·Investigation·

Epidemiological investigation on age related macular degeneration in rural area of Shaanxi Province, China

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Abstract

• AIM: To assess the prevalence and risk factors for age related macular degeneration (AMD) in a rural population in Shaanxi Province of China.

• METHODS: A total of 2 835 (81.00%) people aged 40 years old or more, from Fuping county, Jingbian county and Yang county of Shaanxi Province, China, underwent a comprehensive interview and a relative eye examination. The present of AMD was classified into neovascular AMD (NV) and pure geographic atrophy (GA) by using direct ophthalmoscopy for fundus examination according to International Classification System.

• RESULTS: The prevalence (95% CI) of AMD was 3.00% (2.42, 3.71) in this population, of which NV accounted for 1.45% (1.05, 1.98) and 1.55% (1.14, 2.10) for GA. The prevalence of AMD increased significantly with increasing age (P<0.01). AMD was present in 0.47% of participants aged 40 to 49 years, rising to 11.90% of participants older than 80 years, of which the corresponding data increased from 0.28% to 4.76% for NV and from 0.19% to 7.14% for GA. No significant difference was found in the prevalence of NA and GA between genders in this population. With multiple logistic analysis, apart from advancing age, only smoking was found to have a strong association with any type of AMD.

• CONCLUSION: The prevalence of AMD in the rural population of Shaanxi Province of China is lower than that reported from other population-based studies in different provinces of China, less than that reported in whites, more than that reported in blacks. Besides increasing age, smoking is also a significant well-known risk factor for AMD.

• KEYWORDS: age related macular degeneration; epidemiology; prevalence; risk factors; old people

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INTRODUCTION

Age related macular degeneration (AMD) is a disease involving typical lesions in the macular in older people. It is a leading cause of irreversible severe visual loss in older white populations in the Western world [1-11]. The prevalence of AMD has been reported in many population-based studies in recent years, ranging from 1% in black Africans older than 65 to 100% in Fenland population over 90 years old [12-18].

More recent data from the NHANES Ⅲ [13] shows different prevalence among the racial groups that various by age and gender. And Moeller *et al*[19] considered that different ethnic groups exhibit different patterns of intake for some food and nutrients that might be related to ARM risk. Advancing age, smoking, genetic make-up have now been accepted by most investigators as the most important risk factors to AMD [20-26], but other risk factors may also play significant roles in the pathogenesis of AMD, such as cardiovascular disease, dietary fat intake, alcohol consumption and sunlight exposure, have remained controversial [27-34].

Data on the prevalence and risk factors of AMD depended on population-based study is relatively limited in China in recent years. And with Chinese population aging and

socioeconomic situation developing, the prevalence of age-related eye disease, including AMD, is also increased. On account of what mentioned above, from July to December 2003, we started a population-based survey for eye diseases, including AMD, in rural population of Shaanxi Province of China. In this article we mainly reported the prevalence and relative factors associated with AMD in this population.

MATERIALS AND METHODS

From July to December 2003, a population-based survey was performed in the rural population of Shaanxi Province of China to investigate the prevalence, features and risk factors for eye diseases, the causes of blindness and visual impairment, and the problems on eye care services perceived by people in the location. A stratified, cluster-based, random sample of 2 835 people aged 40 years old or more, was selected from three districts of the North, South and Middle Shaanxi Province, Western China, with a response rate of 81.00%.

Participants were interviewed and examined based on documentary evidence if they had left the address for more than 6 months they would not be regarded as participants, whereas institutionalized residents were also examined if they had lived at the address for more than 6 months. The composition of the sample together with the participants' rates according to age, gender and education level achieved was in accordance with the proportion of local population. Therefore, the sample of this rural population was representative.

The elementary schools at local places were set up as temporary clinic centres for interview and eye examination. All participants had a verbal consent after explanations of nature and possible consequence of the study. The participants were interviewed by local interviewers speaking dialect according to the standard questionnaires, including information on participants demographic characteristics, education status, profession, incoming, smoking habits, alcohol intake, family history of cardiovascular diseases, diabetes, and any therapies implemented, sunlight exposure. Two blood pressure readings in the sitting position were taken. Various ophthalmic and other measurements, applanation tonometry, computer perimetry, lens grading were completed by trained research staff using a standard protocol that had been made in the diagnosis criterions of eye diseases among ophthalmologists.

One drop of tropicamide 10g/L was used to dilate pupils except those with occludable angles. The fundus was examined by direct ophthalmoscopy. The present of AMD was classified according to International Classification System.

Diagnostic criteria and definitions According to International Classification System [35], AMD was graded as "wet AMD" (neovascular AMD) or "dry AMD" (pure geographic atrophy). Neovascular AMD (NV) was defined to include serious or hemorrhagic detachment of either the retinal pigment epithelium (RPE) or sensory retina, the presence of subretinal pigment epithelium hemorrhage, or subretinal fibrous tissue, regardless of the degree of surrounding atrophic RPE changes. Pure geographic atrophy (GA) was defined as a discrete area of retinal depigmentation, with a sharp border and visible choroidal vessels, in the absence of signs of neovascular AMD in the same eye.

Other factors definitions Sunlight exposure was interpreted as the hours of an individual spent outdoors every day. The categories listed included $\geqslant$6h/d and <6h/d.

Smoking was defined as to smoke more than one cigarette every day and continue at least one year.

Drinking was defined as to drink distilled spirit (or wine) at least 50 gramme once every day.

Systemic hypertension: fulfillment either one of the following: ① Systolic blood pressure more than 160mmHg; ② Diastolic blood pressure more than 95mmHg; ③ A self-reported history of hypertension.

Stroke, nephropathy, angina, and arthritis: a self-reported history of the diseases.

Statistical Analysis All the questionnaires and examination data recorded were re-reviewed by a senior ophthalmologist after every participant finished the eye examination. When indicated suspicious information or record, it would be checked-up again with original participant, even reexamined if necessary.

Data were double-entered forms in a customized Epi info (centres for Disease Control and Prevention, Atlanta, GA) database with validation, range, and consistency checks. Analysis was performed by using SPSS version 11.0 statistical software. The stratified analysis using the Mantel-Haenszel method was applied to test the difference in age-adjusted prevalence between male and female. Multiple logistic regression was performed to analyze possible risk factors associated with AMD. Statistical significance was assessed if the associated *P* values were less than 0.05.

Table 1 Prevalence, age and gender of AMD cases in rural area of Shaanxi Province

Age (a)	Male			Female			Total		
	N	*n*	*P* (95%CI)	N	*n*	*P* 95%CI)	N	*n*	*P* 95%CI)
40-	438	4	0.91(0.29,2.49)	622	1	0.16(0.01,1.04)	1060	5	0.47(0.17,1.16)
50-	368	11	2.99(1.58,5.44)	493	9	1.93(0.89,3.56)	861	20	2.32(1.46,3.63)
60-	290	15	5.17(3.03,8.57)	308	19	6.17(3.86,9.62)	598	34	5.69(4.03,7.94)
70-	131	11	8.40(4.47,14.87)	143	10	6.99(3.59,12.82)	274	21	7.66(4.92,11.64)
80-	19	3	15.79(4.17,40.49)	23	2	8.70(1.52,29.51)	42	5	11.90(4.47,26.43)
Tota1	1246	44	3.53(2.61,4.75)	1589	41	2.58(1.88,3.52)	2835	85	3.00(2.42,3.71)

AMD: age related macular degeneration;Adjusted for age by stratified analysis using the Mantel-Haenszel method, *P*-value for the difference between males and females: *P* = 0.360, OR = 0.80 (95%CI, 0.52, 1.23)

Table 2 Prevalence of age and gender GA and NV

Age (a)	GA†			NV‡		
	Male *P* (95%CI)	Female *P* (95%CI)	Total *P* (95%CI)	Male *P* (95%CI)	Female *P* (95%CI)	Total *P* (95%CI)
40-	0.46(0.08,1.82)	0（0,0.77）	0.19(0.03,0.76)	0.46(0.08,1.82)	0.16(0.01,1.04)	0.28(0.07,0.90)
50-	2.17(1.01,4.41)	1.01(0.37,2.49)	1.51(0.84,2.64)	0.82(0.21,2.57)	0.81(0.26,2.21)	0.81(0.36,1.75)
60-	2.41(1.06,5.12)	3.25(1.66,6.08)	2.84(1.72,4.61)	2.76(1.29,5.57)	2.92(1.43,5.67)	2.84(1.72,4.61)
70-	3.05(0.98,8.11)	3.50(1.29,8.39)	3.28(1.61,6.36)	5.34(2.36,11.11)	3.50(1.29,8.39)	4.38(2.39,7.72)
80-	5.26(0.28,28.11)	8.70(1.52,29.51)	7.14(1.86,20.55)	10.53(1.84,34.54)	0(0,17.81)	4.76(0.83,17.42)
Total	1.77(1.14,2.71)	1.38(0.89,2.13)	1.55(1.14,2.10)	1.77(1.14,2.71)	1.20(0.74,1.90)	1.45(1.05,1.98)

GA:Geographic atrophy AMD;NV:Neovascular AMD;Adjusted for age by stratified analysis using the Mantel-Haenszel method, between males and females: †*P*= 0.710, OR = 0.85 (95%CI, 0.47, 1.55); ‡*P*= 0.449, OR = 0.75 (95%CI, 0.40, 1.40)

RESULTS

Study participants Totally 2 835 of the eligible 3 500 people aged 40 years old or more were interviewed and examined from July to December 2003, a response rate of 81.00%. The age of these participants ranged from 40 to 91 years (media age: 52 years; mean age: 54.7 years), and 1 589 participants (56.05%) were female. Seven hundred and seventy-three (27.27%) participants were illiteracy, and 2 062 (72.73%) were non-illiteracy; 1 060 participants (37.39%) belonged to the 40-49 years bracket of age, 861 participants (30.37%) belonged to the 50-59 years bracket of age, 598 participants (21.09%) belonged to the 60-69 years bracket of age, and 316 participants (11.15%) were 70 years of age or older.

AMD prevalence Table 1 and Table 2 show the number of AMD cases and the prevalence (95% Confidence Limits) of AMD by age and gender. Both the media and mean age of participants with AMD was 64.0 years (range: 42-86 years). There were 85 participants found to have AMD in our study totally, and its prevalence was 3.00% (95% CI, 2.42, 3.71). The prevalence of NV was 1.45% (95%CI, 1.05, 1.98), and 1.55% (95% CI, 1.14, 2.10) for GA. AMD prevalence increased significantly with increasing age (P <0.001), increasing from 0.47% of participants aged 40 to 49 years to 11.90% of those older than 80 years. NV was present in 0.28% of participants aged 40 to 49 years, rising to 4.76% of those older than 80 years and the corresponding data for GA increased from 0.19% to 7.14% . No significant difference was found in the prevalence of AMD between males and females (P= 0.360), although males (3.53%) had a high rate than females (2.58%).

From the responses to the questionnaire administered to those studied, we obtained the frequencies of five diseases regarded as indicative of possible systemic vascular involvement. As can be seen from Table 3 and Table 4, after using multiple logistic regression analysis (Enter), a multiple logistic regression analysis with possible risk factors was then employed using backward stepwise conditional model building. Only age and smoking both entered the multiple logistic models for any type of AMD at last, indicated increasing age and smoking cigarettes were independent and strong risk factors for AMD. No associations were found with drinking, education level, sunlight, adumbral tools, nephropathy, and cataract surgery in any form of AMD.

Table 3 Multiple logistic regression for possible Effect Factors for AMD

	GA		NV		AMD	
	Odds Ratio(95%CI)	*P*	Odds Ratio (95%CI)	*P*	Odds Ratio (95%CI)	*P*
Age(yr)		0.002		<0.001		<0.001
40-	1.00		1.00		1.00	
50-	8.29(1.83, 37.45)		4.41(1.11, 17.50)		6.31(2.33, 17.13)	
60-	14.09(3.06, 64.81)		22.36(6.04, 82.83)		18.29(6.80, 49.19)	
70-	18.62(3.69, 93.99)		46.98(11.67, 189.04)		30.27(10.52, 87.11)	
80-	39.78(5.62, 281.39)		44.10(6.05, 321.62)		45.05(11.23, 180.68)	
Gender		0.058		0.177		0.022
Male	1.00		1.00		1.00	
Female	3.05(0.96, 9.64)		2.34(0.68, 8.00)		2.75(1.16, 6.53)	
Smoking		0.001		0.034		<0.001
No	1.00		1.00		1.00	
Yes	6.57(2.11, 20.42)		3.55(1.10, 11.46)		4.97(2.15, 11.46)	
Drinking		0.248		0.492		0.673
No	1.00		1.00		1.00	
Yes	0.30(0.04, 2.33)		1.59(0.42, 6.02)		0.79(0.26, 2.37)	
Education		0.615		0.240		0.242
Illiteracy	1.00		1.00		1.00	
Non-Illiteracy	1.21(0.57, 2.57)		1.66(0.71, 3.86)		1.40(0.80, 2.46)	
Incoming		0.870		0.232		0.785
Lower	1.00		1.00		1.00	
Middle	0.004(0, 4.2E+07)		4.00(0.79, 20.36)		0.73(0.16, 3.46)	
Upper	0.003(0, 3.1E+18)		0.001(0, 4.0E+13)		0.008(0, 1.0E+05)	
Sunlight (h)		0.301		0.318		0.113
≤6	1.00		1.00		1.00	
>6	0.56(0.19, 1.68)		0.54(0.16, 1.80)		0.52(0.23, 1.17)	
Adumbral tools		0.748		0.355		0.371
No	1.00		1.00		1.00	
Yes	0.84(0.29, 2.46)		0.55(0.16, 1.94)		0.68(0.30, 1.57)	
Hypertension		0.901		0.002		0.008
No	1.00		1.00		1.00	
Yes	0.96(0.47, 1.95)		0.09(0.02, 0.41)		0.43(0.23, 0.80)	
Stroke		0.903		0.004		0.240
No	1.00		1.00		1.00	
Yes	0.003(0, 4.3E+38)		41.75(3.40, 512.24)		4.04(0.40, 41.57)	
Nephropathy		0.839		0.124		0.513
No	1.00		1.00		1.00	
Yes	0.001(0, 6.4E+24)		7.56(0.57, 99.71)		2.10(0.23, 19.57)	
Angina		0.013		0.822		0.272
No	1.00		1.00		1.00	
Yes	8.16(1.56, 42.78)		0.001(0, 3.3E+23)		2.51(0.49, 12.93)	
Arthritis		0.947		0.074		0.121
No	1.00		1.00		1.00	
Yes	1.04(0.35, 3.05)		0.16(0.02, 1.20)		0.47(0.18, 1.22)	
Cataract surgery		0.546		0.822		0.619
No	1.00		1.00		1.00	
Yes	1.91(0.23, 15.52)		0.001(0, 2.3E+23)		0.59(0.07, 4.84)	
Location		0.474		<0.001		<0.001
Fuping	1.00		1.00		1.00	
Yangxian	0.54(0.16, 1.84)		0.07(0.01, 0.35)		0.23(0.09, 0.61)	
Jingbian	0.61(0.23, 1.61)		0.07(0.02, 0.33)		0.24(0.11, 0.54)	

Of the 85 participants with AMD, only 7 (8.24%) suffered visual impairment in various degrees as a result of AMD, of which 3 (3.53%) participants were blindness in one eye, and another 4 (4.71%) were low vision in one or both eyes. Blindness in both eyes was not found in this population.

DISCUSSION

The study of the distribution of disease in the population can illuminate two points: it gives us an idea that who is the

Table 4 Multiple Logistic Regression (backward stepwise) for Risk Factors for AMD

	GA		NV		AMD	
	Odds Ratio (95%CI)	*P*	Odds Ratio (95%CI)	*P*	Odds Ratio (95%CI)	*P*
Age (a)		0.001		<0.001		<0.001
40-	1.00		1.00		1.00	
50-	7.64(1.72, 33.99)		4.16(1.07, 16.23)		6.21(2.30, 16.74)	
60-	12.47(2.86, 54.44)		22.36(5.18, 62.52)		16.84(6.43, 44.07)	
70-	16.67(3.56, 78.07)		30.81(8.44, 112.48)		26.61(9.75, 72.67)	
80-	39.78(5.83,230.88))		23.63(3.72, 150.06)		36.55(9.84, 135.70)	
Gender		0.047				0.038
Male	1.00				1.00	
Female	2.98(1.02, 8.76)				2.36(1.05, 5.28)	
Smoking		0.001		0.018		<0.001
No	1.00		1.00		1.00	
Yes	6.27(2.10, 18.69)		2.18(1.14, 4.15)		4.55(2.02, 10.28)	
Incoming		0.870				
Lower	1.00					
Middle	0.003(0, 2.9)					
Upper	0.003(0, 6.7)					
Hypertension				0.002		0.016
No			1.00		1.00	
Yes			0.10(0.02, 0.43)		0.48(0.26, 0.87)	
Stroke		0.903		0.023		
No			1.00			
Yes			16.39(1.48, 181.43)			
Angina		0.013				
No	1.00					
Yes	6.99(1.43, 34.10)					
Arthritis				0.051		0.126
No			1.00		1.00	
Yes			0.11(0.01, 1.01)		0.48(0.19, 1.23)	
Location		0.474		<0.001		<0.001
Fuping			1.00		1.00	
Yangxian			0.17(0.06, 0.49)		0.33(0.17, 0.62)	
Jingbian			0.10(0.02, 0.44)		0.27(0.13, 0.58)	

most affected by the disease first-this can guide the delivery of health services; then, it can help to develop or confirm hypotheses on aetiology [36]. AMD is a leading cause of blindness in the western world in individuals over 60 years old. And with Chinese population aging and socioeconomic situation developing, the prevalence of age related eye disease, including AMD, is also increased. However, there has not been effective treatment that can restore vision in age-related macular degeneration until now. On account of this reason, it appears to be significant to identify possible risk factors for preventing the disease developing in the first place.

The wide variation in the prevalence of AMD across groups of people with a lot of ethnic backgrounds suggests the possibility that there may be differences in genetic susceptibility or environmental risk factors (such as lifestyle or diet). However, the evaluation of prevalence of AMD in various ethnic populations is fairly difficult because of inconsistent definitions of AMD, the methods to assess AMD, and the age of the study sample. Considering stereo photographs examination for all participants in population-based study might not be feasible in developing country, direct ophthalmoscopy was performed to assess fundus in this rural population of Shaanxi Province. Therefore, the prevalence of AMD in this population would possibly be underestimated, and the comparison between data from our study and that reported in other populations defining AMD by grading of stereo photographs is improper. We can but evaluate prevalence of AMD across ethnic groups roughly. In the rural population of Shaanxi Province in China, among people aged 40 years old or more, we found the total prevalence of AMD was 3.00% (95% CI, 2.42, 3.71), of which NV accounted for 1.45% (95% CI, 1.05, 1.98), and GA accounted for 1.55% (95% CI, 1.14, 2.10). In our study the prevalence of AMD in various brackets of age in response other studies to be compared was roughly less than that of any ARM observed in the Visual Impairment Project (VIP) (15.7%) [16] in persons over

40 years, Blue Mountains Eye Study (6.4%) [2] in residents aged 49 and older, the Beaver Dam Eye Study (15.3%) [5] in those aged 43-84 and the Colorado-Wisconsin Study (11.9%) in local residents aged 43-74, more than that reported in blacks [14, 17-19]. We also found the prevalence of AMD in our study was less than that reported in other population-based studies in different Provinces of China, such as 8.4% [37] of AMD was reported in the population aged 50 years old or more in Doumen County of Guangdong Province in the south of China according to the criteria of National Academic Group of Fundus Disease combined with the visual criteria of Framingham Eye Study, and 7.4% [38] persons with AMD were found from the population more than 50 years old in a epidemiologic survey performed in Zhejiang Province of Southern China. The difference in the prevalence of AMD in these populations in China was possibly due to the differences in diagnostic standards, examination technique of the studies, different regions, life styles, occupation, socioeconomic situation and environments in these study populations.

Although only 7 participants (8.24%) were found to have visual impairment because of AMD in this population, lower than that reported in other previous survey, it also would not be ignored the significant eye health problem led from AMD, on account of irreversible vision loss in persons all over 70 years old in this population.

As most studies reported a strong increase in the prevalence of AMD with age and smoking [20-26], we found the similar results in this population that advancing age and smoking cigarettes were significant and strong risk factors for AMD by using a multiple logistic regression analysis (backward stepwise conditional model building) with possible risk factors because age and smoking both entered the multiple logistic models for any type of AMD at last. A higher prevalence of AMD among people aged 80 years and older in our study is also in consistence with the findings from previous studies [2, 3, 5-18]. The risk of AMD associated with smoking was 4.55 (95% CI, 2.02, 10.28) in our study, strengthening the argument that this is likely to be a true association. And the magnitude of risk with smoking was higher in the data for GA (odds ratio, 6.27) compared with NV (odds ratio, 2.18).

The finding of only two significant associations with AMD in the data (age and smoking) may be due to relatively greater measurement error associated with the other exposures investigated. The higher measurement error or insufficient to evaluate dose would lead to larger biases toward the null, deceasing the possibility of finding true associations with AMD. Self-reported education status, profession, incoming, alcohol intake, sunlight exposure, history of cardiovascular diseases, and any therapies implemented in our survey also possibly attributed to recall and information biases.

There were also some exposures found to have a possible association with NV or GA. Data from our study showed, apart from age and smoking, gender, incoming and angina also entered the multiple logistic backward stepwise conditional model for GA, whereas hypertension, stroke, arthritis and location in the model for NA, indicted that women, lower socioeconomic situation and those with angina are at greater risk of GA, stroke and lived in Fuping County for increased risk of NV. Interesting to us, different to general idea that raised blood pressure or hypertension may have an effect on the developing of AMD, we found an inconsistent result that persons with hypertension and arthritis are less likely to have NV. The explanation to this negative association with blood pressure and the apparent difference in risk factors between NV and GA would possibly be due to the limited sampling size and recall and information biases led from self-reported without the knowledge about diseases of participants. Therefore, some possible potential risk factors for AMD presented an inconsistent association with NV and GA. It is commonly considered that women are at increases risk of developing AMD, however, few studies have demonstrated this increased risk unequivocally. The findings for reported history of cardiovascular disease are also inconsistent with some studies finding an association [23, 28] and others not [24, 27, 30].

The difference in NV prevalence among three counties from the north, south and middle of Shaanxi Province, respectively, may be due to the different sunlight exposure, as reported in some published studies [23,39]. Although we failed to identify significant association between sunlight exposure and AMD, measurement and information biases would decrease the association of these two variables. And whether or not expose to sunlight is a significant factor for developing AMD in human is not clear. It is different to measure lifetime light exposure, and little convincing evidence has been found [36]. In our survey, self-reported of the participants' activities in relation to time spent out doors

and use of ambient light exposure was performed to measure sunlight exposure roughly. However, such crude evaluation of the effects of these factors can vary enormously in deed. There are also possibly other factors affected the prevalence of NV in these three counties, such as differences in lifestyle, diet and environment, as suggested by Moeller.

Association of drinking alcohol and AMD has remained unclear. Few studies found that alcohol intake associated with AMD [29-30,33,34], whereas possible effects of beer drinking with NV or retinal drusen were reported 31, 32. In the Physicians Health study, the authors speculated that alcohol did not appear to have the same effect in AMD [40]. We also did not find the significant association of drinking alcohol and the developing of AMD with crude measurement to evaluate dose.

In conclusion, the prevalence of AMD in the rural population of Shaanxi Province of China is 3.00%, of which the rates of NV and GA are approximately equal. Apart from advancing age, cigarette smoking as a preventable exposure also presents a strong and consistent association with any type of AMD.

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