Primary Angle Closure Glaucoma in East Asia: an Overview of the Mongolia-based Research Programme

Winifred P Nolan[1,2]
[1]National University Hospital, Singapore, and [2]Institute of Ophthalmology, University College London, London, UK

Primary angle closure glaucoma is an important contributor to glaucoma blindness. Recent epidemiological studies have helped to quantify the scale of the potential burden of visual disability due to primary angle closure glaucoma in Asia. While these studies often demonstrate that equal numbers of people are affected by primary angle closure glaucoma and primary open angle glaucoma, the proportion of individuals rendered blind in one or both eyes is higher for primary angle closure glaucoma. A series of studies designed to determine whether it is possible to prevent blindness due to primary angle closure glaucoma in East Asia have been performed. This review will summarise the aims, methodology, and main findings from this research programme.

Key Words: *Glaucoma, angle-closure, Mass screening, Mongolia*

Asian J Ophthalmol 2006;8(1):6-12

Introduction

Glaucoma has been estimated to be the commonest cause of irreversible blindness worldwide.[1] Primary angle closure glaucoma (PACG) has long been suspected to be an important contributor to glaucoma blindness due to its prevalence in the densely populated countries of Asia.[2] However, it is really only in the past decade or so that epidemiological studies have helped us to quantify the scale of the potential burden of visual disability due to PACG in Asia. Prior to the 1990s, research into the prevalence, risk factors, and treatment of PACG in Asians had been concentrated in studies of the Inuit populations of Greenland and Alaska.[3-5] During the past 15 years, the number of well-designed studies investigating the characteristics of PACG in Asia has increased considerably. While these studies often demonstrate that equal numbers of people are affected by PACG and primary open angle glaucoma (POAG), the proportion of individuals rendered blind in one or both eyes is higher for PACG.[6,7]

As with any condition that is common and results in disability there is a need to try and develop a strategy for reducing the impact of the disease, both at an individual and population level. It would be ideal if we could diagnose the disease at an early stage using a simple inexpensive method and then implement a safe intervention that is effective for preventing progression to visual loss. In contrast to POAG, laser iridotomy provides us with a relatively simple non-invasive treatment for PACG and gives those specialists researching the disease some cause for optimism. If we could find a method of screening for angle closure at an early presymptomatic stage, those individuals with angle closure could be treated with laser iridotomy, which may prevent the development of more advanced disease. The World Health Organization and, more recently, the National Screening Committee in the UK have listed the requirements of a disease that should be fulfilled prior to implementing a screening programme (Table 1).[8,9]

With these criteria in mind, a programme of research focusing on PACG has been running in Mongolia since 1991. Collaboration between the International Centre for Eye Health in London and ophthalmologists from the Mongolian Medical University in Ulaanbaatar has resulted in a series of studies designed with the ultimate aim of determining whether it is possible to prevent blindness due to PACG in East Asia. This review will summarise the aims, methodology, and main findings from this research programme to date.

Prevalence and Characteristics of Glaucoma in Mongolia

An initial survey of 4000 adults was conducted in 1992 to ascertain the causes of blindness in Mongolia.[10] This survey showed that glaucoma was responsible for 35% of blindness.

The next project was designed to answer the important question: What is the mechanism of glaucoma in this population? A population-based survey of Mongolian adults aged 40 years and older was conducted in the northern Mongolian province of Hövsgöl by Foster et al.[11] An important feature of this study was the gonioscopic examination of all participants by a single observer. Of the selected 1000 participants, 942 underwent a comprehensive examination, including visual field testing and optic nerve head examination.

When the International Society of Geographic and Epidemiological Ophthalmology (ISGEO) classification of glaucoma[12] (Table 2) was used, the prevalence of PACG was calculated as 0.8% and was equivalent to that of POAG. These definitions require the presence of glaucomatous

Table 1. Criteria that should be fulfilled prior to implementing screening for a disease.[8,9]

Requirements of the disease being screened for
- The disease or condition should be a significant health problem as measured by the prevalence, the degree of morbidity and/or mortality associated with it, and the economic impact of the disease
- The epidemiology and natural history of the disease should be understood
- Early diagnosis should be beneficial and should have a favourable effect on outcome

Requirements of the screening test
- The test should have acceptable sensitivity and specificity and the distribution of these values in the target population should be known
- The test should be non-invasive, safe, and acceptable to the population being screened
- The test should be simple and inexpensive with the capability of being performed by trained non-medical personnel with robust equipment
- There should be an agreed policy on the management and further diagnostic investigation of test-positive cases

Requirements of the treatment
- There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

Table 2. International Society of Geographic and Epidemiological Ophthalmology classification of glaucoma for use in population-based surveys.[12]
Abbreviation: CDR = cup-disc ratio.

Category 1 diagnosis (structural and functional evidence)
- CDR or CDR symmetry ≥97.5th percentile for the normal population
  or
- Neuroretinal rim width reduced to ≤0.1 CDR (between 11 and 1 o'clock or 5 and 7 o'clock)
  plus
- A definite visual field defect consistent with glaucoma

Category 2 diagnosis (advanced structural damage with unproved field loss)
- CDR or CDR asymmetry ≥99.5th percentile for the normal population

Category 3 diagnosis (optic disc not seen)
- Visual acuity <3/60 and intraocular pressure >99.5th percentile
  or
- Visual acuity <3/60 and evidence of glaucoma filtering surgery

Primary angle closure glaucoma
- Any of the above 3 categories in the presence of an occludable angle (posterior trabecular meshwork not visible for ≥270° angle)

optic neuropathy for a diagnosis of glaucoma to be made. In addition to the diagnosis of PACG, 2.7% of the participants were diagnosed with primary angle closure (PAC; evidence of synechial closure or elevated intraocular pressure [IOP] in the presence of an occludable angle) and 3% were diagnosed with occludable angles (posterior trabecular meshwork not visible without indentation for ≥270°), also known as primary angle closure suspects (PACS).

Although these latter groups did not have evidence of glaucomatous optic neuropathy on visual field or optic nerve head examination, their presence suggested that PAC is the predominant mechanism of glaucoma in Mongolia. The majority of patients with PACG and PAC were asymptomatic (with no ischaemic sequelae of acute angle closure) as is typical of angle closure in Asia, and women were more often affected than men. Another important finding was that a significantly greater proportion of participants with PACG were bilaterally or unilaterally blind compared with those with a diagnosis of POAG. This feature of PACG, also shown by the Singapore-based Tanjong Pagar survey,[6] highlights the aggressive and visually destructive nature of the disease. By using the data collected during the Mongolian and Singaporean surveys, Foster and Johnson were able to estimate that there may be as many as 1.6 million people in China who are bilaterally blind due to PACG.[7]

Risk Factors for Primary Angle Closure Glaucoma

The Danish ophthalmologists Clemmenson[3] and Alsbirk,[13] who conducted research in the Greenland Inuit population, found that PAC was more likely to be present in eyes with shallow peripheral and central anterior chambers and a smaller radius of corneal curvature. This association between a crowded anterior segment and an increased risk of angle closure was also shown by Lowe.[14]

Anterior chamber depth (ACD) as a risk factor for angle closure was explored further in Mongolia. The values for age-specific mean central ACDs measured from the Hövsgöl sample were shown by Foster et al to lie between those found in Caucasian populations (who have deeper anterior chambers) and those of the Greenland Inuit (who have shallower anterior chambers), supporting the previously reported inverse relationship between mean population central ACD and the prevalence of PACG.[15]

Devereux et al demonstrated that even within the Mongolian population, individuals with occludable angles had shallower anterior chambers than the rest of the population (Figure 1).[16] The anterior chamber tends to be shallower in women and decreases with increasing age, rendering these subgroups at higher risk for angle closure.

The relationship between a shallow ACD and risk for angle closure has been quantified by using the Mongolia data and measurements later collected in Chinese Singaporean people to estimate the odds of angle closure at decreasing ACDs.[17] Figure 2 shows that the risk of having peripheral anterior synechiae (PAS) increases significantly in eyes with shallower ACDs for both the Mongolian and Singaporean populations.

Figure 1. Lowess curve showing distribution of optical pachymetry anterior chamber depth by age. The large grey dots represent the anterior chamber depth measurements of individuals with occludable angles.[16] Reproduced with permission from the American Medical Association.

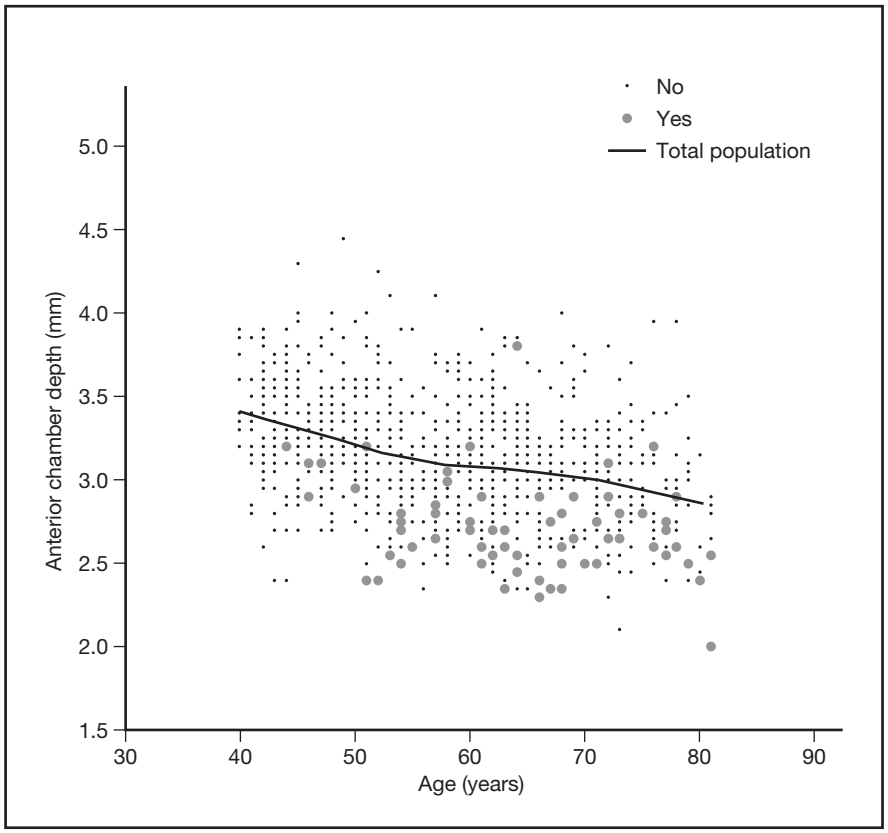
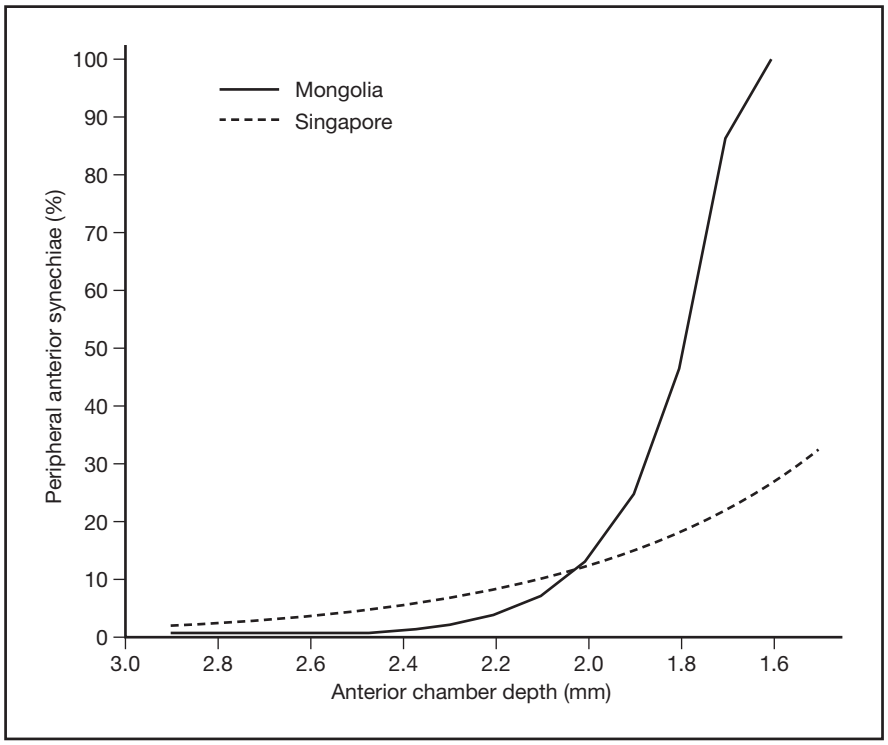


Figure 2. Graph showing proportion of Mongolian and Chinese Singaporean patients with peripheral anterior synechiae at decreasing central anterior chamber depths as measured by optical pachymetry.



Anterior Chamber Depth Measurement as a Screening Tool for Angle Closure

Alsbirk had previously used the van Herick method of estimating peripheral ACD as a ratio to corneal thickness to screen for angle closure in Greenland,[18] and Congdon et al reported good sensitivities and specificities for ultrasound measurement of central ACD in detecting angle closure in a Taiwanese population.[19]

Devereux et al[16] and Foster et al[20] evaluated several methods of measuring ACD as screening tests by comparing them with gonioscopy (the reference standard) in the Mongolian population. These studies were carried out in a population-based sample in southern Mongolia (Omnigobi province), using data collected from the Hövsgöl population. All participants underwent measurements of central ACD using A-scan ultrasound biometry and optical pachymetry methods and limbal ACD. At the beginning of the Hövsgöl glaucoma survey, Foster et al[20] refined and modified the traditional van Herick[21] method of measuring the peripheral or limbal ACD. The modified limbal chamber depth (LCD) grading scheme differed from the van Herick method by having 7 grades (0%, 5%, 15%, 25%, 40%, 75%, and ≥100%) instead of the usual 5 (0, 1/4,1/2, 3/4, 1).

The performances of the different ACD measurement methods for detecting occludable angles are presented in the form of receiver operating characteristic (ROC) curve analysis in Figures 3 and 4. The area under the curve (AUC) gives a measure of the overall performance of the test. The modified LCD method gave good sensitivities and specificities (83.7% and 85.7%, respectively, for 15% cut-off grade) for detecting patients with occludable angles and established angle closure (PAC). Optical pachymetry and ultrasound methods of measuring ACD

Figure 3. Receiver operating characteristic curve comparing the performance of traditional (van Herick) and modified limbal chamber depth grading schemes for the detection of gonioscopically occludable angles. Br J Ophthalmol 2000;84:186-192. Reproduced with permission from the BMJ Publishing Group.
Abbreviation: AUC = area under the curve.

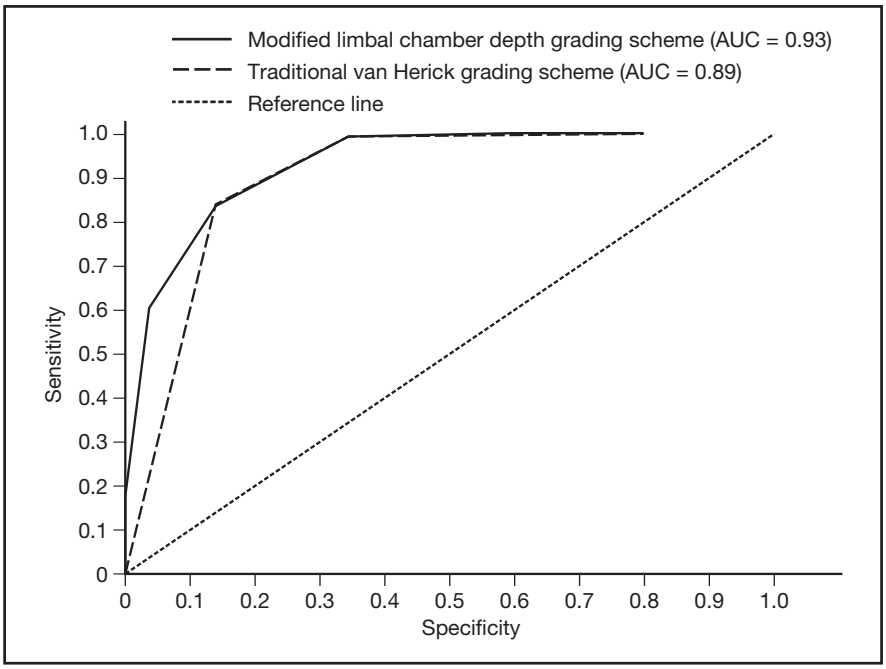
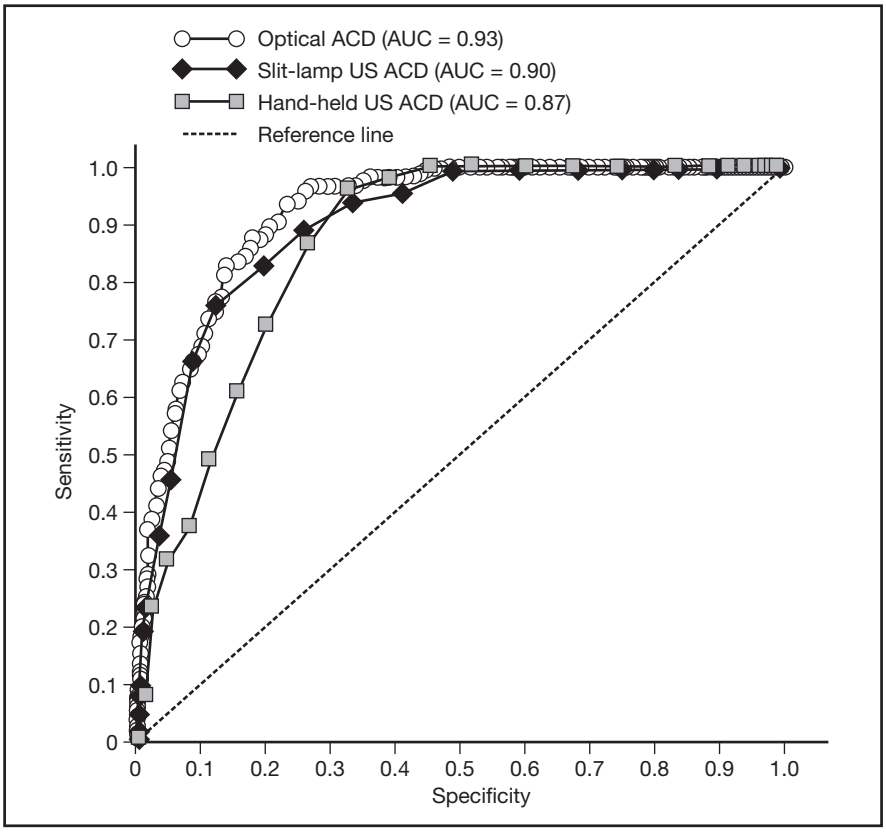


Figure 4. Receiver operating characteristic curve comparing the performance of different methods of measuring central anterior chamber depth for the detection of gonioscopically occludable angles.[16] Reproduced with permission from the American Medical Association.
Abbreviations: ACD = anterior chamber depth; AUC = area under the curve; US = ultrasound.



both performed well for detecting occludable angles, with pachymetry giving slightly better values.

Although the LCD and pachymetry methods gave better sensitivities and specificities than the ACD measurements obtained using A-scan ultrasound they have limited potential as screening tools. Both require the use of a slit-lamp and so would be more expensive and cumbersome, and require a greater level of expertise than the ultrasound method. Two techniques — mounting the probe on a tonometer of a slit-lamp, and a hand-held method — were employed to measure the central ACD using the A-scan ultrasound. The hand-held method performed less well than the slit-lamp mounted method as a screening tool (Figure 4). This was disappointing as it is a simpler method of obtaining the measurements and therefore would be a more ideal way of screening. The reason for the poor performance was likely to be due to instability of the hand-held probe resulting in indentation of the cornea and consequently the detection of a greater number of false-positive cases. However, this was easily overcome by using a specially designed table-top device, which provided more stability for the probe but avoided the need for a slit-lamp (Figure 5).

While the LCD measurements seemed to detect more cases of angle closure in this population, the ultrasound method has the advantage of being easier to perform with simpler equipment. LCD may have a role in the early detection of angle closure in a clinic setting, but in terms of community or population-based screening, the simpler but effective ultrasound method would be the more pragmatic and inexpensive option.

Effectiveness of Treatment for Angle Closure

There is little point in screening for a condition unless there is an intervention that is

Figure 5. Photograph showing the table-top device specially designed for obtaining measurements of central anterior chamber depth in Mongolia in the screening trial. The A-scan ultrasound probe was mounted on the device, providing it with more stability while avoiding the need for a slit-lamp.

effective for preventing disease progression when implemented at this presymptomatic stage. Laser peripheral iridotomy is established as a first-line treatment for the management of angle closure. However, it is not clear whether angle closure in Asian eyes is caused predominantly by pupil block mechanisms and is responsive to treatment with iridotomy.

Using a portable YAG laser all individuals diagnosed as PACS, or with PAC and PACG during the 1995 and 1997 glaucoma surveys were treated with laser iridotomy (using a portable YAG laser) at the time of examination. As many as possible of those treated were re-examined in 1998. The main findings at follow-up were as follows:[22]

- the iridotomy was still patent in 98.1% (157/160) of treated eyes
- comparison of pre- and post-laser gonioscopy found that the angle width was a median of 2 Shaffer grades wider at follow-up; the angle was no longer defined as occludable in all but 3 of the laser treated eyes
- in 55% (15/27) of eyes with an elevated IOP at the time of iridotomy (>19 mm Hg), there was IOP reduction to normal levels without medication at follow up.

The latter 2 findings suggest that pupil block must be the primary mechanism of angle closure in this particular Asian population. When IOP control was analysed by diagnostic subgroup, 97% (65/67) of eyes with PAC showed effective IOP control compared with 52% (12/23) of eyes with PACG, leading us to conclude that laser iridotomy is most effective when administered in the earlier stages of the angle closure process, prior to the development of glaucomatous optic neuropathy. Logistic regression analysis of factors determining the success of iridotomy support this hypothesis (Table 3). Similar findings have previously been reported in studies of iridotomy in South Africa and Korea.[23,24]

The results from the laser iridotomy study were encouraging. They suggested that if patients with angle closure are treated early, it may be possible to prevent them progressing to advanced glaucoma.

Randomised Controlled Trial of Screening

The work presented so far provided the basis for running a randomised controlled trial of screening in Mongolia. The aim of this trial was to determine whether screening for individuals with occludable angles (either PACS or PAC) and treatment with laser iridotomy could prevent progression to PACG.

Participants were recruited in the Bayanhongor area of southern Mongolia and the capital city Ulaanbaatar. They were randomised on an individual basis to screening (with A-scan ACD measurement and tonopen IOP) or control groups. Individuals in the screened group who tested positive were examined with a slit-lamp and gonioscopy and those found to have occludable angles were treated with bilateral YAG laser iridotomies. All participants recruited to the trial first underwent optic disc examination and non-mydriatic disc photography to determine whether they had any evidence of glaucoma at baseline. Participants with evidence of glaucomatous optic neuropathy were excluded from the remainder of the trial. After excluding the patients with glaucoma, 4598 participants were recruited to the trial in 1999.[25] 156 participants in the intervention group were treated with iridotomy following screening (Figure 6). Six years later, the recruited individuals were examined again to determine whether there was a significant difference in the primary outcome (incidence of PACG over 6 years) between the intervention and control groups. This second stage of the trial has just been completed and the data is currently undergoing analysis. An economic analysis of screening for angle closure based on this trial is currently underway.

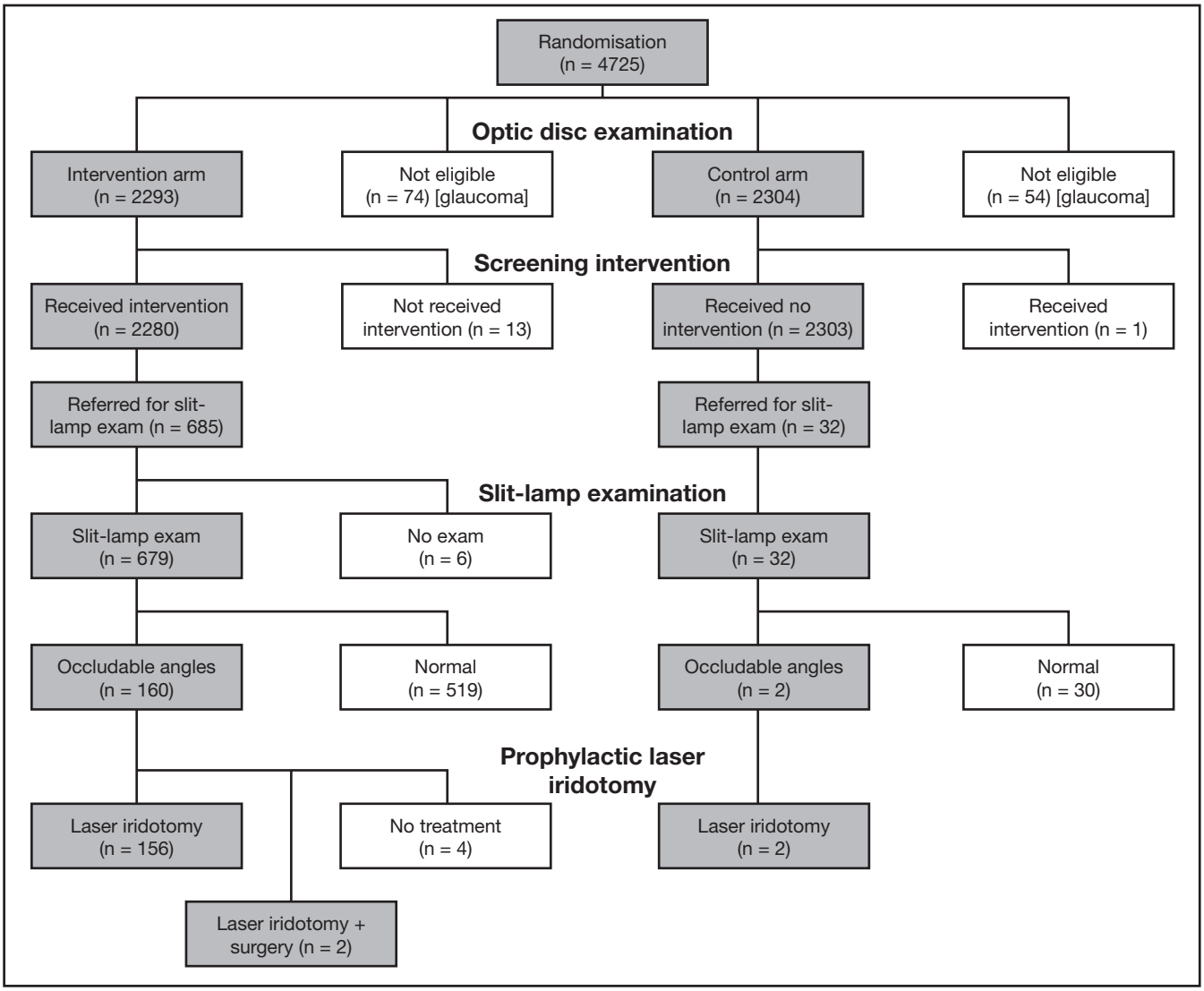
This is the first reported trial of screening for glaucoma and the results should give us some idea of whether there is potential

Table 3. Logistic regression analysis of predictive findings for outcome of failure with iridotomy. Br J Ophthalmol 2000;84:1255-1259. Reproduced with permission from the BMJ Publishing Group.

Factor	Odds ratio	95% Confidence interval	p Value
Univariate analysis			
PAS (3-4)	7.78	1.87-32.33	0.005
CDR ≥0.8	26.43	5.56-125.62	<0.0001
IOP >19 mm Hg	31.70	3.70-266.93	0.002
Multivariate analysis			
PAS (3-4)	2.47	0.38-15.97	0.34
CDR ≥0.8	15.04	2.28-99.29	0.005
IOP >19 mm Hg	19.80	1.85-212.49	0.01

Abbreviations: CDR = cup-disc ratio; IOP = intraocular pressure; PAS = number of quadrants containing peripheral anterior synechiae.

Figure 6. Profile for randomised controlled trial of screening for angle closure. Br J Ophthalmol 2003;87:271-274. Reproduced with permission from the BMJ Publishing Group.



for angle closure screening programmes in East Asian populations.

Current Priorities for Angle Closure Research

The programme of research conducted in Mongolia during the past 10 years has coincided with and helped to stimulate an increased awareness of the importance of PACG in Asia and the need for well-conducted research into the disease. We now have prevalence data on PACG from Singapore, Thailand, and India acquired using the standardised international glaucoma classification.[6,26-28] The prevalence of PACG in these South and South East Asian populations is remarkably similar to that found in the Mongolian surveys. However, the pathophysiology of angle closure may be different; non-pupil block mechanisms seem to play more of a role in PAC in Chinese people[29] and it is likely that this applies to South East Asia as well. If this is the case, then laser iridotomy may be less effective either as treatment of, or prophylaxis for, angle closure in these groups.

New technologies such as anterior segment optical coherence tomography may provide more objective and precise methods of detecting people with angle closure. In parallel with the discovery of more sensitive diagnostic methods, research programmes need to focus on determining the natural history and mechanisms of PACG, and the effectiveness and safety of laser and surgical treatment in different Asian populations. Much of this work is in progress and the results will help shape future prevention of blindness programmes targeted at glaucoma in Asia.

Acknowledgements

Financial support for this research was provided by: The International Glaucoma Association, London; The British Council

for the Prevention of Blindness; The Danish Association for the Blind, Copenhagen; Velux foundation, Copenhagen; National Lottery Charities Board (UK); Fight for Sight; and The Wellcome Trust.

References

1. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. Bull World Health Organ 2004; 82:844-851.
2. Quigley HA. Number of people with glaucoma worldwide. Br J Ophthalmol 1996;80:389-393.
3. Clemmeson V, Alsbirk PH. Primary angle-closure glaucoma (a.c.g) in Greenland. Acta Ophthalmol 1971;49:47-58.
4. Alsbirk PH. Primary angle-closure glaucoma. Oculometry, epidemiology and genetics in a high-risk population. Acta Ophthalmol 1976;54:5-31.
5. Van Rens GH, Arkell SM, Charlton W, Doesburg W. Primary angle-closure among Alaskan Eskimos. Doc Ophthalmol 1988; 70:265-236.
6. Foster PJ, Oen FT, Machin D, et al. The prevalence of glaucoma in Chinese residents of Singapore: a cross-sectional population survey of the Tanjong Pagar district. Arch Ophthalmol 2000;118: 1105-1111.
7. Foster PJ, Johnson GJ. Glaucoma in China: how big is the problem? Br J Ophthalmol 2001;85:1277-1282.
8. Wilson JM, Jungner G. Principles and practice of screening for disease. Public Health Papers No 34. Geneva: World Health Organization; 1968.
9. Health departments of the United Kingdom. First report of the National Screening Committee. Publication of Department of Health. 1-4-1998.
10. Baasanhu J, Johnson GJ, Burendei G, Minassian DC. Prevalence and causes of blindness and visual impairment Mongolia: a survey of populations aged 40 years and older. Bull World Health Organ 1994;72: 771-776.
11. Foster PJ, Baasanhu J, Alsbirk PH, Munkhbayar D, Uranchimeg D, Johnson GJ. Glaucoma in Mongolia. A population-based survey in Hövsgöl province, northern Mongolia. Arch Ophthalmol 1996; 114:1235-1241.
12. Foster PJ, Burhmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol 2002;86:238-242.
13. Alsbirk PH. Anterior chamber depth and primary angle-closure glaucoma. I. An epidemiologic study in Greenland Eskimos. Acta Ophthalmol 1975;53:89-104.
14. Lowe RF. Aetiology of the anatomical basis for primary angle-closure glaucoma: biometrical comparisons between normal eyes and eyes with primary angle-closure glaucoma. Br J Ophthalmol 1970;54: 161-169.
15. Foster PJ, Alsbirk PH, Baasanhu J, Munkhbayar D, Uranchimeg D, Johnson GJ. Anterior chamber depth in Mongolians: variation with age, sex, and method of measurement. Am J Ophthalmol 1997;124: 53-60.
16. Devereux JG, Foster PJ, Baasanhu J, et al. Anterior chamber depth measurement as a screening tool for primary angle-closure glaucoma in an East Asian population. Arch Ophthalmol 2000;118:257-263.
17. Aung T, Nolan WP, Machin D, et al. Anterior chamber depth and the risk of primary angle closure in 2 East Asian populations. Arch Ophthalmol 2005;123: 527-532.
18. Alsbirk PH. Early detection of primary angle-closure glaucoma. Limbal and axial chamber depth screening in a high risk population (Greenland Eskimos). Acta Ophthalmol 1988;66:556-564.
19. Congdon NG, Quigley HA, Hung PT, Wang TH, Ho TC, Glovinsky Y. Screening techniques for angle-closure glaucoma in rural Taiwan. Acta Ophthalmol Scand 1996; 74:113-119.
20. Foster PJ, Devereux JG, Alsbirk PH, et al. Detection of gonioscopically occludable angles and primary angle-closure glaucoma by estimation of limbal chamber depth in Asians: modified grading scheme. Br J Ophthalmol 2000;84:186-192.
21. Van Herick W, Shaffer RN, Schwartz A. Estimation of width of angle of anterior chamber. Incidence and significance of the narrow angle. Am J Ophthalmol 1969;54 (Suppl 127):1-31.
22. Nolan WP, Foster PJ, Devereux JG, Uranchimeg D, Johnson GJ, Baasanhu J. YAG laser iridotomy treatment for primary angle-closure in East Asian eyes. Br J Ophthalmol 2000;84:1255-1259.
23. Salmon JF. Long-term intraocular pressure control after Nd-YAG laser iridotomy in chronic angle-closure glaucoma. J Glaucoma 1993;2:291-296.
24. Kim YY, Jung HR. Dilated miotic-resistant pupil and laser iridotomy in primary angle-closure glaucoma. Ophthalmologica 1997; 211:205-208.
25. Nolan WP, Baasanhu J, Undraa A, Uranchimeg D, Ganzorig S, Johnson GJ. Screening for primary angle-closure in Mongolia: a randomized controlled trial to determine whether screening and prophylactic treatment will reduce the incidence of primary angle-closure glaucoma in an East Asian population. Br J Ophthalmol 2003;87:271-274.
26. Bourne RR, Sukudom P, Foster PJ, et al. Prevalence of glaucoma in Thailand: a population based survey in Rom Klao District, Bangkok. Br J Ophthalmol 2003; 87:1069-1074.
27. Dandona L, Dandona R, Mandal P, et al. Angle-closure glaucoma in an urban population in Southern India. The Andhra Pradesh eye disease study. Ophthalmology 2000;107:1710-1716.
28. Ramakrishnan R, Nirmalan PK, Krishnadas R, et al. Glaucoma in a rural population of southern India: the Aravind comprehensive eye survey. Ophthalmology 2003;110: 1484-1490.
29. He M, Foster PJ, Johnson GJ, Khaw PT. Angle-closure glaucoma in East Asian and European people. Different diseases? Eye 2006;20:3-12.

Address for Correspondence

Dr Winifred Nolan
Department of Epidemiology
Institute of Ophthalmology
Bath Street
London EC1V 9EL
UK
E-mail: winnie_nolan@yahoo.com