter as a proportion and the 95% confidence interval (CI)) and calculated the mean values of linear parameters such as ocular axial length (expressed mean ± standard deviation). We then assessed differences between the stroke group and the non-stroke group in age and gender. As second step, we performed a binary regression analysis with the prevalence of stroke as dependent parameter and with other measured parameters as independent variables, after adjusting for age and gender. As a third step, we conducted an extended multivariable binary analysis which included as independent parameters all those variables which were correlated (P<0.10) with stroke prevalence in the previous analysis. We then dropped step-by-step all those parameters which either showed a collinearity with one of the other independent variables or which were no longer statistically significantly correlated with the prevalence of previous stroke. We first started with the systemic independent parameters, such as age and blood pressure. We calculated the odds ratio (OR) and its 95% CIs. All P-values were two-sided and considered statistically significant, if the values were less than 0.05.

Patient and Public Involvement statement: Patients were not involved in this study

Results

Out of 3468 study participants, 3205 (92.4%) individuals participated in the interview with available information on previous stroke and underwent the systemic and ophthalmologic examination. The participating group as compared to the group of individuals without available information on previous stroke or without systemic and ocular examination was significantly younger (64.4 ± 9.7 years (median: 63 years; range: 50 – 93 years) versus 67.1 ± 11.1 years; *P*<0.001) and came significantly more often from the urban region than from the rural area (rural / urban region of habitation: 1439 / 1766 versus 194 / 69; *P*<0.001), while the differences in gender (men / women: 1386 / 1819 versus 119 / 144; *P*=0.56), axial length (23.3 ± 1.1 mm versus 23.2 ± 1.9 mm; *P*=0.31) and refractive error (-0.22 ± 2.12 diopters versus -0.31 ± 2.17 diopters; *P*=0.59) were not statistically significant.

A previous stroke was reported by 235 individuals (235 / 3205 or 7.33% [95%CI: 6.43, 8.24]). Among the 235 patients, 192 individuals were on oral medication for the prophylaxis of a recurrence of the stroke. The stroke had taken place 7.5 ± 5.7 years ago (median: 7 years; range: 1 month to 26 years).

In the stroke group as compared with the non-stroke group (control group), age was significantly older (71.1 ± 9.2 years versus 63.9 ± 9.5 years; *P*<0.001) and had a higher proportion of men than women (men / women: 128 / 107 versus 1258 / 1712; *P*<0.001) (Fig. 1). The prevalence of a previous stroke increased from 2.0% (95%CI: 0.9, 3.1) in the age group of 50 to <55 years, to 6.9% (95%CI: 4.5, 9.2) in the age group of 65 to <70 years and to 21.9% (95%CI: 16.4, 27.4) in the age group of 80+ years (Table 1).

Since many systemic and ocular parameters were age-related, we performed in a next step of the statistical examination a binary regression analysis with the prevalence of stroke as the dependent parameter and other systemic and ocular parameters as single independent variables, with adjusting for age and gender (Table 2). In that analysis, a higher prevalence of stroke was associated with the systemic parameters of higher body mass index (*P*=0.03), lower frequency of alcohol consumption (*P*=0.001), lower number of days with vigorous physical activities (*P*=0.05) or moderately intensive physical activities (*P*=0.01) and higher number of hours spent with sitting per day (*P*=0.04), lower life quality score (*P*<0.001), higher depression score (*P*<0.001), higher blood concentration of glucose (*P*=0.01) and glycosylated hemoglobin HbA1c (*P*=0.008), and higher prevalence of diabetes mellitus (*P*<0.001) and

arterial hypertension (*P*<0.001); and with the ocular parameters of thicker central corneal thickness (*P*=0.09), lower foveal thickness (*P*=0.04), higher incidence of localized retinal nerve fiber layer defects (*P*=0.06), dry eye feeling (*P*=0.08), and higher prevalence of keratoconus (≥49 diopters) (*P*=0.02), nuclear cataract (*P*=0.06) and presence and stage diabetic retinopathy (*P*<0.001) (Table 2) (Fig. 2).

The multivariable analysis included the prevalence of previous stroke as dependent variable and as independent variables all those systemic parameters for which the *P*-value in the previous analysis was <0.10 (Table 2). We then dropped in step-by-step manner all independent parameters which either showed a collinearity with one of the other independent variables or which were no longer statistically significantly correlated with the prevalence of a previous stroke. In the final model, a higher prevalence of previous stroke was correlated (Nagelkerke R^2: 0.20) with older age (*P*<0.001), male gender (*P*<0.001), lower quality of life score (*P*<0.001), higher prevalence of arterial hypertension (*P*<0.001) and cardiovascular disease (*P*<0.001), and higher prevalence of diabetic retinopathy (*P*<0.001) (Table 3). If the parameter of prevalence of diabetic retinopathy was replaced by the diabetic retinopathy stage, the latter was associated with previous stroke (*P*<0.001; OR: 1.64; 95%CI: 1.26, 2.14).

Discussion

In our population-based study on a population aged 50+ years in Greater Beijing, the prevalence of a previous stroke was 7.33% (95%CI:6.43,8.24). After adjusting for the systemic risk factors of older age, male gender and a higher prevalence of arterial hypertension and cardiovascular disease, a higher prevalence of a previous stroke was significantly correlated with the presence and a higher stage of diabetic retinopathy (Fig. 2). The prevalence of a previous stroke increased for each increase in the stage of diabetic retinopathy (with altogether 4 stages) by an odds ratio of 1.64 (95%CI: 1.26, 2.14), and for the presence of diabetic retinopathy by an odds ratio of 4.41 (95%CI: 2.38, 8.18).

The findings obtained in our study agree with the results of previous investigations. In a review of studies conducted since 1990 in Chinese populations, Tsai and colleagues reported on an age-standardized annual first-ever stroke incidence of 205-584 per 100,000 in

Chinese for the age group of 45-74 years.[13] Li and colleagues performing a population-based stroke surveillance on more than 14,000 residents in Tianjin, China from 1992 to 2012, reported on an increase in the age-standardized incidence for both intracerebral hemorrhage (37.8 per 100,000 person-years in 1992-1998, 46.5 in 1999-2005, and 76.5 in 2006-2012) and for ischemic stroke (83.9 in 1992-1998, 135.3 in 1999-2005, and 238.0 in 2006-2012).[14] The age-standardized incidence of first-ever stroke increased annually by 4.9% for intracerebral hemorrhage and by 7.3% for ischemic stroke. In a similar study, Ning and associates found that the age-standardized incidence of first-ever stroke per 100 000 person-years increased significantly, from 122 in the years 1992 to 1999, to 216 in 2000 to 2007, and to 471.8 in 2008 to 2015.[15] The greatest increases were observed in adults aged 55 to 64 years. In the China National Stroke Screening Survey as reported by Guan and coworkers, the adjusted stroke prevalence in 2014 was 2.06% in adults aged 40 years and older.[16] The incidence of first-ever stroke in adults aged 40-74 years increased from 189/100,000 individuals in 2002 to 379/100,000 in 2013-an overall annual increase of 8.3%.

The systemic factors associated with the prevalence of a previous Stroke in our study population were similar to those reported in previous investigations: older age, male gender and a higher prevalence of arterial hypertension and cardiovascular disease. In the China National Stroke Screening Survey, the largest contributor as risk factor was arterial hypertension (population-attributable risk 53.2%), followed by family history, dyslipidemia, atrial fibrillation, diabetes, physical inactivity, smoking, and overweight/obesity.[16]

The interesting finding in our study is that, after adjusting for other systemic risk factors, the presence of diabetic of diabetic retinopathy increased the likelihood of a previous stroke by an odds ratio of 4.41, and in a parallel manner, that an increase by one step in the stage of diabetic retinopathy increased the probability of a previous stroke by an odds ratio of 1.64. In previous studies by Cheung et al. and by Petitti and colleagues a similar association was described..[17,18] In a population-based, prospective cohort study of 1617 middle-aged persons with diabetes, Cheung found that after a mean follow-up of 7.8 years diabetic retinopathy was associated with an increased risk of ischemic stroke (hazard rate ratio, 2.34; 95% CI, 1.13 to 4.86), after adjusting for systemic parameters such as age, gender, race, arterial blood pressure, duration and therapy of diabetes, blood lipid concentrations and levels and cigarette

smoking status.[17] In an earlier study, Petitti and associates found in a nested case-control study, that the estimated relative risk of stroke in diabetic subjects with retinopathy was 4.0 (95%CI: 1.0 , 14.5) after adjustment for systemic risk factors.[18] The reason for this association may be that diabetic retinopathy as a microangiopathy indicates a wide-spread vascular disorder.

When discussing the results of our study, its limitations have to be taken into account. First, the data on the prevalence of a previous self-reported stroke depended on the information provided by the study participants in the face-to-face interviews. Since stroke is a dramatic event, it is unlikely to be under-reported. Transient ischemic attacks might occur unnoticed by the individuals so that transient ischemic attacks might be under-reported in an interview of previous cerebral strokes. Our study was based however primarily on previous cerebral strokes which were defined as an occurrence of typical neurological symptoms for at least 24 hours. It may make it unlikely that unnoticed previous transient ischemic attacks might have markedly influenced the results of our study. Second, patients who had died as a sequel of a previous stroke were not included into the study. The results of our study are therefore valid primarily only for stroke survivors. Third, due to regional differences in China, findings obtained in our study may not completely be transferable to South China or pother world regions.[19] Fourth, we did not differentiate between intracerebral hemorrhage and ischemic stroke.[20] Fifth, we did not assess the role of atrial fibrillation as risk factor for stroke in our study. Fifth, the study population with an age of 50+ years had experienced major societal changes and economic developments in China during their lifetime. This elderly generation may differ from the young generations in China and from populations in other countries. Sixth, our investigation was a cross-sectional observational study, so that a reverse causality may have existed in the sense that diabetic retinopathy might have been the sequel of stroke.

In conclusion, in this North Chinese population aged 50+ years, the prevalence of a previous stroke was 7.33% (95%CI:6.43,8.24). The presence and stage of diabetic retinopathy were ocular risk factors for a higher prevalence of a previous stroke, after adjusting for the systemic risk factors of older age, male gender and a higher prevalence of diabetes mellitus and cardiovascular disease. The prevalence of previous stroke increased for each

increase in the stage of diabetic retinopathy by an odds ratio of 1.64 (95%CI: 1.26, 2.14), and for the presence of diabetic retinopathy by an odds ratio of 4.41 (95%CI: 2.38, 8.18). Individuals with diabetic retinopathy appear to be a group at particularly high risk of cerebral stroke.

A. contributor ship statement: Design and conception: Ya Xing Wang, Wen Bin Wei, Liang Xu , Jost B. Jonas; Statistical analysis: Ya Xing Wang, Jost B. Jonas; Writing of the manuscript: Jost B. Jonas; Editing and final approval of the manuscript: Ya Xing Wang, Wen Bin Wei, Liang Xu , Jost B. Jonas;

B. competing interests: None

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D. Data sharing statement: The datafile will be available on request.

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Table 1

Prevalence (Mean and 95% Confidence Interval) of previous stroke in the Beijing Eye Study

Age Group (Years)	Men		Women		Total	
	n	Prevalence	n	Prevalence	n	Prevalence
50 to <55	250	2.5% (0.5, 4.3)	363	1.7% (0.3, 3.0)	613	2.0% (0.9, 3.1)
55 to <60	237	3.0% (0.8, 5.1)	366	3.0% (1.3, 4.8)	603	3.0% (1.6, 4.4)
60 to <65	196	7.7% (3.9, 11.4)	282	6.7% (3.8, 9.7)	478	7.1% (4.8, 9.4)
65 to <70	168	8.3% (4.1, 12.6)	270	5.9% (3.1, 8.8)	438	6.9% (4.5, 9.2)
70 to <75	247	10.9% (7.0, 14.9)	256	8.6% (5.1, 12.1)	503	9.7% (7.1, 12.3)
75 to <80	169	16.6 (10.9, 22.2)	182	8.8% (4.6, 12.9)	351	12.5% (9.1, 16.0)
80+	119	18.1, 34.1)	100	17.0% (9.5, 24.5)	219	21.9% (16.4, 27.4)

Table 2

Associations between the prevalence of cerebral stroke and systemic and ocular parameters after adjusting for age and gender in the Beijing Eye Study 2011

Parameter	*P*-Value	Odds Ratio	95% Confidence Interval
Systemic Parameters			
Rural / Urban Region of Habitation	0.11	1.29	0.95, 1.75
Body Mass Index (kg/m^2)	0.03	1.04	1.001, 1.08
Level of Education (1-5)	0.64	1.04	0.92, 1.18
Self-Reported Income	0.73	0.99	0.93, 1.05
Cognitive Score	0.77	1.00	0.96, 1.03
Alcohol Consumption Frequency	0.001	0.85	0.77, 0.94
Smoking Never / Former/ Current	0.19	0.87	0.71, 1.07
Smoking Never / Ever	0.98	1.00	0.72, 1.38
Smoking Package Years	0.38	1.00	1.00, 1.01
Physical Activity			
“How Many Days Do you Walk?”	0.51	0.98	0.92, 1.04
“How Many Days Do You Do Vigorously Intensive Sport or Activities?”	0.05	0.81	0.66, 1.00
“How Many Days Do You Do Moderately Intensive Sport or Activities?”	0.01	0.94	0.89, 0.99
“How Many Hours Do You Sit Per Day?”	0.04	1.06	1.004, 1.12
Quality of Life			
Summed Score	<0.001	1.44	1.31, 1.59

Mobility: I have no / some problems in walking about / I am confined to bed	<0.001	2.79	2.01, 3.86
Self-Care: I have I have no / some problems in washing or dressing myself / I am unable to wash or dress myself	<0.001	3.33	2.33, 4.75
Usual Activities (e.g. Work, study, housework, family or leisure activities): I am able to wash or dress myself / I have some problems with performing my usual activities / I am unable to perform my usual activities	<0.001	3.27	2.36, 4.53
Pain/Discomfort:	0.001	1.62	1.22, 2.14
Anxiety/Depression: I am not / moderately / extremely anxious or depressed	<0.001	2.07	1.45, 2.95
Depression Score	<0.001	1.06	1.04, 1.08
Blood Concentration of:			
Glucose (mmol/L)	0.01	1.11	1.02, 1.21
Glycosylated hemoglobin HbA1c	0.008	1.18	1.04, 1.33
High-Density Lipoproteins (mmol/L)	0.11	0.70	0.45, 1.09
Low-Density Lipoproteins (mmol/L)	0.28	0.90	0.74, 1.09
Triglycerides (mmol/L)	0.95	1.01	0.86, 1.17
Cholesterol (mmol/L)	0.18	0.88	0.74, 1.06
C-reactive Protein	0.47	1.01	0.98, 1.04
Diabetes Mellitus, Prevalence	<0.001	1.86	1.32, 2.61
Diabetes Mellitus, Duration (Years)	0.08	1.02	1.00, 1.04
Systolic Blood Pressure (mmHg)	0.14	1.01	1.00,1.02
Diastolic Blood Pressure (mmHg)	0.82	1.00	0.99, 1.01

Mean Blood Pressure (mmHg)	0.40	1.00	0.99, 1.01
Arterial Hypertension	<0.001	2.42	1.76, 3.34
Estimated Cerebrospinal Fluid Pressure (mm Hg)	0.17	1.03	0.99, 1.09
Creatinine (mmol/L)	0.67	1.00	0.99, 1.02
Estimated Glomerular Filtration Rate (GFR) (mL/min / 1·73 m²) (MDRD Formula)	0.79	1.00	0.99, 1.01
Estimated Glomerular Filtration Rate (mL/min / 1·73 m²) (CKDE Formula)	0.79	1.00	0.98, 1.01
Ocular Parameters			
Refractive Error (Diopters)	0.47	0.98	0.92, 1.04
Axial Length (mm)	0.70	0.98	0.86, 1.11
Anterior Corneal Curvature Radius (mm)	0.16	0.66	0.37, 1.18
Central Corneal Thickness (µm)	0.09	1.004	0.999, 1.008
Anterior Chamber Depth (mm)	0.92	1.01	0.79, 1.29
Lens Thickness (mm)	0.14	1.41	0.89, 2.22
Intraocular Pressure mmHg)	0.66	1.01	0.96, 1.06
Retinal Nerve Fiber Layer Thickness (µm)	0.62	1.00	0.99, 1.01
Localized Defects of the Retinal Nerve Fiber Layer, Prevalence	0.42	1.18	0.79, 1.77
Localized Defects of the Retinal Nerve Fiber Layer, 10-Year Incidence	0.06	1.83	0.98, 3.42
Subfoveal Choroidal Thickness (µm)	0.83	1.00	1.00, 1.00
Fundus Tessellation	0.66	1.02	0.92, 1.13
Macular Retinal Thickness (µm)	0.04	0.994	0.989, 1.000
Optic Disc Size (mm^2)	0.69	1.09	0.71, 1.70

Neuroretinal Rim Area (mm^2)	0.52	1.15	0.75, 1.77
Dry Eye, Yes or No	0.80	1.04	0.79, 1.36
Dry Eye, Number of Days	0.08	1.04	0.995, 1.10
Keratoconus (Anterior Corneal Curvature refractive Power ≥48 Diopters)	0.27	2.04	0.58, 7.18
Keratoconus (Anterior Corneal Curvature refractive Power ≥49 Diopters)	0.02	8.00	1.31, 48.9
Pseudoexfoliation Syndrome	0.49	0.82	0.47, 1.43
Nuclear Cataract	0.06	0.72	0.51, 1.02
Cortical Cataract	0.87	0.97	0.66, 1.43
Subcapsular Posterior Cataract	0.34	1.29	0.77, 2.16
Glaucoma, Prevalence, Total	0.61	0.87	0.52, 1.47
Open-Angle Glaucoma	0.26	0.63	0.28, 1.40
Primary Angle-Closure Glaucoma	0.36	0.57	0.17, 1.89
Age-Related Macular Degeneration, Prevalence, Total	0.60	0.92	0.68, 1.25
Age-Related Macular Degeneration, Early Stage	0.29	0.75	0.44, 1.28
Age-Related Macular Degeneration, Intermediate Stage	0.75	0.95	0.67, 1.34
Age-Related Macular Degeneration, Late Stage	0.11	2.26	0.84, 6.06
Diabetic Retinopathy, Prevalence	<0.001	1.63	1.27, 2.08
Diabetic Retinopathy, Score	<0.001	4.75	2.67, 8.46
Retinal Vein Occlusion, Total	0.18	1.55	0.82, 2.93
Branch Retinal Vein Occlusion	0.65	1.25	0.48, 3.29
Myopic Retinopathy	0.77	1.20	0.36, 4.03

Table 3

Associations (multivariable analysis) between the prevalence of cerebral stroke and systemic and ocular parameters in the Beijing Eye Study 2011

Parameter	*P*-Value	Odds Ratio (OR)	95% Confidence Interval of OR
Age (Years)	<0.001	1.06	1.04, 1.08
Gender (Men / Women)	<0.001	0.54	0.40, 0.74
Inverse Quality of Life Score	<0.001	1.39	1.25, 1.55
Prevalence of Arterial Hypertension	<0.001	2.86	2.05, 3.98
Cardiovascular Disease	<0.001	1.85	1.34, 2.56
Prevalence of Diabetic Retinopathy	<0.001	4.41	2.38, 8.18
(Alternatively: Stage of Diabetic Retinopathy)	*P*<0.001	1.64	1.26, 2.14

Fig. 1

Graph showing the distribution of the prevalence of a previous cerebral stroke stratified by age and gender in the Beijing Eye Study

Fig. 2

Graph showing the distribution of the prevalence of a previous cerebral stroke stratified by age and presence of diabetic retinopathy in the Beijing Eye Study

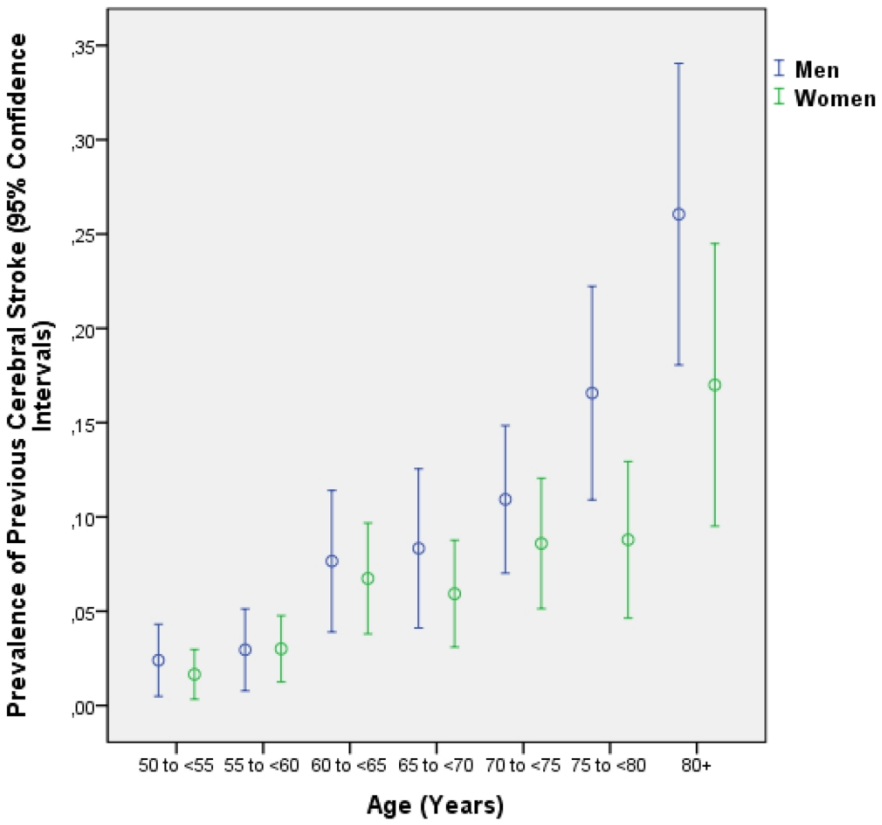

Fig. 1
Graph showing the distribution of the prevalence of a previous cerebral stroke stratified by age and gender in the Beijing Eye Study

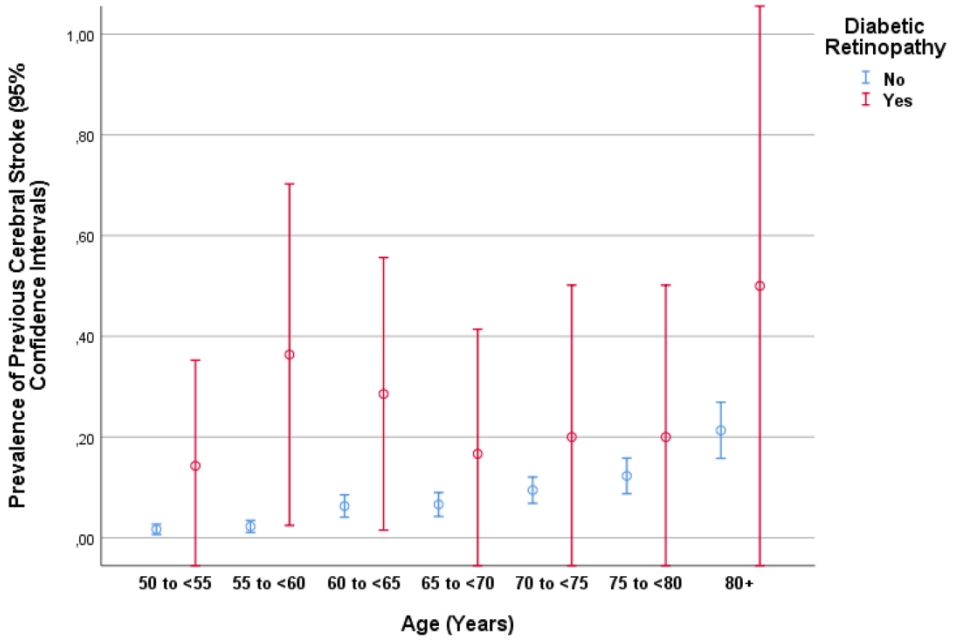

Fig. 2
Graph showing the distribution of the prevalence of a previous cerebral stroke stratified by age and presence of diabetic retinopathy in the Beijing Eye Study

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page: Line
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1: 4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2: 52-58
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4: 72-86
Objectives	3	State specific objectives, including any prespecified hypotheses	4: 72-86
Methods			
Study design	4	Present key elements of study design early in the paper	4: 91-100
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4: 91-100
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4: 91-100
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5: 101-168
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5: 101-168
Bias	9	Describe any efforts to address potential sources of bias	5: 101-168
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7: 169-184
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7: 169-184
		(*b*) Describe any methods used to examine subgroups and interactions	7: 169-184
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7: 169-184
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7: 189-198
		(b) Give reasons for non-participation at each stage	7: 189-198
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7: 189-202
		(b) Indicate number of participants with missing data for each variable of interest	7: 189-202
Outcome data	15*	Report numbers of outcome events or summary measures	8: 205-234
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	8: 205-234

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	8: 205-234
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8: 205-234
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	9: 238-246
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11: 284-303
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9:246-283
Generalisability	21	Discuss the generalisability (external validity) of the study results	9:246-283
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12: 320

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence, Risk Factors and Associated Ocular Diseases of Cerebral Stroke: The Population-based Beijing Eye Study

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Running title: Stroke and Eye Diseases

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Abstract

Objective: To assess the prevalence of cerebral stroke in the general population of Beijing and its association with systemic risk factors and ocular diseases.

Setting: The population-based Beijing Eye Study was conducted in a rural and urban region of Beijing.

Participants: With an eligibility criterion of an age of 50+ years and living in the study regions, 3468 subjects (78.8%) out of 4403 eligible individuals participated.

Primary and secondary outcome measures: The study participants underwent a detailed systemic and ophthalmological examination and an interview in which the occurrence of a previous stroke was assessed.

Results: A previous stroke was reported by 235 individuals (7.33%;95% confidence interval [CI]:6.43,8.24). The prevalence of previous stroke increased from 2.0% (95%CI:0.9,3.1) in the age group of 50 to <55 years to 21.9% (95%CI:16.4,27.4) in the age group of 80+ years. In multivariable regression analysis, a higher prevalence of previous stroke was correlated (Nagelkerke R^2:0.20) with the systemic parameters of older age (*P*<0.001;odds ratio [OR]:1.06;95%CI:1.04,1.08), male gender (*P*<0.001;OR:0.54;95%CI:0.40,0.74), lower quality of life score (*P*<0.001;OR:1.39;95%CI:1.25,1.55), higher prevalence of arterial hypertension (*P*<0.001;OR:2.86;95%CI:2.05,3.98), and cardiovascular disease (*P*<0.001;OR:1.8554;95%CI:1.34,2.56), and with the ocular parameter of higher prevalence of diabetic retinopathy (*P*<0.001;OR:4.41;95%CI:2.38,8.18) (or alternatively, with higher stage of diabetic retinopathy (*P*<0.001;OR:1.64;95%CI:1.26,2.14).

Conclusions: In this North Chinese population aged 50+ years, the prevalence of a previous stroke was 7.33% (95%CI:6.43,8.24). After adjusting for systemic risk factors of older age, male gender and higher prevalence of arterial hypertension and cardiovascular disease, a higher prevalence of a previous stroke was significantly correlated with a higher prevalence and stage of diabetic retinopathy. The prevalence of a previous stroke increased for each step of an increase in the stage of diabetic retinopathy with an odds ratio of 1.64 (95%CI:1.26,2.14), and it increased by the presence of diabetic retinopathy with an odds ratio of 4.41 (95%CI:2.38,8.18).

Article Summary

Strengths and limitations of this study:

- Limitation: Data on the prevalence of a previous stroke depended on self-reported information; patients who had died as a sequel of a previous stroke were not included into the study; the results of our study are therefore valid primarily only for stroke survivors.
- Limitation: Intracerebral hemorrhage was not differentiated from ischemic stroke.
- Limitation: Cross-sectional analysis
- Strength: Population-based study design
- Strength: Large number of parameters including ophthalmological variables assessed

Introduction

Cerebral stroke as one of the main contributors of the global burden of disease has caused 116 million or 4.8% of all DALYs (Disability-Adjusted Life Years) and 14.5 million or 1.8% of all YLDs (Years Lived with Disability) worldwide in the year 2013.[1-4] In particular China has witnessed a marked increase in the importance of stroke in the spectrum of diseases causing DALYS and years of life lost (YLLs). While in 1990, lower respiratory infections or preterm birth complications were the leading causes of YLLs in almost half of the provinces of China (16 out of 33), cerebrovascular disease were the leading cause in 27 of the 33 provinces in 2013.[5,6] Since the eye and brain share the same arterial blood supply through the inner carotid artery and since the retina and optic nerve as former outgrowth of the anterior end of the embryological neural groove are of neuro-ectodermal origin, a major cerebral disease such as stroke may be associated with ocular diseases, in particular disorders of the optic nerve and retina. Since comprehensive population-based studies on associations between stroke and ocular parameters have been scare so far and have not been conducted for the population of China, we investigated the prevalence of cerebral stroke and its potential associations with ocular diseases, after adjusting for systemic factors, in a population-based study performed in China.

Methods

The Beijing Eye Study 2011 is a population-based study which was conducted in a rural region and an urban area of Greater Beijing. The Medical Ethics Committee of the Beijing Tongren Hospital approved the study design, and all study participants gave an informed consent. The eligibility criteria for inclusion into the study were an age of 50+ years and living in the study regions. Out of 4403 eligible individuals, 3468 subjects (1963 (56.6%) women) participated (response rate: 78.8%). The mean age was 64.6 ± 9.8 years (median 64 years; range: 50–93 years). There were 1633 (47.1%) individuals (943 (57.7%) women) coming from the rural region, with the remaining 1835 (52.9%) study participants (1020 (55.6%) women) living in the urban region. The study design has been described in detail previously.[7,8]

All study participants underwent a structured interview by trained research technicians. The interview included more than 200 standardized questions on demographic parameters, socioeconomic background, diet and alcohol consumption, smoking habits, known major systemic diseases and current systemic medical therapies. Using the mini–mental state examination (MMSE) scale, we assessed the cognitive function. Fasting blood samples were collected for measurement of blood lipids, glucose, glycosylated hemoglobin HbA1c and serum creatinine. The blood pressure was measured with the participant sitting for at least 5 min. We also measured body height and weight and the circumference of the waist and hip.

Arterial hypertension was defined by a systolic blood pressure ≥160 mm Hg and/or a diastolic blood pressure ≥95 mm Hg, and/or self-reported current treatment for arterial hypertension with antihypertensive medication. Diabetes mellitus was characterized by a blood glucose concentration ≥7.0 mmol/L, an HbA1c value ≥6%, by a self-reported history of physician diagnosis of diabetes mellitus, or by a history of drug treatment for diabetes (insulin or oral hypoglycemic agents). Depressive symptoms were evaluated using a Chinese depression scale adapted from the Zung self-rated depression scale.[9] The prevalence of previous stroke was examined in the interview by standardized questions on whether a previous cerebral stroke had occurred with typical symptoms such as sudden-onset face weakness, arm drift, abnormal speech hemiplegia, or numbness for at least 24 hours, when such a stroke had occurred, and whether it had been treated.

The ophthalmological examination consisted of automatic refractometry (Auto Refractometer AR-610; Nidek Co., Ltd, Tokyo, Japan), measurement of presenting visual acuity, uncorrected visual acuity and best-corrected visual acuity, tonometry, slit lamp based biomicroscopy of the anterior and posterior segment of the eyes, and photography of the cornea and lens (Neitz CT-R camera; Neitz Instruments Co., Tokyo, Japan) and of the macula and optic disc (fundus camera; Type CR6-45MM; Canon Inc., Tokyo, Japan) in medical mydriasis. Using the photographs, we measured the dimensions of the optic disc, optic cup and parapapillary alpha, beta and gamma zones. The optic nerve head and macula were additionally examined by spectral-domain optical coherence tomography (OCT) using the enhanced depth imaging modality (Spectralis; Heidelberg Engineering, Heidelberg, Germany).

We determined the thickness of the peripapillary retinal nerve fiber layer, of the retina in the foveal region and of the subfoveal choroid. Applying optical low-coherence reflectometry (Lenstar 900 Optical Biometer; Haag-Streit, Koeniz, Switzerland), we measured ocular biometric parameters such as the anterior corneal curvature, central corneal thickness, anterior chamber depth, lens thickness and axial length. The degree of cataract was determined using the lens photographs. The degree of nuclear opacities was assessed in 6 grades using the grading system of the Age-Related Eye Disease Study.[10] In addition, retro-illuminated photographs of the lens were obtained (Neitz CT-R camera; Neitz Instruments Co., Tokyo, Japan), and the percentage of the areas with cortical and posterior subcapsular lens opacities was measured using a grid. The standard to diagnose a nuclear cataract was a nuclear cataract grade of 4 or more, the standard to diagnose a posterior subcapsular cataract was an amount of posterior subcapsular opacities of 0.01 or more, and the standard to diagnose a cortical cataract was an amount of cortical opacities of 0.05 or more. The degree of fundus tessellation defined as the visibility of the large choroidal vessels was assessed on the fundus photographs of the macula and of the optic disc as described in detail previously.[8] It was graded using a scale which ranged from “0” for “no tessellation” to ”3” for “marked tessellation”. Diabetic retinopathy was assessed on the fundus photographs using the Early Treatment of Diabetic Retinopathy Study (ETDRS) criteria. The minimum criterion for diagnosis of diabetic retinopathy was the presence of at least one microaneurysm. The diagnosis for each individual was based on the grading of the individual´s eye with the highest stage of diabetic retinopathy. We differentiated between the mild non-proliferative stage, the moderate non-proliferative stage, the advanced non-proliferative stage, and the proliferative stage of diabetic retinopathy. Glaucomatous optic neuropathy was defined using the criteria of the International Society of Geographic and Epidemiological Ophthalmology ISGEO.[11] Pseudoexfoliation was assessed by an experienced ophthalmologist during the slit lamp assisted biomicroscopy of the anterior segment after pupillary dilation. The diagnosis of pseudoexfoliation was definite, if the lens surface showed a central whitish coating with a diameter of little less than the normal pupillary diameter, or if the periphery of the lens surface showed a whitish coating which was anteriorly bordered by a darker ring-like region on the lens surface. The assessment of

pseudoexfoliation was performed only in phakic eyes. For the diagnosis of age-related macular degeneration, the International ARM (Age-related Maculopathy Epidemiological Study Group) Grading system was used. The subjective symptoms of dry eye were evaluated using a questionnaire composed of three questions: “Do your eyes ever feel dry?”; “Do you ever feel a gritty or sandy sensation in your eyes?”; and “Do your eyes ever have a burning sensation?” Possible answers to the questions were none (0), less than once a month (1), once or twice a week (2), at least once every day (3), all the time (4). The presence of dry eye symptoms was defined as having one or more symptoms at least once every day (3 and 4). A quantitative grading score of subjective dry eye symptoms was obtained by summarizing the answers to the different questions (0–12).[12]

The statistical analysis was performed using a commercially available statistical software package (SPSS for Windows, version 25.0, IBM-SPSS, Chicago, IL, USA). Date were shown as mean (standard deviation), frequency (%, 95% confidence interval [CI]), or median (interquartile range) where appropriate. The differences in parameters such as age and sex between participants with stroke and participants without stroke were assessed by the student t-test for unpaired samples or by the chi-square test. We tested associations between baseline characteristics and stroke with logistic regression adjusting for age and sex. Significant covariates from the step above (P <0.10) were included in multivariable models. We reduced the full model by successively removing non-significant covariates until all remaining predictors remained statistically significant (P <0.05). We calculated the odds ratio (OR). All P-values were two-sided and considered statistically significant, if the values were less than 0.05.

Patient and Public Involvement statement: Patients were not involved in this study

Results

Out of 3468 study participants, 3205 (92.4%) individuals participated in the interview with available information on previous stroke and underwent the systemic and ophthalmologic examination. The participating group as compared to the group of individuals without available information on previous stroke or without systemic and ocular examination was

significantly younger (64.4 ± 9.7 years (median: 63 years; range: 50 – 93 years) versus 67.1 ± 11.1 years; *P*<0.001) and came significantly more often from the urban region than from the rural area (rural / urban region of habitation: 1439 / 1766 versus 194 / 69; *P*<0.001), while the differences in gender (men / women: 1386 / 1819 versus 119 / 144; *P*=0.56), axial length (23.3 ± 1.1 mm versus 23.2 ± 1.9 mm; *P*=0.31) and refractive error (-0.22 ± 2.12 diopters versus -0.31 ± 2.17 diopters; *P*=0.59) were not statistically significant.

A previous stroke was reported by 235 individuals (235 / 3205 or 7.33% [95%CI: 6.43, 8.24]). Among the 235 patients, 192 individuals were on oral medication for the prophylaxis of a recurrence of the stroke. The stroke had taken place 7.5 ± 5.7 years ago (median: 7 years; range: 1 month to 26 years).

In the stroke group as compared with the non-stroke group (control group), age was significantly older (71.1 ± 9.2 years versus 63.9 ± 9.5 years; *P*<0.001) and had a higher proportion of men than women (men / women: 128 / 107 versus 1258 / 1712; *P*<0.001) (Fig. 1). The prevalence of a previous stroke increased from 2.0% (95%CI: 0.9, 3.1) in the age group of 50 to <55 years, to 6.9% (95%CI: 4.5, 9.2) in the age group of 65 to <70 years and to 21.9% (95%CI: 16.4, 27.4) in the age group of 80+ years (Table 1).

Since many systemic and ocular parameters were age-related, we performed in a next step of the statistical examination a binary regression analysis with the prevalence of stroke as the dependent parameter and other systemic and ocular parameters as single independent variables, with adjusting for age and gender (Table 2). In that analysis, a higher prevalence of stroke was associated with the systemic parameters of higher body mass index (*P*=0.03), lower frequency of alcohol consumption (*P*=0.001), lower number of days with vigorous physical activities (*P*=0.05) or moderately intensive physical activities (*P*=0.01) and higher number of hours spent with sitting per day (*P*=0.04), lower life quality score (*P*<0.001), higher depression score (*P*<0.001), higher blood concentration of glucose (*P*=0.01) and glycosylated hemoglobin HbA1c (*P*=0.008), and higher prevalence of diabetes mellitus (*P*<0.001) and arterial hypertension (*P*<0.001); and with the ocular parameters of thicker central corneal thickness (*P*=0.09), lower foveal thickness (*P*=0.04), higher incidence of localized retinal nerve fiber layer defects (*P*=0.06), dry eye feeling (*P*=0.08), and higher prevalence of keratoconus (≥49 diopters) (*P*=0.02), nuclear cataract (*P*=0.06) and presence and stage diabetic

retinopathy (*P*<0.001) (Table 2) (Fig. 2).

The multivariable analysis included the prevalence of previous stroke as dependent variable and as independent variables all those systemic parameters for which the *P*-value in the previous analysis was <0.10 (Table 2). We then dropped in step-by-step manner all independent parameters (such as the prevalence of diabetes mellitus) which either showed a collinearity with one of the other independent variables or which were no longer statistically significantly correlated with the prevalence of a previous stroke. In the final model, a higher prevalence of previous stroke was correlated (Nagelkerke R^2: 0.20) with older age (*P*<0.001), male gender (*P*<0.001), lower quality of life score (*P*<0.001), higher prevalence of arterial hypertension (*P*<0.001) and cardiovascular disease (*P*<0.001), and higher prevalence of diabetic retinopathy (*P*<0.001) (Table 3). If the parameter of prevalence of diabetic retinopathy was replaced by the diabetic retinopathy stage, the latter was associated with previous stroke (*P*<0.001; OR: 1.64; 95%CI: 1.26, 2.14).

Discussion

In our population-based study on a population aged 50+ years in Greater Beijing, the prevalence of a previous stroke was 7.33% (95%CI:6.43,8.24). After adjusting for the systemic risk factors of older age, male gender and a higher prevalence of arterial hypertension and cardiovascular disease, a higher prevalence of a previous stroke was significantly correlated with the presence and a higher stage of diabetic retinopathy (Fig. 2). The prevalence of a previous stroke increased for each increase in the stage of diabetic retinopathy (with altogether 4 stages) by an odds ratio of 1.64 (95%CI: 1.26, 2.14), and for the presence of diabetic retinopathy by an odds ratio of 4.41 (95%CI: 2.38, 8.18).

The findings obtained in our study agree with the results of previous investigations. In a review of studies conducted since 1990 in Chinese populations, Tsai and colleagues reported on an age-standardized annual first-ever stroke incidence of 205-584 per 100,000 in Chinese for the age group of 45-74 years.[13] Li and colleagues performing a population-based stroke surveillance on more than 14,000 residents in Tianjin, China from 1992 to 2012, reported on an increase in the age-standardized incidence for both intracerebral hemorrhage

(37.8 per 100,000 person-years in 1992-1998, 46.5 in 1999-2005, and 76.5 in 2006-2012) and for ischemic stroke (83.9 in 1992-1998, 135.3 in 1999-2005, and 238.0 in 2006-2012).[14] The age-standardized incidence of first-ever stroke increased annually by 4.9% for intracerebral hemorrhage and by 7.3% for ischemic stroke. In a similar study, Ning and associates found that the age-standardized incidence of first-ever stroke per 100 000 person-years increased significantly, from 122 in the years 1992 to 1999, to 216 in 2000 to 2007, and to 471.8 in 2008 to 2015.[15] The greatest increases were observed in adults aged 55 to 64 years. In the China National Stroke Screening Survey as reported by Guan and coworkers, the adjusted stroke prevalence in 2014 was 2.06% in adults aged 40 years and older.[16] The incidence of first-ever stroke in adults aged 40-74 years increased from 189/100,000 individuals in 2002 to 379/100,000 in 2013-an overall annual increase of 8.3%.

The systemic factors associated with the prevalence of a previous Stroke in our study population were similar to those reported in previous investigations: older age, male gender and a higher prevalence of arterial hypertension and cardiovascular disease. In the China National Stroke Screening Survey, the largest contributor as risk factor was arterial hypertension (population-attributable risk 53.2%), followed by family history, dyslipidemia, atrial fibrillation, diabetes, physical inactivity, smoking, and overweight/obesity.[16]

The interesting finding in our study is that, after adjusting for other systemic risk factors, the presence of diabetic of diabetic retinopathy increased the likelihood of a previous stroke by an odds ratio of 4.41, and in a parallel manner, that an increase by one step in the stage of diabetic retinopathy increased the probability of a previous stroke by an odds ratio of 1.64. In previous studies by Cheung et al. and by Petitti and colleagues a similar association was described..[17,18] In a population-based, prospective cohort study of 1617 middle-aged persons with diabetes, Cheung found that after a mean follow-up of 7.8 years diabetic retinopathy was associated with an increased risk of ischemic stroke (hazard rate ratio, 2.34; 95% CI, 1.13 to 4.86), after adjusting for systemic parameters such as age, gender, race, arterial blood pressure, duration and therapy of diabetes, blood lipid concentrations and levels and cigarette smoking status.[17] In an earlier study, Petitti and associates found in a nested case-control study, that the estimated relative risk of stroke in diabetic subjects with retinopathy was 4.0 (95%CI: 1.0 , 14.5) after adjustment for systemic risk factors.[18] The reason for this

association may be that diabetic retinopathy as a microangiopathy indicates a wide-spread vascular disorder.

When discussing the results of our study, its limitations have to be taken into account. First, the data on the prevalence of a previous self-reported stroke depended on the information provided by the study participants in the face-to-face interviews. Since stroke is a dramatic event, it is unlikely to be under-reported. Transient ischemic attacks might occur unnoticed by the individuals so that transient ischemic attacks might be under-reported in an interview of previous cerebral strokes. Our study was based however primarily on previous cerebral strokes which were defined as an occurrence of typical neurological symptoms for at least 24 hours. It may make it unlikely that unnoticed previous transient ischemic attacks might have markedly influenced the results of our study. Second, patients who had died as a sequel of a previous stroke were not included into the study. The results of our study are therefore valid primarily only for stroke survivors. Third, due to regional differences in China, findings obtained in our study may not completely be transferable to South China or pother world regions.[19] Fourth, we did not differentiate between intracerebral hemorrhage and ischemic stroke.[20] Fifth, we did not assess the role of atrial fibrillation as risk factor for stroke in our study. Fifth, the study population with an age of 50+ years had experienced major societal changes and economic developments in China during their lifetime. This elderly generation may differ from the young generations in China and from populations in other countries. Sixth, our investigation was a cross-sectional observational study, so that a reverse causality may have existed in the sense that diabetic retinopathy might have been the sequel of stroke.

In conclusion, in this North Chinese population aged 50+ years, the prevalence of a previous stroke was 7.33% (95%CI:6.43,8.24). The presence and stage of diabetic retinopathy were ocular risk factors for a higher prevalence of a previous stroke, after adjusting for the systemic risk factors of older age, male gender and a higher prevalence of diabetes mellitus and cardiovascular disease. The prevalence of a previous stroke increased for each step of an increase in the stage of diabetic retinopathy with an odds ratio of 1.64 (95%CI:1.26,2.14), and it increased by the presence of diabetic retinopathy with an odds ratio

of 4.41 (95%CI:2.38,8.18). Individuals with diabetic retinopathy appear to be a group at particularly high risk of cerebral stroke.

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Table 1

Prevalence (Mean and 95% Confidence Interval) of previous stroke in the Beijing Eye Study

Age Group (Years)	Men		Women		Total	
	n	Prevalence	n	Prevalence	n	Prevalence
50 to <55	250	2.5% (0.5, 4.3)	363	1.7% (0.3, 3.0)	613	2.0% (0.9, 3.1)
55 to <60	237	3.0% (0.8, 5.1)	366	3.0% (1.3, 4.8)	603	3.0% (1.6, 4.4)
60 to <65	196	7.7% (3.9, 11.4)	282	6.7% (3.8, 9.7)	478	7.1% (4.8, 9.4)
65 to <70	168	8.3% (4.1, 12.6)	270	5.9% (3.1, 8.8)	438	6.9% (4.5, 9.2)
70 to <75	247	10.9% (7.0, 14.9)	256	8.6% (5.1, 12.1)	503	9.7% (7.1, 12.3)
75 to <80	169	16.6 (10.9, 22.2)	182	8.8% (4.6, 12.9)	351	12.5% (9.1, 16.0)
80+	119	18.1, 34.1)	100	17.0% (9.5, 24.5)	219	21.9% (16.4, 27.4)

Table 2

Associations between the prevalence of cerebral stroke and systemic and ocular parameters after adjusting for age and gender in the Beijing Eye Study 2011

Parameter	*P*-Value	Odds Ratio	95% Confidence Interval
Systemic Parameters			
Rural / Urban Region of Habitation	0.11	1.29	0.95, 1.75
Body Mass Index (kg/m^2)	0.03	1.04	1.001, 1.08
Level of Education (1-5)	0.64	1.04	0.92, 1.18
Self-Reported Income	0.73	0.99	0.93, 1.05
Cognitive Score	0.77	1.00	0.96, 1.03
Alcohol Consumption Frequency	0.001	0.85	0.77, 0.94
Smoking Never / Former/ Current	0.19	0.87	0.71, 1.07
Smoking Never / Ever	0.98	1.00	0.72, 1.38
Smoking Package Years	0.38	1.00	1.00, 1.01
Physical Activity			
“How Many Days Do you Walk?”	0.51	0.98	0.92, 1.04
“How Many Days Do You Do Vigorously Intensive Sport or Activities?”	0.05	0.81	0.66, 1.00
“How Many Days Do You Do Moderately Intensive Sport or Activities?”	0.01	0.94	0.89, 0.99
“How Many Hours Do You Sit Per Day?”	0.04	1.06	1.004, 1.12
Quality of Life			
Summed Score	<0.001	1.44	1.31, 1.59

Mobility: I have no / some problems in walking about / I am confined to bed	<0.001	2.79	2.01, 3.86
Self-Care: I have I have no / some problems in washing or dressing myself / I am unable to wash or dress myself	<0.001	3.33	2.33, 4.75
Usual Activities (e.g. Work, study, housework, family or leisure activities): I am able to wash or dress myself / I have some problems with performing my usual activities / I am unable to perform my usual activities	<0.001	3.27	2.36, 4.53
Pain/Discomfort:	0.001	1.62	1.22, 2.14
Anxiety/Depression: I am not / moderately / extremely anxious or depressed	<0.001	2.07	1.45, 2.95
Depression Score	<0.001	1.06	1.04, 1.08
Blood Concentration of:			
Glucose (mmol/L)	0.01	1.11	1.02, 1.21
Glycosylated hemoglobin HbA1c	0.008	1.18	1.04, 1.33
High-Density Lipoproteins (mmol/L)	0.11	0.70	0.45, 1.09
Low-Density Lipoproteins (mmol/L)	0.28	0.90	0.74, 1.09
Triglycerides (mmol/L)	0.95	1.01	0.86, 1.17
Cholesterol (mmol/L)	0.18	0.88	0.74, 1.06
C-reactive Protein	0.47	1.01	0.98, 1.04
Diabetes Mellitus, Prevalence	<0.001	1.86	1.32, 2.61
Diabetes Mellitus, Duration (Years)	0.08	1.02	1.00, 1.04
Systolic Blood Pressure (mmHg)	0.14	1.01	1.00,1.02
Diastolic Blood Pressure (mmHg)	0.82	1.00	0.99, 1.01

Mean Blood Pressure (mmHg)	0.40	1.00	0.99, 1.01
Arterial Hypertension	<0.001	2.42	1.76, 3.34
Estimated Cerebrospinal Fluid Pressure (mm Hg)	0.17	1.03	0.99, 1.09
Creatinine (mmol/L)	0.67	1.00	0.99, 1.02
Estimated Glomerular Filtration Rate (GFR) (mL/min / 1·73 m²) (MDRD Formula)	0.79	1.00	0.99, 1.01
Estimated Glomerular Filtration Rate (mL/min / 1·73 m²) (CKDE Formula)	0.79	1.00	0.98, 1.01
Ocular Parameters			
Refractive Error (Diopters)	0.47	0.98	0.92, 1.04
Axial Length (mm)	0.70	0.98	0.86, 1.11
Anterior Corneal Curvature Radius (mm)	0.16	0.66	0.37, 1.18
Central Corneal Thickness (µm)	0.09	1.004	0.999, 1.008
Anterior Chamber Depth (mm)	0.92	1.01	0.79, 1.29
Lens Thickness (mm)	0.14	1.41	0.89, 2.22
Intraocular Pressure mmHg)	0.66	1.01	0.96, 1.06
Retinal Nerve Fiber Layer Thickness (µm)	0.62	1.00	0.99, 1.01
Localized Defects of the Retinal Nerve Fiber Layer, Prevalence	0.42	1.18	0.79, 1.77
Localized Defects of the Retinal Nerve Fiber Layer, 10-Year Incidence	0.06	1.83	0.98, 3.42
Subfoveal Choroidal Thickness (µm)	0.83	1.00	1.00, 1.00
Fundus Tessellation	0.66	1.02	0.92, 1.13
Macular Retinal Thickness (µm)	0.04	0.994	0.989, 1.000
Optic Disc Size (mm^2)	0.69	1.09	0.71, 1.70

Neuroretinal Rim Area (mm^2)	0.52	1.15	0.75, 1.77
Dry Eye, Yes or No	0.80	1.04	0.79, 1.36
Dry Eye, Number of Days	0.08	1.04	0.995, 1.10
Keratoconus (Anterior Corneal Curvature refractive Power ≥48 Diopters)	0.27	2.04	0.58, 7.18
Keratoconus (Anterior Corneal Curvature refractive Power ≥49 Diopters)	0.02	8.00	1.31, 48.9
Pseudoexfoliation Syndrome	0.49	0.82	0.47, 1.43
Nuclear Cataract	0.06	0.72	0.51, 1.02
Cortical Cataract	0.87	0.97	0.66, 1.43
Subcapsular Posterior Cataract	0.34	1.29	0.77, 2.16
Glaucoma, Prevalence, Total	0.61	0.87	0.52, 1.47
Open-Angle Glaucoma	0.26	0.63	0.28, 1.40
Primary Angle-Closure Glaucoma	0.36	0.57	0.17, 1.89
Age-Related Macular Degeneration, Prevalence, Total	0.60	0.92	0.68, 1.25
Age-Related Macular Degeneration, Early Stage	0.29	0.75	0.44, 1.28
Age-Related Macular Degeneration, Intermediate Stage	0.75	0.95	0.67, 1.34
Age-Related Macular Degeneration, Late Stage	0.11	2.26	0.84, 6.06
Diabetic Retinopathy, Prevalence	<0.001	1.63	1.27, 2.08
Diabetic Retinopathy, Score	<0.001	4.75	2.67, 8.46
Retinal Vein Occlusion, Total	0.18	1.55	0.82, 2.93
Branch Retinal Vein Occlusion	0.65	1.25	0.48, 3.29
Myopic Retinopathy	0.77	1.20	0.36, 4.03

Table 3

Associations (multivariable analysis) between the prevalence of cerebral stroke and systemic and ocular parameters in the Beijing Eye Study 2011

Parameter	*P*-Value	Odds Ratio (OR)	95% Confidence Interval of OR
Age (Years)	<0.001	1.06	1.04, 1.08
Gender (Men / Women)	<0.001	0.54	0.40, 0.74
Inverse Quality of Life Score	<0.001	1.39	1.25, 1.55
Prevalence of Arterial Hypertension	<0.001	2.86	2.05, 3.98
Cardiovascular Disease	<0.001	1.85	1.34, 2.56
Prevalence of Diabetic Retinopathy	<0.001	4.41	2.38, 8.18
(Alternatively: Stage of Diabetic Retinopathy)	*P*<0.001	1.64	1.26, 2.14

Fig. 1

Graph showing the distribution of the prevalence of a previous cerebral stroke stratified by age and gender in the Beijing Eye Study

Fig. 2

Graph showing the distribution of the prevalence of a previous cerebral stroke stratified by age and presence of diabetic retinopathy in the Beijing Eye Study

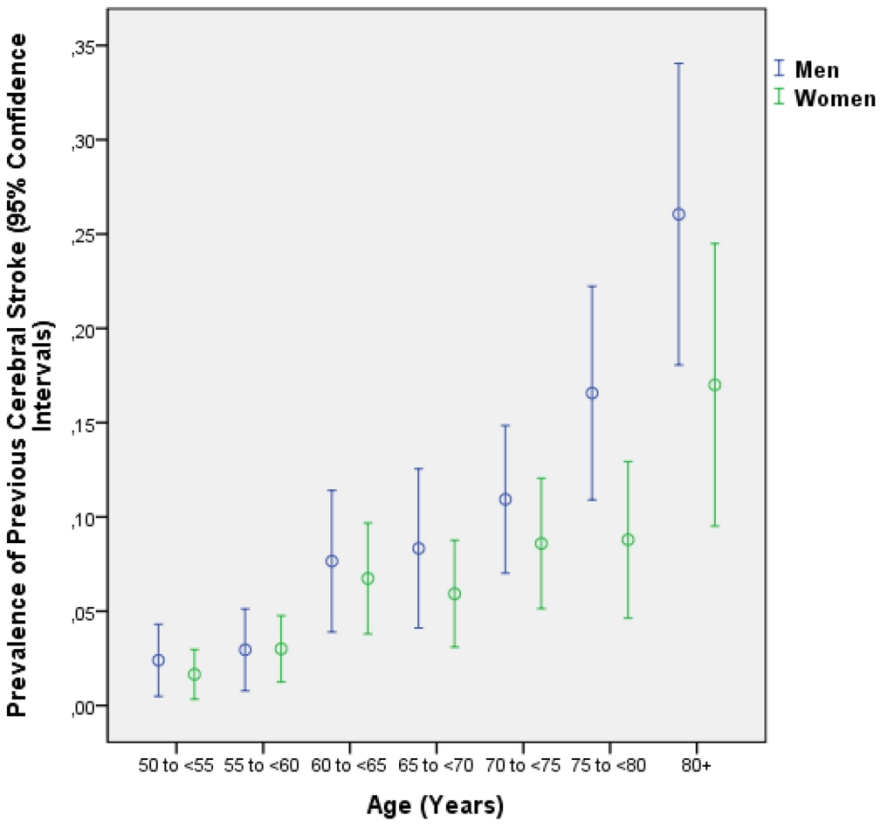

Fig. 1
Graph showing the distribution of the prevalence of a previous cerebral stroke stratified by age and gender in the Beijing Eye Study

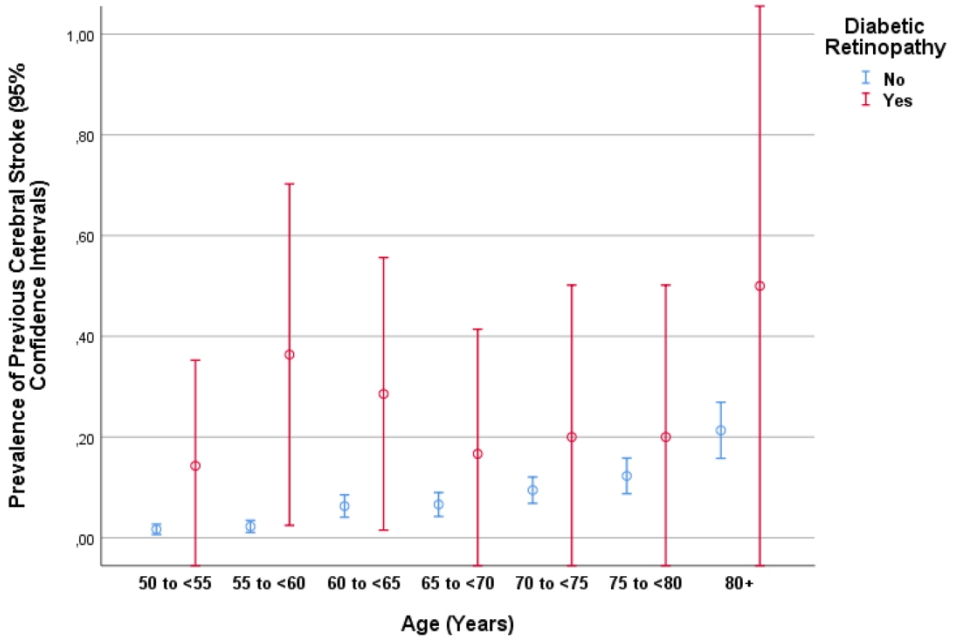

Fig. 2
Graph showing the distribution of the prevalence of a previous cerebral stroke stratified by age and presence of diabetic retinopathy in the Beijing Eye Study

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page: Line
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1: 4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2: 52-58
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4: 72-86
Objectives	3	State specific objectives, including any prespecified hypotheses	4: 72-86
Methods			
Study design	4	Present key elements of study design early in the paper	4: 91-100
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4: 91-100
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4: 91-100
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5: 101-168
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5: 101-168
Bias	9	Describe any efforts to address potential sources of bias	5: 101-168
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7: 169-184
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7: 169-184
		(*b*) Describe any methods used to examine subgroups and interactions	7: 169-184
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7: 169-184
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7: 189-198
		(b) Give reasons for non-participation at each stage	7: 189-198
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7: 189-202
		(b) Indicate number of participants with missing data for each variable of interest	7: 189-202
Outcome data	15*	Report numbers of outcome events or summary measures	8: 205-234
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	8: 205-234

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	8: 205-234
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8: 205-234
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	9: 238-246
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11: 284-303
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9:246-283
Generalisability	21	Discuss the generalisability (external validity) of the study results	9:246-283
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12: 320

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.