City Research Online

City, University of London Institutional Repository

This is the accepted version of the paper.

This version of the publication may differ from the final published version.

Permanent repository link: http://openaccess.city.ac.uk/17760/

Link to published version: http://dx.doi.org/10.1111/opo.12328

City Research Online: http://openaccess.city.ac.uk/   publications@city.ac.uk

Cases of advanced visual field loss at referral to glaucoma clinics – More men than women?

Authors:

David P. Crabb [1], Luke J. Saunders [1], Laura A. Edwards [1]

Affiliation:

1. Division of Optometry and Visual Science, School of Health Sciences, City University London.

Corresponding Author:

Professor David Crabb,

Division of Optometry and Visual Science,

School of Health Sciences,

City University London,

Northampton Square, London EC1V 0HB

Email:: david.crabb.1@city.ac.uk

Phone:: +44 207 040 0191

Abstract

Purpose: In many medical conditions 'late presentation' of disease is more of a problem for men than women. Risk of sight loss from glaucoma is certainly greater in those detected with advanced disease. We performed a retrospective study to test the hypothesis that men are more likely than women to have advanced visual field loss at referral to glaucoma clinics. .

Methods: We used 152,918 Humphrey visual fields from 32,147 patients from three regionally different hospitals in England; no other clinical data was made available apart from patient's age, sex and examination dates. The study population was defined as patients with measureable visual field loss in at least one eye at referral to glaucoma clinics. Cases of advanced visual field loss as defined by the Enhanced Glaucoma Severity Staging (eGSS) method at the first visit to secondary care were used as a proxy measure for late presentation of glaucoma. Age-adjusted relative risk (RR) was calculated as the ratio of the proportion of men to women with this proxy measure.

Results: Median (interquartile range) age and MD (worse eye) for 3733 men and 4264 women was 72 (63, 78) and 74 (64, 81) years and -6.4 (-11.7, -3.8) and -6.3 (-11.0, -3.8) dB respectively. Overall proportion of patients with advanced visual field loss at referral to glaucoma clinics was slightly higher in men (25.0%) than in women (22.3%); this difference was statistically significant (p<0.01). Overall age-standardised RR was statistically significant (1.16; p<0.001); a person with late presentation of glaucoma is 16% (95% confidence interval: 7 to 25%) more likely to be a man than a woman.

Conclusions: A large number of patients with glaucomatous visual field defects are estimated to have advanced loss in at least one eye on referral to secondary care in England; risk for men more likely presenting with late disease is slightly greater than for women.

Introduction

People at greatest risk of sight loss from glaucoma are often those detected at a late stage in the disease process. [1] [2] [3] [4] In these cases asymptomatic visual field (VF) loss in one eye might already be advanced at the time of diagnosis. These patients are more likely to have VF loss that progresses more quickly and have less time to benefit from treatment. This delayed diagnosis is sometimes referred to as 'late presentation'.

In many diseases and medical conditions late presentation is more of a problem for men than women. [5] [6] Men have a greater tendency to explain away early symptoms of morbidity and are more likely not to seek medical attention until disease is significant. [7] [8] [9] In the United Kingdom (UK) men go to their general practitioner (GP; primary care doctor) half as often, on average, as women. [10] Other evidence from the UK suggests men go to the dentist less often and ask the pharmacist for information less frequently than women. [5] [11] The College of Optometrists recently reported women place a higher value on sight tests and visit their community optometrist more than men. [12] Of course, for most people, it is at these routine visits to the community optometrist when glaucoma is mainly detected. We therefore speculate men are less likely than women to be exposed to spontaneous case-finding for glaucoma. In turn we hypothesise that men are more likely to be at risk of late presentation of glaucoma and this is the main idea explored in this paper.

Only a handful of studies have examined differences in risk of late presentation of glaucoma between men and women. In the UK the evidence base for this question is scant with some studies reporting a difference and others not. [13] [14] [15] New knowledge about potential differences between men and women in late presentation of glaucoma could influence case-finding strategies and would be useful information for optometrists carrying out routine sight tests that include examinations for case finding glaucoma.

In this study, cases of advanced VF loss recorded by automated perimetry at the first visit at secondary care are used as a surrogate measure for late presentation of glaucoma. These data are acquired retrospectively from very large archives of VF records from three regionally different glaucoma clinics in England. We examine the

relative risk of this proxy measure of late presentation of disease in this population by sex, as stratified by age, in order to test the hypothesis that men, when compared to women, are more likely to have more advanced glaucoma at the time of referral to glaucoma clinics.

Materials and Methods

We analysed 152,918 VFs from 32,147 patients extracted from Medisoft visual field (VF) databases (Medisoft Ltd., Leeds, UK) from three regionally different clinics (Cheltenham General Hospital Gloucestershire Eye Unit (50,144 VFs), Queen Alexandra Hospital in Portsmouth (31,879 VFs) and the Calderdale and Huddersfield NHS Foundation Trust Hospital (70,955 VFs)).   These datasets have been described in detail previously [16] and were recorded during a period of about 12 years before the extraction date in 2012. Data access was granted by the Caldicott Guardian at each centre. All patient data was anonymised and transferred to a single secure database held at the university. No other clinical data was made available apart from patient's age, sex and the dates of the VF examinations. Subsequent analyses of the data were approved by a research ethics committee of City University London and this study adhered to the Declaration of Helsinki.

Only VFs recorded by patients older than 40 years on the Humphrey Field Analyzer (HFA, Carl Zeiss Meditec, CA, USA www.zeiss.com/meditec) using a Goldmann size III stimulus with a 24-2 test pattern acquired with the Swedish Interactive Testing Algorithm (SITA Fast) were included. The study population comprised of patients with measurable VF loss in at least one eye at diagnosis (at presentation to clinic) as defined using standard HFA VF indices. HFA mean deviation (MD) is a measure of the overall severity of a VF defect, relative to healthy age-matched observers, with more negative values indicating greater VF loss. HFA pattern standard deviation (PSD) is another global measure reflecting irregularities in the VF, such as those caused by localised sensitivity loss. To a certain extent PSD is robust to VF loss caused by cataract or media opacity. Patients were only included if they had a VF with a MD and PSD flagged as outside the 95% normative limits by the HFA VF analysis software. This criterion had to be satisfied for at least two visits to the clinic to improve the likelihood that an included individual has glaucomatous VF loss, in the absence of any other clinical record.

A study eye for each patient was defined as the eye with worse MD (the one with the more negative value) at the first clinic visit. The Enhanced Glaucoma Severity Staging (eGSS) system was then used to classify study eyes as having advanced VF loss or not. [17] In short, eGSS combines information from MD and PSD; it is designed to better

estimates VF loss attributable to glaucoma than say using MD alone, which in turn may be more affected by sensitivity loss resulting from cataract. [18] Eyes were defined as having advanced loss if they were stage 4 (very advanced and absolute defects) or worse on the eGSS chart and this was the surrogate used for a patient having late presentation. Typically these eyes would have MD worse than -15 dB or PSD worse than 14dB. Other combinations where both MD and PSD have to be worse than a criterion (e.g. -12dB for MD and 10dB for PSD) are also flagged as stage 4. It is important to note we chose the worse eye as a surrogate measure to represent the 'detectable' level of glaucomatous VF loss. This definition is appropriate for our methods but is different to a classification of advanced VF loss in the better eye; such patients have advanced bilateral VF loss and would, for example, more likely be symptomatic and would likely fail the VF component for legal fitness to drive in the UK. [19]

Proportions of men and women, stratified by age, presenting with the attribute of advanced VF loss were then calculated. Relative Risk (RR) was calculated as the ratio of the proportion of men to the proportion of women with late presentation for each ten year age group from 40 to 100 years. RR is expected to have a value of one under the null hypothesis that men and women are equally affected by late presentation of glaucoma. An overall age-standardised RR was calculated using the direct method. [20] All statistical analyses were carried out in R (www.R-project.org) including use of the epitools package (http://medepi.com/epitools).

6

Results

Inclusion criteria for this study yielded 3,733 male and 4,264 female patients for analysis (Figure 1). Median (interquartile range; IQR) ages for men and women was 72 (63, 79) and 74 (64, 81) years respectively. Median (IQR) MDs for the worse eye (study eye) for men and women were -6.4 (-11.7, -3.8) and -6.3 (-11.0, -3.8) dB respectively. (Median (IQR) MDs for the better eye for men and women were -2.5 (-4.8,-1.1) and -2.8 (-5.3,-1.5) dB respectively.) The proportion of patients with advanced VF loss using the eGSS criterion (late presentation of glaucoma) was slightly higher in men (932/3733; 25.0%) than in women (949/4264; 22.3%) and this difference was statistically significant (Chi-Square Test; p=0.004).
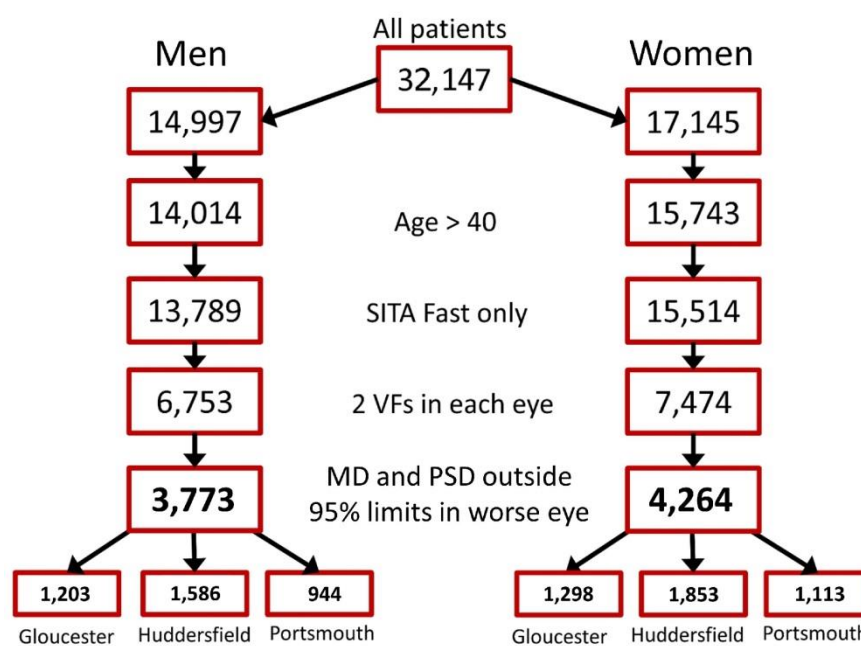

Figure 1: *Flow chart showing the inclusion criteria leading to a study sample of 3,773 men and 4,264 women representing a population of patients in glaucoma clinics with visual field defects in at least one eye.*

Proportions of men and women presenting with advanced VF loss stratified by age is shown in Table 1. Crude RRs stratified into ten year intervals are also reported along

with their 95% confidence intervals. Grouping by age is necessary because late presentation of glaucoma as estimated by our surrogate measure is more prevalent with older age. Further, the age distribution for males and females is different, with more elderly women patients than elderly men. RR is greater than one (indicating greater risk for men) for two of the age strata (60-69 and 70-79 years) and the confidence intervals do not overlap with one indicating these values to be statistically significant. There were no age strata with a statistically significant RR less than one (indicating greater risk for women).

Overall age-standardised RR was 1.16 (95% confidence interval [CI]: 1.07 to 1.25) indicating risk is greater in men; the difference from one cannot be ascribed to chance (p=0.0003) [20]. This means a patient of any age (>40 years) referred to glaucoma clinics with advanced VF loss (late presentation of glaucoma) is, on average, 16% (95% CI: 7 to 25%) more likely to be a man rather than a woman. This RR is statistically significant and estimated with high precision but it is not a large effect from a clinical or practical standpoint; this is illustrated in figure 2. Here, if we imagine a sample of 100 people newly referred to glaucoma clinics with advanced VF loss (late presentation of glaucoma) then our data indicates approximately 54 of them are likely to be men and 46 to be women.

Table 1: *Percentage of patients presenting with advanced visual field loss (in the study eye) stratified by age (decades) and crude relative risks for the attribute for men compared to women. Crude relative risk is only statistically significant (*) for the 60-69 and 70-79 years age groups (P<0.001).*

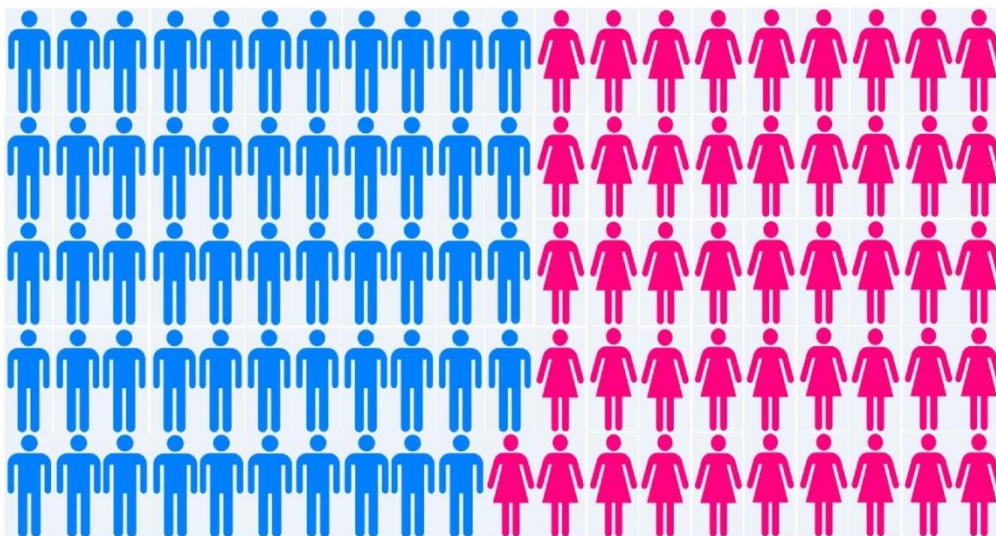| Age (y)	Patients presenting with advanced visual field loss		Crude Relative Risk (95% CI)
	Men	**Women**	
40-49	**23.4%** (n=244)	**20.8%** (n=265)	**1.13** (0.81, 1.56)
50-59	**23.0%** (n=478)	**20.7%** (n=469)	**1.11** (0.87, 1.42)
60-69	**22.6%** (n=945)	**16.3%** (n=909)	**1.39** (1.15, 1.68) *
70-79	**24.8%** (n=1324)	**19.2%** (n=1465)	**1.30** (1.13, 1.49) *
80-89	**29.0%** (n=692)	**31.8%** (n=1061)	**0.91** (0.79, 1.06)
90-99	**42.0%** (n=50)	**32.6%** (n=95)	**1.29** (0.83, 1.99)

Figure 2: *Overall age-standardised relative risk of the ratio of the proportion of men to the proportion of women with late presentation was 1.16 (95% confidence interval: 1.07 to 1.25). This schematic illustrates the size of this statistically significant effect: in a sample of 100 people presenting with advanced VF loss approximately 54 are likely to be men.*

Discussion

Our results suggest at least one in five patients in glaucoma clinics in England referred with VF loss had advanced loss (eGSS criterion) in at least one eye at referral. This statistic has remained approximately at this level for some time [21] and it is a clinical concern because late presentation of glaucoma is associated with a greater risk of visual impairment during a person's lifetime. [1] In this study we have specifically shown that a man is, on average, 16% more likely to be one of these late presenting patients than a woman. This result represents new knowledge about spontaneous case finding and health service delivery of glaucoma in England. The crude relative risk of late presentation in men is greater in people aged between 60-79 years than in other age groups. Yet the magnitude of the overall relative risk is practically quite small. Therefore, this finding will likely not directly affect the evidence base driving strategies for glaucoma case finding but we believe it is useful information for community optometrists carrying out routine sight tests that include glaucoma screening. This finding ought to precipitate a prospective investigation into late presentation of glaucoma with a potential focus on gender differences and other factors, especially about access to services.

The influence of a patient's sex on glaucoma diagnosis is a contentious debate. Yet, a recent well-conducted systematic review of the literature indicated age-adjusted prevalence of glaucoma (globally) is higher in men compared with women. [22] Our study was not designed to contribute to this debate. In contrast we were concerned with the precise idea that men, when compared to women, are more likely to present with advanced VF loss at the point of glaucoma diagnosis, as stratified by age. To our knowledge only a few studies have considered this question and findings are mixed. [23] [24] There are only a few UK reports on this question looking at small numbers of people. One study, investigating patients registering with sight impairment, found that most patients with this level of vision loss when first presenting with glaucoma were men. [13] Two studies by the same London-based group investigated risk factors for late presentation through collecting two cohorts of glaucoma patients; cases had VF loss in one or both eyes; controls had no absolute VF loss within 20 degrees of fixation. Retrospective analysis of the data revealed men to be significantly more likely to be a case rather than a control once adjusting for other variables. [14] However, a later follow-

up study recruiting patients as they were diagnosed did not find sex to be a significant factor in late presentation with glaucoma.[15]

Our study took advantage of a large repository of electronically recorded VF data and was novel because it was based on a sample of several thousands of patients from three regionally different areas in England. These sample sizes, large enough to be readily stratified by age, provide a useful experimental design and give confidence about statistical estimates. This 'big data' method is useful for auditing aspects of health service delivery in glaucoma and for testing hypotheses about the management of patients. Our report, and others like it [1] [21] [25], therefore serve as a stimulus for others to use routinely collected electronically stored resources in eye clinics. Of course this is still only analysis of retrospectively collected data and estimates will not be as valid as those garnered from prospective studies.

The methodology used in this study has several limitations. For example, it was multicentre but the sampling was not done systematically and the data is not particularly current because the extractions were done in 2012. Critically, the study only considers data retrospectively and information about exact diagnosis of glaucoma, intraocular pressure and types of treatment was not available. Our estimate for late presentation of disease is very much a proxy measure. For example, it is not known for certain that a patient's first VF is the first one after diagnosis, because a person may have simply moved area or hospitals, for example. Moreover, our surrogate for advanced VF loss could be affected by a patient having concomitant eye disease like advanced cataract, for example. (Indeed, age-related cataract is more prevalent in women, [26] so this limitation isn't easily dismissed.) Such information was not available in this retrospective study. Lack of clinical information restricts level of certainty about the underlying diagnosis. The methodology of only including patients with serial VF assessments however should exclude most cases of non-glaucoma diagnosis. Furthermore, HFA reliability indices are sometimes used to exclude poorly carried out examinations in clinical practice, but these were not used in this study because many were missing from the original database. Nevertheless, there is no reason why such biases would be associated with the sex of the patient and the sheer size of the data ensures robust estimates. More importantly perhaps, these data represent unselected

people in glaucoma clinics that are receiving routine care and therefore estimates are directly meaningful to 'real-world' practice.

In conclusion there is some evidence of an association between late presentation of VF loss consistent with glaucoma and patient's gender. Our data, based on several thousands of patients with VF loss, indicates men are slightly more at risk of being diagnosed with more advanced VF loss at the point of diagnosis than women. The risk is precisely estimated and statistically significant. Of course statistical significance isn't the same as clinical or practical significance and the reported effect is likely not large enough to impact on case finding strategies in glaucoma. Still, knowledge of this small increased risk in men might be useful for the practicing optometrist as they do their best to detect the condition. At the very least this report further highlights that many patients with VF loss present to secondary care with advanced defects in at least one eye; we suggest a health service delivery focus on ameliorating this statistic ought to help prevent sight loss from glaucoma.

Acknowledgements

Contributions

The study was conceived and designed by DPC. Data was organised by LJS. Data was analysed and interpreted by DPC and LJS. The manuscript was prepared and written by DPC, LJS and LAE.

References

1. Saunders LJ, Russell RA, Kirwan JF, McNaught AI, Crabb DP. Examining visual field loss in patients in glaucoma clinics during their predicted remaining lifetime. Invest Ophthalmol Vis Sci. 2014 Jan;55(1):102–9.

2. Peters D, Bengtsson B, Heijl A. Factors associated with lifetime risk of open-angle glaucoma blindness. Acta Ophthalmol (Copenh). 2014 Aug;92(5):421–5.

3. Forsman E, Kivelä T, Vesti E. Lifetime visual disability in open-angle glaucoma and ocular hypertension. J Glaucoma. 2007 May;16(3):313–9.

4. Chen PP. Blindness in patients with treated open-angle glaucoma. Ophthalmology. 2003 Apr;110(4):726–33.

5. Banks I. No man's land: men, illness, and the NHS. BMJ. 2001 Nov 3;323(7320):1058–60.

6. Macleod U, Mitchell ED, Burgess C, Macdonald S, Ramirez AJ. Risk factors for delayed presentation and referral of symptomatic cancer: evidence for common cancers. Br J Cancer. 2009 Dec 3;101(Suppl 2):S92–101.

7. White AK, Johnson M. Men making sense of their chest pain--niggles, doubts and denials. J Clin Nurs. 2000 Jul;9(4):534–41.

8. Juel K, Christensen K. Are men seeking medical advice too late? Contacts to general practitioners and hospital admissions in Denmark 2005. J Public Health. 2008 Jan 3;30(1):111–3.

9. Galdas PM, Cheater F, Marshall P. Men and health help-seeking behaviour: literature review. J Adv Nurs. 2005 Mar;49(6):616–23.

10. Hippisley-Cox J, Fenty J, Heaps M. Trends in consultation rates in general practice 1995 to 2006: analysis of the QRESEARCH database. [Internet]. Final Rep Inf Cent Dep Health. 2007. Available from: http://www.hscic.gov.uk/catalogue/PUB01077/tren-cons-rate-gene-prac-95-09-95-09-rep.pdf

11. Steele JG, Treasure ET, O'Sullivan I, Morris J, Murray JJ. Adult Dental Health Survey 2009: transformations in British oral health 1968-2009. Br Dent J. 2012 Nov;213(10):523–7.

12. The College of Optometrists. Britain's Eye Health in Focus - A snapshot of consumer attitudes and behaviour towards eye health care. [Internet]. London: The College of Optometrists; 2013. Available from: http://www.college-optometrists.org/en/utilities/document-summary.cfm?docid=A60DE8E4-B6CF-49ED-8E0FE694FCF4B426

13. Kotecha A, Fernandes S, Bunce C, Franks WA. Avoidable sight loss from glaucoma: is it unavoidable? Br J Ophthalmol. 2012 Jun;96(6):816–20.

14. Fraser S, Bunce C, Wormald R. Retrospective analysis of risk factors for late presentation of chronic glaucoma. Br J Ophthalmol. 1999 Jan;83(1):24–8.

15. Fraser S, Bunce C, Wormald R. Risk factors for late presentation in chronic glaucoma. Invest Ophthalmol Vis Sci. 1999 Sep;40(10):2251–7.

16. Saunders LJ, Russell RA, Crabb DP. Measurement precision in a series of visual fields acquired by the standard and fast versions of the Swedish interactive thresholding algorithm: analysis of large-scale data from clinics. JAMA Ophthalmol. 2015 Jan;133(1):74–80.

17. Brusini P, Filacorda S. Enhanced Glaucoma Staging System (GSS 2) for classifying functional damage in glaucoma. J Glaucoma. 2006 Feb;15(1):40–6.

18. Ng M, Sample PA, Pascual JP, Zangwill LM, Girkin CA, Liebmann JM, et al. Comparison of visual field severity classification systems for glaucoma. J Glaucoma. 2012 Nov;21(8):551–61.

19. Saunders LJ, Russell RA, Crabb DP. Practical landmarks for visual field disability in glaucoma. Br J Ophthalmol. 2012 Sep;96(9):1185–9.

20. Fay MP, Feuer EJ. Confidence intervals for directly standardized rates: a method based on the gamma distribution. Stat Med. 1997 Apr 15;16(7):791–801.

21. Boodhna T, Crabb DP. Disease severity in newly diagnosed glaucoma patients with visual field loss: trends from more than a decade of data. Ophthalmic Physiol Opt J Br Coll Ophthalmic Opt Optom. 2015 Mar;35(2):225–30.

22. Kapetanakis VV, Chan MPY, Foster PJ, Cook DG, Owen CG, Rudnicka AR. Global variations and time trends in the prevalence of primary open angle glaucoma (POAG): a systematic review and meta-analysis. Br J Ophthalmol. 2016 Jan;100(1):86–93.

23. Gogate P, Deshpande R, Chelerkar V, Deshpande S, Deshpande M. Is glaucoma blindness a disease of deprivation and ignorance? A case-control study for late presentation of glaucoma in India. Indian J Ophthalmol. 2011 Feb;59(1):29–35.

24. Deva NC, Insull E, Gamble G, Danesh-Meyer HV. Risk factors for first presentation of glaucoma with significant visual field loss. Clin Experiment Ophthalmol. 2008 Apr;36(3):217–21.

25. Boodhna T, Saunders LJ, Crabb DP. Are rates of vision loss in patients in English glaucoma clinics slowing down over time? Trends from a decade of data. Eye Lond Engl. 2015 Dec;29(12):1613–9.

26. Kanthan GL, Wang JJ, Rochtchina E, Tan AG, Lee A, Chia E-M, et al. Ten-year incidence of age-related cataract and cataract surgery in an older Australian population. The Blue Mountains Eye Study. Ophthalmology. 2008 May;115(5):808–814.e1.