WORLD VIEW

Associated factors for age related maculopathy in the adult population in China: the Beijing eye study

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Background: To evaluate factors associated with the prevalence of age related maculopathy (ARM) in the adult Chinese population.

Methods: The Beijing Eye Study, a population based prevalence study, included 4439 out of 5324 subjects from a rural area and an urban region of greater Beijing, aged 40+ years and invited to participate (response rate 83.4%). Fundus photographs were graded using the Wisconsin Age-Related Maculopathy Grading system. The following parameters were graded: drusen size, drusen type, and the area covered by drusen; pigmentary abnormalities; geographic atrophy; and exudative ARM.

Results: Fundus photographs were available for 8655 eyes of 4376 (98.6%) subjects. Early age related macular degeneration (ARD), late ARD, and exudative ARD, respectively, were present in 1.4%, 0.20%, and 0.10% of the subjects. In a binary logistic regression analysis, early ARM was statistically associated with age ($p<0.001$; 95% CI: 1.04 to 1.08), hyperopic refractive error ($p=0.008$; 95% CI: 1.04 to 1.28), rural region ($p<0.001$; 95% CI: 0.17 to 0.49), and lower level of education ($p=0.01$; 95% CI: 1.07 to 1.65). Early ARM was not significantly associated with the optic disc size ($p=0.42$), and size of beta zone of peripapillary atrophy ($p=0.28$), the self reported diagnosis of diabetes mellitus ($p=0.39$; OR: 1.37; 95% CI: 0.66 to 2.85), amount of cortical cataract ($p=0.72$), subcapsular cataract ($p=0.98$), nuclear cataract ($p=0.26$), sex ($p=0.23$), cataract surgery ($p=1.0$; OR: 0.96; 95% CI: 0.13 to 6.95), glaucomatous optic nerve damage ($p=0.77$; OR: 0.62; 95% CI: 0.15 to 2.52), and history of smoking ($p=0.66$; OR: 1.14; 95% CI: 0.65 to 2.00).

Conclusions: Hyperopic refractive error besides age was the single most important risk factor for ARM in adult Chinese. Other associated factors were rural region and lower level of education.

Large scaled population based studies performed in the past 15 years have revealed that age related maculopathy (ARM) belongs to the most common causes for visual impairment in elderly white populations.^{1–8} The list of risk factors for the development and progression of the disease included hyperopic refractive error, smoking, family history, and ethnic background.^{9–21} Since all these parameters may differ between populations of various continents, and because population based data for the Chinese population living in mainland China are only scarcely available as yet, it was the purpose of the present population based investigation to assess factors associated with age related macular degeneration (ARD) in mainland Chinese people.

METHODS

The Beijing Eye Study, a population based cohort study in northern China, was carried out in seven communities, four communities from the urban district Haidian in the northern part of central Beijing, and three communities from a rural district in the village area of Yufa (Daxing District) in the south of Beijing. The medical ethics committee of the Beijing Tongren Hospital had approved the study protocol and all participants had given informed consent. The study has been described in detail previously.^{22–25} In total, 4439 individuals participated in the eye examination, corresponding to a response rate of 83.4%. The study was divided into the rural part (1918 (43.8%) subjects) and the urban part (2460 (56.2%) subjects).

All examinations were carried out in the communities, either in schoolhouses or in community houses. After measurement of visual acuity, digital photographs of the cornea and lens were taken using the Neitz CT-R camera (Neitz Instruments Co, Tokyo, Japan). The degree of nuclear

cataract was scored using the cataract grading system of the Age-Related Eye Disease Study.^{26–27} Additionally, monoscopic colour film photographs of the macula and optic disc were taken using a fundus camera (Type CR6-45NM, Canon Inc, USA). The optic disc photographs were digitised and were measured by outlining the optic disc border on the computer screen using a planimetric software program. The method has been described in detail recently.^{28–30} Additionally, smoking habits were assessed by asking whether the individuals were actual smokers or whether they had smoked in the past, and how many cigarettes they smoked per day.

For the assessment of ARD, the Wisconsin Age-Related Maculopathy Grading system was used as described in detail previously.^{31–32} The macula photographs were examined by an ophthalmologist with special training in retinal diseases (YL). Senior investigators (LX, JBJ) adjudicated all photographs graded as late ARD, and all photographs with questionable grading. Five types of late ARD lesions were considered—geographic atrophy, pigment epithelial detachment, detachment of sensory retina, subretinal haemorrhage, and subretinal disciform scar. Exudative ARD was considered present if any of the following lesions were present—pigment epithelial detachment, detachment of sensory retina, subretinal haemorrhage, or subretinal disciform scar. Late ARD was present if there were signs of exudative ARD or pure geographic atrophy. Early ARM was present if late ARD was absent and there were signs of soft indistinct drusen or any drusen (except hard distinct drusen) combined with pigmentary changes in the macular area.

Abbreviations: ARD, age related macular degeneration; ARM, age related maculopathy

Statistical analysis was performed by using a commercially available statistical software package (SPSS for Windows, version 11.5, SPSS, Chicago, IL, USA). Only one randomly selected eye per subject was taken for statistical analysis.

RESULTS

Fundus photographs with sufficient quality for examination were available for 8655 eyes of 4376 participants (98.6% of the original sample). The mean age was 56.1 (SD 10.5) years, ranging from 40–101 years. The percentage of the population in the various age groups decreased from 16.8% in the group aged 40–44 years, to 16.2% in the group aged 45–49 years, to 13.6% in the group aged 50–54 years, to 13.2% in the group aged 55–59 years, to 16.6% in the group aged 60–64 years, to 12.7% in the group aged 65–69 years, to 6.9% in the group aged 70–74 years, and to 4.1% in the group aged 75+ years. The mean refractive error was -0.37 (2.21) dioptres, ranging from -20.13 dioptres to $+7.50$ dioptres. For 63 (1.4%) subjects, fundus photographs could not be examined. The main reasons for not having photographs taken were inability to have the pupil dilated and significant lens opacity. Participants not included in the analysis because the photographs were not available or were of insufficient quality to grade drusen characteristics were significantly older (66.4 (11.1) years versus 56.1 (10.5) years; $p < 0.001$; 95% CI: 9.10 to 11.89), were significantly more myopic (-1.24 (3.5) dioptres versus -0.37 (2.21) dioptres; $p < 0.001$; 95% CI: -1.26 to -0.58), had lower best corrected visual acuity (0.58 (0.37) versus 0.91 (0.21); $p < 0.001$; 95% CI: -0.36 to 0.31), and more marked nuclear cataract $p < 0.001$; 95% CI: 0.07 to 0.19).

Early ARM, late ARD, and exudative ARD, respectively, were present in 1.4%, 0.20%, and 0.10% of the subjects. The prevalence of early ARM, late ARD, and exudative ARD, respectively, increased from 0.61%, 0.07%, and 0.07%, respectively, in the 40–44 year age group, to 1.66%, 0.26%, and 0.26%, respectively, in the 55–59 years old group, and to 2.99%, 0.90%, and 0.60%, respectively, in the group aged 75 years and older.

Early age related maculopathy

In bivariate analysis, presence of early ARM was significantly associated with age, hyperopic refractive error, lower level of education, and rural area (table 1). The association between early ARM and the following parameters showed a statistically marginally significance: self reported diagnosis of arterial hypertension, cerebral haemorrhage, intraocular pressure, optic disc size, and size of beta zone of peripapillary atrophy (table 1).

The association between early ARD and the following parameters was statistically not significant: self reported diagnosis of diabetes mellitus, hyperlipidaemia, coronary heart disease, amount of cortical cataract, degree of subcapsular cataract, degree of nuclear cataract, sex, cataract surgery, size of alpha zone of peripapillary atrophy, diagnosis of glaucomatous optic nerve damage, history of smoking, current smoking, and daily quantity of current smoking or former smoking. In the study population, 23% of the subjects were current smokers, and 28% were former smokers. From the current smokers, 38% smoked up to 10 cigarettes per day, 34% smoked 10–20 cigarettes per day, and 28% smoked more than 20 cigarettes per day. From the former smokers, 35% smoked up to 10 cigarettes per day, 36% smoked 10–20 cigarettes per day, and 30% smoked more than 20 cigarettes per day.

In a binary logistic regression analysis, early ARD remained to be statistically associated with age ($p < 0.001$; 95% CI: 1.04 to 1.08), hyperopic refractive error ($p = 0.008$; 95% CI: 1.04 to 1.28), rural region ($p < 0.001$; 95% CI: 0.17 to 0.49), and lower level of education ($p = 0.01$; 95% CI: 1.07 to 1.65). Early ARD was no longer significantly associated with the self reported diagnosis of arterial hypertension ($p = 0.56$; 95% CI: 0.41 to 1.61), cerebral haemorrhage ($p = 0.93$; 95% CI: 0.28 to 3.24), intraocular pressure ($p = 0.14$; 95% CI: 0.90 to 1.02), optic disc size ($p = 0.42$; 95% CI: 0.44 to 1.41), and size of beta zone of peripapillary atrophy ($p = 0.28$; 95% CI: 0.49 to 1.23).

Late age related macular degeneration

In bivariate analysis, presence of late ARD was significantly associated with age ($p < 0.002$). The association between late

Table 1 Statistical data (bivariate analysis) on the associations of the prevalence of early age related maculopathy (ARM) and late ARM with ocular and general parameters

	Early ARM	Late ARM
Number	63/4376 (1.4%)	7/4376 (0.2%)
Age	$p < 0.001$ (95% CI: 1.02 to 1.06)	$p < 0.002$ (95% CI: 1.03 to 1.15)
Hyperopic refractive error	$p < 0.001$ (95% CI: 1.10 to 1.34)	$p = 0.16$ (95% CI: 0.76 to 1.05)
Lower level of education	$p = 0.04$ (95% CI: 0.75 to 0.99)	$p = 0.22$ (95% CI: 0.51 to 1.19)
Rural area	$p = 0.001$ (95% CI: 0.38 to 0.79)	$p = 0.77$ (OR: 0.79; 95% CI: 0.25 to 2.45)
Self reported diagnosis		
Arterial hypertension	$p = 0.08$ (OR: 1.48; 95% CI: 0.99 to 2.24)	$p = 0.30$ (OR: 1.82; 95% CI: 0.55 to 6.00)
Cerebral haemorrhage	$p = 0.14$ (OR: 1.83; 95% CI: 0.89 to 3.79)	$p = 1.00$ (OR: 1.00; 95% CI: 1.00 to 1.00)
Intraocular pressure	$p = 0.10$ (95% CI: 0.90 to 1.01)	$p = 0.95$ (95% CI: 0.86 to 1.18)
Optic disc size	$p = 0.10$ (95% CI: 0.38; 1.10)	$p = 0.80$ (95% CI: 0.29; 4.96)
Size of beta zone of peripapillary atrophy	$p = 0.20$ (95% CI: 0.50 to 1.15)	$p = 0.05$ (95% CI: 1.00 to 1.29)
Self reported diagnosis of diabetes mellitus	$p = 0.39$ (OR: 1.37; 95% CI: 0.66 to 2.85)	$p = 0.35$ (OR: 2.68; 95% CI: 0.32 to 22.3)
Hyperlipidaemia	$p = 1.0$ (OR: 1.00; 95% CI: 0.60 to 1.68)	$p = 1.0$ (OR: 0.58; 95% CI: 0.07 to 4.84)
Coronary heart disease	$p = 0.39$ (OR: 1.23; 95% CI: 0.73 to 2.07)	$p = 0.19$ (OR: 2.27; 95% CI: 0.61 to 8.38)
Cortical cataract	$p = 0.72$ (95% CI: 0.88 to 1.21)	$p = 0.89$ (95% CI: 0.99; 1.01)
Subcapsular cataract	$p = 0.98$ (95% CI: 0.85 to 1.18)	$p = 0.67$
Nuclear cataract	$p = 0.26$ (95% CI: 0.96 to 1.17)	$p = 0.30$ (95% CI: 0.04; 1.97)
Sex	$p = 0.23$ (OR: 0.80; 95% CI: 0.56 to 1.14)	$p = 0.57$ (OR: 1.56; 95% CI: 0.47 to 5.17)
Cataract surgery	$p = 1.0$ (OR: 0.96; 95% CI: 0.13 to 6.95)	$p = 1.00$ (OR: 1.00; 95% CI: 1.00 to 1.00)
Alpha zone of peripapillary atrophy	$p = 0.46$ (95% CI: 0.49; 1.38)	$p = 0.65$ (95% CI: 0.07; 4.71)
Diagnosis of glaucomatous optic nerve damage	$p = 0.77$ (OR: 0.62; 95% CI: 0.15 to 2.52)	$p = 1.00$ (OR: 1.00; 95% CI: 1.00 to 1.00)
History of smoking	$p = 0.66$ (OR: 1.14; 95% CI: 0.65 to 2.00)	$p = 1.00$ (OR: 1.01; 95% CI: 0.20 to 5.23)
Current smoking	$p = 0.87$ (OR: 0.89; 95% CI: 0.47 to 1.69)	$p = 1.00$ (OR: 0.57; 95% CI: 0.07 to 4.73)
Daily amount of current smoking or former smoking	$p = 0.36$ (95% CI: 0.34 to 19.63)	$p = 0.33$ (95% CI: 0.34 to 19.63)

OR, odds ratio; 95% CI, 95% confidence interval.

ARD and the following parameters showed a statistically marginal significance with the size of beta zone of peripapillary atrophy ($p = 0.05$) and hyperopic refractive error ($p = 0.16$) (table 1). In a binary logistic regression analysis, late ARD was statistically associated only with age ($p = 0.001$; 95% CI: 1.04 to 1.17), and marginally significantly associated with hyperopic refractive error ($p = 0.08$; 95% CI: 0.76 to 1.02). The size of beta zone of peripapillary atrophy was no longer significantly ($p = 0.99$; 0.79; 1.27) associated.

To further explore the relation between the prevalence of ARM and smoking, a logistic regression analysis was performed, with the prevalence of ARD (early and late type combined) as dependent variable and age, refractive error, current smoking and former smoking as independent parameters. In that analysis, prevalence of ARM was statistically not significantly associated with current smoking ($p = 0.43$; 95% CI: 0.26 to 1.77) or former smoking ($p = 0.31$; 95% CI: 0.67 to 3.49). In a similar manner, if the study population was stratified into age groups each spanning 10 years, the smoker group did not vary significantly from the non-smoker group in the frequency of ARM (age group 40–49 years: $p = 0.76$; OR: 1.14 (95% CI: 0.34 to 3.81); age group 50–59 years: $p = 1.00$; OR: 1.03 (95% CI: 0.36 to 2.96); age group 60–69 years: $p = 0.80$; OR: 1.17 95% CI: 0.45 to 3.04); age group 70+ years: $p = 0.57$; OR: 1.34 (95% CI: 0.45 to 4.01).

DISCUSSION

Data from this population based study demonstrated the expected association between age and ARD in its early stage and its late stage. Hyperopic refractive error besides age was the single most important risk factor for the disease in adult Chinese confirming previous studies on other populations.³³ In addition, early ARD was associated with rural region versus urban region and with a lower degree of education. In contrast with previous population based studies in Western countries as well as in south India, ARD in adult Chinese living in Greater Beijing was markedly not associated with former smoking, current smoking, any type of cataract or status after cataract surgery, and diagnosis of arterial hypertension or diabetes mellitus.

The question arises as to why, in the present study on adult Chinese living in the northern part of mainland China ARD, was not clearly associated with smoking, in contrast with the recent studies on other population groups.^{10 11 13 20} One of the possible reasons could be the markedly lower prevalence of the early stage and the late stage of ARD in mainland China than in Western countries.^{1–8} One may argue that the relatively low prevalence of ARD in the present study might have prevented a statistically significant result. The p values of the associations between smoking data and the presence of ARD were, however, so high that it may be unlikely that with an even larger number of participants in the study the association between smoking and ARD might have become statistically significant. It also has to be taken into account, however, that several studies in Western countries have not found a significant association between smoking and ARD until a meta-analysis clearly showed the relation between smoking and ARD.

There are conflicting reports of an association of arterial hypertension and ARD in the literature.^{34–36} We did not find the self reported diagnosis of arterial hypertension to be associated with ARD in our sample.

In the present study, presence and amount of any type of cataract and previous cataract surgery were not significantly associated with an increased risk of ARD. It is in contrast with a previous study from south India in which a higher prevalence of ARD was found in the presence of cortical cataract.²⁰ Also in other population based studies, the

association between ARD and cataract has been partially controversial.³⁷ In a similar manner, significant associations of ARD with previous cataract surgery have been reported in some studies, while other investigations did not find such relations.^{9 14 17 20 38–40}

In contrast with previous population based studies,^{2 16 37 41 42} we found in the present investigation an association between ARM and lower level of education as well as a relation between ARD and rural region independently of confounding factors such as refractive error and level of education. The reasons for these discrepancies between the Beijing Eye Study and investigations on other population have remained unclear so far. One may speculate that difference in life style, particularly in food, obesity, and physical activity may have had an influence.

The prevalence rates of ARM reported in the present investigations on adult Chinese in Greater Beijing are relatively low compared with the frequency figures of ARM reported for white populations in Western countries.^{43–46} To cite some examples, in the Baltimore Eye Survey,⁴³ the second most common cause of visual impairment was ARM in 14.2% of the impaired eyes. In a study on a population based sample of Hispanic individuals in Arizona,⁶ prevalence of late ARM increased from 0.1% in the 50–59 year age group to 4.3% in the group aged 80+ years. The prevalence of early ARD increased from 20% in the 50–59 year age group to 54% in the group aged 80+ years. The prevalence estimates of ARM in the Beijing Eye Study are not markedly different from figures from Barbados,⁴⁷ where 60% of blindness was the result of open angle glaucoma and age related cataract, and none of the cases with blindness was the result of ARM. The prevalence estimates of ARM in the present study on mainland Chinese in the Greater Beijing area were lower than estimates from the Chinese population group examined in the Taiwanese Shih-Pai Eye Study,⁴⁸ in which ARD was the third most common cause of visual impairment, accounting for 10.4% of the cases. The prevalence estimates of ARD in the present study were also markedly lower than the figures from a previous study carried out in Shanghai on 1023 subjects older than 50 years,⁴⁹ where 15.5% of the included population had ARD and with 19 (1.9%) out of 1023 subjects having exudative ARD.

There are limitations of the present study. Since the diagnosis of the systemic diseases such as diabetes mellitus were self reported by the subjects, it is questionable how valid are the associations, or the lack of significant associations, between the frequency of these diseases and ARM. Another limitation includes the relatively few cases of ARM. It decreases the power of the study to identify all significant risk factors. The results of the present investigation may, therefore, be taken as practical evidence for those associations that were statistically significant, and not as proof that those associations, which did not reach a statistically significant level, were clinically or pathogenetically not relevant. Another limiting factor of the present study, as in any study on the same topic, is that subjects for whom a dense cataract was considered to be the reason for the visual impairment might additionally have had ARD. It may have artificially reduced the prevalence figures for ARD in the present study and might have influenced the statistical analysis of the associations of ARD with other parameters. The strengths of this study are the representativeness of the sample population, the high response rate, and the standardised protocol, including the photographic documentation of the macula.

In conclusion, the single most important risk factor for ARD in adult Chinese from Greater Beijing, besides age, was hyperopic refractive error. Rural region versus urban region and lower level of education were other factors association

with ARD. Current smoking, history of previous smoking, and the quantity of smoking as well as the self reported diagnosis of systemic diseases such as arterial hypertension, diabetes mellitus, and cerebrovascular diseases did not have a pronounced influence on the prevalence of ARD.

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