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

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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).

61

62 **Article Summary**

63 Strengths and limitations of this study:

64 - In this North Chinese population aged 50+ years, the prevalence of a previous stroke was  
65 7.33% (95%CI:6.43,8.24).

66 - Besides known systemic risk factors of older age, male gender and a higher prevalence of  
67 diabetes mellitus and arterial hypertension, the presence and stage of diabetic retinopathy  
68 were additional risk factors.

69 - The prevalence of previous stroke increased for each increase in the stage of diabetic  
70 retinopathy by a factor of 1.67 (95%CI:1.20,1.33), and for the presence of diabetic retinopathy  
71 by a factor of 3.97 (95%CI:1.87,8.43).

72 - Limitations of our study were that the data on the prevalence of a previous self-reported  
73 stroke depended on the information provided by the study participants in the face-to-face  
74 interviews, and that patients who had died as a sequel of a previous stroke were not included  
75 into the study. The results of our study are therefore valid primarily only for stroke survivors.

76 - Another limitation was intracerebral hemorrhage was not differentiated from ischemic stroke.

77

78

## 79 Introduction

80 Cerebral stroke as one of the main contributors of the global burden of disease has caused  
81 116 million or 4.8% of all DALYs (Disability-Adjusted Life Years) and 14.5 million or 1.8% of all  
82 YLDs (Years Lived with Disability) worldwide in the year 2013.<sup>1-4</sup> In particular China has  
83 witnessed a marked increase in the importance of stroke in the spectrum of diseases causing  
84 YLLs. While in 1990, lower respiratory infections or preterm birth complications were the  
85 leading causes of YLLs in almost half of the provinces of China (16 out of 33), cerebrovascular  
86 disease were the leading cause in 27 of the 33 provinces in 2013.<sup>5,6</sup> Since the eye and the  
87 brain share the same arterial blood supply through the inner carotid artery and since the retina  
88 and optic nerve as former outgrowth of the anterior end of the embryological neural groove are  
89 of neuro-ectodermal origin, a major cerebral disease such as a stroke may be associated with  
90 ocular diseases, in particular disorders of the optic nerve and retina. Since comprehensive  
91 population-based studies on associations between stroke and eye have been scarce so far and  
92 have not been conducted for the population of China, we investigated the prevalence of  
93 cerebral stroke and its relationships between systemic factors and ocular diseases in a  
94 Chinese population.

## 97 Methods

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

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

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2  
3 109 The interview included more than 200 standardized questions on demographic parameters,  
4 110 the socioeconomic background, the diet and alcohol consumption, smoking habits, known  
5 111 major systemic diseases and current systemic medical therapies. Using the mini-mental  
6 112 state examination (MMSE) scale, we assessed the cognitive function. Fasting blood samples  
7 113 were collected for measurement of blood lipids, glucose, glycosylated hemoglobin HbA1c and  
8 114 serum creatinine. The blood pressure was measured with the participant sitting for at least 5  
9 115 min. We also measured body height and weight and the circumference of the waist and hip.

16 116 Arterial hypertension was defined as a systolic blood pressure  $\geq 160$  mm Hg and/or a  
17 117 diastolic blood pressure  $\geq 95$  mm Hg, and/or self-reported current treatment for arterial  
18 118 hypertension with antihypertensive medication. Diabetes mellitus was characterized by a  
19 119 blood glucose concentration  $\geq 7.0$  mmol/L, an HbA1c value  $\geq 6\%$ , by a self-reported history of  
20 120 physician diagnosis of diabetes mellitus, or by a history of drug treatment for diabetes (insulin  
21 121 or oral hypoglycemic agents). Depressive symptoms were evaluated using a Chinese  
22 122 depression scale adapted from the Zung self-rated depression scale.<sup>9</sup> The prevalence of  
23 123 previous stroke was examined in the interview by standardized questions on whether a  
24 124 previous cerebral stroke had occurred with typical symptoms such as sudden-onset face  
25 125 weakness, arm drift, abnormal speech, hemiplegia, or numbness for at least 24 hours, when  
26 126 such a stroke had occurred and whether it had been treated.

36 127 The ophthalmological examination consisted of automatic refractometry (Auto  
37 128 Refractometer AR-610; Nidek Co., Ltd, Tokyo, Japan), measurement of presenting visual  
38 129 acuity, uncorrected visual acuity and best-corrected visual acuity, tonometry, slit lamp based  
39 130 biomicroscopy of the anterior and posterior segment of the eyes, and photography of the  
40 131 cornea and lens (Neitz CT-R camera; Neitz Instruments Co., Tokyo, Japan) and of the macula  
41 132 and optic disc (fundus camera; Type CR6-45MM; Canon Inc., Tokyo, Japan) in medical  
42 133 mydriasis. Using the photographs, we measured the dimensions of the optic disc, optic cup  
43 134 and parapapillary alpha, beta and gamma zones. The optic nerve head and macula were  
44 135 additionally examined by spectral-domain optical coherence tomography (OCT) using the  
45 136 enhanced depth imaging modality (Spectralis; Heidelberg Engineering, Heidelberg, Germany).  
46 137 We determined the thickness of the peripapillary retinal nerve fiber layer, of the retina in the  
47 138 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.<sup>10</sup> 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.<sup>8</sup> 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.<sup>11</sup> 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



1  
2  
3 169 symptoms of dry eye were evaluated using a questionnaire composed of three questions: “Do  
4  
5 170 your eyes ever feel dry?”; “Do you ever feel a gritty or sandy sensation in your eyes?”; and “Do  
6  
7 171 your eyes ever have a burning sensation?” Possible answers to the questions were none (0),  
8  
9 172 less than once a month (1), once or twice a week (2), at least once every day (3), all the time  
10  
11 173 (4). The presence of dry eye symptoms was defined as having one or more symptoms at least  
12  
13 174 once every day (3 and 4). A quantitative grading score of subjective dry eye symptoms was  
14  
15 175 obtained by summarizing the answers to the different questions (0–12).<sup>12</sup>

16 176 Statistical analysis was performed using a commercially available statistical software  
17  
18 177 package (SPSS for Windows, version 22.0, IBM-SPSS, Chicago, IL, USA). As a first step, we  
19  
20 178 examined the mean value of the main outcome parameter, i.e. the prevalence of stroke  
21  
22 179 (presented as mean and 95% confidence intervals (CI)) and assessed differences between the  
23  
24 180 stroke group and the non-stroke group in age and gender. As second step, we performed a  
25  
26 181 binary regression analysis with the prevalence of stroke as dependent parameter after  
27  
28 182 adjusting for age and gender. As a third step, we conducted an extended multivariate binary  
29  
30 183 analysis which included as independent parameters all those systemic variables which were  
31  
32 184 correlated ( $P<0.10$ ) with the stroke prevalence in the previous analysis. We then dropped all  
33  
34 185 those parameters which were no longer significantly associated with the stroke prevalence.  
35  
36 186 We first started with the systemic independent parameters, such as age and blood pressure.  
37  
38 187 We calculated the odds ratio (OR) and its 95% CIs. All  $P$ -values were two-sided and  
39  
40 188 considered statistically significant, if the values were less than 0.05.

41 189 Patient and Public Involvement statement: Patients were not involved in this study

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## 44 192 **Results**

45 193 Out of 3468 study participants, 3205 (92.4%) individuals participated in the interview with  
46  
47 194 available information on previous stroke and underwent the systemic and ophthalmologic  
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49 195 examination. The participating group as compared to the group of individuals without  
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51 196 available information on previous stroke or without systemic and ocular examination was  
52  
53 197 significantly younger ( $64.4 \pm 9.7$  years (median: 63 years; range: 50 – 93 years) versus  $67.1 \pm$   
54  
55 198  $11.1$  years;  $P<0.001$ ) and came significantly more often from the urban region than from the

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2  
3 rural area (rural / urban region of habitation: 1439 / 1766 versus 194 / 69;  $P<0.001$ ), while the  
4  
5 differences in gender (men / women: 1386 / 1819 versus 119 / 144;  $P=0.56$ ), axial length ( $23.3$   
6  
7  $\pm 1.1$  mm versus  $23.2 \pm 1.9$  mm;  $P=0.31$ ) and refractive error ( $-0.22 \pm 2.12$  diopters versus  
8  
9  $-0.31 \pm 2.17$  diopters;  $P=0.59$ ) were not statistically significant.

10  
11 A previous stroke was reported by 235 individuals (235 / 3205 or 7.33% [95%CI: 6.43,  
12  
13 8.24]). Among the 235 patients, 192 individuals were on oral medication for the prophylaxis  
14  
15 of a recurrence of the stroke. The stroke had taken place  $7.5 \pm 5.7$  years ago (median: 7  
16  
17 years; range: 1 month to 26 years).

18  
19 In the stroke group as compared with the non-stroke group (control group), age was  
20  
21 significantly older ( $71.1 \pm 9.2$  years versus  $63.9 \pm 9.5$  years;  $P<0.001$ ) and had a higher  
22  
23 proportion of men than women (men / women: 128 / 107 versus 1258 / 1712;  $P<0.001$ ) (Fig. 1).  
24  
25 The prevalence of a previous stroke increased from 2.0% (95%CI: 0.9, 3.1) in the age group of  
26  
27 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%  
28  
29 (95%CI: 16.4, 27.4) in the age group of 80+ years (Table 1).

30  
31 Since many systemic and ocular parameters were age-related, we performed in a next  
32  
33 step of the statistical examination a binary regression analysis with the prevalence of stroke as  
34  
35 the dependent parameter and other systemic and ocular parameters as single independent  
36  
37 variables, with adjusting for age and gender (Table 2). In that analysis, a higher prevalence  
38  
39 of stroke was associated with the systemic parameters of higher body mass index ( $P=0.03$ ),  
40  
41 lower frequency of alcohol consumption ( $P=0.001$ ), lower number of days with vigorous  
42  
43 physical activities ( $P=0.05$ ) or moderately intensive physical activities ( $P=0.01$ ) and higher  
44  
45 number of hours spent with sitting per day ( $P=0.04$ ), lower life quality score ( $P<0.001$ ), higher  
46  
47 depression score ( $P<0.001$ ), higher blood concentration of glucose ( $P=0.01$ ) and glycosylated  
48  
49 hemoglobin HbA1c ( $P=0.008$ ), and higher prevalence of diabetes mellitus ( $P<0.001$ ) and  
50  
51 arterial hypertension ( $P<0.001$ ); and with the ocular parameters of thicker central corneal  
52  
53 thickness ( $P=0.09$ ), lower foveal thickness ( $P=0.04$ ), higher incidence of localized retinal nerve  
54  
55 fiber layer defects ( $P=0.06$ ), dry eye feeling ( $P=0.08$ ), and higher prevalence of keratoconus  
56  
57 ( $\geq 49$  diopters) ( $P=0.02$ ), nuclear cataract ( $P=0.06$ ) and diabetic retinopathy ( $P<0.001$ ) (Table  
58  
59 2).

228 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

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

268 The findings obtained in our study agree with the results of previous investigations.  
269 In a review of studies conducted since 1990 in Chinese populations, Tsai and colleagues  
270 reported on an age-standardized annual first-ever stroke incidence of 205-584 per 100,000 in  
271 Chinese for the age group of 45-74 years.<sup>13</sup> Li and colleagues performing a population-based  
272 stroke surveillance on more than 14,000 residents in Tianjin, China from 1992 to 2012,  
273 reported on an increase in the age-standardized incidence for both intracerebral hemorrhage  
274 (37.8 per 100,000 person-years in 1992-1998, 46.5 in 1999-2005, and 76.5 in 2006-2012) and  
275 for ischemic stroke (83.9 in 1992-1998, 135.3 in 1999-2005, and 238.0 in 2006-2012).<sup>14</sup> The  
276 age-standardized incidence of first-ever stroke increased annually by 4.9% for intracerebral  
277 hemorrhage and by 7.3% for ischemic stroke. In a similar study, Ning and associates found  
278 that the age-standardized incidence of first-ever stroke per 100 000 person-years increased  
279 significantly, from 122 in the years 1992 to 1999, to 216 in 2000 to 2007, and to 471.8 in 2008  
280 to 2015.<sup>15</sup> The greatest increases were observed in adults aged 55 to 64 years. In the  
281 China National Stroke Screening Survey as reported by Guan and coworkers, the adjusted  
282 stroke prevalence in 2014 was 2.06% in adults aged 40 years and older.<sup>16</sup> The incidence of  
283 first-ever stroke in adults aged 40-74 years increased from 189/100,000 individuals in 2002 to  
284 379/100,000 in 2013-an overall annual increase of 8.3%.

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

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3 289 (population-attributable risk 53.2%), followed by family history, dyslipidemia, atrial fibrillation,  
4  
5 290 diabetes, physical inactivity, smoking, and overweight/obesity.<sup>16</sup> As in our study, the review  
6  
7 291 by Kyu and colleagues revealed that individuals with a higher level of physical activity had a  
8  
9 292 lower risk of ischemic stroke.<sup>17</sup> Interestingly, self-reported alcohol consumption was not  
10  
11 293 significantly associated with the prevalence of previous stroke in our study population.

12  
13 294 The interesting finding in our study is that, after adjusting for other systemic risk factors,  
14  
15 295 the presence of diabetic of diabetic retinopathy increased the likelihood of a previous stroke by  
16  
17 296 a factor of 3.97, and in a parallel manner, that an increase by one step in the stage of diabetic  
18  
19 297 retinopathy increased the probability of a previous stroke by a factor of 1.67. In previous  
20  
21 298 studies by Cheung et al. and by Petitti and colleagues a similar association was described..<sup>18,19</sup>  
22  
23 299 In a population-based, prospective cohort study of 1617 middle-aged persons with diabetes,  
24  
25 300 Cheung found that after a mean follow-up of 7.8 years diabetic retinopathy was associated  
26  
27 301 with an increased risk of ischemic stroke (hazard rate ratio, 2.34; 95% CI, 1.13 to 4.86), after  
28  
29 302 adjusting for systemic parameters such as age, gender, race, arterial blood pressure, duration  
30  
31 303 and therapy of diabetes, blood lipid concentrations and levels and cigarette smoking status.<sup>18</sup>  
32  
33 304 In an earlier study, Petitti and associates found in a nested case-control study, that the  
34  
35 305 estimated relative risk of stroke in diabetic subjects with retinopathy was 4.0 (95%CI: 1.0 , 14.5)  
36  
37 306 after adjustment for systemic risk factors.<sup>19</sup> The reason for this association may be that  
38  
39 307 diabetic retinopathy as a microangiopathy indicates a wide-spread vascular disorder.

40  
41 308 When discussing the results of our study, its limitations have to be taken into account.  
42  
43 309 First, the data on the prevalence of a previous self-reported stroke depended on the  
44  
45 310 information provided by the study participants in the face-to-face interviews. Second,  
46  
47 311 patients who had died as a sequel of a previous stroke were not included into the study. The  
48  
49 312 results of our study are therefore valid primarily only for stroke survivors. Third, due to  
50  
51 313 regional differences in China, findings obtained in our study may not completely be  
52  
53 314 transferable to South China or pother world regions.<sup>20</sup> Fourth, we did not differentiate  
54  
55 315 between intracerebral hemorrhage and ischemic stroke.<sup>21</sup> Fifth, we did not assess the role of  
56  
57 316 atrial fibrillation as risk factor for stroke in our study. Fifth, the study population with an age of  
58  
59 317 50+ years had experienced major societal changes and economic developments in China

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

320 In conclusion, in this North Chinese population aged 50+ years, the prevalence of a  
321 previous stroke was 7.33% (95%CI:6.43,8.24). Besides known systemic risk factors of older  
322 age, male gender and a higher prevalence of diabetes mellitus and arterial hypertension, the  
323 presence and stage of diabetic retinopathy were additional risk factors. The prevalence of  
324 previous stroke increased for each increase in the stage of diabetic retinopathy by a factor of  
325 1.67 (95%CI:1.20,1.33), and for the presence of diabetic retinopathy by a factor of 3.97  
326 (95%CI:1.87,8.43). Diabetic subjects with retinopathy appear to be a group at particularly  
327 high risk of ischemic stroke. Development of preventive interventions may focus on this group.

328

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330 Jost B. Jonas; Statistical analysis: Ya Xing Wang, Jost B. Jonas; Writing of the manuscript:  
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395 Table 1

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

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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)

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399

400 Table 2  
 401 Associations between the prevalence of cerebral stroke and systemic and ocular parameters  
 402 after adjusting for age and gender in the Beijing Eye Study 2011  
 403

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 <sup>2</sup> )	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

## 18 Stroke and Eye Diseases

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 m <sup>2</sup> ) (MDRD Formula)	0.79	1.00	0.99, 1.01
Estimated Glomerular Filtration Rate (mL/min / 1.73 m <sup>2</sup> ) (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 <sup>2</sup> )	0.69	1.09	0.71, 1.70
Neuroretinal Rim Area (mm <sup>2</sup> )	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 $\geq$ 48 Diopters)	0.27	2.04	0.58, 7.18
Keratoconus (Anterior Corneal Curvature refractive Power $\geq$ 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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406 Table 3  
 407 Associations (multivariate analysis) between the prevalence of cerebral stroke and systemic  
 408 and ocular parameters in the Beijing Eye Study 2011

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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, 3.46
Prevalence of Nuclear Cataract	0.01	0.58	0.38, 0.89

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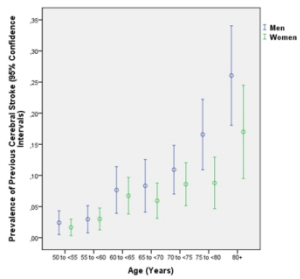


Fig. 1: Graph showing the distribution of the prevalence of a previous stroke stratified by age and gender in the Beijing Eye Study

323x199mm (120 x 120 DPI)



# BMJ Open

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

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10 4 **Prevalence, Risk Factors and Associated Ocular Diseases of Cerebral Stroke: The**  
11 5 **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).

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4 61 **Article Summary**

5 62 Strengths and limitations of this study:

- 6 63 - Limitation: Data on the prevalence of a previous stroke depended on self-reported  
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8 64 information; patients who had died as a sequel of a previous stroke were not included into the  
9  
10 65 study; the results of our study are therefore valid primarily only for stroke survivors.  
11  
12 66 - Limitation: Intracerebral hemorrhage was not differentiated from ischemic stroke.  
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14 67 - Limitation: Cross-sectional analysis  
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16 68 - Strength: Population-based study design  
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18 69 - Strength: Large number of parameters including ophthalmological variables assessed  
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## 71 Introduction

72 Cerebral stroke as one of the main contributors of the global burden of disease has caused  
73 116 million or 4.8% of all DALYs (Disability-Adjusted Life Years) and 14.5 million or 1.8% of all  
74 YLDs (Years Lived with Disability) worldwide in the year 2013.<sup>1-4</sup> In particular China has  
75 witnessed a marked increase in the importance of stroke in the spectrum of diseases causing  
76 DALYS and years of life lost (YLLs). While in 1990, lower respiratory infections or preterm  
77 birth complications were the leading causes of YLLs in almost half of the provinces of China  
78 (16 out of 33), cerebrovascular disease were the leading cause in 27 of the 33 provinces in  
79 2013.<sup>5,6</sup> Since the eye and brain share the same arterial blood supply through the inner  
80 carotid artery and since the retina and optic nerve as former outgrowth of the anterior end of  
81 the embryological neural groove are of neuro-ectodermal origin, a major cerebral disease such  
82 as stroke may be associated with ocular diseases, in particular disorders of the optic nerve and  
83 retina. Since comprehensive population-based studies on associations between stroke and  
84 ocular parameters have been scarce so far and have not been conducted for the population of  
85 China, we investigated the prevalence of cerebral stroke and its potential associations with  
86 ocular diseases, after adjusting for systemic factors, in a population-based study performed in  
87 China.

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## 90 Methods

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

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

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

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

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

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

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

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

188

189

190 **Results**



191 Out of 3468 study participants, 3205 (92.4%) individuals participated in the interview with  
192 available information on previous stroke and underwent the systemic and ophthalmologic  
193 examination. The participating group as compared to the group of individuals without  
194 available information on previous stroke or without systemic and ocular examination was  
195 significantly younger ( $64.4 \pm 9.7$  years (median: 63 years; range: 50 – 93 years) versus  $67.1 \pm$   
196  $11.1$  years;  $P < 0.001$ ) and came significantly more often from the urban region than from the  
197 rural area (rural / urban region of habitation: 1439 / 1766 versus 194 / 69;  $P < 0.001$ ), while the  
198 differences in gender (men / women: 1386 / 1819 versus 119 / 144;  $P = 0.56$ ), axial length ( $23.3$   
199  $\pm 1.1$  mm versus  $23.2 \pm 1.9$  mm;  $P = 0.31$ ) and refractive error ( $-0.22 \pm 2.12$  diopters versus  
200  $-0.31 \pm 2.17$  diopters;  $P = 0.59$ ) were not statistically significant.

201 A previous stroke was reported by 235 individuals (235 / 3205 or 7.33% [95%CI: 6.43,  
202 8.24]). Among the 235 patients, 192 individuals were on oral medication for the prophylaxis  
203 of a recurrence of the stroke. The stroke had taken place  $7.5 \pm 5.7$  years ago (median: 7  
204 years; range: 1 month to 26 years).

205 In the stroke group as compared with the non-stroke group (control group), age was  
206 significantly older ( $71.1 \pm 9.2$  years versus  $63.9 \pm 9.5$  years;  $P < 0.001$ ) and had a higher  
207 proportion of men than women (men / women: 128 / 107 versus 1258 / 1712;  $P < 0.001$ ) (Fig. 1).  
208 The prevalence of a previous stroke increased from 2.0% (95%CI: 0.9, 3.1) in the age group of  
209 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%  
210 (95%CI: 16.4, 27.4) in the age group of 80+ years (Table 1).

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

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

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

237

238

### 239 Discussion

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

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

251 Chinese for the age group of 45-74 years.<sup>13</sup> Li and colleagues performing a population-based  
252 stroke surveillance on more than 14,000 residents in Tianjin, China from 1992 to 2012,  
253 reported on an increase in the age-standardized incidence for both intracerebral hemorrhage  
254 (37.8 per 100,000 person-years in 1992-1998, 46.5 in 1999-2005, and 76.5 in 2006-2012) and  
255 for ischemic stroke (83.9 in 1992-1998, 135.3 in 1999-2005, and 238.0 in 2006-2012).<sup>14</sup> The  
256 age-standardized incidence of first-ever stroke increased annually by 4.9% for intracerebral  
257 hemorrhage and by 7.3% for ischemic stroke. In a similar study, Ning and associates found  
258 that the age-standardized incidence of first-ever stroke per 100 000 person-years increased  
259 significantly, from 122 in the years 1992 to 1999, to 216 in 2000 to 2007, and to 471.8 in 2008  
260 to 2015.<sup>15</sup> The greatest increases were observed in adults aged 55 to 64 years. In the  
261 China National Stroke Screening Survey as reported by Guan and coworkers, the adjusted  
262 stroke prevalence in 2014 was 2.06% in adults aged 40 years and older.<sup>16</sup> The incidence of  
263 first-ever stroke in adults aged 40-74 years increased from 189/100,000 individuals in 2002 to  
264 379/100,000 in 2013-an overall annual increase of 8.3%.

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

271 The interesting finding in our study is that, after adjusting for other systemic risk factors,  
272 the presence of diabetic of diabetic retinopathy increased the likelihood of a previous stroke by  
273 an odds ratio of 4.41, and in a parallel manner, that an increase by one step in the stage of  
274 diabetic retinopathy increased the probability of a previous stroke by an odds ratio of 1.64. In  
275 previous studies by Cheung et al. and by Petitti and colleagues a similar association was  
276 described..<sup>17,18</sup> In a population-based, prospective cohort study of 1617 middle-aged persons  
277 with diabetes, Cheung found that after a mean follow-up of 7.8 years diabetic retinopathy was  
278 associated with an increased risk of ischemic stroke (hazard rate ratio, 2.34; 95% CI, 1.13 to  
279 4.86), after adjusting for systemic parameters such as age, gender, race, arterial blood  
280 pressure, duration and therapy of diabetes, blood lipid concentrations and levels and cigarette

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4 281 smoking status.<sup>17</sup> In an earlier study, Petitti and associates found in a nested case-control  
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6 282 study, that the estimated relative risk of stroke in diabetic subjects with retinopathy was 4.0  
7  
8 283 (95%CI: 1.0 , 14.5) after adjustment for systemic risk factors.<sup>18</sup> The reason for this  
9  
10 284 association may be that diabetic retinopathy as a microangiopathy indicates a wide-spread  
11  
12 285 vascular disorder.

13  
14 286 When discussing the results of our study, its limitations have to be taken into account.  
15  
16 287 First, the data on the prevalence of a previous self-reported stroke depended on the  
17  
18 288 information provided by the study participants in the face-to-face interviews. Since stroke is a  
19  
20 289 dramatic event, it is unlikely to be under-reported. Transient ischemic attacks might occur  
21  
22 290 unnoticed by the individuals so that transient ischemic attacks might be under-reported in an  
23  
24 291 interview of previous cerebral strokes. Our study was based however primarily on previous  
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26 292 cerebral strokes which were defined as an occurrence of typical neurological symptoms for at  
27  
28 293 least 24 hours. It may make it unlikely that unnoticed previous transient ischemic attacks  
29  
30 294 might have markedly influenced the results of our study. Second, patients who had died as a  
31  
32 295 sequel of a previous stroke were not included into the study. The results of our study are  
33  
34 296 therefore valid primarily only for stroke survivors. Third, due to regional differences in China,  
35  
36 297 findings obtained in our study may not completely be transferable to South China or pother  
37  
38 298 world regions.<sup>19</sup> Fourth, we did not differentiate between intracerebral hemorrhage and  
39  
40 299 ischemic stroke.<sup>20</sup> Fifth, we did not assess the role of atrial fibrillation as risk factor for stroke  
41  
42 300 in our study. Fifth, the study population with an age of 50+ years had experienced major  
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44 301 societal changes and economic developments in China during their lifetime. This elderly  
45  
46 302 generation may differ from the young generations in China and from populations in other  
47  
48 303 countries. Sixth, our investigation was a cross-sectional observational study, so that a  
49  
50 304 reverse causality may have existed in the sense that diabetic retinopathy might have been the  
51  
52 305 sequel of stroke.

53  
54 306 In conclusion, in this North Chinese population aged 50+ years, the prevalence of a  
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56 307 previous stroke was 7.33% (95%CI:6.43,8.24). The presence and stage of diabetic  
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58 308 retinopathy were ocular risk factors for a higher prevalence of a previous stroke, after adjusting  
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60 309 for the systemic risk factors of older age, male gender and a higher prevalence of diabetes  
310 mellitus and cardiovascular disease. The prevalence of previous stroke increased for each

311 increase in the stage of diabetic retinopathy by an odds ratio of 1.64 (95%CI: 1.26, 2.14), and  
312 for the presence of diabetic retinopathy by an odds ratio of 4.41 (95%CI: 2.38, 8.18).

313 Individuals with diabetic retinopathy appear to be a group at particularly high risk of cerebral  
314 stroke.

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318 Jost B. Jonas; Statistical analysis: Ya Xing Wang, Jost B. Jonas; Writing of the manuscript:  
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320 Liang Xu , Jost B. Jonas;

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378 Table 1

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

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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)

381



383 Table 2  
 384 Associations between the prevalence of cerebral stroke and systemic and ocular parameters  
 385 after adjusting for age and gender in the Beijing Eye Study 2011  
 386

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 <sup>2</sup> )	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

## 18 Stroke and Eye Diseases

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 m <sup>2</sup> ) (MDRD Formula)	0.79	1.00	0.99, 1.01
Estimated Glomerular Filtration Rate (mL/min / 1.73 m <sup>2</sup> ) (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 <sup>2</sup> )	0.69	1.09	0.71, 1.70

Neuroretinal Rim Area (mm <sup>2</sup> )	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 $\geq$ 48 Diopters)	0.27	2.04	0.58, 7.18
Keratoconus (Anterior Corneal Curvature refractive Power $\geq$ 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

388 Table 3  
 389 Associations (multivariable analysis) between the prevalence of cerebral stroke and systemic  
 390 and ocular parameters in the Beijing Eye Study 2011

Parameter	<i>P</i> -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)	<i>P</i> <0.001	1.64	1.26, 2.14

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3  
4 410 Fig. 1  
5 411 Graph showing the distribution of the prevalence of a previous cerebral stroke stratified by age  
6 412 and gender in the Beijing Eye Study  
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9 413  
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11 414 Fig. 2  
12 415 Graph showing the distribution of the prevalence of a previous cerebral stroke stratified by age  
13 416 and presence of diabetic retinopathy in the Beijing Eye Study  
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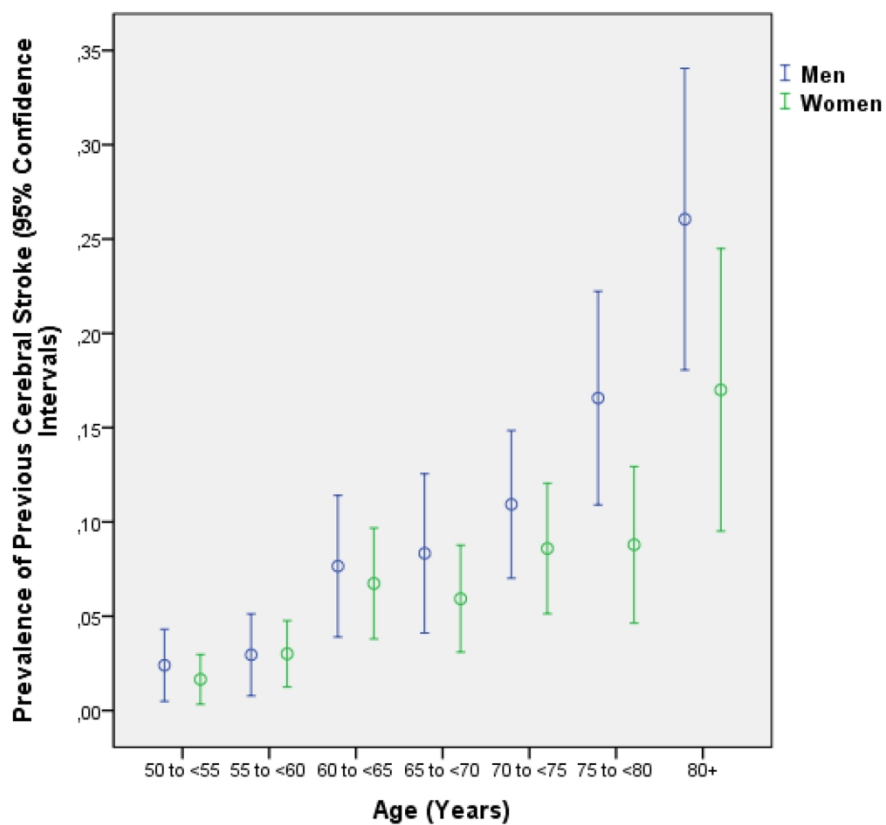


Fig. 1  
 Graph showing the distribution of the prevalence of a previous cerebral stroke stratified by age and gender in the Beijing Eye Study

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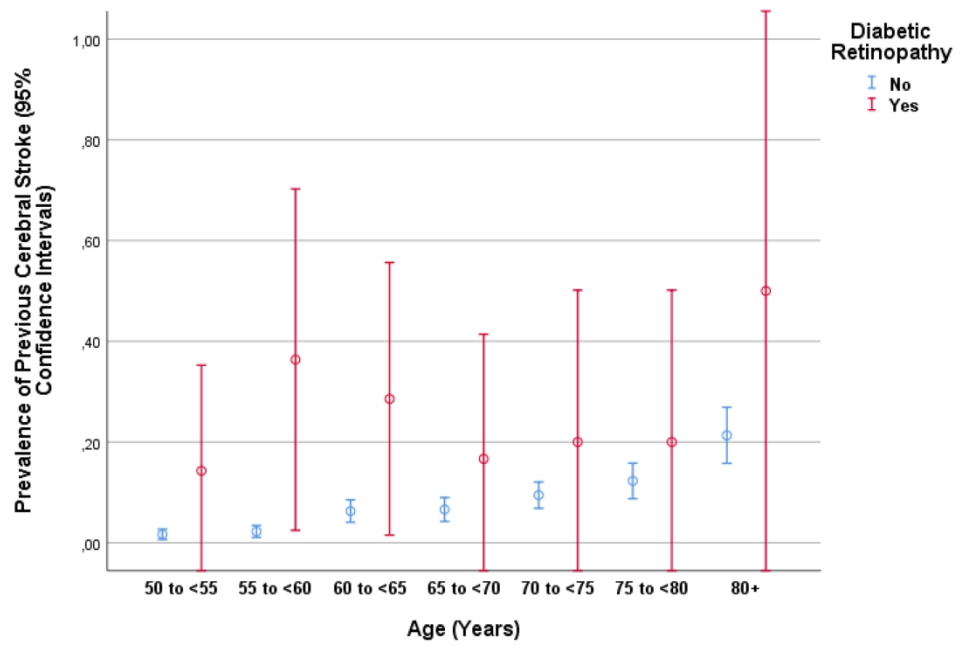


Fig. 2  
Graph showing the distribution of the prevalence of a previous cerebral stroke stratified by age and presence of diabetic retinopathy in the Beijing Eye Study



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

	Item No	Recommendation	Page: Line
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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	
<b>Results</b>			
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	
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).

# BMJ Open

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

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Manuscripts

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8 3 **Prevalence, Risk Factors and Associated Ocular Diseases of Cerebral Stroke: The**  
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10 4 **Population-based Beijing Eye Study**  
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17 8 Ya Xing Wang, MD(1), Wen Bin Wei, MD (2), Liang Xu , MD(1), Jost B. Jonas, MD(1,3)  
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45 22 Running title: Stroke and Eye Diseases

46 23 Keywords: Stroke; Retinal nerve fiber layer; Optic nerve; Glaucoma; Age-related macular  
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48 24 degeneration; Diabetic retinopathy; Diabetes mellitus; 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 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).

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5 62 **Article Summary**

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7 63 Strengths and limitations of this study:

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9 64 - Limitation: Data on the prevalence of a previous stroke depended on self-reported  
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11 65 information; patients who had died as a sequel of a previous stroke were not included into the  
12  
13 66 study; the results of our study are therefore valid primarily only for stroke survivors.

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15 67 - Limitation: Intracerebral hemorrhage was not differentiated from ischemic stroke.

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17 68 - Limitation: Cross-sectional analysis

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19 69 - Strength: Population-based study design

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21 70 - Strength: Large number of parameters including ophthalmological variables assessed  
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## 72 Introduction

73 Cerebral stroke as one of the main contributors of the global burden of disease has caused  
74 116 million or 4.8% of all DALYs (Disability-Adjusted Life Years) and 14.5 million or 1.8% of all  
75 YLDs (Years Lived with Disability) worldwide in the year 2013.<sup>1-4</sup> In particular China has  
76 witnessed a marked increase in the importance of stroke in the spectrum of diseases causing  
77 DALYS and years of life lost (YLLs). While in 1990, lower respiratory infections or preterm  
78 birth complications were the leading causes of YLLs in almost half of the provinces of China  
79 (16 out of 33), cerebrovascular disease were the leading cause in 27 of the 33 provinces in  
80 2013.<sup>5,6</sup> Since the eye and brain share the same arterial blood supply through the inner  
81 carotid artery and since the retina and optic nerve as former outgrowth of the anterior end of  
82 the embryological neural groove are of neuro-ectodermal origin, a major cerebral disease such  
83 as stroke may be associated with ocular diseases, in particular disorders of the optic nerve and  
84 retina. Since comprehensive population-based studies on associations between stroke and  
85 ocular parameters have been scarce so far and have not been conducted for the population of  
86 China, we investigated the prevalence of cerebral stroke and its potential associations with  
87 ocular diseases, after adjusting for systemic factors, in a population-based study performed in  
88 China.

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## 91 Methods

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

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4 102 All study participants underwent a structured interview by trained research  
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6 103 technicians. The interview included more than 200 standardized questions on demographic  
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8 104 parameters, socioeconomic background, diet and alcohol consumption, smoking habits,  
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10 105 known major systemic diseases and current systemic medical therapies. Using the mini-  
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12 106 mental state examination (MMSE) scale, we assessed the cognitive function. Fasting blood  
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14 107 samples were collected for measurement of blood lipids, glucose, glycosylated hemoglobin  
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16 108 HbA1c and serum creatinine. The blood pressure was measured with the participant sitting  
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18 109 for at least 5 min. We also measured body height and weight and the circumference of the  
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20 110 waist and hip.

21 111 Arterial hypertension was defined by a systolic blood pressure  $\geq 160$  mm Hg and/or a  
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23 112 diastolic blood pressure  $\geq 95$  mm Hg, and/or self-reported current treatment for arterial  
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25 113 hypertension with antihypertensive medication. Diabetes mellitus was characterized by a  
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27 114 blood glucose concentration  $\geq 7.0$  mmol/L, an HbA1c value  $\geq 6\%$ , by a self-reported history of  
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29 115 physician diagnosis of diabetes mellitus, or by a history of drug treatment for diabetes (insulin  
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31 116 or oral hypoglycemic agents). Depressive symptoms were evaluated using a Chinese  
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33 117 depression scale adapted from the Zung self-rated depression scale.<sup>9</sup> The prevalence of  
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35 118 previous stroke was examined in the interview by standardized questions on whether a  
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37 119 previous cerebral stroke had occurred with typical symptoms such as sudden-onset face  
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39 120 weakness, arm drift, abnormal speech hemiplegia, or numbness for at least 24 hours, when  
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41 121 such a stroke had occurred, and whether it had been treated.

42 122 The ophthalmological examination consisted of automatic refractometry (Auto  
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44 123 Refractometer AR-610; Nidek Co., Ltd, Tokyo, Japan), measurement of presenting visual  
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46 124 acuity, uncorrected visual acuity and best-corrected visual acuity, tonometry, slit lamp based  
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48 125 biomicroscopy of the anterior and posterior segment of the eyes, and photography of the  
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50 126 cornea and lens (Neitz CT-R camera; Neitz Instruments Co., Tokyo, Japan) and of the macula  
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52 127 and optic disc (fundus camera; Type CR6-45MM; Canon Inc., Tokyo, Japan) in medical  
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54 128 mydriasis. Using the photographs, we measured the dimensions of the optic disc, optic cup  
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56 129 and parapapillary alpha, beta and gamma zones. The optic nerve head and macula were  
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58 130 additionally examined by spectral-domain optical coherence tomography (OCT) using the  
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60 131 enhanced depth imaging modality (Spectralis; Heidelberg Engineering, Heidelberg, Germany).



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4 132 We determined the thickness of the peripapillary retinal nerve fiber layer, of the retina in the  
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6 133 foveal region and of the subfoveal choroid. Applying optical low-coherence reflectometry  
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8 134 (Lenstar 900 Optical Biometer; Haag-Streit, Koeniz, Switzerland), we measured ocular  
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10 135 biometric parameters such as the anterior corneal curvature, central corneal thickness,  
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12 136 anterior chamber depth, lens thickness and axial length. The degree of cataract was  
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14 137 determined using the lens photographs. The degree of nuclear opacities was assessed in 6  
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16 138 grades using the grading system of the Age-Related Eye Disease Study.<sup>10</sup> In addition,  
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18 139 retro-illuminated photographs of the lens were obtained (Neitz CT-R camera; Neitz  
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20 140 Instruments Co., Tokyo, Japan), and the percentage of the areas with cortical and posterior  
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22 141 subcapsular lens opacities was measured using a grid. The standard to diagnose a nuclear  
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24 142 cataract was a nuclear cataract grade of 4 or more, the standard to diagnose a posterior  
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26 143 subcapsular cataract was an amount of posterior subcapsular opacities of 0.01 or more, and  
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28 144 the standard to diagnose a cortical cataract was an amount of cortical opacities of 0.05 or  
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30 145 more. The degree of fundus tessellation defined as the visibility of the large choroidal vessels  
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32 146 was assessed on the fundus photographs of the macula and of the optic disc as described in  
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34 147 detail previously.<sup>8</sup> It was graded using a scale which ranged from “0” for “no tessellation”  
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36 148 to “3” for “marked tessellation”. Diabetic retinopathy was assessed on the fundus  
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38 149 photographs using the Early Treatment of Diabetic Retinopathy Study (ETDRS) criteria. The  
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40 150 minimum criterion for diagnosis of diabetic retinopathy was the presence of at least one  
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42 151 microaneurysm. The diagnosis for each individual was based on the grading of the  
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44 152 individual’s eye with the highest stage of diabetic retinopathy. We differentiated between the  
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46 153 mild non-proliferative stage, the moderate non-proliferative stage, the advanced  
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48 154 non-proliferative stage, and the proliferative stage of diabetic retinopathy. Glaucomatous  
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50 155 optic neuropathy was defined using the criteria of the International Society of Geographic and  
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52 156 Epidemiological Ophthalmology ISGEO.<sup>11</sup> Pseudoexfoliation was assessed by an  
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54 157 experienced ophthalmologist during the slit lamp assisted biomicroscopy of the anterior  
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56 158 segment after pupillary dilation. The diagnosis of pseudoexfoliation was definite, if the lens  
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58 159 surface showed a central whitish coating with a diameter of little less than the normal pupillary  
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60 160 diameter, or if the periphery of the lens surface showed a whitish coating which was anteriorly  
161 bordered by a darker ring-like region on the lens surface. The assessment of

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4 162 pseudoexfoliation was performed only in phakic eyes. For the diagnosis of age-related  
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6 163 macular degeneration, the International ARM (Age-related Maculopathy Epidemiological Study  
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8 164 Group) Grading system was used. The subjective symptoms of dry eye were evaluated using  
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10 165 a questionnaire composed of three questions: "Do your eyes ever feel dry?"; "Do you ever feel  
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12 166 a gritty or sandy sensation in your eyes?"; and "Do your eyes ever have a burning sensation?"  
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14 167 Possible answers to the questions were none (0), less than once a month (1), once or twice a  
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16 168 week (2), at least once every day (3), all the time (4). The presence of dry eye symptoms was  
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18 169 defined as having one or more symptoms at least once every day (3 and 4). A quantitative  
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20 170 grading score of subjective dry eye symptoms was obtained by summarizing the answers to  
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22 171 the different questions (0–12).<sup>12</sup>

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24 172 The statistical analysis was performed using a commercially available statistical  
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26 173 software package (SPSS for Windows, version 25.0, IBM-SPSS, Chicago, IL, USA). Data  
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28 174 were shown as mean (standard deviation), frequency (%), 95% confidence interval [CI], or  
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30 175 median (interquartile range) where appropriate. The differences in parameters such as age  
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32 176 and sex between participants with stroke and participants without stroke were assessed by the  
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34 177 student t-test for unpaired samples or by the chi-square test. We tested associations  
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36 178 between baseline characteristics and stroke with logistic regression adjusting for age and sex.  
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38 179 Significant covariates from the step above ( $P < 0.10$ ) were included in multivariable models.  
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40 180 We reduced the full model by successively removing non-significant covariates until all  
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42 181 remaining predictors remained statistically significant ( $P < 0.05$ ). We calculated the odds ratio  
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44 182 (OR). All  $P$ -values were two-sided and considered statistically significant, if the values were  
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46 183 less than 0.05.

47 184 Patient and Public Involvement statement: Patients were not involved in this study  
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## 52 187 **Results**

53  
54 188 Out of 3468 study participants, 3205 (92.4%) individuals participated in the interview with  
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56 189 available information on previous stroke and underwent the systemic and ophthalmologic  
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58 190 examination. The participating group as compared to the group of individuals without  
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60 191 available information on previous stroke or without systemic and ocular examination was

192 significantly younger ( $64.4 \pm 9.7$  years (median: 63 years; range: 50 – 93 years) versus  $67.1 \pm$   
193  $11.1$  years;  $P < 0.001$ ) and came significantly more often from the urban region than from the  
194 rural area (rural / urban region of habitation: 1439 / 1766 versus 194 / 69;  $P < 0.001$ ), while the  
195 differences in gender (men / women: 1386 / 1819 versus 119 / 144;  $P = 0.56$ ), axial length ( $23.3$   
196  $\pm 1.1$  mm versus  $23.2 \pm 1.9$  mm;  $P = 0.31$ ) and refractive error ( $-0.22 \pm 2.12$  diopters versus  
197  $-0.31 \pm 2.17$  diopters;  $P = 0.59$ ) were not statistically significant.

198 A previous stroke was reported by 235 individuals (235 / 3205 or 7.33% [95%CI: 6.43,  
199 8.24]). Among the 235 patients, 192 individuals were on oral medication for the prophylaxis  
200 of a recurrence of the stroke. The stroke had taken place  $7.5 \pm 5.7$  years ago (median: 7  
201 years; range: 1 month to 26 years).

202 In the stroke group as compared with the non-stroke group (control group), age was  
203 significantly older ( $71.1 \pm 9.2$  years versus  $63.9 \pm 9.5$  years;  $P < 0.001$ ) and had a higher  
204 proportion of men than women (men / women: 128 / 107 versus 1258 / 1712;  $P < 0.001$ ) (Fig. 1).  
205 The prevalence of a previous stroke increased from 2.0% (95%CI: 0.9, 3.1) in the age group of  
206 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%  
207 (95%CI: 16.4, 27.4) in the age group of 80+ years (Table 1).

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

222 retinopathy ( $P<0.001$ ) (Table 2) (Fig. 2).

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

235

236

### 237 Discussion

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

246 The findings obtained in our study agree with the results of previous investigations.  
247 In a review of studies conducted since 1990 in Chinese populations, Tsai and colleagues  
248 reported on an age-standardized annual first-ever stroke incidence of 205-584 per 100,000 in  
249 Chinese for the age group of 45-74 years.<sup>13</sup> Li and colleagues performing a population-based  
250 stroke surveillance on more than 14,000 residents in Tianjin, China from 1992 to 2012,  
251 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).<sup>14</sup> 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.<sup>15</sup> 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.<sup>16</sup> 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.<sup>16</sup>

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..<sup>17,18</sup> 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.<sup>17</sup> 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.<sup>18</sup> The reason for this

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

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

304       In conclusion, in this North Chinese population aged 50+ years, the prevalence of a  
305 previous stroke was 7.33% (95%CI:6.43,8.24). The presence and stage of diabetic  
306 retinopathy were ocular risk factors for a higher prevalence of a previous stroke, after adjusting  
307 for the systemic risk factors of older age, male gender and a higher prevalence of diabetes  
308 mellitus and cardiovascular disease. The prevalence of a previous stroke increased for each  
309 step of an increase in the stage of diabetic retinopathy with an odds ratio of 1.64  
310 (95%CI:1.26,2.14), and it increased by the presence of diabetic retinopathy with an odds ratio

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

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315 A. contributor ship statement: Design and conception: Ya Xing Wang, Wen Bin Wei, Liang Xu ,

316 Jost B. Jonas; Statistical analysis: Ya Xing Wang, Jost B. Jonas; Writing of the manuscript:

317 Jost B. Jonas; Editing and final approval of the manuscript: Ya Xing Wang, Wen Bin Wei,

318 Liang Xu , Jost B. Jonas;

319 B. competing interests: None

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322 data collection and analysis, decision to publish, or preparation of the manuscript.

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



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376 Table 1

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

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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)

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381 Table 2  
 382 Associations between the prevalence of cerebral stroke and systemic and ocular parameters  
 383 after adjusting for age and gender in the Beijing Eye Study 2011  
 384

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 <sup>2</sup> )	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

## 18 Stroke and Eye Diseases

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 m <sup>2</sup> ) (MDRD Formula)	0.79	1.00	0.99, 1.01
Estimated Glomerular Filtration Rate (mL/min / 1.73 m <sup>2</sup> ) (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 <sup>2</sup> )	0.69	1.09	0.71, 1.70

Neuroretinal Rim Area (mm <sup>2</sup> )	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 $\geq$ 48 Diopters)	0.27	2.04	0.58, 7.18
Keratoconus (Anterior Corneal Curvature refractive Power $\geq$ 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

386 Table 3  
 387 Associations (multivariable analysis) between the prevalence of cerebral stroke and systemic  
 388 and ocular parameters in the Beijing Eye Study 2011

Parameter	<i>P</i> -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)	<i>P</i> <0.001	1.64	1.26, 2.14

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4 408 Fig. 1  
5 409 Graph showing the distribution of the prevalence of a previous cerebral stroke stratified by age  
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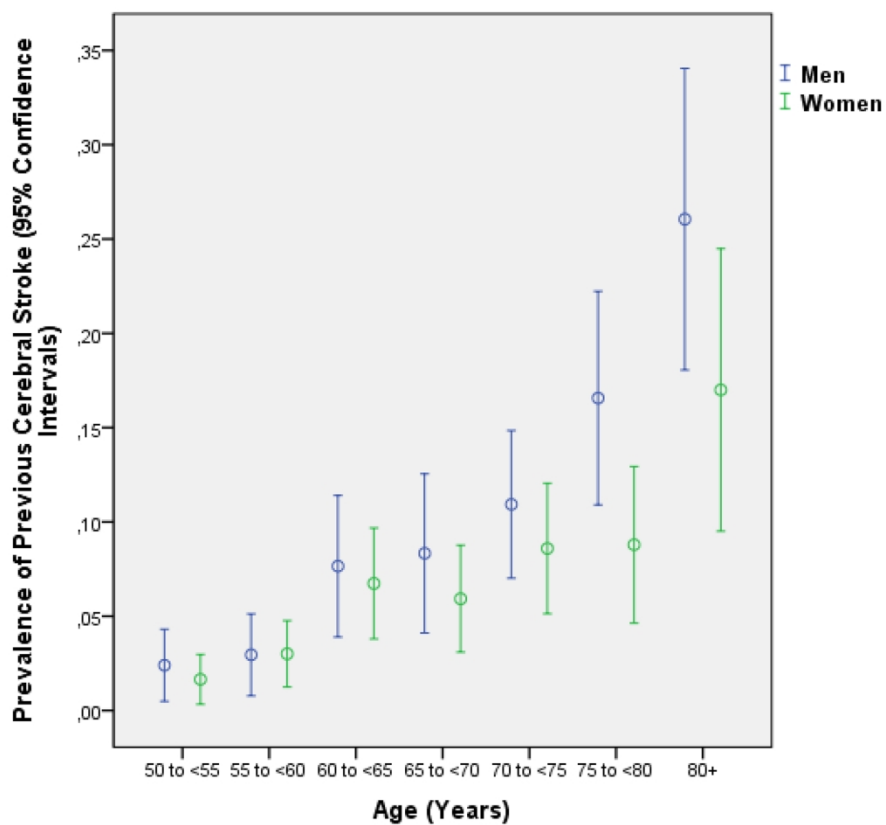


Fig. 1  
Graph showing the distribution of the prevalence of a previous cerebral stroke stratified by age and gender in the Beijing Eye Study

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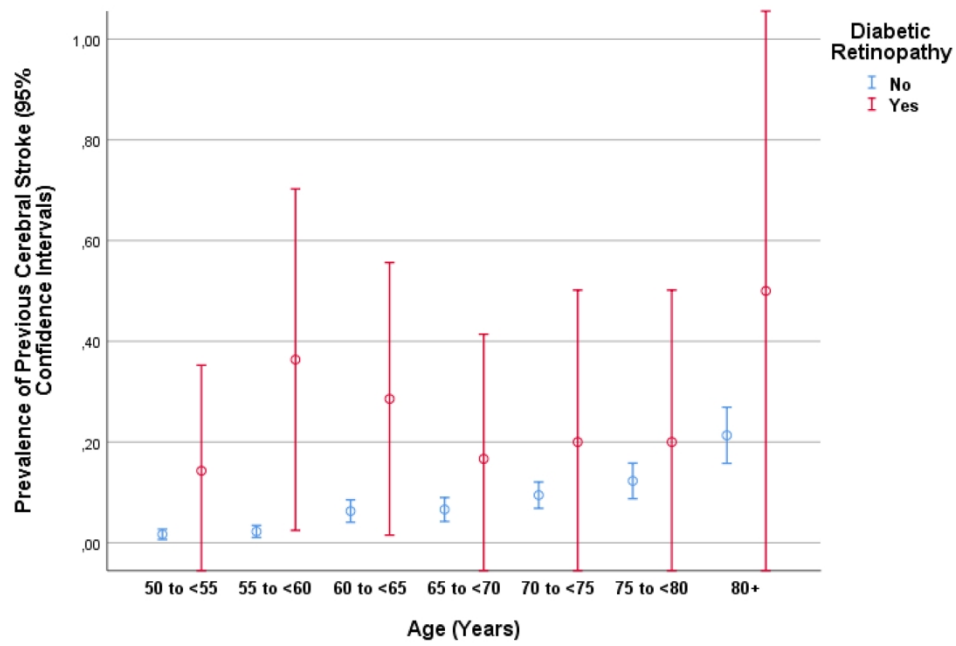


Fig. 2  
Graph showing the distribution of the prevalence of a previous cerebral stroke stratified by age and presence of diabetic retinopathy in the Beijing Eye Study

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

	Item No	Recommendation	Page: Line
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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	
<b>Results</b>			
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	
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).