THE EPIDEMIOLOGY OF NUCLEAR CATARACT IN MELTON MOWBRAY A POPULATION BASED STUDY OF THE AGEING EYE

Thesis submitted for the degree of
Doctor of Medicine
at the University of Leicester

by

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The Epidemiology of Nuclear Cataract in Melton Mowbray, a population based study of the ageing eye.

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Objectives
(1) to measure the prevalence of nuclear cataract, (2) to investigate the effects of established and suspected risk factors on nuclear cataract including those comprising the insulin resistance syndrome.

Participants and Methods
The Melton Eye Study is a community-based study of the ageing eye. A random sample of 1205 people aged 55 to 74 years was selected from a general practice list covering the whole town of Melton Mowbray in England. A standardised protocol was used for interviews and examinations. Lenses were graded at the slit-lamp using both LOCS III and the Oxford Clinical Cataract Classification and Grading System. 826 subjects participated in the examination.

Results
89 (9.33%) of subjects had significant White Scatter (95% CI 7.42% to 11.53%), and 90 (11.04%) had significant Brunescence (95% CI 8.97% to 13.40%). 0.49% of the population were visually impaired (95% CI 0.13% to 1.24%). In Regression analyses on possible risk factors Brunescence was positively associated with age ($p<0.0001$) (Coefficient =0.037) (95% CI for Co-ef, 0.031 to 0.043), a history of light cigarette smoking ($p=0.005$) (Coef = 0.1, 95% CI 0.03 to 0.17) and heavy cigarette smoking ($p=0.035$) (Coef = 0.12, 95% CI 0.009 to 0.24), a history of heavy drinking ($p=0.002$), (Coef = 0.21, 95% CI 0.08 to 0.35), being diabetic ($p<0.0001$) (Coef = 0.33, 95% CI 0.17 to 0.48) and with an insulin resistance syndrome score ($p=0.042$) (Coef = 0.08, 95% CI 0.003 to 0.17). Brunescence was negatively associated with Beta carotene ($p=0.011$) (Coef = -0.19, 95% CI -0.33 to -0.04) and Vitamin A ($p=0.046$) (Coef = -0.18, 95% CI -0.35 to -0.003). White Scatter was associated with age ($p< 0.0001$) (Coefficient =0.035) (95% CI, 0.028 to 0.041), a history of light cigarette smoking ($p=0.048$) (Coef = 0.08, 95% CI 0.0005 to 0.16), and with myopes who started wearing glasses in their youth. ($p<0.0001$) (Coef = -0.09, 95% CI -0.13 to -0.04)

Conclusions
The Melton Eye Study is the first population-based study to establish the prevalence of lens opacities in the UK and examine the association with risk factors. These data can be used to provide health care planning for the UK population.

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1. Literature Review

1.1 Prevalence

Cataract, which may be defined as opacification of the lens that impairs vision, is the leading cause of blindness worldwide (Thylefors, Negrel et al. 1995). In the developing world, it accounts for untold suffering.

The World Health Organisation (WHO) estimates that in 1990 there were 38 million blind people in the world (Thylefors, Negrel et al. 1995), of which cataract sufferers accounted for 41.8%, totalling nearly 16 million people. (Table LRI)

The term "age-related cataract" implies that it is the elderly who are most vulnerable. Throughout the world the elderly population is increasing. For the period of 1980 to 2020 the projected increase in population ageing for the developed world is 186%, whilst in developing countries it is projected to increase at a rate of 356%. WHO estimates that there will be 54 million blind people aged 60 years or more by the year 2020 (Thylefors, Negrel et al. 1995). Consequently, cataract surgery will continue to consume an increasing proportion of health care budgets in developed nations. In the USA cataract related spending is currently estimated at over $3.4 billion annually (West and Valmadrid 1995). In the developing world the number of new cataract cases far outstrips the rate of surgical removal. In Africa alone cataract accounts for 500,000 new cases of blindness each year, yet only 10% of these are likely to have their sight surgically restored (Foster 1991).

Table LR1. World blindness: percentage of blindness from cataract by region, ranked according to proportion of blindness attributable to cataract.

World blindness from cataract by region

Region	Reference population ($x10^3$)	Number of blind ($x10^3$)	Prevalence of blindness (all causes) (%)	No. of blind from cataract	
				($x10^3$)	(%)
Latin America the Caribbean	444297	2300	0.5	1326	57.6
India	849515	8900	1	5120	57.5
Middle Eastern Crescent	503075	3600	0.7	1627	45.2
Sub-Saharan Africa	510271	7100	1.4	3101	43.7
Other Asia and islands	682533	5800	0.8	2314	39.9
China	1133698	6700	0.6	2166	32.3
Former socialist economies of Europe	346237	1100	0.3	91	8.3
Established market economies	797788	2400	0.3	84	3.5
Total	5267414	37900	0.7	15829	
Percentage of world blindness					41.8

Discussing the prevalence of blinding cataract requires population-based surveys, which, while taxing from an organisational point of view, may use relatively simple grading or screening methods (Mehra and Minassian 1988). It is not straightforward describing the prevalence of any lens opacity or opacities that cause visual loss. The former requires accurate lens grading systems and the latter, careful examination of the eye to exclude other causes of visual loss. However, accurate population-based data are important to planning for health services specific to cataract (Klein, Klein et al. 1992).

A review of the some of the major surveys conducted in attempt to answer the question of the prevalence of lens opacity in various populations follows.

The 1971–1972 National Health and Nutrition Examination Survey (Hiller, Sperduto et al. 1983), included a lens examination, performed by 91 residents in ophthalmology, which included dilated examination of the lens with slit lamp and direct ophthalmoscope. Hiller et al used these examination data and defined cataract as senile lens changes consistent with best corrected visual acuity of 20/30 (6/9) or worse. Using this definition 413 (18.6%) out of 2225 persons, aged 45 to 74, had cataract.

A similar definition was used in the Framingham Eye Study (Sperduto and Seigel 1980), which found lens opacities in 21% of persons between the ages of 52 and 64 years, 53% of those between the ages of 65 and 74 years, and 80% of those between the ages of 75 and 85 years. This study also divided cataracts into subtypes and found that nuclear cataract was present in 65.5% of persons over the age of 75 (Sperduto and Hiller 1984)

Population-based studies in the United Kingdom predate modern lens grading methods: Gibson et al examined 677 subjects aged 76 years of age and older living in the Melton Mowbray area (Gibson, Rosenthal et al. 1985). They found a prevalence of cataract of 46.1% using the Framingham Eye Study definition of cataract (lens opacity consistent with best corrected visual acuity of 20/30 (6/9) or worse). A random sample of 487 persons living in Edinburgh aged 62 years and over showed a cataract prevalence of 22% for ages 62 to 69 years, and a prevalence of 40% for those of 70 years and older (Milne and Williamson 1972). A geriatric assessment survey carried out in East Kilbride used different selection and examination criteria and found a prevalence of cataract for those aged 65 to 74 years of 14% (McWilliam 1975)

Wormald et al (Wormald RP 1992), examined 207 people 65 years and over in a random sample from inner London. Cataract was not graded. They reported that cataract accounted for 75% of cases of low vision.

The North London Study (Reidy, Minassian et al. 1998), was a population-based study of 1547 people aged 65 years and older. Subjects were from a random sample of

people registered with 17 general practice groups in North London. WHO criteria for blindness and low vision were not used. Although the examiners report using LOCS II photographs to record cataract type and density, prevalence of cataract causing visual impairment was defined as visual acuity in one or both eyes less than 6/12 attributable to lens opacity. They found the estimated population prevalence of cataract according to this definition to be 30 %. 10% of subjects had had cataract surgery in one or both eyes. They also included subjects in whom both macular degeneration and cataract were deemed to contribute to the loss of vision. Prevalence of cataract in terms of LOCS II grading was not reported.

The Beaver Dam Eye Study (BDES) was one of the first population-based studies to use modern lens grading methods and lens photography. They defined an early nuclear cataract as opacity of level 3 and a late nuclear cataract as levels 4 or 5 on a scale of severity ranging from 1 to 5. The levels of severity were assessed by comparison with a set of four standard photographs. Women had significantly more nuclear cataract than men in all age ranges. Overall, 17.3% of subjects had nuclear sclerosis more severe than level 3.

The Blue Mountains Eye Study a population-based study of eye disease in the Blue Mountains, west of Sydney, examined 3654 people aged 49 to 96 years (Mitchell, Cumming et al. 1997). Subjects' lenses were photographed and graded using the Wisconsin cataract grading system. Due to camera difficulties only 70% of subjects had gradable nuclear photographs. A decimalised version of the grading system was used (Bailey, Bullimore et al. 1991). Moderate or advanced nuclear opacities were present in 53.3% of women and 49.7% of men. The age-specific prevalence rates found for early and late cataract, or for past cataract surgery, are very similar to rates reported in the Beaver Dam Eye Study, using the same definitions. There were however significantly lower age-specific rates for nuclear cataract compared with the Beaver Dam Eye Study. Table LR2 summarises the differences between the two studies.

Table LR2. Comparison of Nuclear cataract prevalence in Beaver Dam and Blue Mountain Studies (male and female combined) (Mitchell, Cumming et al. 1997).

Age group (yrs)	BDES	BMES
55–64	6.6	3.9
65–74	27.4	21.8
75–84	57.0	48.5

A cross-sectional population study of inhabitants 70 years of age or older in Finland (Hirvela, Luukinen et al. 1995), used LOCS II (Chylack, Leske et al. 1989), to grade lens opacities in 560 subjects with a response rate of 89.3%. Grading of lenses was done at the slit lamp rather than from photographs. Cataract, aphakia, or pseudophakia was recorded in one or both of the eyes in 64.4% (322 persons) of the participants. A total of 56.4% of persons had cataract, aphakia, or pseudophakia in both eyes. Nuclear lens opacities in particular were detected in 38.5% of the participants. A cataract was defined as LOCS II nuclear grade 2-4 or nuclear colour grade 2. Some of the studies and their findings are summarised in Table LR3.

Table LR3. Prevalence studies of different types of cataract using cataract grading systems (without visual acuity loss criteria).

Study	Age range	Race of study population	No.	Classification	Type	Prevalence (male/female if reported)	
Framingham Eye Study		White	2239	Slit lamp evaluation with standardised system (written protocol)	PSC Nuclear Cortical	8.3 25.6 14.3	
Watermen Study (Taylor, West et al. 1988)		White	831	Slit lamp evaluation with standardised system	PSC Nuclear Cortical	1.7 27.6 13.4	
Beaver Dam Eye Study (Klein, Klein et al. 1992)	43-84	White	4600	Photographic evaluation with standardised system (Wisconsin)	PSC Nuclear Cortical	6.0 17.3 16.3	
Finland (Hirvela, Luukinen et al. 1995)	70 or older	White	500	Slit lamp evaluation with LOCS II	PSC Nuclear Cortical	27.7 38.5 37.6	
Barbados Eye Study (Leske, Connell et al. 1997)	40-84	Black	4250	Slit lamp evaluation with LOCS II	PSC Nuclear Cortical	3.9 19.2 34.0	
Blue Mountains Eye Study (Mitchell, Cumming et al. 1997) Australia	49-96	White	3654	Photographic evaluation with standardised system (Wisconsin)	PSC Nuclear Cortical	6.5 49.7 21.1	6.2 53.3 25.9
Melbourne Visual Impairment Project (McCarty, Mukesh et al. 1999) Australia	40 or older	White	3271	Photographic evaluation with standardised system (Wilmer)	PSC Nuclear Cortical	4.08 11.6 11.3 (age standardised)	
The Salisbury Eye Evaluation Project (West, Munoz et al. 1998) USA	65-84	White and Black- (26.4%)	2520	Photographic evaluation with standardised system (Wilmer – decimalised)	PSC Nuclear Cortical	Black 5.5 33.5 54.2	White 13.0 50.7 24.2

The above table is helpful to the extent that it highlights the different studies undertaken. However, there are serious limitations: the age ranges of each study are critical to the overall prevalence of a lens opacity. For example, the age range in the BDES is 43 to 84 and in the BMES it is 49 to 96. The overall prevalence of nuclear opacity reported in the BDES is only 19.2% considerably lower than the 51.7% overall prevalence (involving one or both eyes) reported in the BMES. However, if age-specific prevalences are studied then the BMES, in fact, recorded a significantly lower rate of nuclear cataract than the BDES in each age group. (Table LR1) The higher overall prevalence in the BMES is due to the age range extending up to 96.

The Salisbury Eye Evaluation project (SEE) found that nuclear cataract was more prevalent amongst Caucasians than African Americans (West, Munoz et al. 1998). Early nuclear cataract was present in around 10% of 43- to 54-year-olds, rising to over 40% of over 75-year-olds. The percentage of level 4 or 5 nuclear cataract (late) rose from near 1% in the youngest group to nearly 50% of those in the over 75 years category.

1.2 Lens grading

There has been a proliferation in cataract grading systems in the last two decades (Chylack, Lee et al. 1983; Sparrow, Bron et al. 1986, ; Chylack, Leske et al. 1988; Chylack, Leske et al. 1989; Taylor and West 1989; Klein, Klein et al. 1990; Sasaki, Shibata et al. 1990; Chylack, Wolfe et al. 1993; Hall, Lempert et al. 1999). Prior to 1976 most classification of cataract was achieved using inconsistently applied clinical definitions couched in terms of anatomical changes (nuclear, cortical) or according to the aetiology. In 1976, the National Eye Institute funded the Cooperative Cataract Research Group, which developed a consistent method of classifying extracted intracapsular cataracts (Chylack, Lee et al. 1983; Chylack, Ransil et al. 1984; Chylack, White et al. 1984; Chylack, Wolfe et al. 1993).

The advent of extracapsular cataract surgery meant that in vivo classification systems had to be developed. Many of these were based on the use of standard photographs against which the cataract to be graded is compared (Klein, Klein et al. 1990; Sasaki, Shibata et al. 1990; Chylack, Wolfe et al. 1993). Others used standard images (colour samples and charts) to grade the opacity (Sparrow, Bron et al. 1986). Some required the use of cameras to photograph the lens opacity prior to grading (Chylack, Leske et al. 1988; Chylack, Leske et al. 1989; Sasaki, Shibata et al. 1989; Klein, Klein et al. 1990; Sasaki, Shibata et al. 1990; Chylack, Wolfe et al. 1993). While others could be graded at the slit

lamp (Sparrow, Bron et al. 1986; Chylack, Leske et al. 1989; Taylor and West 1989, Chylack, 1989 #346; Chylack, Wolfe et al. 1993).

The two gradings systems used in The Melton Eye Study, the Oxford Clinical Cataract Classification and Grading System (OCCCGS) and the Lens Opacities Classification System III (LOCS III) are reviewed below.

The Oxford Clinical Cataract Classification and Grading System

The Oxford Clinical Cataract Classification and Grading System (OCCCGS) was designed for slit lamp classification of lens opacities in clinical studies. The original system classified 10 lenticular features on an integer scale with even grading steps (Sparrow, Bron et al. 1986). The original system gave good inter- and intra-observer measures of repeatability (Sparrow, Ayliffe et al. 1988). The system has been modified to describe two further lens features (fibre-folds and coronary flakes) and does not classify anterior clear zone thickness as a feature (Sparrow, Frost et al. 2000). This later version has been decimalised according to the principles of Bailey (Bailey, Bullimore et al. 1991). The features recorded were pupil diameter, measured in the vertical axis, and 11 features in the lens. Complete grading definitions require reference to the original paper (Sparrow, Bron et al. 1986), but for those unfamiliar with the Oxford terminology these abnormalities were summarised by Deane and Hall (Deane, Hall et al. 1997): **Anterior subcapsular opacity (ASC):** Opacities just posterior to the anterior capsule and visible in either retro illumination or focal illumination. These are graded against diameter scale reference standards. **Posterior subcapsular opacity (PSC):** Opacities just anterior to the posterior capsule and visible in either retro illumination or focal illumination. These are graded against diameter scale reference standards. **Cortical spoke (CS):** Base out wedges, visible in retro illumination as dark areas and in focal illumination as scattering opacities. These are graded against reference "pie charts". **Fibre-folds (FF):** Originally these were termed lamellar separations. Fibre-folds are seen as parallel lines in the lens cortex, both anteriorly and posteriorly, running in the plane of the capsule at right angles to a meridian. They are best seen in focal illumination and graded against the same "pie charts" as cortical spokes (Brown, Vrensen et al. 1989). **Waterclefts (WC):** Radial, fusiform or base out areas producing localised areas of altered refraction. Waterclefts are variably seen in retro illumination and full extent is best assessed as optically empty spaces on slit illumination. These are graded against the same scoring plates as cortical spokes. **Vacuoles:** Small round cystic spaces in the cortex, optically behaving as a diverging lens. These are graded against standard diagrams. **Perinuclear Retro-dots:** Rounded features, distinguished from vacuoles by their larger size, perinuclear position, poorly demarcated edges and refractive

properties, behaving as converging lenses. These are graded against standard plates. **Coronary flakes (CF):** Discrete white circular or ovoid lesions in the peripheral cortex with clearly demarcated edges, often overlapping other deeper coronary flakes. These are graded against standard plates. **Focal dots (FD):** Fine punctate opacities in the peripheral cortex, graded against standard plates in a defined grading patch. **White nuclear scatter (WNS):** The degree of nuclear opalescence in the anterior foetal nucleus, graded using standard Munsell neutral density grey scales. **Brunescence:** The degree of nuclear colour in the posterior foetal nucleus, graded using standard Munsell colour scales.

The separate quantification of these different clinico-pathological subtypes is a key difference between the Oxford System and many other systems, which tend to group certain subtypes of opacity together (Sparrow, Frost et al. 2000).

In recent years, cataract grading methods have converged towards a common differentiation of cortical spokes, posterior subcapsular cataract and nuclear cataract (opalescence and/or colour) (Sparrow, Bron et al. 1986; Chylack, Leske et al. 1989; Klein, Klein et al. 1990; Sasaki, Shibata et al. 1990). Several systems have recognised the need for finer scale intervals (Chylack, Wolfe et al. 1993; West, Munoz et al. 1993). The OCCCGS system has been decimalised according to the principles of Bailey (Bailey, Bullimore et al. 1991), thereby increasing the sensitivity to detect small changes and narrowing confidence intervals (Sparrow, Frost et al. 2000). Coarse scales are frequently wasteful of available information because they fail to utilise the ability of a grader to make fine judgements (Bailey, Bullimore et al. 1991). The ideal scale should be sensitive enough to impose little restriction on the ability of the grader to record judgements. This enhanced scale sensitivity is more suitable for longitudinal studies and for studies comparing groups by allowing more precise comparison of individual pairs of measurements (Sparrow, Frost et al. 2000).

Theoretical considerations, followed by iterative piloting, were used to define a set of rules for the decimalisation of grading for the 10 cataract features of the OCCCGS. These rules maintained the direct relationship between the original integer grades and the new decimal grades thereby retaining the important principle of equal interval steps of the original Oxford System. The original integer grades ran from Grade 0 (feature absent) to Grade 5 (maximum extent). Decimal values were inserted between each integer grade to provide scale intervals 10 times smaller. This resulted in 50 steps of 0.1 each. The performance of the decimal version was then formally tested by means of inter- and intra-observer comparisons of repeated measurements. Repeatability of the decimal system was found to be good amongst multiple users of differing clinical experience. The use of finer

scale intervals improved the system's ability to detect change (reduced 95% tolerance limits for change) by a factor of around two for most features (Sparrow, Frost et al. 2000).

The Lens Opacities Classification System III (LOCS III)

The Lens Opacities Classification System II (LOCS II) was introduced in 1989 (Chylack, Leske et al. 1989), but was found to have several limitations (Chylack, Wolfe et al. 1993). These included a scale for nuclear colour grading that was too small and coarse, the guidelines for colour grading were not linked to parameters of colour such as hue and purity, and the scaling intervals were unequal. Chylack et al therefore attempted to rectify these deficiencies by developing LOCS III (Chylack, Wolfe et al. 1993). The improvements included expanding the scale for nuclear colour grading from three to six steps and linking the subjective scaling of the colour to objective measures of colour. Furthermore, equal scaling intervals were introduced between the reference standards, and decimalised, rather than integer, grading was used to reduce the size of the 95% tolerance limits.

The LOCS III standards are all boundaries of scaling intervals. There are no zero standards or grades in LOCS III, thus the lowest cortical cataract score in LOCS III would be assigned a score of 0.1 while the same lens in the OCCCGS system would be given a score of 0. The range of the scale in LOCS III nuclear lens opacity assessment is from 0.1 to 6.9, representing 68 steps to Oxford's 50. To assess nuclear opalescence in LOCS III the grader evaluates the average opalescence of the entire nucleus, this includes an assessment of the areas of increased scatter, known as the "figure" and the scatter in the background regions, known as the "ground". In assessing colour, the grader is required to focus on two regions of the lens: both the entire cross-sectional view of the nucleus and the posterior subcapsular reflex. The opalescence and colour are compared with the standard nuclear images and a decimal value given.

The LOCS III was developed and standardised using photograding. Karbassi et al assessed the validity of LOCS III at the slit lamp and compared slit lamp with photograding (Karbassi, Khu et al. 1993). This was felt to be necessary because of concerns that at the slit lamp the new system may be oversensitive. In addition, slit lamp grading was found to be more difficult than photograding in early validation studies of LOCS II.

Two independent observers graded cataract at the slit lamp and in photographs from two sets of patients. The 95% tolerance limits (TL) for grading at the slit lamp ranged from 0.9 to 1.8 for the first set and 0.6 to 1.2 for the second (intraclass correlation coefficients 0.79 to 0.91 versus 0.70 to 0.97, respectively). Specifically, there was a

significant decrease in 95% TL for cortical and nuclear colour. For the first set of photograding, the 95% TL were 0.3 to 0.6 between the two observers and 0.6 to 0.8 for the same observer at two different sessions. Similar results were found for photograding the second set. The 95% TL for comparing slit lamp and photograding were generally > 1.0. The results suggest that:

(1) LOCS III at the slit lamp has 95% TL only slightly worse than those for LOCS III photogradings;

(2) LOCS III slit lamp grading for cortical and nuclear colour improves with practice; and

(3) the slit lamp and photographic gradings cannot be used interchangeably. Karbassi felt that the differences between slit lamp and photograding of the same cataract arose from the increased complexity of the in vivo grading procedure and the unavoidable dissimilarity between the in vivo slit lamp image and the photographic image.

Other grading systems have been devised and have been used to varying extents in epidemiological surveys. They are mentioned briefly below with reference to the nuclear grading method.

Klein at al developed a photographic system for grading lens opacities (Klein, Klein et al. 1990; Panchapakesan, Cumming et al. 1997), which has been used in a number of surveys into cataract epidemiology (Klein, Klein et al. 1992, Panchapakesan, 1997 #86; Mitchell, Cumming et al. 1997; Panchapakesan, Cumming et al. 1997). Taylor and West (West, Rosenthal et al. 1988; Taylor and West 1989, West, 1988 #599), developed a simple system for the clinical grading of the presence and severity of lens opacities. The densities of nuclear opacities as seen on clinical slit lamp examination are graded in comparison with a set of four standard photographs. The extent of cortical opacities seen on retro illumination is estimated in terms of segments involved.

They described this system for use at the slit lamp (Taylor and West 1989), and for photograding (West, Rosenthal et al. 1988, West, 1993 #573; West, Munoz et al. 1993). This system has also been used for large cataract epidemiology studies in both the United States of America and Australia (West, Duncan et al. 1998; West, Munoz et al. 1998; McCarty, Mukesh et al. 1999). In Australia the original integer method was used. However in the Salisbury Eye Evaluation Project (SEE) (West, Munoz et al. 1998), Bailey's principles of decimalisation were applied (Bailey, Bullimore et al. 1991). The Wilmer and Wisconsin systems do not give separate attention to grading the colour of the nucleus to the degree that the Oxford and LOCS systems do. Colour in the SEE project was graded as less than, equal to or greater than one nuclear standard (West, Duncan et al. 1998; West,

Munoz et al. 1998; McCarty, Mukesh et al. 1999). Similarly in the Wisconsin system nuclear colour is judged against a standard slit lamp photograph (Klein, Klein et al. 1990).

The lack of an archival copy for regrading is the principal disadvantage of a slit lamp based grading system. This means that drift of grading criteria over time, and assessing both inter-observer and intra-observer error is more difficult than photographically-based systems. A further potential problem is that of misclassification of lesions, with one feature being misrecorded as another (Deane, Hall et al. 1997). Despite these drawbacks clinical grading systems have a role in longitudinal studies as there is no other currently available system to accurately describe features such as fibre-folds and perinuclear Retro-dots. Without a description of these lesions, it would be impossible to assess their role in the development of the more widely recognised features, and answer questions such as "Do cortical spokes arise from fibre-folds?".

The disadvantages of slit lamp grading may be countered by simultaneously making objective measurements. Digital images, such as those taken by the Marcher CASE 2000 Oxford cataract camera (Sparrow, Brown et al. 1990), are a useful complement to clinical grading schemes. Use of photographic systems will allows some assessment of drift over time and consistency of grading.

1.3 Visual acuity and nuclear lens opacities

The existing population-based estimates of best corrected visual acuity (VA) for the United Kingdom tend to focus on older people. Gibson, Lavery and Rosenthal (Gibson, Lavery et al. 1986), examined 529 persons of 75 years and over during a two-year study of the elderly in the market town of Melton Mowbray. 25.7% had visual acuity of less than 6/18 in their better eye, therefore defining them as visually impaired according to the World Health Organisation classification. 3.8% were found to have visual acuities of less than 6/60.

The data show that typically, persons aged 75 years and older have poor uncorrected vision (6/36 Snellen acuity), but good corrected acuity, 73.8% gaining 6/12 binocular Snellen acuity or better (Lavery, Gibson et al. 1988)

Wormald et al (Wormald RP 1992), examined 207 people 65 years and over in a random sample from inner London. The prevalence of blindness was 1% and low vision was 7.7%. using WHO criteria. This rose to 3.9% and 10.6% respectively if American criteria were used.

The North London Study (Reidy, Minassian et al. 1998), was a population based study of 1547 people aged 65 years and older. Subjects were from a random sample of

people registered with 17 general practice groups in North London. WHO criteria for blindness and low vision were not used. They defined visual impairment as visual acuity < 6/12. The prevalence of visual impairment in both eyes was 30.2%. Differences between men and women were not reported.

The MRC trial of assessment and management of older people in the community (Evans, Fletcher et al. 2002), measured the prevalence of visual impairment in 14600 people age 75 years and over. They used WHO definitions of visual impairment and blindness. However they focused on presenting acuity rather than best corrected acuity. Overall 10.3% had low vision and 2.1% were blind Low vision ranged from 6.2% in those aged 75-79 to 36.9 % in those over 90. Similarly blindness increased from 0.6% to 6.9%. Women were more likely to be affected than men with an overall prevalence of low vision of 9.1% for men and 14.4% for women

The National Diet and Nutrition Survey of people aged 65 and over (van der Pols, Bates et al. 2000), measured visual acuity in 1362 participants. They used WHO definitions of low vision and blindness using a pinhole to assess best corrected visual acuity. Overall 14.3% had low vision or blindness. This ranged form 3.1% in the 65-74 year age group to 35.5% in those over 85.There was significantly more visual impairment in women than in men with 10.4% of men affected as compared to 18.3 % of women.

Population-based studies with a wider range of age groups were undertaken in America (Klein, Klein et al. 1991), and Australia (Attebo, Mitchell et al. 1996). The Blue Mountains Eye Study is a population-based study which examined an Australian population of 49 years of age and older (Attebo, Mitchell et al. 1996). The logarithm of the minimum angle of resolution (logMAR) visual acuity was measured before and after refraction in 3647 persons. Refraction improved visual acuity by one or more lines in 45% of participants and by three or more lines in 13%. Levels of visual impairment were not described according to World Health Organisation criteria but were divided into mild, moderate and severe or blind. Visual impairment (visual acuity 20/40 or worse in the better eye) was found in 170 participants (4.7%). Mild visual impairment (Snellen equivalent 20/40 to 20/60 in the better eye) was found in 3.4%, moderate visual impairment (20/80 to 20/160 in the better eye) in 0.6%, and severe visual impairment or blindness (20/200 or worse in the better eye) in 0.7%. Visual impairment was significantly more frequent in females at all ages. Among persons with severe visual impairment, 79% were female. The Beaver Dam Eye Study used similar definitions and found mild impairment in 3.9%, moderate in 0.8% and severe in 0.5% of subjects (Klein, Klein et al. 1991). The age range in the Beaver Dam Eye Study was 43 to 86 years. Both the Beaver Dam Eye Study and

Blue Mountains Eye Study found that levels of visual impairment increase with age and female sex.

Visual acuity measurement has been the standard tool for assessing the state of visual deterioration in cataract patients (Weatherill 1993; Maraini, Rosmini et al. 1994). Maraini et al's assessment of the effect of pure forms of age-related cataract on visual acuity used data from 1076 eyes. Classification of lenses was done at the slit lamp using LOCS II colour of the lens was not graded for this study. Conditions other than cataract, which might affect the vision, were excluded. Cataract-specific multiple regression analyses were done with VA or CS as dependent variables. Age was adjusted for as an independent continuous variable. They found that increasing severity of nuclear cataract was associated with the greatest increase in logMAR visual acuity (a decrease in visual acuity). They concluded that increasing severity along the LOCS II scale for nuclear and posterior subcapsular cataract had a more detrimental effect on vision than similar changes along the LOCS II cortical scale.

1.4 Contrast sensitivity and nuclear lens opacities

Visual acuity (VA) measurements have been the gold standard for assessing visual function in patients with cataract (Maraini, Rosmini et al. 1994). However, cataracts imperfectly refract incoming light causing intraocular scatter and therefore a reduction in the contrast of the retinal image (Lasa, Datiles et al. 1992; Brown 1993). The development of clinical contrast sensitivity (CS) tests (Pelli 1988), has lead to the call, by some, for these to be used in the routine assessment of cataract patients – because they provide more information than visual acuity alone and may be a more reliable guide to the likely benefits of cataract surgery (Weatherill 1993). The Pelli-Robson chart explores CS at low spatial frequencies. Inter test (test/retest) repeatability is reported to be excellent (Rubin 1988). Limited data are available on the associations of contrast sensitivity tests with cataract type and severity.

Elliot and Gilchrist (Elliott, Gilchrist et al. 1989), found that in cortical and nuclear cataract, medium and high spatial frequency CS scores correlated with VA. They found no significant CS loss at low spatial frequency. A decade later they assessed large and small letter contrast sensitivity and visual acuity in 37 elderly eyes with early lens opacities. (mean VA -0.01 logMAR, Snellen 6/6). Lens opacities were graded using the LOCS III system. They found that large letter contrast sensitivity was often not reduced in cataract from age-matched normal values and provided limited information. Small letter contrast sensitivity was shown to be a more sensitive measure of early cataract than visual acuity

and large letter contrast sensitivity. They suggested that its usefulness may be limited by its strong correlation with visual acuity (r2 = 0.70), which is the standard and traditional measure of vision in cataract (Elliott and Situ 1998)

In a population of 188 non-diabetic patients with early cataracts or nuclear brunescence, Chylack et al (Chylack, Jakubicz et al. 1993), assessed the degree to which contrast sensitivity function provided more information about a patient's visual disability than high contrast visual acuity measurements. Using data collected on: – LOCS II cataract classification; Bailey-Lovie visual acuity (LogMAR score); LogMAR interferometric visual acuity (LI VA); and distance contrast sensitivity function (CSF) using the Vistech 6500 – they used regression models, in which CS was the dependent variable, to ascertain whether CSF provided additional information about visual disability to that provided by LogMAR score or LI VA. They concluded that contrast sensitivity function was decreased only by nuclear opalescence at high frequencies (12 to 18 cycles per degree); for all other cataract types and nuclear colour, CSF testing provided no more information about cataract-related visual loss than LI VA or LogMAR score. They felt that in patients with nuclear opalescence, the additional information may not be clinically significant (Chylack, Jakubicz et al. 1993)

Adamsons et al (Adamsons, Rubin et al. 1992), examined 78 eyes with early cataract and found that CS scores were significantly affected by age and VA. Contrast sensitivity scores were lower for all patients with lens opacities than for patients with clear lenses at high frequencies only; all lens opacity groups scored similarly with each other.

Williamson et al (Williamson, Strong et al. 1992), found that the addition of a glare source (a disposable pen torch) led to a significant reduction in CS in subjects with early cataract. Cortical cataracts were most affected followed by posterior subcapsular opacities. CS was suggested to be a more sensitive measure of glare disability than VA.

Lasa et al (Lasa, Datiles et al. 1992), performed Pelli-Robson CS tests on 128 patients with cataracts and no other ocular disease and on 29 control volunteers. The cataracts were graded using the Lens Opacities Classification System II (LOCS II). Data from the left eyes were analysed using logistic regression models. They found that contrast sensitivity loss was associated with cataract severity for cortical ($p < 0.0001$) and posterior subcapsular ($p = 0.0001$) cataracts and with decreased visual acuity ($p = 0.0001$). There was no associations found between CS and nuclear opacity. They suggested that the Pelli-Robson chart was good for evaluating visual function in moderate to advanced cataracts. However, for early cataracts, other techniques need to be explored to assess visual function loss. The Italian-American Study of Age Related Cataract (Maraini, Rosmini et al. 1994),

examined the effect of pure forms of age-related cataract on visual acuity and contrast sensitivity in 1076 eyes. Classification of lenses was done at the slit lamp using LOCS II. Conditions other than cataract, which might affect the vision, were excluded. Cataract-specific multiple regression analyses were done with VA or CS as dependent variables. Age was adjusted for as an independent continuous variable. They found that increasing severity of nuclear cataract was associated with the greatest increase in logMAR visual acuity (a decrease in visual acuity) and lower CS scores. After adjusting for age and VA, CS scores at low spatial frequency were no longer associated with cataract type and severity, and therefore provided no additional information.

The Blue Mountains Eye Study (Ivers, Cumming et al. 1998), measured CS in a geographically distinct cohort of their study population. They found that contrast sensitivity and visual acuity were the tests that most strongly correlated elderly people falling. It is not clear from their description of statistical methods whether VA was included as an independent variable in the model exploring the relationship between falls and CS.

The Beaver Dam Eye Study used the Pelli-Robson charts in a cohort of their study population. They reported the population-based means of log contrast sensitivity by age and sex. Log CS ranged from 1.7 in 40- to 49-year-olds to 1.4 in those over 80 (Klein, Klein et al. 1999). No mention of an examination of the effect of cataract on contrast sensitivity in either study was found.

1.5 Refractive errors and nuclear lens opacities

High myopia has a known association with age-related cataract (Brown and Hill 1987). Many studies have suggested that low myopia may also be an important risk factor for cataract (Weale 1980; Harding and van Heyningen 1987; Harding, Harding et al. 1989). This relationship has been disputed (Brown and Hill 1987), on the grounds that nuclear sclerotic cataract itself causes a change towards myopia. The refractive index of the lens is increased by nuclear sclerosis, so increasing lens power (Brown 1993)

The earlier studies used subjects drawn from cataract surgical populations. Perkins (Perkins 1984), studied patients who had undergone cataract surgery and found an incidence of myopia in over 25% of subjects with refraction records. The study was limited by the availability of past refraction records for only 17% of patients.

Gibson et al in the Melton Mowbray Study of all Melton residents aged 75 years and over, found an association between cataract and myopia (Gibson, Shaw et al. 1986).

They postulated that the association was probably due to the association of index myopia with senile cataract.

Brown (Brown and Hill 1987), used 100 cataract patients in whom the refractive error was known four years prior to first presentation with cataract. He points out that this differs from patients in other studies who were assessed at the time of cataract surgery, in that the cataracts were likely to be less advanced than those needing surgery. These patients were compared with a group of aged-matched controls in which the refraction was also known for the four previous years. He found that the myopic shift in nuclear cataract occurred independently of whether the eye was myopic or hypermetropic. Myopic shift occurred only in nuclear cataract. He concluded that simple myopia did not predispose to cataract.

Harding reported an association between self reported childhood myopia and cataract but did not subdivide the types of age-related cataract (Harding, Harding et al. 1989). Weale (Weale 1980), did not divide the cataract subtypes either, he did not have early records of refractive error but used the patients preoperative refractive error and applied a correction for "myopisation" to try and estimate the pre-cataractous refractive state.

The Lens Opacities Case Control Study used a history of use of eye glasses by the age of 20 as a proxy for myopia (Leske, Chylack et al. 1991). They found an increased risk of mixed cataract but not for either cortical nuclear or posterior subcapsular cataract. There seemed to be no attempt to differentiate those people who might have used glasses before the age of 20 because of significant hypermetropia.

The Beaver Dam Eye Study (Cruickshanks, Klein et al. 1992), found an increased risk of PSC in women but not in men with the use of distance glasses before the age of 21 years (odds ratio, OR 1.20). However, in men of this age a history of wearing distance glasses was associated with a significantly lower risk of nuclear cataract (OR 0.77). In this study the history of use of glasses described above was to determine whether there was a protective effect of glasses against ultraviolet light, and therefore young hypermetropes were not separated from myopes. Wearing glasses was interpreted as protective against lens damage from ultraviolet radiation.

The Blue Mountains Eye Study (Lim, Mitchell et al. 1999), is the first population-based study to explore the association of myopia with cataract. They examined 3654 people according to a well defined protocol. They defined myopia as a spherical equivalent of less than –1D. Data was available on history of glasses use in the past, as well as the age at which glasses were first used, in over 99% of subjects. Subjects were assumed to have

myopia if they gave a history of wearing distance glasses excluding eyes with a current hypermetropic refraction. With regard to nuclear cataract, as expected, they found an association between any current myopia and nuclear cataract. Any history of wearing glasses was associated with nuclear cataract; however, after stratification by age at which glasses were first worn, the relationship was only significant for person who began wearing glasses after the age of 40 years. They felt that this confirmed the previous observations by Brown and Hill (Brown and Hill 1987), that the myopic shift caused by the nuclear sclerosis that leads to the need for myopic correction..

Posterior subcapsular cataract was found to be associated with any myopia even after adjusting for nuclear cataract. After excluding eyes with a current hypermetropic refraction, a significant relationship was found between a history of wearing distance glasses and posterior subcapsular cataract, with the strongest association being found in people with early-onset myopia. These findings suggested that early-onset myopia may be a risk factor for the development of posterior subcapsular cataract in later life (Lim, Mitchell et al. 1999)

The Visual Impairment Project, a large population-based study in Victoria Australia, reported an association between nuclear cataract and myopia (McCarty, Mukesh et al. 1999; Wensor, McCarty et al. 1999). They did not report on any association with early-onset myopia. Cataract was graded using the Wilmer grading scheme and dichotomised into present or absent. Myopia was defined as greater (more negative) than –1.0 D. The association was attributed to the myopic shift occurring with nuclear cataract.

The Barbados Eye Study (Wu, Nemesure et al. 1999), reported on the prevalence of myopia in the predominantly black population of Barbados. They reported the expected association between current myopia and nuclear cataract. However, no report is made of an attempt to analyse previous history of myopia, in particular early-onset myopia with nuclear cataract. No population-based study has yet found an association between early myopia and nuclear cataract.

1.6 Cigarette smoking and nuclear lens opacities

Smoking tobacco is recognised as a leading cause of death and disability (Solberg, Rosner et al. 1998). More than 15% of deaths in the United States are attributed to smoking. Tobacco smoke has some 4000 active compounds (Solberg, Rosner et al. 1998). Many of these are toxic and a hazard to human health. They include carcinogens and heavy metals such as lead and cadmium. In addition, numerous compounds have oxidative

properties. These may cause direct oxidative stress to the lens (Hiller, Sperduto et al. 1997).

The association between cigarette smoking and the increased risk of developing age-related cataract was first reported in case-control studies (Clayton, Cuthbert et al. 1982; Harding and van Heyningen 1989; Leske, Chylack et al. 1991). Subsequently both cross-sectional (Klein, Klein et al. 1985; Flaye, Sullivan et al. 1989), and prospective (Christen, Manson et al. 1992; Hankinson, Willett et al. 1992; West, Munoz et al. 1995; Klein, Klein et al. 1997), epidemiological studies confirmed the relationship. The most consistent association was for nuclear lens opacities.

When a further case-control study was carried out in Edinburgh by Phillips and Clayton (Phillips, Clayton et al. 1996), they found an association between nuclear cataract and alcohol consumption but were surprised not to find one for smoking.

Klein (Klein, Klein et al. 1985), found that smoking increased the risk of cataract in Type II diabetics.

The City Eye Study was a nine-year longitudinal study of over 1000 volunteers recruited in the City of London. The initial cross-sectional observation study found an association between cigarette smoking and nuclear lens opacities. The relative risk for smokers compared to non-smokers was 2.5 for light smokers rising to 3.0 for heavy smokers. The analysis corrected for use of steroids, alcohol intake, cholesterol, fasting triglycerides, glucose, social class and occupation (Flaye, Sullivan et al. 1989). Although an attempt to grade lens opacities into mild, moderate and severe was made, these grades do not appear to have been used in the analysis. The increasing relative risk with increasing severity of smoking was thought by the authors to suggest a dose dependent effect.

The Framingham Eye and Heart Studies (Hiller, Sperduto et al. 1997), examined the incidence of new lens opacities. 660 people who were free of lens opacities at the time of the original eye examination were examined 12 years later. During this period of time lens opacities developed in 381 persons. Most of these were nuclear opacities. Smokers were divided into light and heavy smokers; the latter having smoked more than 20 cigarettes per day at the time of six or more of the Heart Study examinations. In particular, persons who smoked 20 or more cigarettes per day at the time of the first eye examination were at substantially increased risk for the development of nuclear opacities than non-smokers (odds ratio, OR 2.84). Multivariate logistic regression analysis correcting for age, sex, education, and diabetes showed a significant positive association between increased duration and number of cigarettes smoked and increased risk of incident nuclear cataract.

Moreover, those affected tended to be current smokers. Cigarette smoking was not associated with the risk of developing cortical or posterior subcapsular cataract.

In a prospective cohort study of male physicians, Christen et al (Christen, Manson et al. 1992), examined the association between cigarette smoking and the incidence of cataract. An incident cataract was defined as self reported cataract, which was confirmed by review of medical records. 10% of the 22,071 physicians were current smokers at the start of the study. During five years of follow-up, 557 eyes of 371 participants developed cataract. Current smokers of 20 or more cigarettes per day were significantly ($p < 0.001$) more likely to develop both nuclear cataract and posterior subcapsular cataract (relative risk 2.41 and 3.31). Past smokers had a greater risk of posterior subcapsular cataract, but no risk of nuclear cataract. No risk was found for smokers of fewer than 20 cigarettes per day.

A similar study of 50,828 female nurses found 493 incident cataracts (Hankinson, Willett et al. 1992). This study only found an increased risk for posterior subcapsular cataract and not for nuclear cataract.

One of the disadvantages of both studies was the inability to assess incident cataracts by repeated examination of subjects because of the large number of participants. In addition, it was not possible to classify the cataracts in a standardised manner. This may have resulted in some misclassification of cataract and therefore tended to bias relative risks towards the average effect seen with all the types of cataract combined. However, the authors point out that an association was found between posterior subcapsular cataract and diabetes but not with diabetes and nuclear cataract. This relationship has been found in studies with standardised lens examinations, suggesting that the ophthalmologists had tended to report the dominant type of cataract correctly (Hankinson, Willett et al. 1992)

A smaller cohort study, which did use lens grading, found no association between smoking and incident nuclear lens opacities. However pre-existing opacities were more likely to progress in smokers. A cohort of 442 Chesapeake Bay watermen were followed in a prospective study to examine the relationships between smoking and the five-year incidence of nuclear opacities. Photographs of the nucleus of the lens were taken and graded in 1985 and then again in 1990. The risk of progression of nuclear opacities from less than grade 3 at the start of the study to grade 3 or worse was 2.4 times higher in smokers than non-smokers. Their data was consistent with an association between current smoking and progression to severe nuclear lens opacities. There was no association of progression of opacities with the accumulative dose to 1985 or the total dose at the end of the study period, suggesting that progression of opacities was driven by the current

smoking. This finding also suggested that giving up smoking may result in a reduction of risk of nuclear cataract approaching that of non-smokers. Harding (Harding 1997), points out that there were few visually disabling opacities in this population. A further prospective study, which confirmed the relationship between current smoking and nuclear cataract, was the Longitudinal Study of Cataract (Leske, Chylack et al. 1998)

In Australia the Visual Impairment Project, (McCarty, Mukesh et al. 1999), a population-based investigation of the epidemiology of cataract, found a significant association between nuclear cataract and a history of having smoked for more than 30 years. Unlike many of the other studies, they were unable to find an association with current smoking and nuclear cataract. For the purpose of this analysis, nuclear cataract was defined as greater than Wilmer standard 2.0. Stepwise logistic regression analysis was used to evaluate significant univariate risk factors. In the multivariate analyses age, female sex, rural residence, diabetes (diagnosed more than five years previously), brown iris, myopia and age-related macular degeneration were also risk factors for nuclear cataract. As in the Chesapeake Bay Watermen Study (West, Munoz et al. 1995), a decreased risk of nuclear cataract was found 20 years after stopping smoking. This relationship did not, however, remain significant in the multivariate analysis.

Another Australian study is the Blue Mountains Eye Study (Cumming and Mitchell 1997), of an urban community of 3654 people aged 49 to 97 years. After adjusting for multiple potential confounders, the investigators found that people who had ever smoked cigarettes had a higher prevalence than non-smokers of more severe nuclear and posterior subcapsular cataracts. They found the association between pipe smoking and nuclear cataract (adjusted odds ratio OR, 3.1; 95% confidence interval CI, 1.5-8.2) to be even stronger than the association with cigarette smoking.

A dose-response relationship between cumulative amount of smoking exposure and the risk of development of nuclear opacity has been demonstrated in three studies (Flaye, Sullivan et al. 1989; West, Munoz et al. 1989; Hankinson, Willett et al. 1992; West, Munoz et al. 1995).

There are many plausible biological mechanisms for the development of cataract. Cyanide and thiocyanate, which are raised in the blood of smokers can be converted to isocyanate (Harding 1993), as well as free radicals and aldehydes: isocyanate, thiocyanate and aldehydes may reach the lens to attack enzymes and lens proteins by causing aggregation and unfolding of lens proteins (Harding 1993); (Harding 1995). Cadmium has been proposed as a possible agent of cataractogenesis (Ramakrishnan, Sulochana et al. 1995; Cekic 1998), Ramakrishnan (Ramakrishnan, Sulochana et al. 1995), found high

levels of cadmium in both the blood and lenses of smokers. The Vitamin C levels in the blood of their subjects and controls were not significantly decreased suggesting that the cadmium was the agent responsible. Cekic (Cekic 1998), found increased levels of lead cadmium and copper in human lenses of smokers. Cigarette smoke was the probable source of the cadmium. This in turn could promote the accumulation of copper and lead within the lens. He postulated that cadmium may interfere with copper homeostasis within the body. Copper-dependent enzymes, such as super oxide dismutase, would then be affected. In addition to affecting enzymes in the lens the cadmium may interact directly with the lens proteins leading to protein denaturation and ultimately cataract.

Smoking appears to induce and oxidative stress (Taylor, Jacques et al. 1995). The erythrocytes of smokers are prone to increased peroxidation. This tendency is abolished by supplementation with Vitamin E (Duthie, Arthur et al. 1991). Epidemiological studies support the notion that diets rich in antioxidants, or the use of vitamin supplements, protect against the development of cataract (Mares-Perlman, Klein et al. 1994; Mares-Perlman, Brady et al. 1995; Mares-Perlman, Brady et al. 1995)

In addition to the direct oxidative challenge to the lens, smoking seems to contribute to the depletion of endogenous anti-oxidant pools (Solberg, Rosner et al. 1998). Low plasma levels of antioxidant vitamins C and E, and Beta carotene in the blood of smokers was postulated to cause an oxidative stress to the lens leading to increase risk of cataract in two prospective studies of cigarette smoking in health workers (Christen, Manson et al. 1992; Hankinson, Willett et al. 1992)

Evidence from these studies suggests that current smokers are at increased risk of developing nuclear cataract. Some studies have suggested that giving up smoking has a protective effect.

1.7 Alcohol and nuclear lens opacities

An association between alcohol consumption and cataract has been found in several studies: these include case-control studies, (Clayton, Cuthbert et al. 1982; Harding and van Heyningen 1989; Munoz, Tajchman et al. 1993; Phillips, Clayton et al. 1996), and cross-sectional (Ritter, Klein et al. 1993; Cumming and Mitchell 1997), and prospective (Manson, Christen et al. 1994; Klein, Klein et al. 1999), population-based studies.

Clayton et al (Clayton, Cuthbert et al. 1982), observed that there was a U- or J-shaped relationship between cataract and increasing alcohol consumption in their case-control study of surgical patients. They reported that there was a higher risk amongst teetotallers and heavy drinkers than amongst moderate or occasional drinkers. The same

group examined another population of surgical patients and quantified current ethanol consumption by questionnaire (Phillips, Clayton et al. 1996). In this case-control study of 990 cases, "light and infrequent" consumption and "light and frequent" consumption of ethanol were associated with a significantly lower risk of cataract than were total abstention and "occasional" consumption. Although a U-shaped curve was suggested by the prevalence of nuclear cataract rising with further increases in consumption, there was not a significant association between nuclear cataract and increasing alcohol consumption. The J shape suggested a protective effect of light drinking or possibly a misclassification of non-drinkers (West and Valmadrid 1995).

In a case-control study in Oxfordshire (Harding and van Heyningen 1989), heavy beer drinking was associated with a two-fold increased risk of cataract. The subjects were from a surgical population of patients undergoing cataract extraction. The subtype of cataract was not described in this study.

However, three large case-control studies found no association between alcohol consumption and cataract formation (Mohan, Sperduto et al. 1989; 1991; Leske, Chylack et al. 1991). Leske et al followed up their initial case-control study and were unable to find an association after four years of follow-up (Leske, Chylack et al. 1998).

The association of alcohol consumption and a specific cataract subtype was identified by Munoz et al (Munoz, Tajchman et al. 1993). In a follow-up study of 238 surgical cases of posterior subcapsular cataracts and their controls, a matched pair analysis controlling for other known risk factors showed an increased risk associated with heavy alcohol use. Moderate to heavy drinkers were defined as those who drank more than one drink per day. Heavy drinkers were more likely to be cataract surgical cases than were non-drinkers (odds ratio OR, 4.6; $p = 0.05$). Light drinkers were not at increased risk. There was a suggestion of a protective effect in light drinkers compared with non-drinkers, making this another study to find a possible J-shaped relationship between alcohol consumption and risk of cataract.

The relationship that was first established in these case-control studies was then confirmed in cross-sectional population-based studies. The Blue Mountains Eye Study (Cumming and Mitchell 1997), population-based, cross-sectional study close to Sydney, Australia, examined 3654 people aged 49 to 97 years in an urban community. Details of current alcohol consumption and smoking history were assessed by questionnaire. Lenses were graded from photographs for presence and severity of cortical, nuclear, and posterior subcapsular cataracts. Heavy alcohol consumption (defined as greater or equal to four drinks a day in this study) was associated with nuclear cataract in current smokers

(adjusted odds ratio, OR, compared with non-drinkers, 3.9; 95% CI, 0.9-16.6) but not in those who had never smoked: people who smoked and drank heavily had an increased prevalence of nuclear cataract. This relationship persisted after adjusting for the effect of smoking. It may represent a residual confounding effect of smoking, or a real interaction between alcohol, smoking and cataract, demonstrating a synergistic effect between alcohol and tobacco.

However, in Melbourne, Australia, a population-based study of 3271 adults aged 40 or over (McCarty, Mukesh et al. 1999), alcohol consumption was a risk factor for nuclear cataract only in the univariate analysis. Once multivariate analysis, correcting for potential confounders, was done the association was no longer significant.

The Beaver Dam Eye Study, (Ritter, Klein et al. 1993), is a large (N = 4926) population-based study of adults aged 43 to 86 years in Beaver Dam Wisconsin, USA. The relationship between alcohol use and lens opacities was examined using data on alcohol history, and severity of cataract determined by masked grading of photographs. The authors defined heavy drinking as four or more drinks per day. A history of heavy drinking was related to more severe nuclear sclerotic, cortical, and posterior subcapsular opacities (odds ratios, 1.34, 1.38, and 1.57, respectively). These relationships remained after adjusting for other risk factors such as smoking. They found that in both sexes and in every age group a higher percentage of heavy drinkers had late nuclear sclerotic cataract (level 4 out of 5 or worse). Moderate liquor consumption and the consumption of wine were associated with less severe nuclear sclerosis (OR 0.81). The relationships between alcohol consumption and cataract all applied to past heavy drinking and not to current drinking.

When this population was re-examined five years later (Klein, Klein et al. 1999), to evaluate incident cataract, they found significant associations between nuclear cataract and current alcohol intake (OR 1.01, 95% CI 1.00, 1.02 per 10 grams ethanol/week). This significant effect was found for right eyes only and was not present for left eyes. They therefore inferred that the relationship was not strong. They confirmed that the prevalence study had found a strong relationship and surmised that the short term follow-up period of five years may be insufficient to detect risks to the lens in what is described as a "chronic slow process".

A further prospective, although not population-based study, was the Physicians' Health Study (Manson, Christen et al. 1994), – a randomised trial of aspirin and Beta carotene among 22,071 male physicians 40 to 84 years of age at entry in 1982. Data from 17,824 physicians who had provided information about alcohol consumption and other cataract risk factors and had not reported cataract at baseline were used to examine the

association between alcohol consumption and incidence of cataract, as well as cataract extraction, among US male physicians. 371 participants had a confirmed incident cataract, defined as a self report, confirmed by medical record review, and 110 underwent cataract extraction. Compared to physicians consuming alcohol less than once per month, daily consumers of alcohol had an age-adjusted relative risk (RR) of cataract of 1.31 (95% confidence interval, CI = 0.95, 1.81). The risk of cataract extraction for posterior subcapsular cataract was also elevated and of borderline statistical significance – RR was 1.65 (95% CI = 0.99, 2.72) – among daily drinkers compared with those drinking less than daily. Manson concludes that the prospective data suggest that daily consumptions of alcohol is associated with a modest increase in the risk of cataract, particularly posterior subcapsular cataract. Because alcohol consumption was recorded before cataract was diagnosed, the recollection of drinking habits could not have changed with the development of cataract.

The association of alcohol consumption with cataract development may be due to confounding with other risk factors. There is the suggestion that heavy drinking patterns are associated with lower socio-economic status; (Ames and Janes 1987), the latter has been established as a risk factor for cataract in many studies (Leske, Wu et al. 1997; Ughade, Zodpey et al. 1998). Like low education, the association seems to be independent of various likely explanations such as low nutrition, excessive exposure to sunlight or different job exposures, but could be an explanatory confounder of the apparent effect of alcohol on the lens. Excessive alcohol consumption has also been linked to poor nutritional status; associations of nutritional status were not explored in all studies, (Munoz, Tajchman et al. 1993), and poor nutrition in heavy drinkers may therefore be confounder.

It is interesting to note the different levels of alcohol consumption defined as heavy in two of the studies. Ritter (Ritter, Klein et al. 1993), et al define heavy as four or more drinks per day, whereas Munoz et al defined moderate to severe drinkers as those who drank one or more drinks per day.

1.8 Antioxidants and nuclear lens opacities

The lens consists almost entirely of protein. New lens fibres are laid down throughout life. The older lens fibres are retained in the centre of the lens. Lens opacities develop as the proteins are damaged, and aggregate and precipitate (Taylor, Jacques et al. 1995). This damage may result from oxidative stress on lens enzymes, proteins and membranes. Oxidative reactions involving activated oxygen species such as hydrogen peroxide, superoxide anion singlet oxygen and hydroxyl free radical (West and Valmadrid

1995), may be induced by ultraviolet light and smoking (Taylor, West et al. 1988; Christen, Manson et al. 1992). Primary defence systems exist in younger lenses to protect the lens against oxidative insults (Taylor, Jacques et al. 1995). These include small molecule antioxidants (Vitamins C – ascorbic acid, Vitamin E – alpha-tocopherol and carotenoids) and antioxidant enzyme systems (superoxide dismutase, catalase, and glutathione peroxidase) (West and Valmadrid 1995). Secondary defence systems include proteolytic enzymes that remove damaged proteins. As lenses age, these defence mechanisms are no longer able to keep up with the rate of damage to the lens, resulting in the build up of modified proteins in the lens (Taylor, Jacques et al. 1995)

Epidemiologic research has been carried out to determine the role of antioxidants in protecting the lens against damage. These have included case-control studies, (Mohan, Sperduto et al. 1989; 1991; Leske, Chylack et al. 1991), population-based studies (Mares-Perlman, Klein et al. 1994; Mares-Perlman, Brady et al. 1995; Mares-Perlman, Brady et al. 1995; Leske, Wu et al. 1997; Cumming, Mitchell et al. 2000), longitudinal cohort studies, (Leske, Chylack et al. 1998; Brown, Rimm et al. 1999; Lyle, Mares-Perlman et al. 1999; Lyle, Mares-Perlman et al. 1999), and trials of nutritional supplements (Sperduto, Hu et al. 1993; Teikari, Virtamo et al. 1997). Some studies have looked at the content of antioxidants derived from the diet, (Mares-Perlman, Brady et al. 1995; Tavani, Negri et al. 1996; Cumming, Mitchell et al. 2000), while others have examined the role of vitamin supplements (Mares-Perlman, Klein et al. 1994; Jacques, Taylor et al. 1997; Chasan-Taber, Willett et al. 1999; Chasan-Taber, Willett et al. 1999). Yet other studies have assessed the nutritional status of individuals by measuring the antioxidant levels in the serum or red blood cells (Jacques, Hartz et al. 1988; Leske, Wu et al. 1995; Mares-Perlman, Brady et al. 1995; Lyle, Mares-Perlman et al. 1999)

The Lens Opacities Case-Control Study evaluated risk factors for age-related nuclear, cortical, posterior subcapsular and mixed cataracts. The 1380 participants were ophthalmology outpatients, aged 40 to 79 years. They found that the regular use of multivitamin supplements (at least once a week for at least one year) decreased risk (OR = 0.63) for all cataract types. Persons with higher dietary intake of riboflavin, vitamins C, E, and carotene or with a higher level of dietary antioxidant index (OR = 0.40) were also at decreased risk (Leske, Chylack et al. 1991).

Vitamin E levels, red blood cell enzymes and amino acids were measured. Persons with higher levels of Vitamin E had the risk of nuclear opacities reduced to less than one half (odds ratio, 0.44 for nuclear opacities). In addition, lens opacities were associated with lower levels of riboflavin, Vitamin E, iron, and protein nutritional status (Leske, Wu et al.

1995). In parallel with the US case-control study, two other case control studies were carried out with the same common objective of evaluating risk factors for nuclear, cortical and PSC cataracts. One in Italy (1991), and the other in India (Mohan, Sperduto et al. 1989). A total of 1008 cases and 469 controls, aged 45 to 79 years, were included in a clinic-based case-control study of age-related cataract in Parma, Italy, from 1987 to 1989. The Indian study included 1441 patients with age-related cataracts and 549 controls.

The impact of the nutritional findings from these three studies has been reviewed by Schoenfeld, Leske et al (Schoenfeld, Leske et al. 1993). All studies used slit lamp examination to classify cataract. The Indian study used its own grading scheme. The studies developed antioxidant indices, with which to evaluate the relationship of cataract to nutrients. The Indians index was based on red blood cell levels of glutathione peroxidase and glucose-6-phosphate dehydrogenase and plasma levels of ascorbic acid and Vitamin E from blood data. The Americans did not have blood data available and used a dietary index based on groupings of riboflavin, vitamins C and E and carotene. In addition to the antioxidant indices, individual nutrients were also examined. A high blood antioxidant index was associated with decreased risk of PSC and mixed cataract in the Indian study but not in the Italian study. High blood levels of Vitamin C were found to increase risk for mixed cataract in India. Vitamin C was not evaluated in the other two studies. High levels of Vitamin E appeared to reduce the risk of nuclear cataract in the US study only.

Leske (Leske, Chylack et al. 1998), comments that comparing the results of these three studies is difficult. Although they share several design features, there are significant differences. The Indian study had different inclusion and exclusion criteria – excluding diabetics and vitamin supplement users and requiring visual acuity loss in all cases. The Italian Study had few supplement users.

The Longitudinal Study of Cataract group regraded photographs from 764 of the participants of the original case-control study using LOCS III (Leske, Chylack et al. 1998). Nutritional data were available from the baseline assessment. Subjects were then followed yearly with examinations, including lens photographs. Analyses examined whether the nutritional factors at baseline were related to increases in nuclear opacification at follow-up. The risk of nuclear opacification at follow-up was decreased in regular users of multivitamin supplements (RR = 0.69; 0.48-0.99), Vitamin E supplements (RR = 0.43; 0.19-0.99), and in persons with higher plasma levels of Vitamin E (RR = 0.58; 0.36-0.94).

Two of the three studies were in well-nourished populations. The importance of nutritional deprivation in cataract formation was emphasised in the Linxian Cataract Studies (Sperduto, Hu et al. 1993). The studies were of nutritional intervention in

oesophageal dysplasia with an ophthalmic component added. Both studies were randomised, double-masked trials with a duration of five to six years and end-of-trial eye examinations, set in rural communities in Linxian, China. In the first trial, 2141 participants aged 45 to 74 years, were assigned to either multivitamin/mineral supplement or matching placebo. In the second trial, 3249 participants tested the effect of four different vitamin/mineral combinations. The results demonstrated a 36% reduction in the prevalence of nuclear cataract for persons aged 65 to 74 years who received the supplements in the first trial. In the second trial, the same age group had a significantly lower prevalence of nuclear cataract if they received riboflavin/niacin. There was no effect on any other cataract type or in any other age group. The authors comment that additional research is needed in less nutritionally deprived populations before these findings can be translated into general nutritional recommendations.

Reviewing these trials, Hodge et al (Hodge, Whitcher et al. 1995), observed that the trials examined the prevalence, and not the incidence, of cataract when calculating odds ratios but point out that this approach would bias the results towards the null.

The effect of vitamin supplementation has been examined in other studies. There have been conflicting reports of the benefits of supplementation. The Nurses Health Study in early analyses found long-term supplementation with Vitamin C to lower the rate of cataract extraction (Hankinson, Stampfer et al. 1992). In a later study of some of the same population, (Jacques, Taylor et al. 1997), a cohort of 247 women free of cataract or diabetes in the Boston area were examined to determine the cross-sectional relationship between age-related lens opacities and Vitamin C supplement use over a 10 to 12 year period. Supplements were used before assessment of lens status. A 77% reduction in the prevalence of lens opacification, primarily in the nuclear region was observed in women who used Vitamin C supplements for greater than or equal to 10 years. However this apparent protection against early nuclear changes was not translated to a reduced risk of cataract extraction. When the full cohort of 73,956 nurses was examined to determine the association between vitamin supplement intake and the incidence of cataract extraction during 12 years of follow-up (Chasan-Taber, Willett et al. 1999). 1377 senile cataracts were diagnosed and extracted during the study. Those who used multivitamins or separate supplements of vitamin C, E, or A did not have decreased risks of cataract as compared with non-users even for use of 10 or more years. In another prospective study, physicians who were current users of multivitamins had a relative risk of 0.73 for diagnosis of cataract compared with non-users. There was no significant association among users of vitamin C and E supplements alone (Seddon, Christen et al. 1994).

The nurses study also examined the association between carotenoid and Vitamin A intakes and cataract extraction (Chasan-Taber, Willett et al. 1999). There was a 22% decreased risk of cataract extraction for those with the highest intake of lutein and zeaxanthin compared with those in the lowest quintile (relative risk RR: 0.78; 95% CI: 0.63, 0.95). There was no association with cataract and the carotenoids (Alpha carotene, Beta carotene, lycopene, and beta-cryptoxanthin), Vitamin A, or retinol. Foods rich in lutein such as spinach and kale, seemed to be associated with a moderate decrease in risk of cataract.

The Beaver Dam Eye Study has examined the relationship between both diet and supplements in both a cross-sectional and longitudinal manner.

Regular use of multivitamins for 10 years in the past was associated with a decreased risk of nuclear cataract and an increased risk of cortical cataract in persons without diabetes. In those with diabetes there was no association with nuclear sclerosis but there was a deceased risk of cortical cataract (Mares-Perlman, Klein et al. 1994)

Relationships between diet and nuclear opacities were also explored (Mares-Perlman, Brady et al. 1995). Diets were assessed retrospectively with the use of a food frequency questionnaire. The relationships of nuclear sclerosis and nutrients were often qualitatively and quantitatively different between men and women. In men, nutrients in the highest versus lowest quintile were associated with 40-50% reduced odds of more severe nuclear sclerosis. Relations with some nutrients (vitamins A, C, and E, riboflavin, thiamine, niacin) became apparent only after including contributions from supplements. Thus the relationship of dietary nutrients may be at least partly explained by the previously identified inverse associations with multivitamin use (Mares-Perlman, Klein et al. 1994). Relations with other nutrients (folate, Alpha carotene and dietary fibre) appeared to reflect associations with intake of foods, particularly vegetables. Inverse associations with individual nutrients and foods were often weaker or nonexistent in women. However, there was an inverse relationship of spinach intake (a rich source of lutein) and severity of nuclear cataract in women. This finding was consistent with the finding in other studies suggesting a protective effect of spinach (Tavani, Negri et al. 1996; Brown, Rimm et al. 1999; Chasan-Taber, Willett et al. 1999).

The Beaver Dam Eye Study was able to examine the relationship of some of these nutrients with cataract prospectively (Lyle, Mares-Perlman et al. 1999; Lyle, Mares-Perlman et al. 1999). They examined the association of incident nuclear cataracts with antioxidant intake. A strength of this study is that the data on nutrient intake was available at a time before follow-up began on a cohort who were free of cataract at the outset. The

presence of cataract was therefore unlikely to have influenced peoples' diet or nutrient intake. In this analysis they estimated both food and supplemental sources of antioxidants. Persons with the highest intake of lutein in the distant past (10 years before base line) were half as likely to have incident nuclear cataract as persons in the lowest quintile of intake. However, nuclear cataract were not related to intake of vitamins C or E.

In a random sample of 400 of the Beaver Dam Eye Study subjects serum carotenoids and tocopherols were measured (Lyle, Mares-Perlman et al. 1999). There was no association of nuclear cataract with the carotenoids. Serum tocopherol (the sum of alpha and gamma tocopherol) was inversely associated with nuclear cataract.

However, in a longitudinal study of supplementation with alpha-tocopherol or Beta carotene in middle-aged smoking men, there was no association with the end of trial prevalence of nuclear cataract (Teikari, Virtamo et al. 1997).

The Age Related Eye Disease Study (AREDS) and the Vitamin E, Cataract and Age-related Maculopathy Trial (VECAT) are 2 randomised controlled trials of antioxidant Vitamins and cataract. The AREDS group randomised 4757 participants to receive either a high dose antioxidant combination consisting of Vitamins E, C and Beta Carotene or placebo and followed them for 7 years. No effect of the antioxidant combination was observed on the development or progression of any age related lens opacities or on the incidence of cataract surgery. (The Age Related Eye Disease Study Group 2001)

The VECAT trial randomised 1193 eligible subjects to either Vitamin E or placebo. Subjects were followed for 4 years. The study found no difference in cataract incidence or progression between those receiving Vitamin E and those who did not. (McNeil JJ, Robman L et al. 2004)

The results of these two studies suggest that pharmacological doses of Antioxidants have no clinically significant effect on either the incidence or progression of nuclear, cortical or posterior sub-capsular cataract.The evidence for a protective effect of antioxidant vitamins is thus inconsistent reflecting the complex nature of dietary and nutritional assessment in epidemiological studies. The current evidence may be summarised according to the major antioxidants.

Vitamin A and various carotenoids have been found to be inversely associated with nuclear cataract in some studies (Leske, Chylack et al. 1991; Mares-Perlman, Brady et al. 1995). However, other studies including population-based (Mares-Perlman, Brady et al. 1995; Lyle, Mares-Perlman et al. 1999), longitudinal cohort (Chasan-Taber, Willett et al. 1999; Chasan-Taber, Willett et al. 1999), and interventional studies (Teikari, Virtamo et al. 1997), have not found any association.

Vitamin C has been found to have an inverse relationship with cataract in a number of studies (Leske, Chylack et al. 1991; Hankinson, Stampfer et al. 1992; Jacques, Taylor et al. 1997). In other studies there has been no evidence of any association, (1991; Chasan-Taber, Willett et al. 1999; Lyle, Mares-Perlman et al. 1999; Lyle, Mares-Perlman et al. 1999), and in the India-US cases-control study there was in fact increased prevalence of mixed cataract with increased plasma Vitamin C concentrations (Mohan, Sperduto et al. 1989). Some studies have shown this conflicting evidence within the same study for different cataract subtypes; Mares-Perlman et al reported past use of supplements containing Vitamin C was associated with reduced prevalence of nuclear cataract but an increased prevalence of cortical cataract (Mares-Perlman, Klein et al. 1994). Lyle et al (Lyle, Mares-Perlman et al. 1999), reviewed evidence which suggested that there is a potentially glycating effect of ascorbic acid (Podmore, Griffiths et al. 1998), which may be amplified in the presence of elevated glucose levels. They therefore counselled against advocating widespread supplementation with Vitamin C .

Vitamin E has been found to have a significant inverse association with cataract in various studies. These include case-control, (Leske, Chylack et al. 1991; Knekt, Heliovaara et al. 1992), longitudinal (Leske, Chylack et al. 1998), and population based studies (Lyle, Mares-Perlman et al. 1999). The association has been found for all types of cataract (Leske, Chylack et al. 1991), but more commonly for nuclear cataract (Leske, Wu et al. 1995; Leske, Chylack et al. 1998; Lyle, Mares-Perlman et al. 1999). In the latter trial the relationship was for serum tocopherols rather than Vitamin E in particular.

This ambiguity is heightened by the number of studies that have found no relationship between Vitamin E and cataract. Including case-controls studies in nutritionally contrasting communities (Mohan, Sperduto et al. 1989; 1991), and controlled trials of Vitamin A supplementation (Teikari, Virtamo et al. 1997). These conflicting data suggest that further research is required before recommendations on vitamin supplementation to reduce cataract can be made.

1.9 Hypertension and cardiovascular risk factors

The Framingham Eye Study used data from the Framingham Heart Study in 1948 to 1964 together with ophthalmic diagnoses made in the Framingham Eye Study in 1973 to 1975 to examine the association between cataract and, amongst other risk factors, various cardiovascular risk factors (Kahn, Leibowitz et al. 1977). After adjusting for age and sex, systolic blood pressure was found to be significantly higher in those with cataract compared to those without.

Hiller et al (Hiller, Sperduto et al. 1983), used data from the 1971-1972 National Health and Nutrition Examination Survey to examine a number of risk factors for cataract. The significant association of cataract with systolic blood pressure while controlling for sex and age, disappeared after adjusting for race, education, diabetes, rural residence, and ultraviolet B radiation. However, when examined by subtype, a significant association of posterior subcapsular cataract and systolic hypertension was found. A similar association with posterior subcapsular cataract was found in a case-control study designed to explore this relationship.(Burgess and Sowers 1992)

The association of hypertension with cataract has been studied in clinic-based case-control studies with conflicting results. Some have found a positive association, (Clayton, Cuthbert et al. 1982; Tavani, Negri et al. 1995), while other have found no association at all (Bochow, West et al. 1989; Miglior, Marighi et al. 1994). Clayton et al's study in Scotland also found an association with the use of various diuretics. A case-control study amongst women in Northern Italy found a positive association between hypertension and cataract extraction. They also found significant associations with elevated body mass index, diabetes, and hyper-lipidaemia – all risk factors for cardiovascular disease (Tavani, Negri et al. 1995). An earlier case-control study in the same country found no association with hypertension amongst a total of 1008 cases and 469 controls (1991). They examined an extensive range of variables. Those that could be considered to be related to cardiovascular disease included: a history of cardiovascular disease, duration of cardiovascular disease, a history of diabetes, and body mass index. None of these was reported to be associated with cataract.

However, a similarly designed study in India, found that higher blood pressure was associated with nuclear and mixed cataracts (Mohan, Sperduto et al. 1989). In this population a low body mass index, rather than a high one, was associated with nuclear and mixed cataract.

Population-based studies then examined the association of cardiovascular disease with cataract. The Beaver Dam Eye Study found that hypertension was associated with increased risk of posterior subcapsular cataract in the cross-sectional phase of their study (Klein, Klein et al. 1995). They defined hypertension as either a systolic blood pressure of at least 160 mmHg and diastolic pressure of at least 95 mmHg, or a history of use of hypertensive medications at the time of the examination. They were unable to explore the effect of anti-hypertensive drugs on cataract at the cross-sectional stage. When the data were examined further, looking for associations of cataract with cardiovascular disease and cardiovascular disease risk factors they found that higher glycated haemoglobin was

significantly associated with the increased risk of nuclear cataract in women (Klein, Klein et al. 1997). Men had a higher risk of posterior subcapsular cataract if they had high ratios of total to high density lipoprotein cholesterol. A history of cardiovascular disease either alone, or in conjunction with a history of diabetes, was not associated with cataract. A follow-up examination of the same population confirmed the association of a higher glycated haemoglobin and nuclear cataract, but only in diabetics (Klein, Klein et al. 1998). They concluded that cardiovascular disease and associated risk factors were not associated with the incidence of age-related cataract.

The Barbados Eye Study, a population-based study in a largely black community in Barbados, found an association of cataract with diabetes, high diastolic blood pressure, high waist-hip ratio (a marker of abdominal obesity) and glycated haemoglobin. Most of these lens opacities were cortical. They attributed 14% of the prevalence in lens changes to diabetes (Leske, Wu et al. 1999). There was no significant association of nuclear lens opacities with glycated haemoglobin.

In contrast, two recent large population-based studies amongst predominantly Caucasian populations found no association between hypertension and cataract (McCarty, Mukesh et al. 1999; Delcourt, Cristol et al. 2000). The Melbourne Visual Impairment Project did find an association between thiazide diuretics and posterior subcapsular cataract, and other anti-hypertensives and nuclear cataract. Whether these drugs act as markers for cardiovascular disease and hypertension in particular, or whether it represents a direct effect of the drug on the lens, has not been established in this or other cross-sectional studies (Klein, Klein et al. 1997; McCarty, Mukesh et al. 1999; Delcourt, Cristol et al. 2000)

1.10 Diabetes

The association of diabetes and cataract has been reported in both hospital based and population-based studies.

Case-controls studies in the United Kingdom have reported an association between diabetes and cataract (Clayton, Cuthbert et al. 1982; Harding, Egerton et al. 1993). Harding suggested that 11% of cataract in Oxfordshire could be attributed to diabetes.

The Lens Opacities Case Control study found an increased risk of posterior subcapsular, cortical and mixed cataract with diabetes (Leske, Chylack et al. 1991). In a follow-up study of the risk factors for nuclear cataract in the same population they did not report an association of nuclear cataract with diabetes (Leske, Chylack et al. 1998). Not all the case-control studies have been consistent in reporting an association. The Italian-

American study did not find an association, but had excluded any subjects with diabetic retinopathy and also had a relatively older age group (1991). Older diabetics have been found to have a lower risk of cataract compared with younger ones (Ederer, Hiller et al. 1981). However, another hospital-based study in Italy confirmed a strong association between diabetes and the risk of cataract extraction. They also found that the risk was greater amongst those aged less than 60 years (Tavani, Negri et al. 1995). A further Italian case-control study classified cataract and found an increased risk of cortical cataract with diabetes of more than five years duration.(Miglior, Marighi et al. 1994)

Clinic-based case-control studies are subject to the criticism of selection bias because diabetics are under greater medical surveillance than non diabetics and are therefore more likely to have their cataracts extracted (Ederer, Hiller et al. 1981; Hodge, Whitcher et al. 1995). However, the association has also been demonstrated in cross-sectional studies (Kahn, Leibowitz et al. 1977; Hiller, Sperduto et al. 1983). The Framingham Eye Study showed an association between cataract and increasing blood glucose levels (Kahn, Leibowitz et al. 1977). While both the Framingham Eye Study and the National Health and Nutrition Examination Survey confirmed that the risk for diabetes was stronger in younger age groups (Ederer, Hiller et al. 1981)

Large population-based studies have also examined the association. The cross-sectional phase of the Beaver Dam Eye Study found an increased risk of cortical lens opacities in diabetics (Klein, Klein et al. 1995). There was no increased risk of nuclear cataract observed. They confirmed the observation that the effect of diabetes on the lens was greater in younger diabetics. The Pathologies Oculaires Liees a l'Age (POLA) study found a strong association of diabetes with all types of cataract except nuclear. They also found that the risk of cataract increases with the duration of diabetes (Delcourt, Cristol et al. 2000). The Beaver Dam Eye Study was able to explore the relationship prospectively over a five-year interval (Klein, Klein et al. 1998). They found that increased glycated haemoglobin levels were associated with increased risk of nuclear and cortical cataracts in those with diabetes. There was no significant difference in the incidence of nuclear cataract by diabetic status, whereas the incidence of cortical and posterior subcapsular cataract was greater and pre-existing cataracts were more likely to have progressed.

The Barbados Eye Study found a high prevalence of cortical cataract and attributed this to the high prevalence of diabetes in the predominantly black population (Leske, Wu et al. 1999). Glycated haemoglobin levels were associated with all lens opacities as well as cortical lens opacities, but were not statistically significant for nuclear lens opacities.

The weight of epidemiological evidence in conjunction with laboratory evidence suggest that the relationship between diabetes and cataract is causal (Harding, Egerton et al. 1993), the two most likely pathways are the osmotic effect of sorbitol and the non-enzymatic glycation of lens proteins (Harding, Egerton et al. 1993)

1.11 Anthropometric status

Studies in developing countries have found that low body mass index is associated with nuclear and mixed cataract (Mohan, Sperduto et al. 1989). This has been attributed to poor nutrition, (Sperduto, Hu et al. 1993), diarrhoeal disease (Minassian, Mehra et al. 1989), and the association with low socio-economic status (Mohan, Sperduto et al. 1989)

However animal studies have suggested that restricting calories can lower the incidence and delay the onset of cataract (Taylor, Zuliani et al. 1989; Taylor, Lipman et al. 1995). The association of body mass index on cataract was therefore examined in a number of epidemiological studies. Case-control studies such as Tavani et al's study in Italy found an association between higher body mass index and cataract extraction (Tavani, Negri et al. 1995). This relationship received further support from two prospective cohort studies, which showed higher incidence of cataract extraction in nurses (Hankinson, Seddon et al. 1993), and physicians (Glynn, Christen et al. 1995), to be associated with a higher body mass index. The latter study also found a higher incidence of self-reported cataract, particularly posterior subcapsular cataract and nuclear cataract. However, a population-based cohort study found no association at baseline (Klein, Klein et al. 1997), and a marginally significant association with incident posterior subcapsular cataract after five years follow-up (Klein, Klein et al. 1998). Data were used from the Framingham Eye Study to assess the association of body mass index with cataract (Hiller, Podgor et al. 1998). Eye examinations 13 years apart were used to determine incident cataract in those who were free of cataract at the baseline eye examination. They found a strong association of high body mass index at the time of the baseline examination and the development of cortical cataract at follow-up. There was a strong association of increasing body mass index over time and the development of posterior subcapsular cataract. They found no association with nuclear cataract.

A population-based study in a predominantly black population in Barbados found a high prevalence of cortical lens opacities associated with diabetes. However, even in a population with a high prevalence of obesity, body mass index was not associated with lens opacities. A high waist-hip ratio was associated with cortical lens opacities (Leske, Wu et al. 1999)

A population with a mixture of black and white participants (25% African American) is the Salisbury Eye Evaluation project (Caulfield, West et al. 1999). This study found that there was a greater risk of nuclear opacification in those with lower body mass index. In addition individuals with a high body mass index were less likely to have nuclear cataract than the referent group. Conversely, there was a greater risk of cortical cataract in those with higher body mass indexes. There was no relationship of body mass index with posterior subcapsular cataract.

Mention must be made of a study which examined birth weight and weight at one year, with the subsequent development of cataract (Evans, Rauf et al. 1998). There was no association between birth weight and nuclear opacities, however weight at one year was found to be negatively correlated with nuclear lens opacity score as an adult. It was felt that this association might reflect impaired glucose tolerance brought about by impaired development of the islets of Langerhans. Alternatively impaired growth early in life may affect long-lived molecules such as lens crystallins (Evans, Rauf et al. 1998)

In summary, the evidence regarding body mass index and the development of cataract is conflicting. The confusion reflects the way in which other cataract risk factors such as smoking, alcohol consumption and low socio-economic status are associated with a low body mass index, while others such as diabetes, hypertension and African American race are associated with a higher body mass index (Caulfield, West et al. 1999).

1.12 Oestrogens

Animal studies have shown an protective effect of oestrogen against cataract induced by Transforming Growth factor Beta – a model for human posterior subcapsular cataract (Hales, Chamberlain et al. 1997). The Beaver Dam Eye Study (Klein, Klein et al. 1994), found a protective effect of duration of oestrogen exposure and use of hormone replacement therapy (HRT) against cortical and nuclear lens opacities. The prevalence of nuclear lens opacities in women over the age of 70 who had taken oestrogen replacements was 28.6% compared with 39.1% in men of the same age. Fluorophotometric examination of the nucleus showed a statistically significant difference in lens transmittance and autofluorescence suggestive of a protective effect in women taking oestrogens (Benitez del Castillo, del Rio et al. 1997). The Blue Mountains Eye Study found no protective effect amongst all women, but amongst those aged 65 years and over there was a lower prevalence of cortical cataract (Cumming and Mitchell 1997)

1.13 Sunlight

The association between exposure to sunlight and cataract has been reviewed by Dolin.(Dolin and Johnson 1994). Epidemiological studies have provided evidence for the association of ocular exposure to ultraviolet light and cataract by determining the exposure for each individual.

A case-control study amongst surgical posterior subcapsular cataract cases from a large rural ophthalmic practice was undertaken to investigate the role of exposure to ultraviolet light in the B range (UV-B). Using matched-pairs analyses Bochow et al found that a history of relatively high exposure to UV-B was associated with increased risk of PSC cataracts (Bochow, West et al. 1989)

Taylor et al investigated the relation of ultraviolet radiation and cataract formation, in a survey of 838 watermen who worked on Chesapeake Bay (Taylor, West et al. 1988). The annual ocular exposure and cataract grading were obtained for each waterman. High cumulative levels of UV-B exposure significantly increased the risk of cortical cataract. A dose-response was seen. They did not find an association between nuclear cataracts and UV-B exposure. The Beaver Dam Eye Study (Cruickshanks, Klein et al. 1992), found that exposure to UV-B light may be associated with the severity of cortical, but not with nuclear or posterior subcapsular, opacities in men. They did not find an associations with UV-B exposure for women.

The sunlight hypothesis has been criticised (Harding 1994). The criticism is based on the inconsistency in some studies. However, these studies do not give any attention to the assessment of individual exposure. In summary, these studies provide good evidence of a possibly causal relationship between cortical cataract and UV-B exposure but not for nuclear cataract.

1.14 Diarrhoea

Severe diarrhoea, resulting in dehydration, has been put forward as a risk factor for cataract (Minassian, Mehra et al. 1989). The evidence came from two trials in India, which found a strong dose-dependent association between severe diarrhoea and cataract (Minassian, Mehra et al. 1984; Minassian, Mehra et al. 1989). A case-control study in Oxfordshire supported the association (Harding, Harding et al. 1989). Some subsequent studies in India did not support the hypothesis of an increased risk of visually disabling cataract in persons with a positive history of severe diarrhoea (Mohan, Sperduto et al. 1989; Bhatnagar, West et al. 1991), while others did (Ughade, Zodpey et al. 1998). Prospective studies of people who have had severe diarrhoea could clarify the issue (West and Valmadrid 1995)

1.15 Drugs

Steroids

Posterior subcapsular cataract has been found to be strongly associated with the use of steroids in numerous studies. These include case-control studies (Harding and van Heyningen 1988; Bochow, West et al. 1989; Miglior, Marighi et al. 1994), and population-based studies (Cumming, Mitchell et al. 1997; Delcourt, Cristol et al. 2000). The association has even been found for inhaled corticosteroids (Cumming, Mitchell et al. 1997.)

Aspirin and other analgesics

The role of aspirin in protecting against cataract was proposed following reports of reduced cataract rates amongst regular users of aspirin (Harding and van Heyningen 1988). There were theoretical grounds for this; aspirin inhibits aldose reductase activity and lowers plasma tryptophan levels (West and Valmadrid 1995). However, numerous other studies including population-based and prospective randomised controlled trials have not found a protective effect (Hiller, Sperduto et al. 1986; 1991; Seddon, Christen et al. 1991; Hankinson, Seddon et al. 1993; Cumming and Mitchell 1998)

Allopurinol

The association of Allopurinol use with cataract has been found in some case-control studies (Leske, Chylack et al. 1991). It is difficult to interpret the data from many of the studies because of lack of data on long-term use (West and Valmadrid 1995). Population-based studies have not found an association (Cumming and Mitchell 1998). Long-term duration of gout has been associated with cataract (McCarty, Mukesh et al. 1999).

1.16 Genetic effects

Framingham Eye Study (1973–1975) and the Framingham Offspring Eye Study (1989–1991) were used to study familial associations for nuclear, cortical, and posterior subcapsular lens opacities. The odds of nuclear opacity for one sibling of a sibling pair was estimated to more than triple if the other sibling had a nuclear opacity. There were no associations found for cataract between parents and offspring or between spouses. The clustering of lens opacities in families led to the conclusion that there may be genetic or environmental factors responsible (Framingham Eye Study 1994)

The Beaver Dam Eye Study performed segregation analysis, sibling correlational analysis and commingling analysis on a proportion of the study participants. They found

that a single major gene could account for 58% of the variability in cortical cataract (Heiba, Elston et al. 1995), and for 35% of the variability of nuclear sclerosis after adjusting for age and sex (Heiba, Elston et al. 1993)

Hammond et al studied 506 pairs of female twins aged between 50 to 79 years. (226 monozygotic and 280 dizygotic) They found that the proportion of the variance explained by genetic factors was 48%, while age and unique environmental effects accounted for 38% and 14% of the variance respectively (Hammond, Snieder et al. 2000). These studies suggest that genetic effects are important even in such a clearly age-related disease as cataract, explaining up to almost 50% of the variation in the severity of this disease (Hammond, Snieder et al. 2000).

1.17 Conclusion

Age-related cataract is clearly a multifactorial disease, subject to both genetic and environmental effects. Of the environmental effects, nuclear cataract is associated with smoking and alcohol. Antioxidants and oestrogens may be protective of nuclear cataract. Certain reported risk factors, which depend on personal, possibly inherited factors, include: myopia, diabetes and hypertension.

2. Methods

This chapter aims to

- Introduce the need for a study in eye disease in the United Kingdom.
- State the principle hypothesis of the dissertation.
- Outline the objectives of the Melton eye study and of the dissertation.
- Describe the population studied in the Melton Eye Study.
- Describe the methods used to examine the population, including examples of nuclear lens grading
- Describe the methods used to analyse the data.
- Develop the principal of an insulin resistance score.
- Discus the response rate.
- Describe the characteristics of those who did not take part.
-

2.1 Introduction

There has recently been a proliferation of ophthalmic epidemiology studies. (see Table M5 page 57) Each study has varied slightly in the methods used. Why another study? An editorial in the journal *Ophthalmic Epidemiology* (Klein 1997), points out that there is a need for "thoughtful design of individual studies that are undertaken for a specific geographical area and a particular constellation of public health needs". It goes on to suggest that "homogeneity as well as heterogeneity of results" may give important insight into the understanding of lens opacities. The dearth of population-based information on ageing diseases of the eye for the United Kingdom population has lead to the development of the Melton Eye Study.

2.2 Hypothesis

The insulin resistance syndrome comprises a constellation of factors which include, obesity, central body fat distribution, glucose intolerance, elevated plasma insulin levels, increased triglycerides and decreased high-density lipoprotein cholesterol, cardiovascular disease and hypertension, nephropathy, neuropathy and retinopathy (Austin, Mykkanen et al. 1995; Hansen 1995).

The principle hypothesis of this dissertation is that the insulin resistance syndrome provides a common pathway for many observed risk factors for cataract.

2.3 Objectives

The Melton Eye Study was designed to be longitudinal with the aims of:

- measuring the incidence of common eye diseases, particularly cataract and age-related macular degeneration,
- relating disease incidence to risk factors measured before the onset of disease,
- describing the natural history of the ageing eye in order to identify those small changes to the eye that are associated with the eventual development of sight threatening disease.
- The baseline examination was designed to fit in with the study's longitudinal aims but it will in itself:
- provide prevalence estimates for eye disease that will be useful in planning health service provision,
- document the extent of minor lens and macula changes,
- facilitate a preliminary assessment of risk and protective factors.
-

2.4 Objectives of this dissertation:

- provide prevalence estimates for nuclear cataract that will be useful in planning health service provision,
- examine the association between nuclear cataract and the risk factors comprising the insulin resistance syndrome
- examine the association between nuclear cataract and other reported risk and protective factors.

2.5 Research Period

The first subject was seen on the 30 March 1994 and the last subject was seen on the 30 May 1997.

The design of the Study began in April 1993. This period of design included research funding applications, development and piloting of study questionnaires and examination forms. Staff recruitment and training, advertising and promoting the study and recruitment of subjects followed culminating in the first patient being seen..

2.6 Researchers

The Melton Eye Study has been conducted in phases with the input of a number of researchers at different stages.

Concept

The Melton Eye Study in its current form was conceived by Prof AR Rosenthal with Dr J Sparrow and Dr J Thompson as an extension of the earlier study on the same population (Gibson, Rosenthal et al. 1985).

Study Design

Dr A.B. Hall in conjunction with statistical advice and research design from Dr J. Thompson, developed and piloted questionnaires, examination forms and the research protocol. This included recruitment of subjects, advertising and promoting the study.

Staff training.

A research assistant, Mrs R Donegan was recruited and trained by Drs Hall and Thompson. The research assistant was trained to interview subjects and take their blood. She already had the laboratory skills to perform the High Pressure Liquid Chromatography on the serum specimens to determine antioxidant levels.

After 18 months a second ophthalmologist Dr J Deane was trained by Dr Hall in all aspects of the research protocol, including lens grading.

Research Clinic

The research clinic was initially run by Dr Hall. Following Dr Deane's training the 2 ophthalmologists worked together for a period, running clinics on different days. The study examinations were completed by Dr Deane.

Data Entry

Dr Thompson supervised the training of research assistants in data entry. This included double entry to check for errors.

Statistical analysis

The statistical analysis for this dissertation has been performed by the author.

2.7 The study population

Melton Mowbray is a market town with a population of about 35,000, situated in Leicestershire midway between Nottingham and Leicester. Over the last 15 years it has been used in a number of epidemiological surveys particularly of the needs of elderly people and of eye disease (Clarke, Clarke et al. 1984; Gibson, Rosenthal et al. 1985; Gibson, Lavery et al. 1986; Gibson, Shaw et al. 1986; Jagger and Clarke 1988; Lavery, Gibson et al. 1988; Lavery, Gibson et al. 1988; Sparrow, McLeod et al. 1993). It was originally chosen because it is a very stable community and virtually all the town and the surrounding countryside is served by a single 14 doctor general practice which had one of

England's first computerised age-sex registers. This has enabled researchers to draw representative random samples of the town's population. Local ethics committee approval was obtained before commencing the study.

Characteristics of the population

The population is predominantly a Caucasian one. Table M1 Describes the racial composition of the Melton Eye Study subjects. Table M2 describes the breakdown of the population by social class. Data were available on social class for 802 of the subjects examined. 40.4 % of the population could be described as in a non-manual class (Classes I – III). The remainder were in the manual classes IV – VI. Table M3 gives the number of years of higher education for 810 of the subjects who had this information available. 73.7% of subjects had no higher education. 16 subjects had had cataract surgery: 20 cataract surgeries had been performed, 12 in the right eye and 8 in the left, with 4 subjects having had surgery in both eyes. 5 Subjects had had retinal detachment surgery and a further 3 had had glaucoma surgery. These data on surgery other than cataract surgery, are summarised in Table M4

Table M1 Racial composition of the Melton Eye Study subjects

ORIGIN	Frequency.	Percent	Cumulative.	95% Conf. Interval
Caucasian	820	99.27	99.27	98.42 % to 99.73 %
South Asian	5	0.61	99.88	0.19 % to 1.40 %
Oriental	1	0.12	100.00	0.003 % to 0.67 %
Total	826	100.00		

Table M2 Social Classes of the Melton Eye Study subjects

Social Class	Frequency	Percent	Cumulative	95% Conf. Interval
1	72	8.98	8.98	7.09 % to 11.17 %
2	161	20.7	29.05	17.35% to 23.02 %
3	91	11.35	40.40	9.23% to 13.75 %
4	220	27.43	67.83	24.37% to 30.66 %
5	206	25.69	93.52	22.69% to 28.85 %
6	52	6.48	100.00	4.88% to 8.42 %
	802	100		

Table M3 Years of higher education

Years of higher education	Frequency.	Percent	Cumulative.	95% Conf. Interval
None	597	73.70	73.70	70.53 % to 76.70 %
Up to 3 years	169	20.86	94.57	18.11 % to 23.83 %
Greater than 3 years	44	5.43	100.00	3.9 % to 7.22 %
Total	810	100.00		

Table M4 Intra-ocular surgeries other than cataract:
Type of Surgery, Eye operated, Brunescence and White Scatter cataract grading scores by eye. (operated eye in bold)

	Eye Involved	Brunescence RE	White Scatter RE	Brunescence LE	White Scatter LE
Retinal Detachment	Right	**3.5**	**4.0**	2.5	3.0
	Right	**1.3**	**2.2**	1.1	1.4
	Right	**Had Cataract Surgery**		N/A	
	Left	1.7	2.8	**2**	**3.2**
	Left	1.3	1.1	**1.5**	**0.9**
Glaucoma	Right	**1.6**	**1.3**	1.6	1.2
	Right	**0.4**	**2.4**	0.3	2.2
	Both	**1.3**	**1.6**	**1.5**	**1.7**

Eligibility for the study

Anyone registered with the general practice at the time of sampling and aged between 55 and 74 years inclusive was considered to be eligible for the study. Residents of nursing homes and those housebound due to mental or physical disability were included. This age range was chosen as a previous study had investigated the eyes of the 75 and over age group (Gibson, Rosenthal et al. 1985; Gibson, Lavery et al. 1986; Gibson, Shaw et al. 1986). The 55 to 74 age group was also felt to represent the age range in which early pre-symptomatic changes develop, enabling prospective analysis of risk factors in future assessments of the subjects.

The sample

On four occasions, separated by about six months, up-to-date lists of all patients aged 55 to 74 years were obtained from the general practice. Subjects were drawn at random from these lists. When a subject was selected any other eligible person recorded as living at the same address was also included in the sample. On each of the 4 occasions the process was continued until the sample size reached at least 300. The total sample size thus obtained was 1204.

2.8 Recruitment strategy

Recruitment

In order to maximise the response rate a publicity campaign was undertaken at the start of the project. Posters and leaflets were placed in the doctors' surgery and on the premises of local optometrists. Local newspapers, television and radio were contacted and they carried features describing the aims of the study.

Subjects were contacted by letter, coming jointly from the University of Leicester and their own general practitioner. The letter invited them to participate in the study and outlined its aims. Subjects who did not reply to the letter were contacted by phone, repeat letter or if no other contact was possible, by home visit. Subjects not prepared to come for eye examinations were sent a shortened version of the questionnaire used in the research clinic. A number of people agreed to come to the research clinic after completing the postal questionnaire. Subjects who could be contacted by telephone but who were not willing to attend the research clinic or to return a postal questionnaire were asked to answer the questions in the postal questionnaire over the telephone. Subjects who were unable to travel were visited at home. The home visit included an assessment of visual acuity, an interview and an eye examination following dilation of pupils. Photography was not performed on those having home visits.

Apart from the free complete eye examination and a prescription for glasses, if required, no financial incentives were offered to persuade reluctant subjects to attend the research clinic. If the subject had a problem getting to the research clinic, a taxi or volunteer driver from the local Lions Club was contacted to transport them.

Appointments

Appointments for the research clinic were sent out with the invitation letter and information leaflets. When possible this was followed by a telephone call confirming the appointment. Clinic appointments were offered after working hours and on Saturdays if subjects indicated that they could not attend because of work commitments.

2.9 Research clinic procedure

Subjects were welcomed to the clinic, the procedure explained to them, and any questions answered. After written informed consent was obtained, standard examination and interviewing protocols were followed. The time that the subjects spent in the clinic averaged one-and-a-half hours for a single person and two hours for a couple.

Visual acuity

The subject's current spectacle prescription was measured on a Topcon LM6 focimeter. The visual acuity was assessed using their current refractive correction on retro-illuminated Early Treatment of Diabetic Retinopathy (ETDRS) letter 4 metre charts, which are based on the Bailie-Lovie LogMAR charts (Ferris FL 1982). An initial chart was used to determine the best corrected visual acuity, using auto refraction and subjective refinement as necessary. Once best correction was achieved, two further charts were used to record the final visual acuities. The visual acuity was recorded in LogMAR notation and

the total number of letters correctly read. At least four of five letters had to be identified correctly per line.

If the visual acuity fell below 54 letters (LogMAR 0.0 or 6/6 Snellen) in either eye then an auto refraction, using a Nidek AR-1100 auto refractor, was performed and the visual acuity reassessed using that correction placed in a trial frame. If the acuity remained below LogMAR 0.0, a subjective refractive correction was performed before a final best-corrected visual acuity accepted. If the subject was unable to read any letters on the top line (1.0 or 6/60) at 4 metres then the test was repeated at 1 metre. If this was unsuccessful then the subject's ability to count fingers, detect hand movement, or to perceive and project light was assessed.

Near vision was measured using Minread Acuity cards (Mansfield JS 1992), with a separate chart for each eye. The subject's preferred reading distance was used in order that the measurement should relate to functional disability. If a subject was unable to read LogMAR 0.1 (6/7.5) with his or her own near correction then an auto or subjective refraction was used – with an appropriate reading addition for the person's age – placed in a trial frame. Each eye was tested separately under standard fluorescent lighting conditions. The final score was the last complete three-line sentence without error.

Contrast sensitivity

Contrast sensitivity was measured using Pelli-Robson (Pelli 1988), contrast sensitivity charts. These charts consist of 16 groups of three letters at 1-2 cycles/degree, near peak sensitivity. The letters within each triplet each have the same contrast, the contrast decreases from one triplet to the next by a factor of $1/\sqrt{2}$. The first triplet is of maximal contrast (0.05 log units) and the following triplets reduce by 0.15 log units for a total of 2.30 log units, below the threshold for normal observers.

Testing took place under standard lighting conditions using the subjects usual correction at a distance of 1 metre to minimise the effects of visual acuity on contrast sensitivity. Each letter subtends an angle of 1.5 degrees at this distance. A triplet was scored as correct if the subject identified two out of the three letters as instructed by Pelli. Subjects were encouraged to persist for 20 seconds and to identify a given character even if uncertain of its identity, as it takes some time to perceive a letter when the subject approaches threshold. The chart was changed between eyes and again for binocular testing. The subject's score was the log contrast sensitivity corresponding to the last group of letters in which two letters were correctly named.

Photography

After pupil dilatation, subjects were seated on a chair that could swivel between the fundus camera, CCD cataract cameras and the slit lamp. Stereo fundus photography was performed using a Zeiss FF5 fundus camera and 50 ASA Fuji Velvia reversal film. Stereo views were taken of the optic disc, macula and the area temporal to the macula. All macular photographs were subsequently graded using the International Grading System for age-related macular degeneration (Bird, Bressler et al. 1995).

The lens was imaged using the Marcher CASE 2000 cataract imaging system with both Scheimpflug and retro-illumination digital images (Sparrow, Brown et al. 1990). These were stored on the hard disc until they were processed later in the day and the images transferred to optical discs. The software used to analyse the images obtained by the Scheimpflug cameras was unfortunately not perfected during the period of the study. This meant that we were unable to use the digital image data in the analysis of the study.

Slit lamp examination

A detailed slit lamp examination was performed. Lids were examined for signs of blepharitis (Bron, Benjamin et al. 1991), including meibomian gland plugging, retroplacement of meibomian gland orifices, vascularisation and keratinisation of the lid margin. The lids were examined for any other signs of disease, particularly the presence of lesions that were suspicious of basal cell or squamous cell carcinoma. The cornea was examined for signs of climatic droplet keratopathy (Johnson and Ghosh 1975). A note was made of any other corneal lesions, distinguishing those that involved the central area and may have affected visual acuity.

Pterygium was measured in millimetres from the tip of the pterygium to the middle of the base at the limbus. The presence of any pinguecula and corneal arcus senilis was noted. The latter was categorised as involving more or less than 180 degrees of the cornea. The iris colour was graded by comparison with standard photographs supplied by the Beaver Dam Eye Study (Klein, Klein et al. 1991).

The presence of pseudoexfoliation, defined as dandruff-like material on the lens capsule or iris margin, was noted during lens grading. If a subject was aphakic the presence or absence of an intra-ocular ocular lens was noted.

Slit lamp biomicroscopy of the vitreous, disc and retina was performed using a Volk 90D or 78D lens. The presence or absence of a posterior vitreous detachment was noted. A record of the vertical cup disc ratio was made. Presence of peri-papillary atrophy and any features suggestive of glaucomatous disc damage such as notching of the disc margin or disc margin haemorrhages were also noted. The presence of features of age related macular

degeneration such as soft drusen, soft confluent drusen, large hard drusen, atrophy and hypertrophy of the retinal pigment epithelium, geographic atrophy, exudative macular degeneration and disciform scarring were noted. Any features of diabetic retinopathy were recorded. Any other ocular abnormalities were recorded. The examiner then correlated the clinical findings with any reduction in visual acuity.

Intra-ocular pressure

Slit lamp examination ended with tonometry using benoxinate and fluorescein instilled in each eye. Intra-ocular pressure (IOP) was not measured prior to pupil dilatation as the taking of such measurements would affect the quality of photographs, particularly the Marcher CCD retro-illumination pictures of the crystalline lens that are very sensitive to abnormalities in the corneal tear film. IOP was measured using a regularly re-calibrated Goldman contact tonometer. If subjects were found to have an intra-ocular pressure of above 21mm of mercury then they were reviewed in a few weeks for undilated tonometry. If the intra-ocular pressure remained elevated, they were referred to an ophthalmology clinic for further assessment and visual field examination.

Lens grading

The lens was graded using both LOCS III (Chylack, Wolfe et al. 1993), and the decimalised version of the Oxford Clinical Cataract Grading and Classification System (OCCCGS) (Sparrow, Bron et al. 1986; Sparrow, Frost et al. 2000). Details of the grading systems are given in the Literature review. The purpose of this section is to give actual examples of nuclear grading.

Figures M1-M3 are examples of lenses that may have been graded in the Melton Eye Study. (The photographs are of patients that were seen at the Leicester Royal Infirmary). The lenses have been graded by both LOCS III and OCCCGS. The grading has been done from the photographs. The grades given are therefore merely to demonstrate the grading process. There are unavoidable differences between the in vivo slit lamp image and the photographic image that mean that the grades given here would not be the same as those found in slit lamp grading.

Figure M1 is of a relatively clear lens typical of that found in younger Melton Study subjects. There is very little colour in the lens, which was graded as 0.7 LOCS Nuclear Colour and 0.1 OCCCGS Brunescence. The dip in the centre of the lens is clearly visible and there is very little light being scattered by the lens. This was graded as 0.9 LOCS Opalescence and 0.2 OCCCGS White Scatter.

Figure M1 Relatively clear lens with little Colour (Brunescence) or Opalescence (White Scatter).

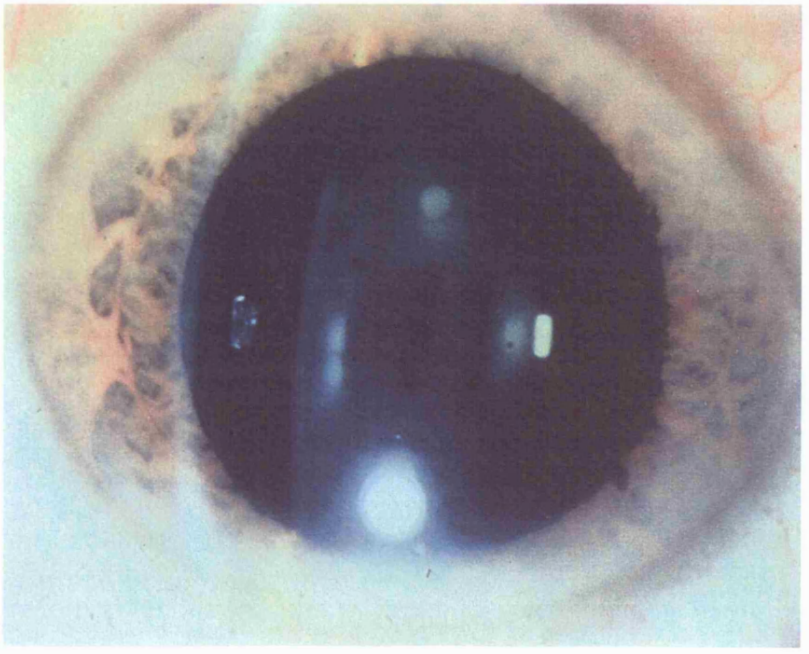


Figure M2 depicts a lens with changes in the nucleus that are predominantly in the LOCS Opalescent or OCCCGS White Scatter category. The dip in the centre of the lens has largely disappeared, and the whole of the centre of the lens is scattering a considerable amount of light. However, the amount of the colour in the lens is relatively low. This lens was graded as LOCS grade 3.3 Nuclear Opalescence OCCCGS 2.9 White Scatter. The LOCS Nuclear Colour grade was 2.2 and the OCCCGS Brunescence grade 0.8.

Figure M2 Predominantly Opalescent (White Scatter) lens with little Nuclear Colour (Brunescence)

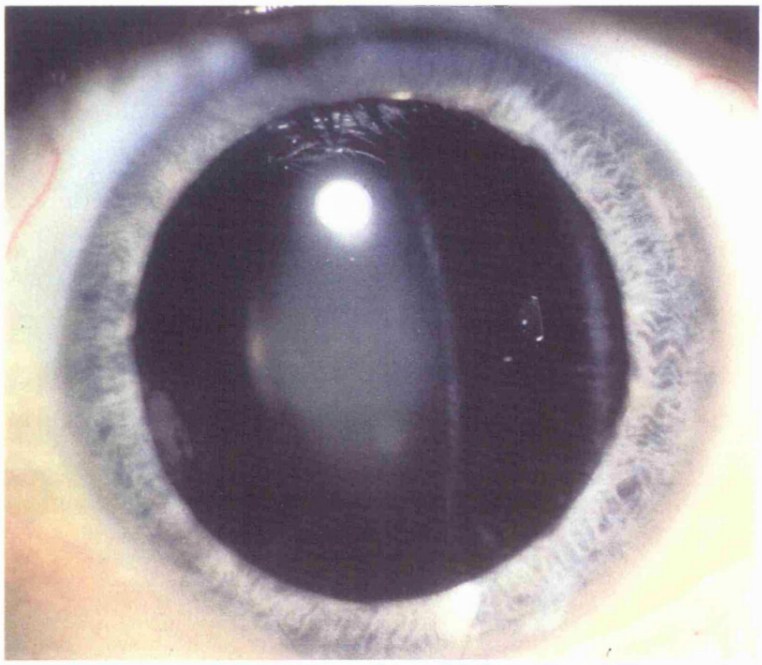
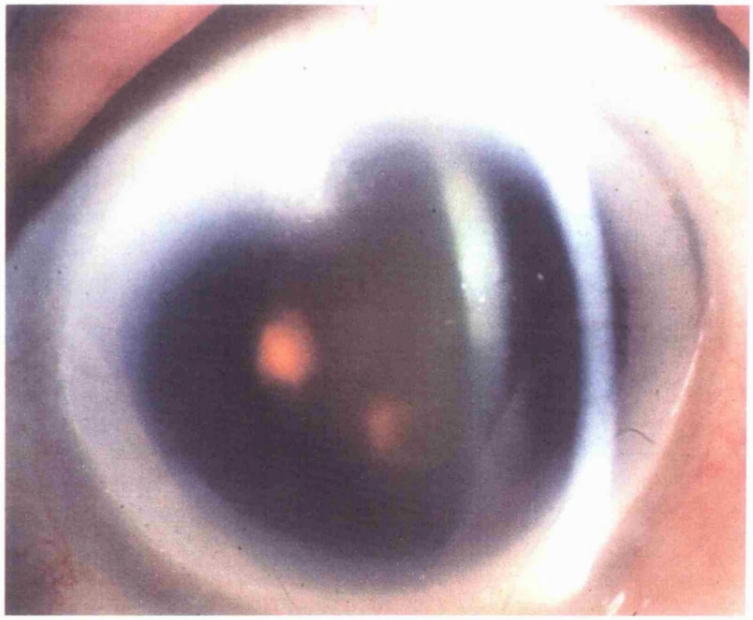


Figure M3 is of a lens with more colour or brunescent changes than Figure M2. There is also less Opalescence. This lens was graded as LOCS Nuclear Colour grade 4.7 and as OCCCGS Brunescence 2.9. The grades for Opalescence and White Scatter were 3.1 and 2.1 respectively.

Figure M3 Lens with Nuclear Colour (Brunescence) predominating



Blood samples

Blood was taken to determine levels of antioxidants including Vitamins A , C, and E and Beta Carotene, glucose, and lipids. Samples were immediately centrifuged in the clinic and the serum frozen at minus 20 degrees centigrade. At the end of the day the frozen samples were taken to Leicester and stored at minus 70 degrees centigrade. The frozen samples were processed in batches by High Pressure Liquid Chromatography (HPLC)

2.10 Quality control

A group of people from Leicester were used to pilot the questionnaire and clinic procedures. The strict protocol ensured that the variation between examiners was kept to a minimum. Systematic variation in slit lamp grading between the two observers was assessed in a reproducibility trial (Hall, Thompson et al. 1997).

The quality of images taken on the CCD cameras can be assessed immediately and new ones taken if the images are inadequate. Assessment of the images is computerised. The development of fundus transparencies was all undertaken by the Department of Ophthalmology Photographic Unit at the Leicester Royal Infirmary – ensuring uniformity of quality. The graders of the photographs received training in Rotterdam or Madison in the International Grading System for age-related macular degeneration (Bird, Bressler et al. 1995). Standard photographs were periodically regarded to ensure that there was no shift in the way grading criteria were applied.

2.11 Data handling and statistical methods.

Interviews and patient examination data were recorded on paper questionnaires and examination forms in the research clinic. These data were then entered into a computer database. Double entry of data was used to minimise transcription errors. Subsequently variables were checked visually using either tables, graphs or summary statistics to look for unexplained outliers that could signify an error in data entry.

A statistical graphics and data management package called STATA*(. 1999.) was used for all statistical analysis and to generate most of the graphs. The relevant statistical methods are given in each chapter. However in summary: summary statistics were generated by STATA. (. 1999.) The associations between cataract and various risk factors were analysed using regression analysis.

Risk factors comprising the insulin resistance syndrome were analysed first in a univariate analysis using regression analysis, examining the association of the risk factor with the various subtypes of nuclear cataract.

Factors included in this section of the analysis include: Diabetes, Glucose, body mass index, triglycerides, cholesterol, hypertension, and oestrogen. [1]

An insulin resistance score was created by taking glucose, body mass index, cholesterol, low levels of high-density lipoprotein cholesterol, and triglycerides as key

[1] StataCorp. 1999. *Stata Statistical Software: Release 6.0.* College Station, TX: Stata Corporation

elements of the syndrome and dividing each variable into 4 evenly distributed quartiles. The lowest quartile scored 1 and the highest 4. However as low levels of HDL cholesterol are the insulin resistance syndrome risk factor; a high level of HDL cholesterol was given a score of 1 while a low level was given a score of 4. The insulin resistance score was created by taking the mean of each subject's quartiles as the score. The insulin resistance score was then included in the regression analyses.

Other known risk factors and protective factors were also analysed in a univariate model. These factors comprise cigarette smoking, alcohol, education status, social class, and blood antioxidant levels. Because of the consistent and large effect of age sex and grader on nuclear cataract each analysis was then corrected for age sex and grader. Age was analysed as a continuous variable and sex and grader were analysed as indicator variables. Multivariate models were then built using all the risk factors comprising the insulin resistance syndrome and those know risk and protective factors, which were shown by regression analysis correcting for age, sex and grader to be associated with nuclear cataract in this study. If a known risk factor was not significant in analysis correcting for age, sex and grader it was not included in the final model. Hypertension was examined by looking at systolic and diastolic blood pressure and then attempting to adjust for the effect of possible treatment for hypertension by including a self-report of hypertension in the analysis. Diabetes, hormone replacement therapy, social class, years of higher education smoking, and alcohol consumption were categorised and analysed as indicator variables.

Unlike refractive error or contrast sensitivity, which are eye specific, these risk factors affect both eyes. The data from cataract grading used to analyse risk and protective factors are therefore the average of the grading from both eyes. If for any reason (e.g. pseudophakia) no grading is available then data from the available eye were used.

Hormone replacement therapy (HRT) is only give to women. Inclusion of HRT in the model was done separately for women only. The estimated co-efficients for the various risk factors including HRT are analysed in the final model for women only are therefore presented separately.

In analysing the association of myopia with nuclear cataract, data from the right eyes was used. The various environmental risk factors are included in a final model for myopia; however it was not possible to include myopia in the final model examining the insulin resistance syndrome as myopia is eye specific.

Each nuclear feature was analysed in turn in a regression including all the above associated factors. In all the regressions involving indicator variables STATA

automatically drops an indicator (dummy) variable from the regression. This allows the coefficients to have the interpretation of changes from a base group.

Data from the multivariate regression models is presented in tables giving estimated coefficients, the standard error, probability levels and 95% confidence intervals.

2.12 Discussion

Not all the elements of the methods of the Melton Eye Study described in this chapter are relevant to the epidemiology of nuclear cataract. However, they have been described in detail as most of the data has been examined for an association with nuclear cataract. At first glance age-related macular degeneration and glaucoma may appear to have nothing to do with the lens, yet glaucoma, particularly glaucoma surgery has an association with cataract (Harding, Egerton et al. 1993). The association of age-related macular degeneration and cataract has been examined in some detail (Wang, Mitchell et al. 1999).

The Melton Eye Study will provide up-to-date prevalence data on the eye diseases responsible for much of the visual impairment and blindness in the UK. Incidence data from the longitudinal phase of the study would be invaluable in assessing the ocular health care needs of the community.

The age range for the study was selected in order to give a cohort in whom the early development of disease and other age-related changes to the eye could be observed. The lower limit of 55 years was adopted because age-related eye disease is very rare before this age. For instance, in the Beaver Dam Eye Study cortical opacities involving 5% of the lens were found in only 1.5% of the population aged 43 to 54 years (Klein, Klein et al. 1992). The upper limit of 74 years fits in with the earlier study of eye disease in people aged over 75 years from the same town (Gibson, Rosenthal et al. 1985), a study of older people would be suitable for studying established eye disease but not so helpful for charting disease development. The longitudinal design of the study means that data will eventually become available on ageing eye diseases in older people, with the added advantage of being able to relate it to the earlier data on their eyes.

A critical stage in any population-based study is obtaining a complete sampling frame. The frames used in other studies include: electoral registers (Green, Battistutta et al. 1994), a specially organised household census conducted by telephone (Klein, Klein et al. 1991), and doorstep interviews (Livingston, Carson et al. 1994). While the Melton Study has some advantages over these, there are limitations that must be acknowledged. Melton Mowbray is an ideal location because the community is distinct and the patient list from the single general practice provides an accurate and regularly updated frame. In order to reduce the number of subjects lost to the study due to death or migration, the Melton Eye Study sampled 300 people at a time at intervals throughout the study period, using an updated version of the register on each occasion. The composition of the patient register closely reflects that of the population of the town, as measured by official censuses, and

has been found to be similar to England and Wales in relation to age, sex and social class distributions and standardised mortality ratio (Jagger and Clarke 1988). However, the size of the population used in the study is relatively small and the racial mix of the population is restricted to Caucasians. Therefore, extrapolating the findings of the Melton Eye Study to the general population needs to be done with an element of caution.

A major factor hampering the collaboration between cataract research projects is the lack of any unified grading system. The computerised CCD cameras used in the Melton Eye Study provide a permanent objective record of all subjects' lenses in a form suitable for image processing. However not all the important features show up clearly on photographs and a certain amount of clinical grading is still needed. The Oxford Clinical Cataract Classification and Grading Scheme (OCCCGS) was chosen as the primary grading method because it has features for grading early lenticular changes such as fibre-folds and Retro-dots. In order to aid international comparison with studies aimed more at established disease, LOCS III grading at a slit lamp was also used (Hall, Thompson et al. 1997). LOCS III was chosen as it has a published and clearly described method and uses a decimalised grading system. Decimalised systems were chosen for grading in spite of the scepticism subsequently voiced by Klein (Klein 1997), that subdivision only disperses the grading error over more subunits without getting closer to accurate classification.

The Melton Eye Study also uses Marcher/Oxford CCD retro illumination and Scheimpflug cameras. These have been shown to be very sensitive to small clinical changes (Sparrow, Brown et al. 1990; Harris, Smith et al. 1991; Datiles, Magno et al. 1995), and they are not susceptible to variation in photographic development in the same way as film based methods are. The quality of the CCD images can be immediately assessed and the pictures repeated if necessary. These factors make the CCD cameras ideal for a longitudinal study. The combination of detailed slit lamp assessment of early lenticular changes provided by OCCCGS combined with the sensitivity of the CCD cameras gives the Melton Eye Study a unique opportunity to study the natural history of lens ageing. The software used to analyse the images obtained by the Scheimpflug cameras was unfortunately not perfected during the period of the study. This meant that we were unable to use the digital image data in the analysis of the study. However, the images are available should the planned longitudinal phase of the study be done.

The study of age-related macular degeneration has been helped by the development of an international system of classification (Bird, Bressler et al. 1995). The Melton Eye Study uses the international grading system on paired stereo photographs of the fundus.

Response rate

There was a hierarchy of participation in the Melton Eye Study. Of the 1204 subjects selected, 20 had died and 24 had moved away from the area before being able to attend. Of the 1160 remaining 1013 participated in the questionnaire and 826 in the examination. There were 95 who were contacted and refused any participation, and 52 could not be contacted at all despite multiple attempts. Characteristics of those who were examined, not examined and those who actively refused to participate are summarised in Table M6.

Participation rate may be expressed in a variety of ways depending on the figures chosen for numerator and denominator. The participation rate, including those with questionnaire data only, as a percentage of contacts is 92% and as a percentage of all subjects including sampling frame errors 84%. The participation rate in terms of examination of contacts was 75%. In terms of examination as a percentage of sampling frame including known and possible frame errors the rate would be 69%.

There are ways of reducing non-participation in population-based studies. The Melbourne VIP (Livingston, Lee et al. 1997), used similar strategies to the Melton Eye Study: a clear friendly invitation to participate in the study, detailed explanation of the reasons for and details of the study. Unlike the MVIP a financial incentive was not offered to the final group of non-responders. In the case of the MVIP this strategy lead to an increase in the overall participation by 3% (Livingston, Lee et al. 1997). Table M1 summarises some of the strategies used in recruitment for population-based studies as well as giving details on the numbers seen and the response rate.

Table M5. A selection of population based studies summarising sampling strategies, exclusion criteria and response rates.

	Beaver Dam (Klein, Klein et al. 1991).	Baltimore Eye Survey (Tielsch, Sommer et al. 1990).	Nambour study of ocular disease (Green, Battistutta et al. 1994).	Melbourne Visual Impairment Project (Livingston, Carson et al. 1994).	Blue Mountains Eye Study (Attebo, Mitchell et al. 1996).	Melton Eye Study
Total sample size	5925	6743	3000	3500	4433	1204
Number seen	4926	5341	1626	3271	3654	826
No. aged 55 to 74	2601 seen	2653 (estimated)	568 seen (estimated)	1855 (estimated)	2376 seen	1204
Response rate		79.2%	54.2%	83%-n	82.4%	75% (examined)
Age range	43 –84 years	> 40 years	25-70 years	40 years and older	49 to 96	55 to 74
Sampling strategy	private census of households	cluster sampling of households stratified by race	random sample from state electoral role	Household census	Door to door census	Random sample from computerised general practice age/ sex register
Recruitment strategy		Doorstep interview	Letter of invitation	• Doorstep interview • Financial incentives	Information sheet	• Letter of invitation • Telephone reminder
Exclusions	None	None	None	•institutionalised • dying after initial contact but before exam • no contact after 10 attempts	• institutionalised	None
Ophthalmic exam	All	• Screening exam • Detailed exam if VA < 20/30	All	All	All	All
Lens grading	Photograding Wisconsin System for Classification of Cataracts from Photographs	? method not reported	Photograding: Method not reported	• Photograding: Wilmer standard photography system • Slit lamp grading Wilmer system.	Photograding: Wisconsin System for Classification of Cataracts from Photographs	•Oxford/ Marcher automated CCD retro illumination and Scheimpflug views • Slit lamp grading: Oxford Clinical Grading System and LOCS III

Table M6

Mean Age of Examined Participants by sex

Variable	Observations	Mean age	Std. Dev.	Min	Max
Female					
Age	435	65.30	5.76	54.48	76.63
Male					
Age	391	65.05	5.90	55.15	76.80
Total	**826**	**65.17**	**5.82**	**54.48**	**76.80**

Mean Age of Non-Examined by sex

Variable	Observations	Mean age	Std. Dev.	Min	Max
Female					
Age	180	65.76	6.27	55.73	76.78
Male					
Age	172	64.78	5.93	55.22	75.82
Total	**352**	**65.34**	**6.10**	**55.22**	**76.78**

Mean age of those who refused by sex

Variable	Observations	Mean age	Std. Dev.	Min	Max
Female					
Age	82	65.98	5.59	55.79	76.51
Male					
Age	72	65.12	5.95	55.22	74.76
Total	**154**	**65.72**	**5.78**	**55.22**	**76.51**

Bias

Bias could have affected the study results in a number of ways. The most serious has been alluded to in the above section, namely bias due to selective participation. If those who refused to participate are in any substantial way different to the participants in particular with reference to eye problems than this will affect the results. For example people with know eye disease or under the care of an ophthalmologist may have decided not participate, as they were already being regularly seen. This would have lead to an under estimate of certain eye problems. Alternatively those who refused to participate may have had healthier eyes that the participants and refused because they perceived that they had nothing wrong. This would have lead to an over estimate of eye problems in the population.

Bias may also have crept in during examination. The examiners were responsible for checking the visual acuity of the subjects. If they then found a significant cataract there may have been a temptation to give this a higher grade than it deserved. The difference in application of grading criteria between the 2 graders has been corrected for statistically in the analyses, however this will become more of a problem in a longitudinal study when graders start to see subjects graded by a different observer. The bias due to grading can be reduced by checking for drift with the archived copies of nuclear images.

There may have been a significant but unavoidable selection bias in subjects who had blood samples taken. Data in the chapter on antioxidants show that subjects who did not consent to give blood tended to be older than those who did give blood. Older subjects are more likely to have cardiovascular problems. Furthermore, there was a group of subjects with whom difficulty was experienced in taking blood due to obesity or collapsed veins. These subjects may also have had more cardiovascular risk factors. Finally there was a small number who refused because they had just had blood tests for other illnesses.

A further source of bias may occur at the stage of selection of data to be included in the analysis. This may occur either as the result of "data dredging" that is including all the data in the analysis and seeing what comes out of the analysis, or there may be a bias if important data is left out of the analysis. Examples of the latter in this study include the decisions not to analyse histories of ultra violet exposure and diet. Although the literature suggests that ultra violet light is not a factor in nuclear cataract, it is possible that there is an association in this population that has been missed by its exclusion. Similarly there may be an association of diet with antioxidant status that augments or reduces the association of serum antioxidant levels with nuclear cataract.

Wherever possible, possible sources of bias are discussed in the relevant chapter as well as the steps that were taken to reduce this.

2.13 Conclusion

The Melton Eye Study is the first longitudinally designed population-based study of the natural history of the ageing eye in the United Kingdom and should provide valuable data on the prevalence and incidence of common eye diseases as well as providing data for planning the health care needs of elderly people.

3. LOCS III versus the Oxford Clinical Cataract Classification and Grading System for the assessment of nuclear cataract

3.1 Purpose

The aims of this chapter are:

- to compare two methods of slit lamp grading of cataract for nuclear cataract,
- to develop calibration between the two systems.

We are not attempting to establish the superiority of one system over the other, but rather to assess the feasibility of data conversion.

The subject is important to the thesis in that both systems are used for grading cataract. The OCCCGS has more nuclear features than LOCS III. However, it has not been used in population-based surveys before. It is therefore valuable to have the LOCS III data to compare our prevalence rates with other studies. The issues of comparability and the use of different studies for meta-analysis make this an important enough issue to include the comparison in the thesis.

3.2 Introduction

Research into the development of cataract requires sensitive, repeatable methods of cataract grading (West and Taylor 1986). Grading may be performed on transparencies of the lens taken with slit lamp and retro illumination cameras (West, Rosenthal et al. 1988; Klein, Klein et al. 1990; Chylack, Wolfe et al. 1993). These systems have the advantage of having an archival copy on which grading can be repeated.

Cataract assessment may also be automated using computer driven Charge Couple Device (CCD) cameras taking Scheimpflug and retro illumination views (Sparrow, Brown et al. 1990). These automated systems are not subject to variations in grading technique over time or to fluctuations in film processing. Recent advances in exposure or gain settings have increased the reliability of automated CCD cameras (Vivino, Chintalagiri et al. 1993; Vivino, Mahurkar et al. 1995). However both automated and film based grading are expensive to set up. Photographers need to be trained and certified (Chylack, Wolfe et al. 1993)

Grading systems that can be used at the slit lamp exist, including the Oxford Clinical Cataract Classification and Grading System (OCCCGS) (Sparrow, Bron et al. 1986), and the Lens Opacities Classification System III (LOCS III) (Chylack, Wolfe et al. 1993). These have the advantage of being cheap, readily available and have been shown to be repeatable (Sparrow, Ayliffe et al. 1988; Karbassi, Khu et al. 1993)

The diversity of grading systems hampers any attempts at comparison or pooling of data. If data from different studies are to be compared or pooled for future meta-analysis it will be essential for calibration to be developed.

3.3 Methods

The detailed methods used in the Melton Eye Study have been described. The aspects of the study relevant to this chapter are summarised. The results have already been published for nuclear cortical and posterior subcapsular cataract (Hall, Thompson et al. 1997). Only the results of nuclear cataract are described. The interested reader can find the description of the other lens features in the published work.

This chapter outlines the examination of the first 560 subjects taking part in the Melton Eye Study as reported above (Hall, Thompson et al. 1997). This number of lens gradings is more than sufficient to provide adequate power for comparison of the two systems. It was therefore decided not to repeat the analysis on the remaining subjects. Aphakic and pseudophakic eyes were excluded, as were subjects who refused dilated examination.

The pupils were dilated using Tropicamide 1% and Phenylephrine 10%. A detailed slit lamp examination was then performed. The lenses were also photographed using the Marcher* Case 2000 / Oxford computerised CCD cataract cameras taking both Scheimpflug and retro illumination views.

Subjects had their lenses graded by one of two observers. One observer started the study earlier than the other. The two observers then continued concurrently. Each observer held a clinic on a different day of the week. Clinic appointments were made by a research clerk. There was no systematic bias in the allocation of subjects to different days of the week.

Each observer graded the subjects' lenses using both grading systems: first the OCCCGS and then LOCS III. The OCCCGS was chosen as the primary grading method because it has features for grading early lenticular changes such as fibre-folds and Retro-dots and the examiners had prior experience of using the system. LOCS III was added to facilitate comparison of results with other lens researchers.

Details of both grading systems are described in the literature review section on grading. Examples of nuclear lens grading are given in the chapter on grading. Briefly, the OCCCGS was developed for use at the slit lamp (Sparrow, Bron et al. 1986). It has recently been modified to incorporate a decimalised system of grading (Sparrow, Frost et

*Marcher Enterprises Limited, Twyford Road, Rotherwas Industrial Estate, Hereford HR2 6JR, UK

al. 2000). This has resulted in much finer grading scales with increased sensitivity for detecting clinical change (Bailey, Bullimore et al. 1991). Nuclear brunescence and white scatter are graded separately allowing independent measurement of each variable to be made. The grading standards consist of Munsell colour samples and Munsell neutral density grey samples for the grading of nuclear colour and white scatter respectively. When grading white scatter the brunescence of the lens can be confusing. To counter this, both the lens being graded and the neutral density patches are viewed through the same yellow Wratten filters.

The Lens Opacities Classification System III (LOCS III) (Chylack, Wolfe et al. 1993), can be used at the slit lamp. It differs from LOCS II by using a decimalised grading system and equal scaling intervals. Both opalescence and nuclear colour are graded from the same standard colour transparencies of the lens. Graders used a standard slit beam width when grading nuclear colour and opalescence in order to minimise inter-observer variation. The same width used in the OCCCGS (number 12 = 0.3mm.) was used for LOCS III.

Training

Graders learnt LOCS III grading from the published description using the standard photographs. Patients from wards and clinics were examined at the slit lamp until the graders were satisfied that the procedure was being followed correctly. Both graders had previous cataract slit lamp cataract grading experience using the decimalised version of OCCCGS. Both graders received training in this technique from Dr John Sparrow.

Results from two grading systems and two observers are therefore available. Each observer has used both grading systems. The results of the two systems have been plotted against one another. The plots consist of an amalgamation of both observers results.

Inter-observer variation.

Each observer saw different subjects. It was therefore not possible to calculate inter-observer variation on the subjects seen within the Melton Eye Study. The observers both examined a selection of volunteers with a range of lens opacities from ophthalmic clinics and wards. Forty lenses were examined following pupil dilation. Each subject had their lenses graded by both observers. The grader who examined the subject first was alternated in order to eliminate any bias induced by subject fatigue. Each grader used first the OCCCGS and then LOCS III. The graders were not aware of their colleague's grades until the grading was completed by both graders.

Eyes graded by both observers were analysed by calculating the mean and standard deviation of the difference between grades and then forming 95% tolerance limits. To

check that the size of the difference does not depend on the size of the measurement, the data were plotted in the manner described by Bland and Altman (Bland and Altman 1986).

Calibration curves

The inter-observer analysis in this study suggested that at the slit lamp, the LOCS III and the Oxford grades were subject to similar levels of variability. It is not therefore appropriate to perform simple linear regression, as this assumes that the explanatory variable is measured without error. The appropriate analysis allows for measurement error in both variables as described by Kendall and Stuart, Chapter 29 (Kendall MG and Stuart A. 1973). The calibration lines were calculated assuming equal measurement error on the two scales. Right and left eyes were calculated separately to avoid problems with the correlation between pairs of eyes. The coefficients of these pairs of lines were always very similar and the calibration line quoted is the average of these two lines, which is a consistent estimate of the overall calibration line.

OCCCGS grading of LOCS III images

One observer graded the LOCS III images using the Oxford system. The LOCS III slit lamp grading transparency was mounted on a viewing box and viewed through a magnifier. The LOCS III images were then graded for both brunescence and white scatter by comparing them with the Oxford Munsell standards. For nuclear cataract, the mean of four gradings taken on separate occasions was used.

3.4 Results

Nuclear colour and opalescence

Figure LO 1. shows OCCCGS white scatter plotted against LOCS III opalescence. Figure LO 2 shows the relationship between OCCCGS brunescence and LOCS III colour. The relationships are linear.

The calibration equation for white scatter/ nuclear opalescence is:

OCCCGS = -1.165 + 0.883 (LOCS III).

The equation for brunescence / nuclear colour is:

OCCCGS = - 1.115 + 0.990 (LOCS III).

The calibration lines are plotted on each figure as solid straight lines. The linear relationship for OCCCGS brunescence and LOCS III colour is no longer linear around a value of LOCS III NC3.5. From this point on the in vivo grading results fall below the calibration line.

Figure LO 1. Oxford white scatter plotted against LOCS III opalescence.
Calibration line plotted as straight line. Grading of LOCS III standard images by OCCCGS plotted as open circles.

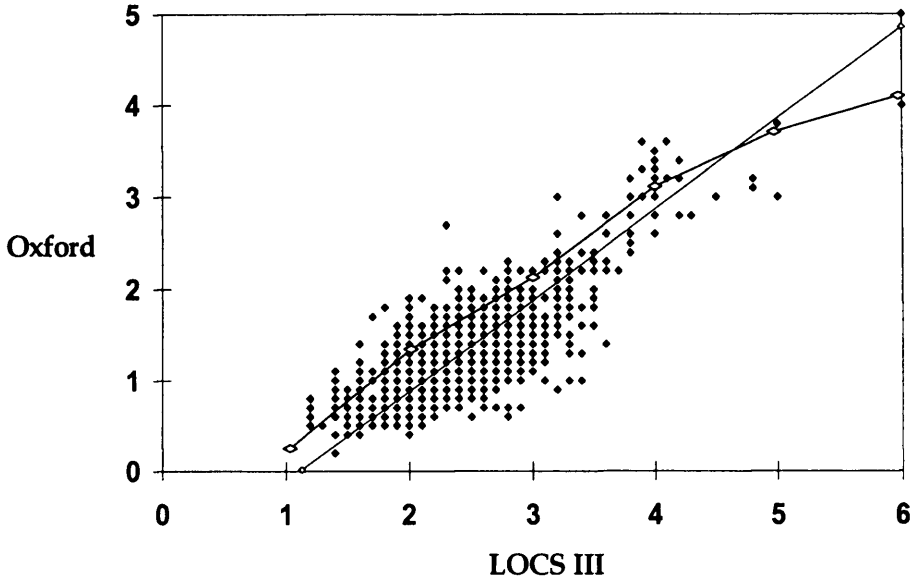
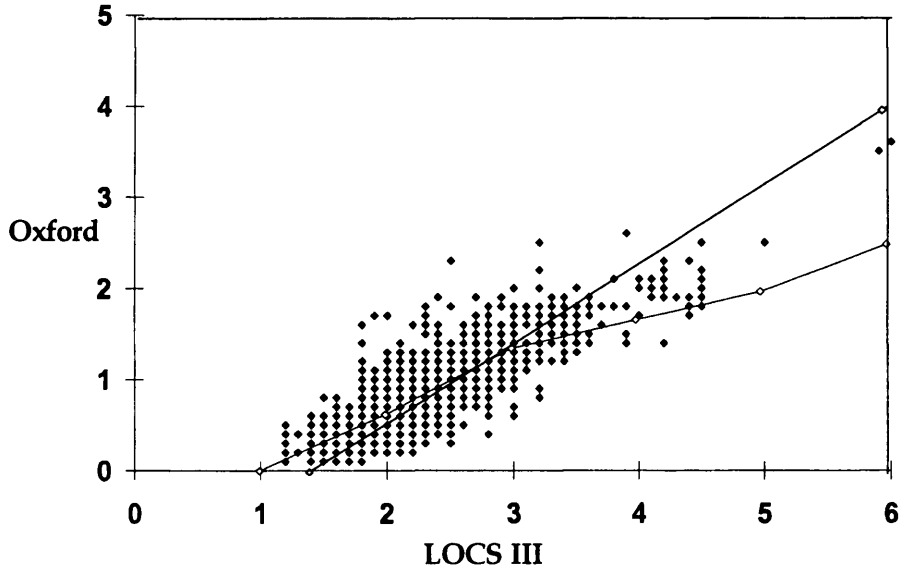


Figure LO 2. Oxford brunescence plotted against LOCS III Nuclear Colour.
Calibration line plotted as straight line. Grading of LOCS III standard images by OCCCGS plotted as open circles.



OCCCGS brunescence was plotted against OCCCGS white scatter (Figure LO 3) and LOCS III Nuclear Colour against LOCS III Nuclear Opalescence. (Figure LO 4) In the OCCCGS there is more variation, with white scatter occurring without colour change. When LOCS III nuclear colour is plotted against opalescence the association between the two is greater with the points arranged more linearly.

OCCCGS grading of LOCS III images

The OCCCGS grades of the LOCS III images are plotted on the graphs (Figure LO 1,2,6,7) as open circles. These graphs show that the intervals between the LOCS III images are nearly linear when ranked by the human eye using the OCCCGS. They are in broad agreement with the calculated calibration lines. There were some minor deviations: In OCCCGS brunescence versus LOCS III nuclear colour, (Figure LO 2) the grading line falls below the calibration line.

Figure LO 3. Oxford brunescence grades plotted against Oxford white scatter grades.

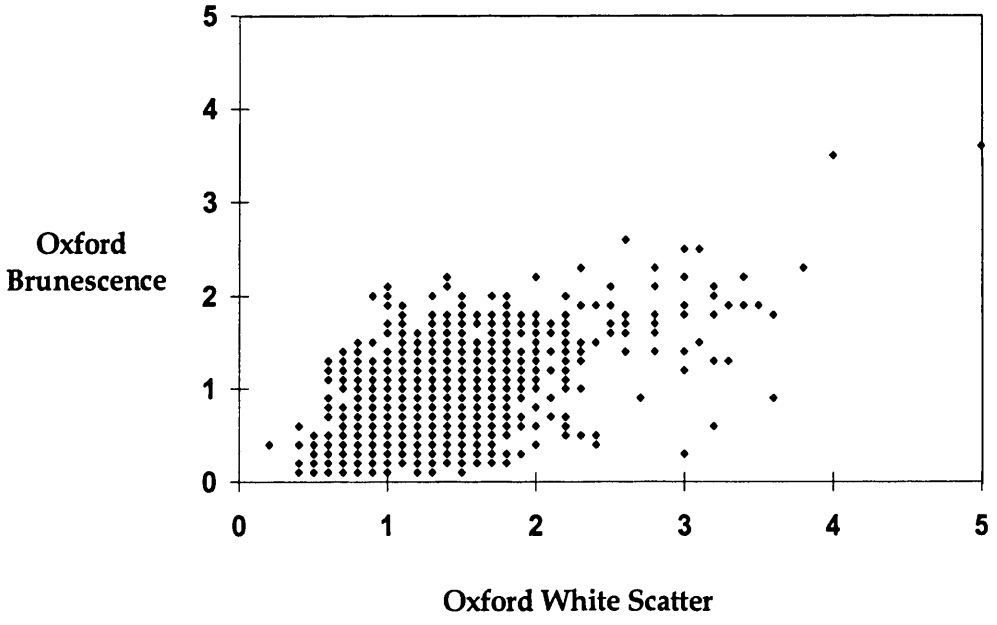
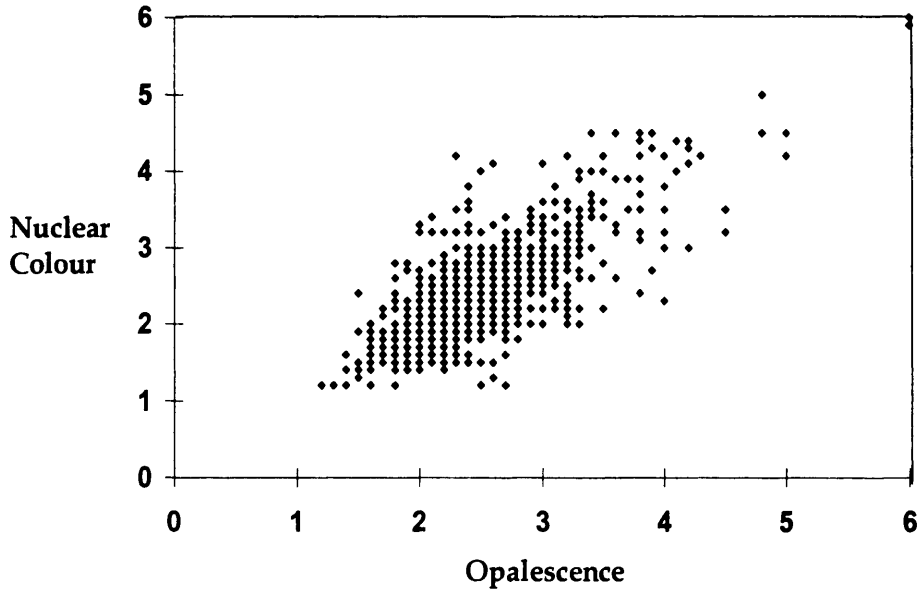


Figure LO 4. LOCS III nuclear colour grades plotted against LOCS III opalescence grades.



Observer populations

Each grader saw a different group of subjects from the same randomly selected population. One grader saw 257 subjects with a mean of 64.2 years; 113 (44%) of these subjects were male. The other grader saw 303 subjects with a mean age of 64.0 years. 149 (49%) of these were male.

Inter-observer variation

Table LO 1 shows the 95% Tolerance Limits (TL) for the two graders for both LOCS III and OCCCGS. The results are also displayed graphically in Figures LO 8-15. Each graph plots the difference between the scores obtained, against the average grade obtained by the two graders. The central dotted line is the mean difference in grades and the two outer lines delineate the 95% TL. All the mean differences are close to zero except for OCCCGS White Scatter (0.26) (fig 8) and LOCS III PSC (0.25) (fig 15). The graphs display the distribution of grades obtained for each type of lens opacity graded in the inter-observer grading exercise. There is no evidence that the difference increases with the size of the observation.

Table LO 1 Inter-observer differences (95% Tolerance Limits) for slit lamp grading of OCCCGS and LOCS III.

Slit lamp Grading Inter-observer Differences (95%TL) for OCCCGS and LOCS III			
LOCS III		OCCCGS	
(N=37)		(N= 37)	
Opalescence	0.93	White Scatter	0.90
Colour	1.12	Brunescence	0.77

Figure LO 8: Inter-observer variation for OCCCGS white scatter:
Average score of 2 observers plotted against the difference between scores

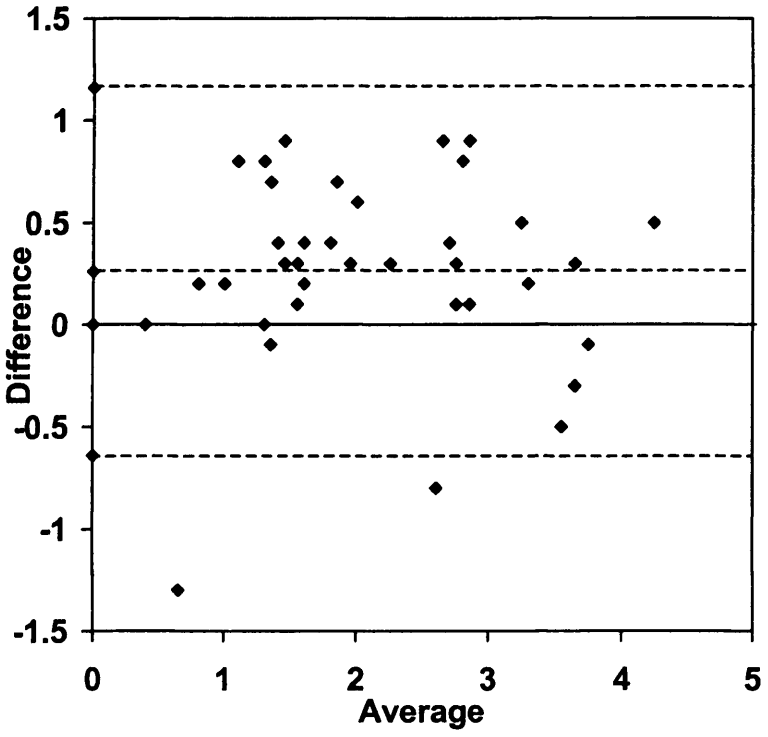


Figure LO 9: Inter-observer variation for LOCS III opalescence:
Average score of 2 observers plotted against the difference between scores

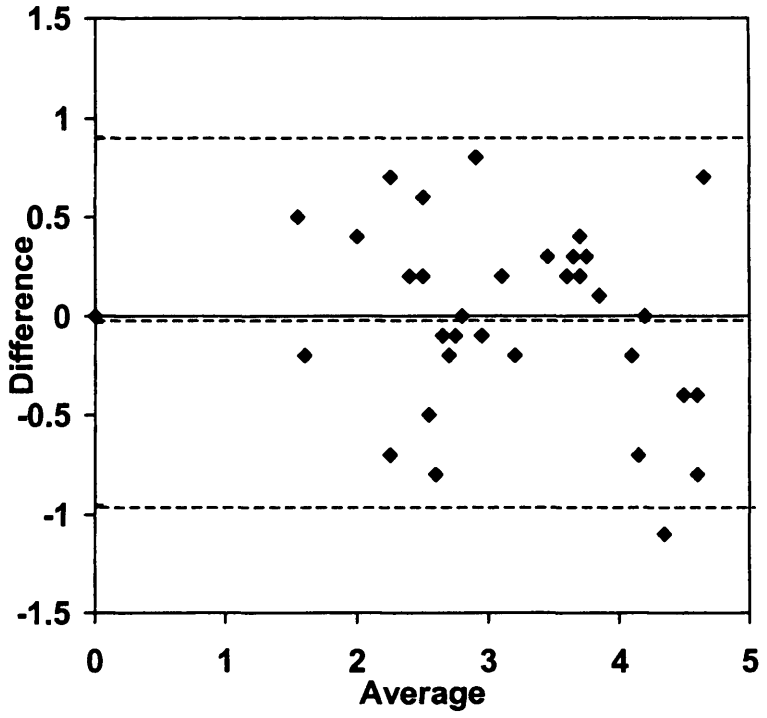


Figure LO 10: Inter-observer variation for OCCCGS brunescence:
Average score of 2 observers plotted against the difference between scores

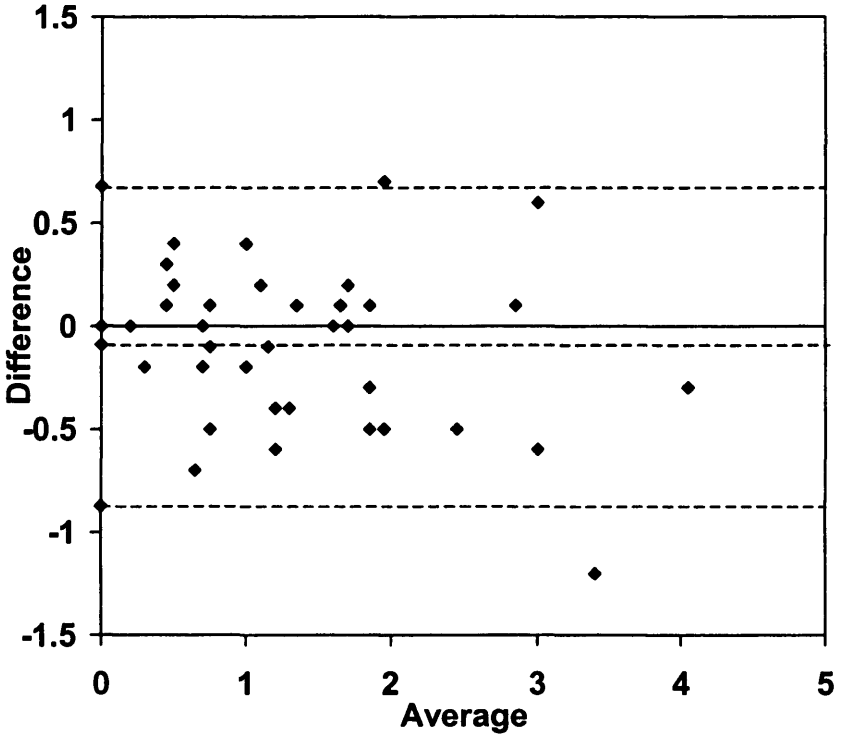
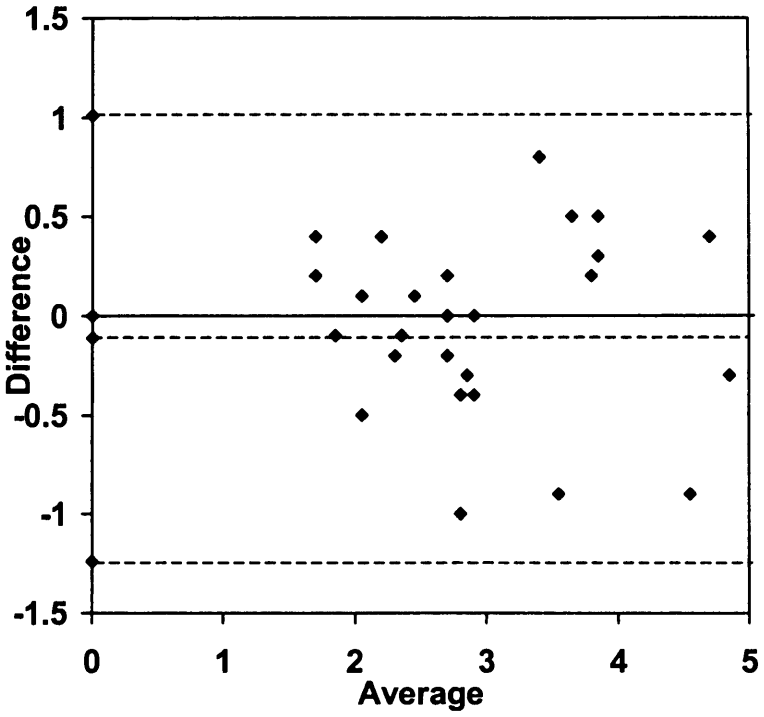


Figure LO 11: Inter-observer variation for LOCS III nuclear colour:
Average score of 2 observers plotted against the difference between scores.



3.5 Discussion

Cataract grading systems have been compared in the past. LOCS II (Chylack, Leske et al. 1989), and the original integer version of the OCCCGS were compared by Sparrow (Sparrow 1990), with particular reference to repeatability. At that stage LOCS II only used three classes for nuclear assessment while Oxford used six. Oxford therefore had a lower repeatability score for nuclear opacities but was more likely to be sensitive to clinical change. Both systems have now changed to a decimalised system, and LOCS III has increased the number of standards for all the categories except cortical cataract (Chylack, Wolfe et al. 1993; Sparrow, Frost et al. 2000)

Taylor compared two photographic methods of cataract grading (Taylor, Lee et al. 1991). He compared LOCS II with the system developed at Johns Hopkins University. One hundred photographs from a population-based study were examined and graded by both systems. As far as we are aware the Melton Eye Study is the first population-based study in which two patient-derived (slit lamp) grading systems are compared.

Nuclear lens opacities

Despite differences in the LOCS III and OCCCGS techniques for grading nuclear colour and opalescence, the agreement between the systems is good. LOCS III uses the same nuclear standard for both nuclear colour and opalescence, whereas OCCCGS uses separate standards. In addition, the observer wears yellow Wratten filters while assessing OCCCGS nuclear white scatter, reducing the confusing effect of brunescence (Sparrow, Bron et al. 1986). The two systems also look at different parts of the nucleus: in OCCCGS the anterior and posterior foetal nuclei are used to assess white scatter and brunescence respectively; whereas in LOCS III the entire nucleus is examined for opalescence and brunescence, including the posterior subcapsular reflex for the latter.

These differences in technique may account for some of the minor discrepancies that arise. The graph for Colour versus brunescence shows a drop in the grading values below the calibration line. There are a number of possible reasons for this: the relationship may not be linear; there may be two different slopes, one from LOCS III 0.1 to around 3.5 and another from 3.5 onwards. Alternatively it may be that the number of subjects with significant brunescence is too low to allow an accurate assessment of this trend. However, the fact that the line produced by the grading of LOCS III standards also drops at this point suggests that the loss of linearity at this point is real. One possible reason is that the colour in the LOCS III standards is leached out or overexposed by the white light scatter or opalescence in the higher grades. Alternatively, one could argue that the OCCCGS intervals beyond a value of 2.5 may be too broad.

In this population-based sample the majority of subjects have normal lenses or early lens changes. The points close to the calibration lines in the lower grades may represent 10 or more subjects. In this population, the LOCS III scale is sensitive. However in populations that do not come to surgery as early, graders may find that they are running out of LOCS III grades. The OCCCGS standards are derived by a process of colour matching of extracted lenses and should therefore reflect the range of brunescence encountered in more advanced cataract, giving a greater range at this end of the scale. A study using hospital-based surgical patients with lenses in the upper range of brunescence / colour would help to determine whether the change in slope is real or a reflection of the low numbers with advanced brunescence seen in the population-based study.

Figure LO 3 shows OCCCGS white scatter against brunescence. The points are widely scattered. This would seem to fit the clinical impression that some lenses scatter white light while remaining fairly colourless. When LOCS III nuclear colour is plotted

against opalescence (Figure LO 4) the points are arranged more linearly. This may reflect the graders difficulty in separating colour and opalescence from the same standard images.

Inter-observer variation

The inter-observer variation obtained in our grading exercise on volunteers from wards and clinics is good for both the OCCCGS and LOCS III. The Tolerance Limits (TL) (Table 1) for LOCS III and OCCCCGS are similar for opalescence but are slightly better in OCCCGS Brunescence than LOCS III colour. The LOCS III TL compare favourably with those found by Karbassi et al (Karbassi, Khu et al. 1993), for slit lamp grading using LOCS III. The mean difference between the graders for OCCCGS white scatter (Figure LO 8) indicates that there may be a degree of bias. That is, one grader may be tending to give a slightly higher value than the other. The bias applies to the two graders in the Melton Eye Study. It is not possible to generalise on how the bias should be applied to other observers. One would need to study more observers and compare the calibration lines from each observer to determine the impact of the bias on grading values.

Table LO2 gives the differences in prevalence and mean scores between the two graders for the first 560 subjects seen. Adapted from Deane 1997 (Deane, Hall et al. 1997).

Table LO2: Mean subject prevalences and scores by grader:

	Grader 1		**Grader 2**	
Feature	Percent prevalence	Mean Oxford score	Percent prevalence	Mean Oxford score
White Nuclear Scatter	100	1.51	100	1.17
Brunescence	100	0.96	100	0.80
Perinuclear Retro-dots	12	1.13	10	1.17
Cortical Spoke	43	0.27	30	0.43
Posterior Subcapsular	11	0.57	11	0.48

Subjects were unable to return for a second examination and therefore there are no data on intra-observer variation. It was felt that the intra observer variation had already been shown to be good for both systems. In addition, it was unlikely that inter-observer agreement would have been so good in the presence of poor intra-observer agreement.

Differences emerged between graders in our study that were not apparent during training and reproducibility studies, but became apparent as a result of the statistical power of such a large study (Deane, Hall et al. 1997). These differences arose from subtly different application of the grading rules.

We did not have lens photographs to be graded by both graders to reach a consensus. This has been shown to decrease inter-observer variation possibly at the expense of intra-observer accuracy (Karbassi, Khu et al. 1993). The lack of an archival copy for regrading is the principal disadvantage of a slit lamp based grading system. This means that assessing drift of grading criteria over time, and assessing both inter-observer and intra-observer error is more difficult than with photographically based systems. A further potential problem is that of misclassification of lesions, with one feature being misreported as another (Deane, Hall et al. 1997). Despite these drawbacks, clinical grading systems have a role in longitudinal studies as there is no other currently available system to accurately describe features such as fibre-folds and perinuclear Retro-dots. Without a description of these lesions, it would be impossible to assess their role in the development of the more widely recognised features, and answer questions such as "Do cortical spokes arise from fibre-folds?"

The disadvantages of slit lamp grading may be countered by simultaneously making objective measurements. The Melton Eye Study has an objective record of the status of the lenses in our subjects in the form of digital images taken by the Marcher CASE 2000 Oxford cataract camera (Sparrow, Brown et al. 1990). Such a system is a useful complement to the OCCCGS (Sparrow, Brown et al. 1990), and will allow some assessment of drift over time and consistency of grading. The software used to analyse the images obtained by the Scheimpflug cameras was unfortunately not perfected during the period of the study. This meant that we were unable to use the digital image data in the analysis of the study. However the data are stored and would be available should the longitudinal phase of the study be completed.

It is not possible at this stage to determine the relative sensitivities and specificities of the two systems. There is at present no gold standard against which to compare them.

3.6 Analysis

These results suggest that it is possible to compare the data from different lens classification systems. The Melton Eye Study has shown that it is possible to develop calibration between two systems. This would, however, be subject to an increase in variability. Use of calibration lines should make meta analysis possible, but not

straightforward. Meta analysis would be useful in various areas of cataract epidemiology, particularly in the areas of UV exposure and nutrition. For example, it is unlikely that any one centre would have sufficient power to examine an association between posterior subcapsular cataract and UV light.

What future developments can be made toward a method of calibration between grading systems? The lens nuclei graded in this study by LOCS III and the OCCCGS have also been photographed using the computerised Scheimpflug CCD cameras. The densitometric measurements should be plotted against the LOCS III and Oxford gradings. Densitometric analysis of the standard images in different grading systems should also be performed, allowing objective comparison of standards.

Fast Spectral Scanning Colourimetry (Chylack, Wolfe et al. 1993), can be used to determine the colour of the standards in various grading schemes. These measurements would help in the development of calibration tables between grading systems. The techniques used in this study could be applied to other grading schemes to facilitate future comparison and pooling of data.

3.7 Conclusions

The linear calibration lines may be used to convert from one system to another and may be useful in comparing studies or performing meta-analysis. These results show that data from cataract studies using different clinical grading schemes can be compared.

4. Prevalence of lenticular abnormalities.

4.1 Purpose

The aim of this chapter is to:

- Describe the epidemiology and distribution of the nuclear features assessed by the Oxford Clinical Cataract Classification and Grading System (OCCCGS) and LOCS III.
- Present the data in graphs and tables
- Describe the prevalence of significant nuclear lens opacities.
- Compare the prevalence of nuclear opacities in the Melton population with other populations

4.2 Introduction

A preliminary report on the prevalence of lenticular abnormalities in the Melton Eye Study has already been published (Deane, Hall et al. 1997). The paper described the distribution of the 11 features assessed by the Oxford Clinical Cataract Classification and Grading System (OCCCGS) in the 560 subjects who had been examined at the time. This chapter describes the prevalence of five of those features: the nuclear features, (White Scatter, Brunescence and perinuclear Retro-dots) as well as cortical and posterior subcapsular lens opacities in all 826 subjects examined. In order to allow for comparison with other studies the prevalence of the nuclear features as measured by the Lens Opacities Classification System III (LOCS III) (Chylack, Wolfe et al. 1993), grading system is also reported.

A review of the different population based surveys carried out to determine the prevalence of cataract is presented in the literature review. Some used visual acuity criteria while others used lens grading schemes. These studies used different grading schemes and therefore have come up with different prevalence rates for nuclear cataract. The prevalences of these and other studies are summarised in Table P12.

4.3 Methods

Subjects had both eyes graded by both LOCS III and OCCCGS. The details of these grading systems are described in full in the Literature Review section on grading. Comparison of the systems is made in the Chapter LOCS III versus the Oxford Clinical Cataract Classification and Grading System for the assessment of nuclear cataract. Regression analyses were performed for severity of the lesions. The analysis was performed on all cataract lesions, based on the mean of both eyes. Estimates of prevalence were calculated using the number of subjects with Retro-dots, posterior subcapsular

cataract, and cortical lens opacity as a percentage of the total who had that feature graded. Prevalence data is presented firstly for the mean score and then for nuclear cataract by eye. If data is missing for one eye of a subject then the data from the other eye is used. One hundred percent of subjects had a nuclear grade for Brunescence or White Scatter. This is a meaningless statistic, as it does not give an estimate of the severity or clinical significance of the lesion. Therefore a significant level for each of these features was set using the mid-point of the LOCS III scale; any subject with a score greater than LOCS III grade 3 was deemed to have significant nuclear opacity. This was then converted to an OCCCGS value for significant lens opacity using calibration equations derived from the first 560 subjects (Hall, Thompson et al. 1997). The inter-observer analysis suggested that at the slit lamp, the LOCS III and the Oxford grades were subject to similar levels of variability. It is not therefore appropriate to perform simple linear regression as this assumes that the explanatory variable is measured without error. The appropriate analysis allows for measurement error in both variables as described by Kendall and Stuart, Chapter 29 (Kendall MG and A. 1973). The calibration lines were calculated assuming equal measurement error on the two scales. Right and left eyes were calculated separately to avoid problems with the correlation between pairs of eyes. The coefficients of these pairs of lines were always very similar and the calibration line quoted is the average of these two lines, a consistent estimate of the overall calibration line.

4.4 Results

Grader

Data on 826 subjects were available for analysis. Grader 2 graded 504 subjects (61.02%), and Grader 1graded 322 (38.98%).

Gradings were available for between 805 to 807 right eyes and 809 to 811 left eyes depending on the nuclear feature. Reasons for no grading included refusal of dilated examination, previous cataract surgery, or enucleation. 12 subjects (1.45%) had had cataract surgery to their right eyes, while 8 (0.97%) had had cataract surgery to their left eyes.

Distribution by age

The graphs in Figures P1 to 5 show the distribution of scores for OCCCGS nuclear features and cortical and posterior subcapsular cataract against age. The graphs are presented by sex with a total for all subjects.

Figure P1. White Scatter.

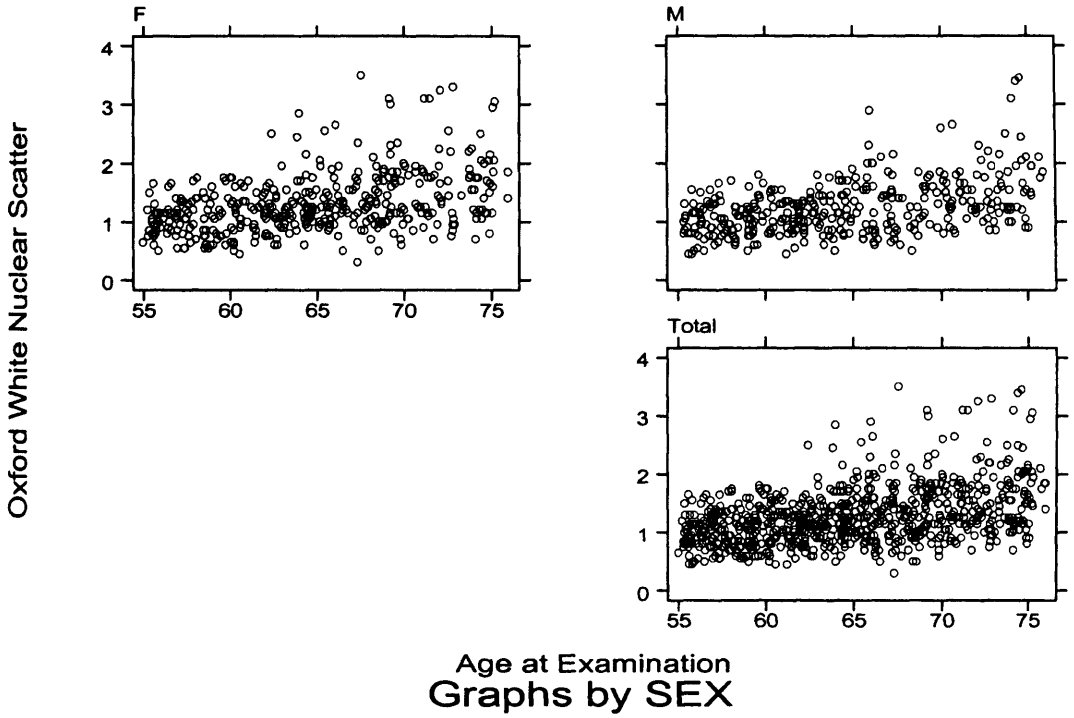


Figure P2. Brunescence.

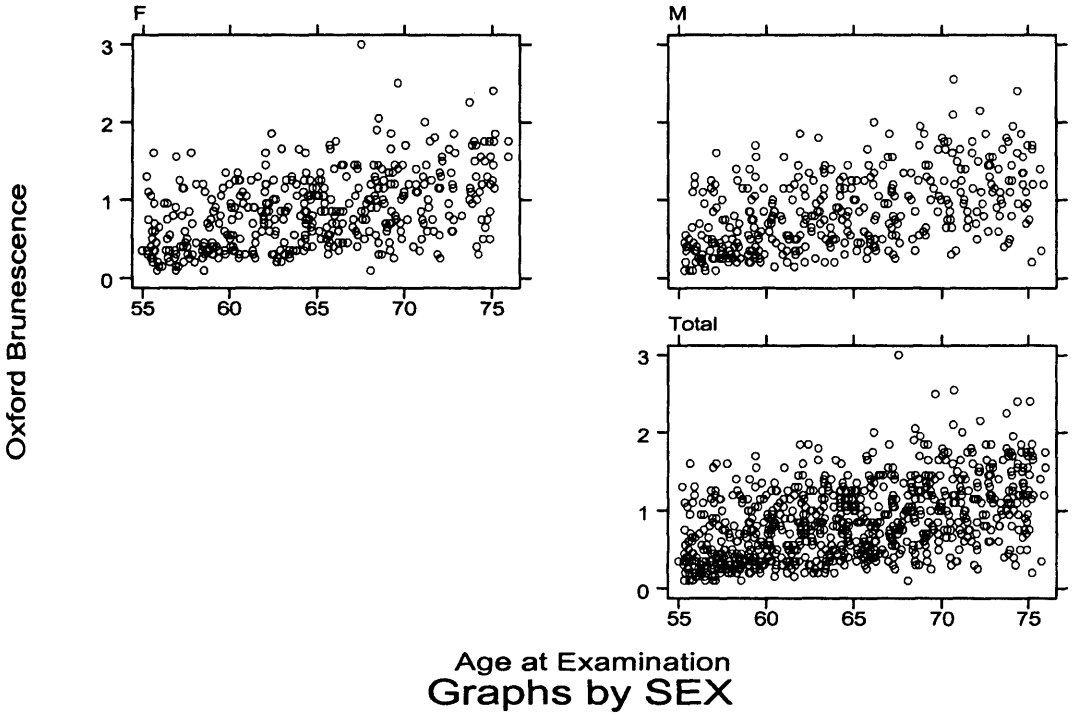


Figure P3. Perinuclear Retro-dots (non zero values).

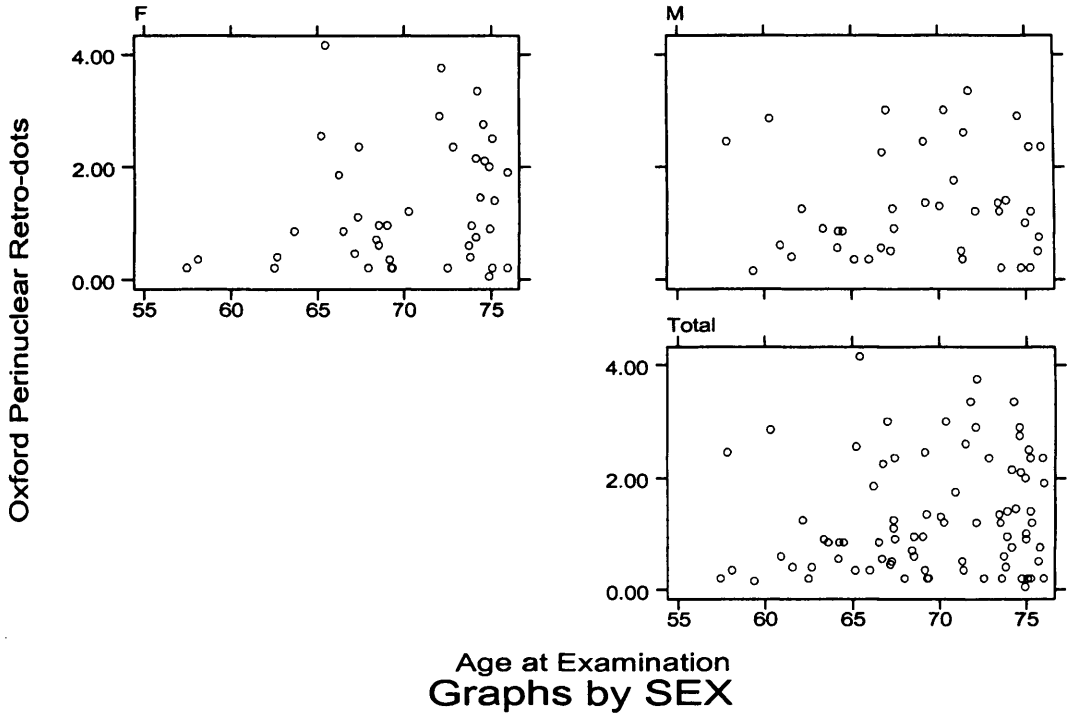


Figure P4. Posterior subcapsular (non zero values)

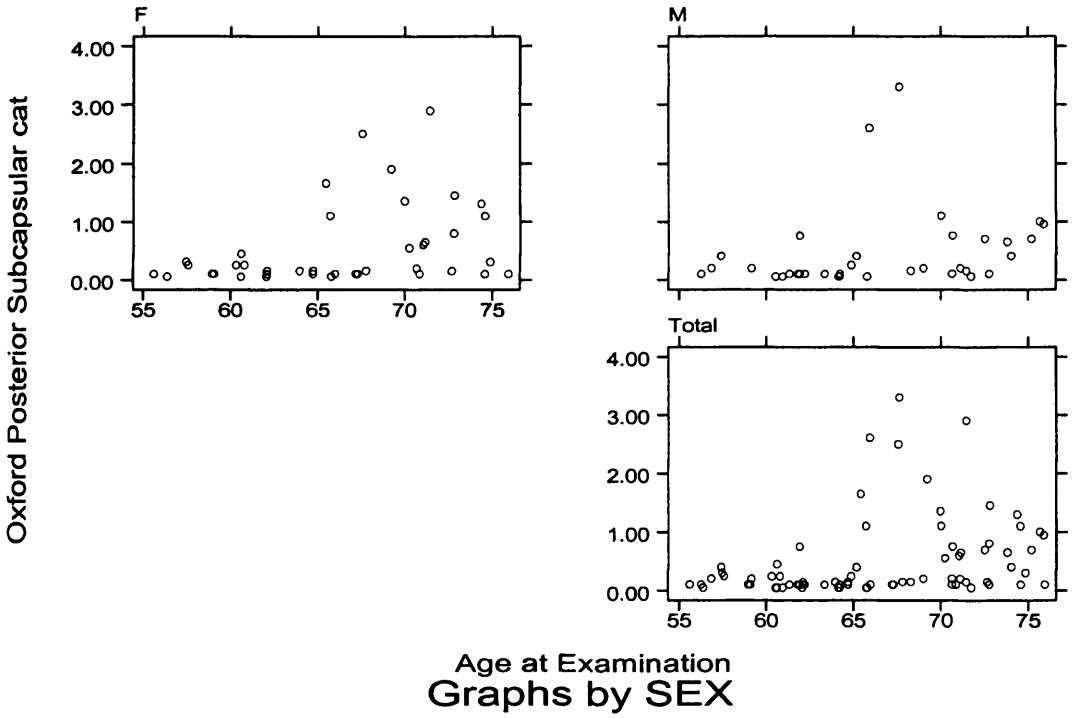
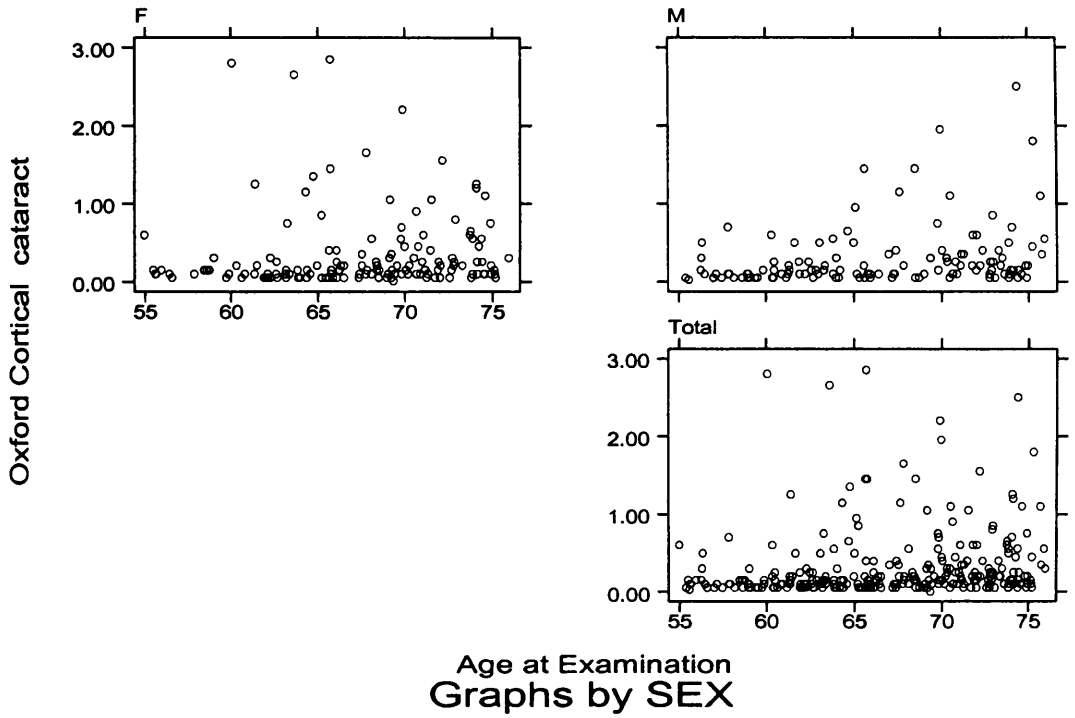


Figure P5. Cortical spoke (non zero values).



Prevalence and mean scores

The prevalence and mean scores with minimum and maximum scores of features for all subjects are displayed in Table P1. Table P2 contains the mean, standard error and 95% confidence intervals for the nuclear features, (White Scatter, Brunescence and Retro-dots), as well as the other major features namely cortical and posterior subcapsular cataract for the whole examined population including subjects in whom some of the features were absent. In a significant number of subjects certain features are not present. The mean, standard error and 95% confidence intervals for the Retro-dots, cortical and posterior subcapsular cataract, when the features were present, is therefore displayed in Table P3. The prevalence of the features (when present) is summarised in Table P4. The estimated prevalence is based on the entire age range of 55 to 74 years.

Table P1 Mean Oxford score, standard deviation and minimum and maximum scores by eye.

Variable	Observations	Mean	Standard Error.	Minimum	Maximum
White Scatter re	807	1.29	0.51	0.20	4.00
White Scatter le	809	1.25	0.51	0.40	5.00
Brunescence re	807	0.86	0.49	0.10	3.50
Brunescence le	811	0.86	0.49	0.10	3.60
Retro dots re	805	0.13	0.50	0.00	3.50
Retro dots le	809	0.15	0.64	0.00	4.90
Cortical re	806	0.11	0.33	0.00	3.20
Cortical le	810	0.12	0.35	0.00	5.00
Posterior Sub-Caps re	807	0.05	0.30	0.00	5.00
Posterior Sub-Caps le	810	0.06	0.33	0.00	3.80

re= Right Eye, le = Left Eye

Table P2. Mean scores and 95% confidence intervals of lenticular features by sex.

Variable	Observations	Mean	Standard Error.	(95% Conf.Interval)	
Female					
White Scatter	429	1.30	0.02	(1.25	1.35)
Brunescence	429	0.87	0.02	(0.83	0.90)
Retro dots	421	0.13	0.02	(0.08	0.18)
Posterior Sub. Cap	422	0.05	0.01	(0.03	0.08)
Cortical	422	0.12	0.02	(0.09	0.16)
Male					
White Scatter	386	1.24	0.02	(1.19	1.29)
Brunescence	386	0.86	0.02	(0.81	0.91)
Retro dots	375	0.14	0.03	(0.09	0.19)
Posterior Sub. Cap.	376	0.04	0.01	(0.02	0.07)
Cortical	376	0.10	0.01	(0.07	0.13)
Total					
White Scatter	815	1.27	0.02	(1.24	1.31)
Brunescence	815	0.86	0.02	(0.83	0.90)
Retro dots	796	0.13	0.02	(0.10	0.17)
Posterior Sub. Cap.	798	0.05	0.01	(0.03	0.07)
Cortical	798	0.11	0.01	(0.09	0.13)

Table P3. Mean scores and 95% confidence intervals of lenticular features by sex.
(Retro-dots, cortical and posterior subcapsular cataract when present).

Variable	Observations	Mean	Standard Error.	(95% Conf.Interval)	
Female					
Retro dots	42	1.27	0.17	(0.93	1.61)
Posterior Sub. Cap.	40	0.55	0.11	(0.32	0.77)
Cortical	151	0.35	0.04	(0.26	0.43)
Male					
Retro dots	41	1.30	0.15	(1.01	1.60)
Posterior Sub. Cap.	35	0.46	0.12	(0.22	0.70)
Cortical	128	0.30	0.03	(0.23	0.37)
Total					
Retro dots	83	1.29	0.11	(1.07	1.51)
Posterior Sub. Cap.	75	0.51	0.08	(0.35	0.67)
Cortical	279	0.32	0.03	(0.27	0.38)

Table P4. Prevalence of lenticular features.

	Number	Cataract %	95% Confidence Interval
White Scatter	815	100.00	99 54 % to 100 % *
Brunescence	815	100.00	99 54 % to 100 % *
Retro-dots	83	10.43	8.39 % to 12.76 %
Posterior Subcapsular	75	9.40	7.4 % to 11. 63 %
Cortical	279	34.96	31.65 % to 38.38 %

* One-sided, 97.5% confidence interval

Table P5 contains the results of regression analysis for the severity of the lens features.

Table P5. Logistic regression coefficients for score severity by age, sex and grader when non zero, (mean of both eyes).

Feature	Number	Age	Sex (M)	Grader 1
White nuclear scatter	815	0.035 (p<0.0001)	-0.037 (p=0.197)	0.305 (p<0.0001)
Brunescence	815	0.038 (p<0.0001)	0.014 (p=0.614)	0.206 (p<0.0001)
Perinuclear Retro-dots	83	0.029 (p=0.189)	0.063 (p=0.781)	-0.124 (p=0.58)
Cortical spoke	279	0.011 (p=0.02)	-0.052 (p=0.34)	-0.095 (p=0.08)
Posterior subcapsular	75	0.037 (p=0.008)	-0.076 (p=0.64)	0.076 (p=0.63)

There is no significant difference between men and women for the different nuclear features in the regression analysis for score severity. A ttest confirms that there is no difference between the mean scores (Table P2) between men and women. (Brunescence, White Scatter and Retro-dots, p = 0.83, 0.063 and 0.67 respectively.)

Prevalence of significant nuclear lens opacities

All subjects have a nuclear grade. However the 100% prevalence of Brunescence and White Scatter does not mean that all subjects have significant nuclear lens opacities. If an opacity of greater than LOCS III standard 3 is chosen to represent a significant nuclear opacity then 98 (12.05 %) of subjects have significant opalescence and 90 (11.07 %) have significant nuclear colour opacities.

Using the calibration equation OCCCGS= – 1.115 + 0.990 (LOCS III) (Hall, Thompson et al. 1997), the equivalent Oxford cut off for significant nuclear White Scatter is 1.85. Using OCCCGS= – 1.165 + 0.883 (LOCS III) the cut off point for a significant Brunescence is 1.48. Using these criteria for significant lens opacity, 89 (9.33%) of subjects had significant White Scatter and 90 (11.04 %) had significant brunescence. These scores are marginally higher if the prevalence is given by eye. They increase to 11.02 % and 8.65 % for White Scatter right and left eyes respectively and to 12.5 % and 11.84 % for Brunescence right and left eyes respectively. Females have a lower prevalence (9.17 %) of Brunescence than males. (11.14%) However, the prevalence of White Scatter is higher in women (10.66 %) than in men (6.9 %.)

Tables P6 and 7 show the significant prevalences by age group for OCCCGS nuclear opacities along with the confidence intervals.

Tables P8 and 9 show the significant prevalences by age group for LOCS III nuclear opacities.

Tables P9 and 10 give the prevalences by sex for OCCCGS nuclear opacities.

Table P6. Prevalence of significant OCCCGS White Scatter by age category.

Age Range	Number	Total	Cataract %	95% Confidence Intervals
55 to 59	0	213	0.00	0.0 % to 1.71 % *
60 to 64	5	224	2.23	0.73 % to 5.13 %
65 to 69	27	194	13.92	9.38 % to 19.60 %
70 upwards	44	184	23.91	17.95 % to 30.74%
Total	76	815	9.33	7.42 % to 11.53%
Total Right	89	807	11.02	8.95 % to 13.39 %
Total Left	70	809	8.65	6.81 % to 10.81 %

* one-sided, 97.5% confidence interval

Table P7. Prevalence of significant OCCCGS Brunescence by age category.

Age Range	Number	Total	Cataract %	95% Confidence Interval
55 to 59	6	213	2.82	1.04 % to 6.03 %
60 to 64	9	224	4.01	1.85 % to 7.49 %
65 to 69	20	194	10.31	6.41 % to 15.47 %
70 upwards	55	184	29.89	23.38 % to 37.07 %
Total	90	815	11.04	8.97% to 13.40 %
Total Right	101	807	12.51	10.31 % to 14.99 %
Total Left	96	811	11.84	9.69 % to 14.26 %

Table P8. Prevalence of significant (>3) LOCS III colour by age category.

Age Range	Number	Total	Cataract %	95% Confidence Interval
55 to 59	1	212	0.47	0.01 % to 2.6 %
60 to 64	10	224	4.46	2.16 % to 8.06 %
65 to 69	24	193	12.44	8.13 % to 17.93 %
70 upwards	55	184	29.89	23.40 % to 37.06 %
Total	90	813	11.07	9.00 % to 13.43 %

Table P9: Prevalence of significant (>3) LOCS III opalescence by age category.

Age Range	Number	Total	Cataract %	95% Confidence Interval
55 to 59	4	212	1.89	0.52 % to 4.80 %
60 to 64	4	224	1.79	0.49 % to 4 51 %
65 to 69	30	193	15.54	10.74 % to 21.44 %
70 upwards	60	184	32.61	25.89 % to 39.89 %
Total	98	813	12.05	9.90 % to 14.49%

Table P10. Prevalence of significant OCCCGS Brunescence by sex

Females

Age Range	Number	Total	Cataract %	95 % Confidence Intervals
55 % to 59	3	101	2.97	0.62 % to 8.4 %
60 % to 64	5	122	4.10	1.34 % to 9.30 %
65 % to 69	9	113	7.96	3.70 % to 14.58 %
70 upwards	24	86	27.90	18.77 % to 38.6 %
Total	41	422	9.7	7.06 % to 12.95 %

Males

Age Range	Number	Total	Cataract %	95 % Confidence Intervals
55 % to 59	3	110	2.72	0.57 % to 7.76 %
60 % to 64	3	99	3.03	0.63 % to 8.60 %
65 % to 69	9	78	11.54	5.41 % to 20.77 %
70 upwards	27	90	30.00	20.78 % to 40.57 %
Total	42	377	11.14	8.14 % to 14 75 %

Table P11. Prevalence of significant OCCCGS White Scatter by sex.

Females

Age Range	Number	Total	Cataract %	95 % Confidence Intervals
55 % to 59	0	101	0	0 % to 3.59 %*
60 % to 64	5	122	4.9	1.34 % to 9.30 %
65 % to 69	17	113	15.04	9.02 % to 22.99 %
70 upwards	23	86	26.74	17.78 % to 37 38 %
Total	45	422	10.66	7.89 % to 14.01 %

Males

Age Range	Number	Total	Cataract %	95 % Confidence Intervals
55 % to 59	0	109	0	0 % to 3.33 %*
60 % to 64	0	99	0	0 % to 3.66 %*
65 % to 69	8	77	10.39	4.59 % to 19.45 %
70 upwards	18	90	20.00	12.31 % to 29.75 %
Total	26	375	6.90	4.58 % to 9.98 %

* one-sided, 97.5% confidence interval

Tables P6-P11 Explanation of column headings.
Number = the number of subjects in each age group with significant nuclear cataract.
Total = the number of subjects in each age category.
Cataract % = the prevalence of cataract

4.5 Discussion

These data are the first available population-based data on the prevalence of lens opacities in a UK population using modern lens grading methods. A report on all the OCCCGS features for part of this population has been published (Deane, Hall et al. 1997). This chapter does not cover all those features described in OCCCGS which do not associate with nuclear features in any way. Comparison with other grading systems is difficult as other systems are either photographically based or do not rate such a comprehensive set of lenticular features as the Oxford system. Comparison of the nuclear features, cortical spoke and posterior subcapsular grading, is possible, but not straightforward, as definitions of what should be graded differ substantially between the

various systems. However, as two systems have been used in this study, it has been possible to report the prevalence in both Oxford and LOCS systems.

Prevalence

Comparing the prevalence of nuclear cataract between the different population-based studies is difficult. Different studies have used different grading schemes and defined a significant nuclear opacity in different ways (Klein, Klein et al. 1990; Chylack, Wolfe et al. 1993; Green, Battistutta et al. 1994; Cumming and Mitchell 1997; McCarty, Mukesh et al. 1999). We are not aware of any population-based study, which uses either LOCS III or Oxford with which to compare the prevalence of nuclear lens opacities in the Melton population. The value of LOCS III standard 3 was chosen as the significant level as this was mid-way along the LOCS scale. This seemed to be a more appropriate level for this population-based sample in which the majority of subjects have normal lenses or early lens changes. The LOCS III scale was found to be sensitive in this population (Hall, Thompson et al. 1997). The OCCCGS standards are derived by a process of colour matching of extracted lenses and should therefore reflect the range of Brunescence encountered in more advanced cataract, giving a greater range at the more advanced end of the scale than LOCS III (Hall, Thompson et al. 1997). However, this end of the scale was not used much in the Melton Eye Study as the population had relatively clear nuclei. The mid-point of the OCCCGS scale would therefore have set a high cut off point for significant nuclear opacity. Clearly, as the grading systems are sensitive at different points, the Oxford system having a greater range, they will give different prevalences. The Oxford grading system will consistently give a lower prevalence than the LOCS III score.

The grade that is set as a significant lens opacity has a dramatic effect on the prevalence of a lens opacity. This is well illustrated by the cortical lens opacity prevalence in our study. The high subject prevalence of cortical spoke (34.96%) and posterior subcapsular cataract (9.4%) in our study is due to the documentation of any lesion and is accounted for by the large number of very low values. If a similar threshold for the presence of these lesions is used to that in the Beaver Dam Eye Study (5% of pupil area) (Klein, Klein et al. 1990), these prevalences fall to 11% and 2% respectively. This range of values is similar to that found for significant nuclear lens opacities once a cut-off threshold is applied.

This difference in threshold definition is critical when attempting to make comparisons between studies. These tiny opacities may not be clinically important, but by recording them, longitudinal follow-up is possible. Comparison with other grading systems

is difficult as other systems are either photographically based or do not rate such a comprehensive set of lenticular features. Many of the features in the Oxford system, such as Retro-dots, are not visible on currently available cameras so cannot be graded photographically. Comparison of the nuclear features, cortical spoke and posterior subcapsular grading is possible, but not straightforward, as definitions of what should be graded differ substantially between the various systems. Table P13 summarises the prevalences of cataract found in various population-based studies

The table is helpful to the extent that it highlights the different studies undertaken. However, it also highlights some of the serious limitations: the age ranges of each study are critical to the overall prevalence of a lens opacity. For example, the age range in the Beaver Dam Eye Study is 43 to 84 and in the Blue Mountains Eye Study it is 49 to 96. The overall prevalence of nuclear opacity reported in the Beaver Dam Eye Study is only 19.2% considerably lower than the 51.7% overall prevalence (involving one or both eyes) reported in the Blue Mountains Eye Study. However, if age specific prevalences are studied then the Blue Mountains Eye Study, in fact, had significantly lower rate of nuclear cataract than BDES in each age group. (Table P12) The higher overall prevalence in the Blue Mountains Eye Study is due to the age range extending up to 96.

Table P12. Comparison of nuclear cataract prevalence in Beaver Dam and Blue Mountain studies (male and female combined) (Data from BMES) (Mitchell, Cumming et al. 1997)

Age group (yrs)	The Beaver Dam Eye Study	Blue Mountains Eye Study
55-64	6.6	3.9
65-74	27.4	21.8
75-84	57.0	48.5

Table P13. Prevalence studies of different types of cataract using cataract grading systems (without visual acuity loss criteria)

Study	Age Range	Race of study population	No	Classification	Type	Prevalence
Framingham Eye Study		White	2239	Slit lamp evaluation with standardised system (written protocol)	PSC Nuclear Cortical	8.3 25.6 14.3
Watermen Study (Taylor, West et al. 1988)		White	831	Slit lamp evaluation with standardised system	PSC Nuclear Cortical	1.7 27.6 13.4
Beaver Dam Eye Study (Klein, Klein et al. 1992)	43-84	White	4600	Photographic evaluation with standardised system (Wisconsin)	PSC Nuclear Cortical	6.0 17.3 16.3
Finland (Hirvela, Luukinen et al. 1995)	70 or older	White	500	Slit lamp evaluation with LOCS II	PSC Nuclear Cortical	27.7 38.5 37.6
Barbados Eye Study (Leske, Connell et al. 1997)	40-84	Black	4250	Slit lamp evaluation with LOCS II	PSC Nuclear Cortical	3.9 19.2 34.0
Blue Mountains Eye Study (Mitchell, Cumming et al. 1997) Australia	49-96	White	3654	Photographic evaluation with standardised system (Wisconsin)	PSC Nuclear Cortical	Male Female 6.5 6.2 49.7 53.3 21.1 25.9
Melbourne Visual Impairment Project (McCarty, Mukesh et al. 1999) Australia	40 or older	White	3271	Photographic evaluation with standardised system (Wilmer)	PSC Nuclear Cortical	4.08 11.6 11.3 (age standardised)
The Salisbury Eye Evaluation Project (West, Munoz et al. 1998) USA	65-84	White and Black- (26.4%)	2520	Photographic evaluation with standardised system (Wilmer - decimalised)	PSC Nuclear Cortical	Black White 5.5 13.0 33.5 50.7 54.2 24.2
Melton Eye Study	55-75	White	826	Slit lamp evaluation with LOCS III and OCCCGS	PSC Nuclear Cortical	2.0 11.07/12.05* 11.0

*LOCS III Colour and Opalescence respectively

Table P13 suggests that the prevalences in the Melton Eye Study are considerably lower than in other studies. However, comparison of the age specific prevalences show that this is due mostly to the lower age range of our cohort. The prevalence of opalescence using LOCS III definitions amongst the 65 to 69-year-olds was 14.89% and amongst 70 to 75-year-olds 31.82%. This correlates much better with the results of the Beaver Dam Eye Study and Blue Mountains Eye Study. (Table P11) However, direct comparison is still difficult because of the different grading systems used and the consequent difficulty in setting the same threshold definition of significant cataract. Like the Blue Mountains Eye study we found a greater prevalence of nuclear cataract in women. However, this was only apparent in the White Scatter component. This again highlights the difference in grading systems with the LOCSIII and OCCCGS systems able to differentiate between opalescence and brunescence.

4.6 Conclusions

From the Melton Eye Study, 91 (11.42%) of subjects have significant Opalescence and 84 (10.53%) have significant nuclear colour opacities. The prevalence of significant opalescence rises to 31.82% amongst 70 to 75 year olds. These age specific prevalences correlate reasonably well with other studies, given the limitations of comparing across grading systems. Women have a higher prevalence of white scatter than men do.

4.7 Public health implications

The high prevalence and incidence (Klein, Klein et al. 1998), of nuclear cataract in Caucasian populations (West, Munoz et al. 1998), has implications for the planning of cataract surgical services. Klein (Klein, Klein et al. 1998), found a rate of incident nuclear cataract of 13.1% compared with only 8.0% in cortical and 3.4% in posterior subcapsular cataract. The incidence of nuclear cataract from baseline was 40.0% in those aged 75 years or older. The demand for cataract surgery in the UK can be estimated using the prevalence of visually disabling nuclear cataract, and the fact that 35% of UK ophthalmology consultants are prepared to consider surgery at levels better than 6/9 (Frost and Sparrow 2000).

5. Visual Acuity and Nuclear Cataract

5.1 Purpose

The aims of this chapter are:

- to describe the levels of visual impairment in the Melton population aged 55 to 75 years;
- to report the level of uncorrected refractive error in the population;
- to describe the effect of nuclear lens opacities on visual acuity.

5.2 Introduction

Existing population-based estimates of best-corrected visual acuity for the United Kingdom focus on older age groups (Gibson, Lavery et al. 1986; Wormald RP 1992; Reidy, Minassian et al. 1998; van der Pols, Bates et al. 2000). Many of the population based studies including those in the UK found uncorrected refractive errors within the population (Gibson, Lavery et al. 1986; Attebo, Mitchell et al. 1996, Reidy, 1998 #708; van der Pols, Bates et al. 2000, Evans, 2002 #706).

Maraini et al (Maraini, Rosmini et al. 1994), found that increasing severity of nuclear cataract was associated with greater decrease in visual acuity than similar changes along the LOCS II cortical scale. A detailed review of these aspects of visual acuity and cataract may be found in the Literature Review.

5.3 Methods

Only the methods relevant to visual acuity measurement are summarised here. In brief: the subject's current spectacle prescription was measured on a Topcon LM6 focimeter. The visual acuity was assessed using their current refractive correction on retro-illuminated Early Treatment of Diabetic Retinopathy (ETDRS) letter 4 metre charts which are based on the Bailie-Lovie LogMAR charts (Ferris FL 1982). An initial chart was used to determine the best corrected visual acuity, using auto refraction and subjective refinement as necessary. Once best correction was achieved, two further charts were used to record the final visual acuities. The visual acuity was recorded in LogMAR notation as the line on which at least four of five letters were identified correctly.

If the visual acuity fell below 54 letters (LogMAR 0.0 or 6/6 Snellen.) in either eye then an auto refraction – using a Nidek AR-1100 – auto refractor was performed and the visual acuity reassessed using that correction placed in a trial frame. If the acuity remained below LogMAR 0.0, a subjective refractive correction was performed before a final best-corrected visual acuity accepted. If the subject was unable to read any letters on the top

line (1.0 or 6/60) at 4 metres, then the test was repeated at 1 metre. If this was unsuccessful, then the subject's ability to count fingers, detect hand movement, or to perceive and project light was assessed.

Statistical methods

When analysing vision in the better eye; the best correction for each eye was first chosen from either the patient's current refraction or the subjective refraction. The better of the two eyes was then chosen. STATA was used to generate categories of visual acuity to allow summaries of visual impairment.

Examining the difference between presenting visual acuity and best-corrected visual acuity enabled the unmet need in terms of refraction to be estimated.

Uncorrected refractive error was examined to see if there was an association with the presence of significant nuclear cataract.

Data on visual acuity was examined in a number of ways. The visual acuity was examined as a continuous variable in a regression analysis which included age, sex and grader. Age was analysed as a continuous variable while sex and grader were analysed as indicator variables. STATA automatically drops an indicator (dummy) variable from the regression. This allows the coefficients to have the interpretation of changes from a base group. Regression analysis was used to examine the association of cataract with the number of letters read correctly in the right eye with best-corrected vision. Data from cataract grading was examined as a continuous variable.

5.4 Results

Mean visual acuity

Results on Visual acuity were available for 824 of the 826 examined subjects. 2 subjects had data missing on VA. 821 subjects had data for the right eye and 820 for the left eye. Data on the best eye was therefore available for 824 subjects. The visual acuity measured using the ETDRS protocol (see Methods) is presented in terms of the numbers of letters read correctly on the LogMAR chart. This allows easy comparison of the UK population with the Beaver Dam Eye Study. Each line of five letters represents 0.1 LogMAR. Table VA1 shows the conversions between letters read correctly on the LogMAR chart, the LogMAR VA and Snellen VA. There was no significant difference in the mean number of letters read with either eye. The mean number of letters read with the right eye was 53.5 and that with the left was 53.6. Table VA2 summarises the data by age group and sex. Table VA3 gives the data with 95% confidence intervals. The data is depicted graphically in Figure VA1.

Table VA1. Conversion between letters read and visual acuity notations.

Letters	LogMAR	Snellen (6m)
5	1.0	6/60
10	0.9	6/48
15	0.8	6/38
20	0.7	6/30
25	0.6	6/24
30	0.5	6/19
35	0.4	6/15
40	0.3	6/12
45	0.2	6/9.5
50	0.1	6/7.5
55	0.0	6/6
60	-0.1	6/4.8
65	-0.2	6/3.8
70	-0.3	6/3

Age and sex

The mean number of letters read decreases with increasing age and is lower in women than in men. In all the regressions female sex ($p = 0.021$) and increasing age ($p < 0.0001$) are significantly associated with decreasing visual acuity.

A ttest of the mean number of letters read confirms that there is a significant difference between the mean number of letters read by men and women ($p = 0.017$)

Figure VA1. Scatter plots of visual acuity and age at examination.

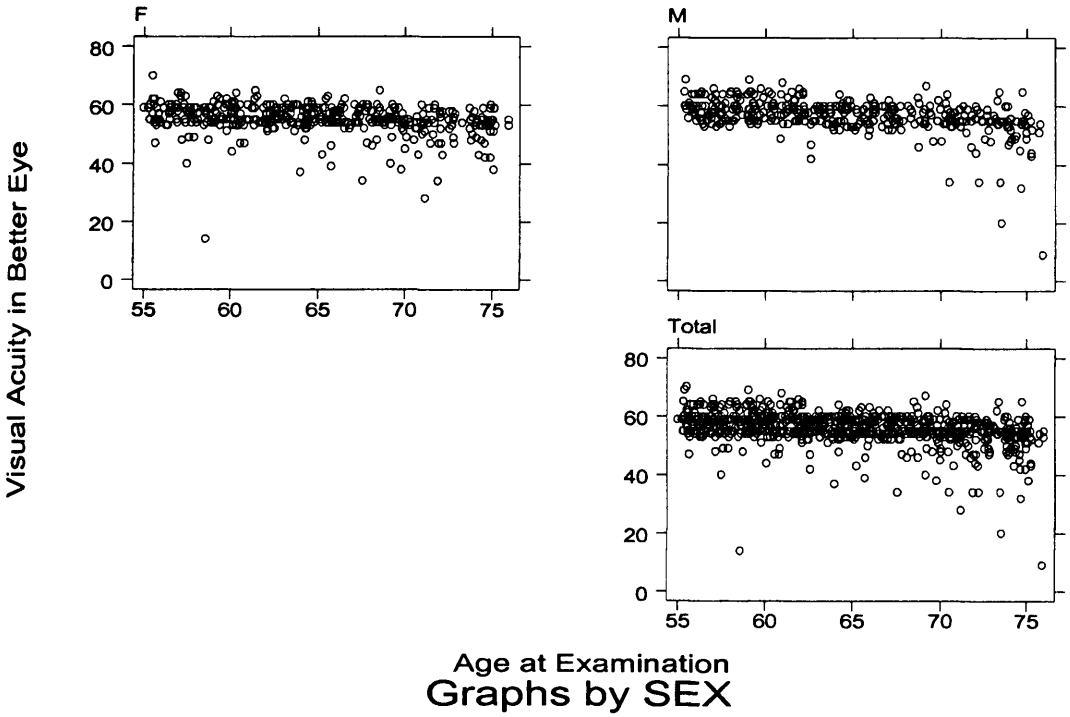


Table VA2. Mean number of letters read correctly by eye and sex. (Minimum and Maximum)

Eye and Age Category	Observations	Mean	Std.Dev.	Min	Max
Females					
Age 55-59					
Best Corrected VA RE	103	55.01	6.90	14.00	70.00
Best Corrected VA LE	103	53.96	7.11	14.00	64.00
Age 60-64					
Best Corrected VA RE	125	54.10	7.31	9.00	65.00
Best Corrected VA LE	124	53.90	6.08	8.00	63.00
Age 65-69					
Best Corrected VA RE	114	53.46	5.70	28.00	62.00
Best Corrected VA LE	115	51.95	10.04	2.00	65.00
Age 70-75					
Best Corrected VA RE	91	47.93	10.71	8.00	60.00
Best Corrected VA LE	91	50.22	8.07	21.00	60.00
Total (Females)					
Best Corrected VA RE	434	52.88	7.97	8.00	70.00
Best Corrected VA LE	434	52.63	8.05	2.00	65.00
Males					
Age 55-59					
Best Corrected VA RE	111	56.72	8.06	2.00	69.00
Best Corrected VA LE	110	57.54	4.34	43.00	69.00
Age 60-64					
Best Corrected VA RE	100	55.85	5.42	25.00	65.00
Best Corrected VA LE	101	56.40	6.78	10.00	68.00
Age 65-69					
Best Corrected VA RE	80	53.58	9.07	4.00	67.00
Best Corrected VA LE	81	53.86	6.89	5.00	63.00
Age 70-75					
Best Corrected VA RE	95	50.48	10.66	7.00	65.00
Best Corrected VA LE	93	50.41	10.93	1.00	65.00
Total (Males)					
Best Corrected VA RE	387	54.28	8.74	2.00	69.00
Best Corrected VA LE	386	54.75	7.96	1.00	69.00
Total (Male and Female)					
Best Corrected VA RE	821	53.51	8.47	2.00	70.00
Best Corrected VA LE	820	53.63	8.07	1.00	69.00

Table VA3 Mean number of letters read by eye according to age group (95%Conf.Interval)

Variable	Observations	Mean	Standard Error.	(95%Conf.Interval)	
Age 55-59					
Best Corrected VA RE	215	55.79	0.53	54.75	56.82
Best Corrected VA LE	214	55.82	0.42	55.00	56.64
Age 60-64					
Best Corrected VA RE	226	54.86	0.44	54.00	55.72
Best Corrected VA LE	226	55.02	0.43	54.17	55.87
Age 65-69					
Best Corrected VA RE	194	53.51	0.52	52.48	54.53
Best Corrected VA LE	196	52.74	0.64	51.48	53.99
Age 70-75					
Best Corrected VA RE	186	49.24	0.79	47.68	50.79
Best Corrected VA LE	184	50.32	0.71	48.92	51.71
Total					
Best Corrected VA RE	821	53.51	0.30	52.93	54.09
Best Corrected VA LE	820	53.63	0.28	53.07	54.18

Prevalence of visual impairment

Levels of impairment of visual function for the individual are defined by the best-corrected visual acuity in the better eye. Only 0.49% of subjects were visually impaired according to WHO criteria (VA <6/18). There were no bilaterally blind people (VA < 3/60) in this population (Table VA4). If the Beaver Dam Eye Study and Blue Mountains Eye Study criteria for mild, moderate, and severe visual impairment are used then 14 (1.69)% had mild impairment (VA<6/12) (Table VA5). Table VA6 shows the distribution of best-corrected visual acuities in the better eye of Melton subjects. If the subjects' current correction (i.e. presenting visual acuity is considered than mild impairment rises to 20 (3.16%) (Table VA8). The figure for WHO visual impairment in the worse eye is 4.65%. If the Beaver Dam criteria for mild impairment are used on the worse eye it rises to 9.67%.) (Table VA7). Although the mean number of letters read is lower in women than in men; in this population there was no difference in the prevalence of visual impairment between men and women.

Table VA4 Visual Impairment in Melton Subjects according to WHO criteria by age and sex. - (Best corrected VA in better eye.)

	All No.		No. 55-59 years		No. 60-64 years		No. 65-69 years		No. 70+ years	
		No. <6/18		No.<6/18		No.<6/18		No.<6/18		No.<6/18
Men	389	2 (0.51%)	112	0	101	0	81	0	95	2 (2.11%)
Women	435	2 (0.46%)	103	1 (0.97%)	126	0	115	0	91	1 (1.10%)
All subjects	824	4 (0.49%)	215	1 (0.47%)	227	0	196	0	186	3 (1.61%)

Table VA 5 Mild Visual Impairment in Melton Subjects according to American criteria (<6/12) by age and sex. - (Best corrected VA in better eye.)

	All No.		No. 55-59 years		No. 60-64 years		No. 65-69 years		No. 70+ years	
		No. <6/12		No.<6/12		No.<6/12		No.<6/12		No.<6/12
Men	389	6 (1.54%)	112	0	101	0	81	0	95	6 (6.3%)
Women	435	8 (1.83%)	103	1 (0.97%)	126	1 (0.79%)	115	3 (2.61)	91	3 (3.3%)
All subjects	824	14 (1.69%)	215	1 (0.47%)	227	1 (0.44%)	196	3 (1.53)	186	9 (4.83%)

Table VA6. Percentage distribution of visual acuity categories: Better eye. (Best Corrected Vision)

Better eye	Number of letters	Freq.	Percent	Cum.
<6/18	29	4	0.49	0.49
<6/12	39	10	1.21	1.70
<6/9	44	13	1.58	3.28
≤6/6	55	364	44.17	47.45
	70	433	52.55	100.00
Total		824	100.00	

Table VA7. Percentage distribution of visual acuity categories: Worse eye. (Best Corrected Vision)

Worse eye	Number of letters	Freq.	Percent	Cum.
≤6/60	5	6	0.73	0.73
<6/18	29	32	3.92	4.65
<6/12	39	41	5.02	9.67
<6/9	44	23	2.82	12.48
≤6/6	55	501	61.32	73.81
	70	214	26.19	100.00
Total		817	100.00	

Table VA8 Best Current (Presenting) Visual Acuity- using better eye.

Best Current Correction Category	Number of letters	Freq.	Percent	Cum.
≤6/60	5	1	0.12	0.12
<6/18	29	5	0.61	0.73
<6/12	39	20	2.43	3.16
<6/9	44	51	6.19	9.34
≤6/6	55	476	57.77	67.11
	70	271	32.89	100.00
Total		824	100.00	

Improvement with refraction

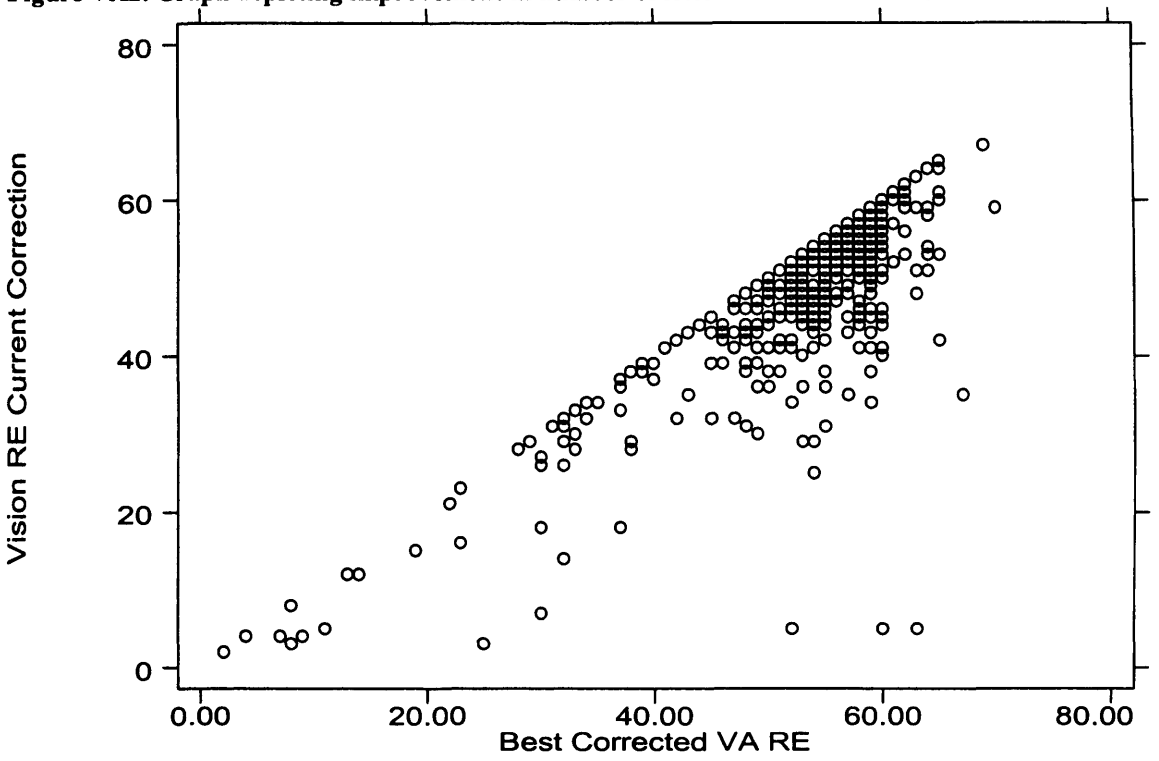
Refraction improved visual acuity by one or more lines in 230 (27.85%) of 824 participants and by three or more lines in 40 (4.84%). This is illustrated in Figure VA2 which plots the current correction against the subjective refraction at the time of examination for right eyes. Table VA9 summarises the improvement in right eyes with refraction and Table VA10 that of left eyes. In right eyes, 8 out of 10 subjects with vision of 6/60 or worse were improved to better than 6/60. Refraction improved the presenting visual acuity as used by the subjects in every day life from 3.16 % to 1.69% seeing <6/12

22 (2.66%) of subjects forgot their glasses. There was no change in the prevalence of visual impairment of either best corrected or presenting visual acuity if these subjects were excluded from the analysis. All 22 had best corrected acuities of 6/6 and only 1 had a presenting acuity of <6/12.

Association of uncorrected refractive error and nuclear cataract

Of 101 significant brunescent cataracts, 92 were not associated with significant uncorrected refractive error (improving by 3 or more lines) while 9 were. Of 89 significant white scatter cataracts, 83 were not associated with significant uncorrected refractive error while 6 were.

Figure VA2. Graph depicting improvement in number of letters read after refraction.



Vision RE Current correction :Le = Vision in right eye -number of letters.

Table VA9. Percentage distribution of visual acuity categories* before and after refraction. Right Eyes.

VA category Current Correction RE	Number of letters	Freq.	Percent	Cum.
≤6/60	5	10	1.22	1.22
<6/18	29	30	3.65	4.87
<6/12	39	45	5.48	10.35
<6/9	44	60	7.31	17.66
≤6/6	55	491	59.81	77.47
	70	185	22.53	100.00
Total		821	100.00	

VA category Best Corrected RE	Number of letters	Freq.	Percent	Cum.
≤6/60	5	2	0.24	0.24
<6/18	29	19	2.31	2.56
<6/12	39	32	3.90	6.46
<6/9	44	15	1.83	8.28
≤6/6	55	411	50.86	58.34
	70	342	41.66	100.00
Total	Total	821	100.00	

Table VA10. Percentage distribution of visual acuity categories* before and after refraction. Left Eyes.

VA category Current Correction LE	Number of letters	Freq.	Percent	Cum.
≤6/60	5	6	0.73	0.73
<6/18	29	29	3.54	4.27
<6/12	39	45	5.49	9.76
<6/9	44	62	7.56	17.32
≤6/6	55	486	59.27	76.59
	70	192	23.41	100.00
Total	Total	820	100.00	

VA category Subjective Refraction LE	Number of letters	Freq.	Percent	Cum.
≤6/60	5	4	0.49	0.49
<6/18	29	23	2.80	3.29
<6/12	39	27	3.29	6.59
<6/9	44	27	3.29	9.88
≤6/6	55	491	59.88	69.76
	70	248	30.24	100.00
Total	Total	820	100.00	

Associations of visual acuity with lens opacity

The association of vision with lens features was assessed by excluding those subjects who had non-cataract causes of visual loss. There were 34 subjects with documented reasons for reduced visual acuity unrelated to cataract. The majority of these had retinal pathology.

The effect of lens opacity on visual acuity was explored correcting for age, sex and grader in each analysis. Each Oxford nuclear feature was associated with a decreasing visual acuity when analysed separately. However, the different nuclear features are so strongly associated with each other that individual analyses are meaningless. When all three nuclear features (white scatter, brunescence, and Retro-dots were analysed together, only white scatter ($p < 0.0001$) and Retro-dots ($p = 0.024$) remained with a significant effect on vision.

If the effect of all cataract sub-types (including cortical and posterior subcapsular cataract) were included, then only white scatter remained significant ($p < 0.0001$) Retro-dots had a greater effect than brunescence but neither were statistically significant ($p = 0.058$) and ($p = 0.154$) respectively (Table VA10).

An attempt was made to analyse the effect of nuclear lens opacities on vision, without any confounding effect from other cataract types. The regression analyses were conducted on pure nuclear lens opacity. The results were essentially the same with only white scatter having a significant effect on vision.

Both cortical ($p < 0.0001$) and posterior subcapsular cataract ($p = 0.004$) were significantly associated with decreasing levels of visual acuity (Table VA10).

Figures VA3-VA7 and Tables VA5-VA9 summarise the associations of visual acuity with each lens feature. The tables are presented as ANOVA tables, with tables of estimated coefficients

Figure VA3. Visual acuity and Oxford white scatter – Right eye.

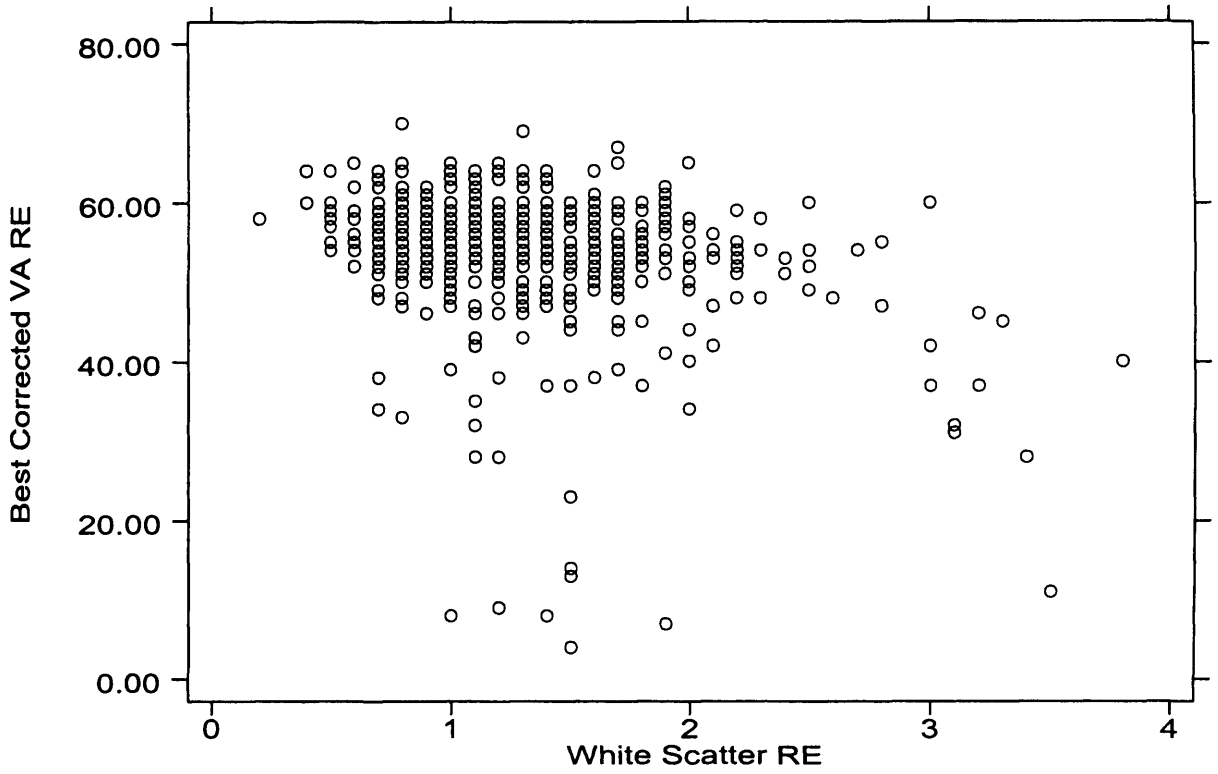


Figure VA4. Visual acuity and Oxford brunescence – Right eye.

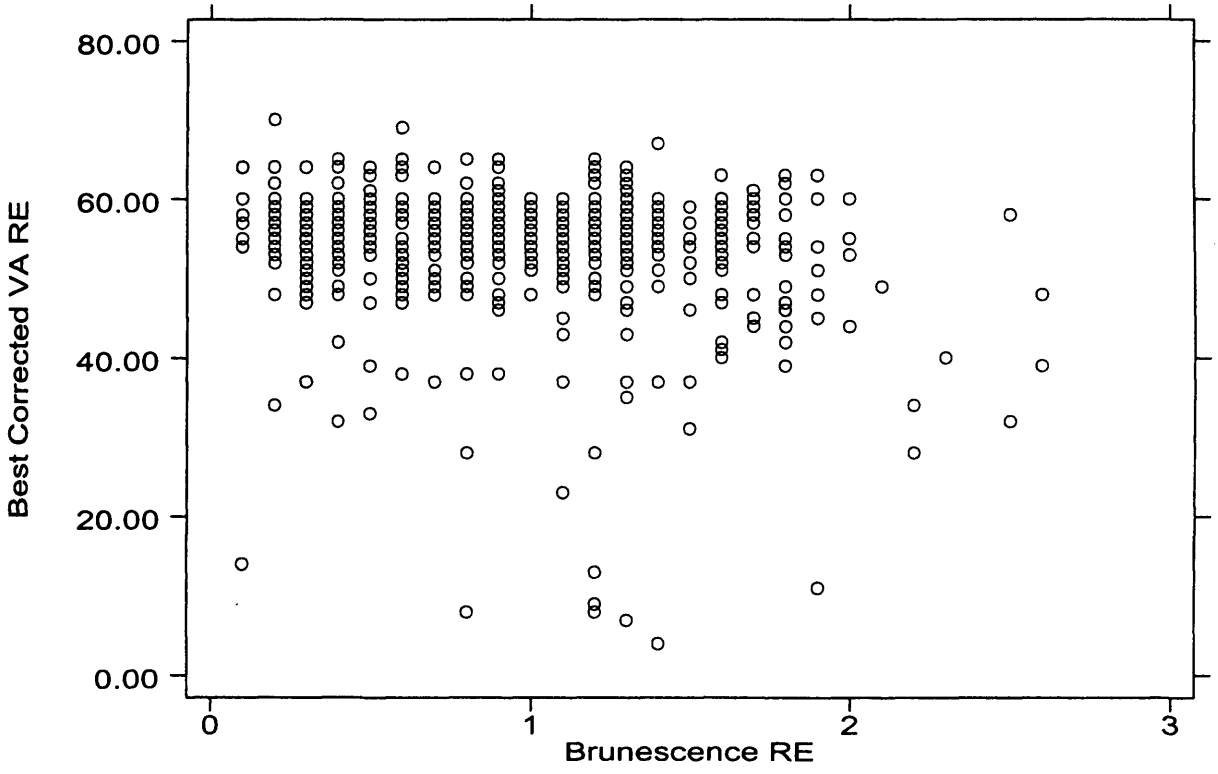


Figure VA5. Visual acuity and Oxford Retro-dots – Right eye.

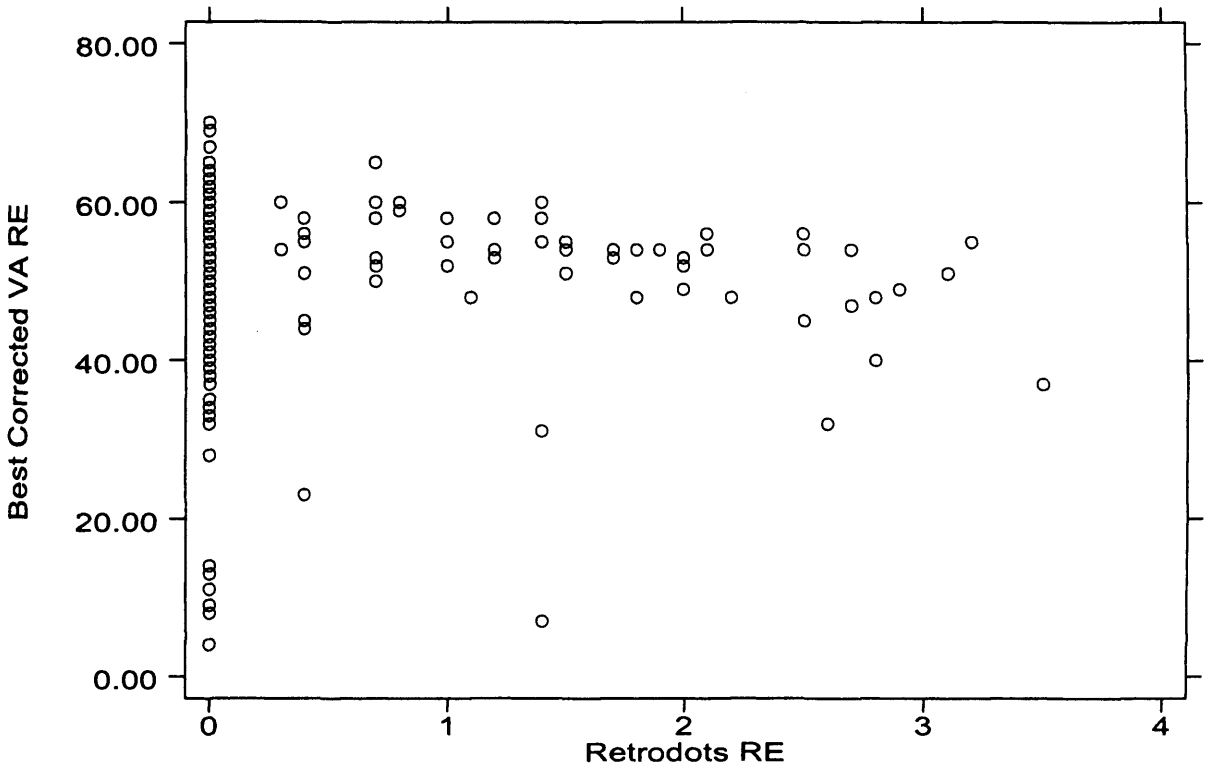


Figure VA6. Visual acuity and Oxford cortical cataract– Right eye.

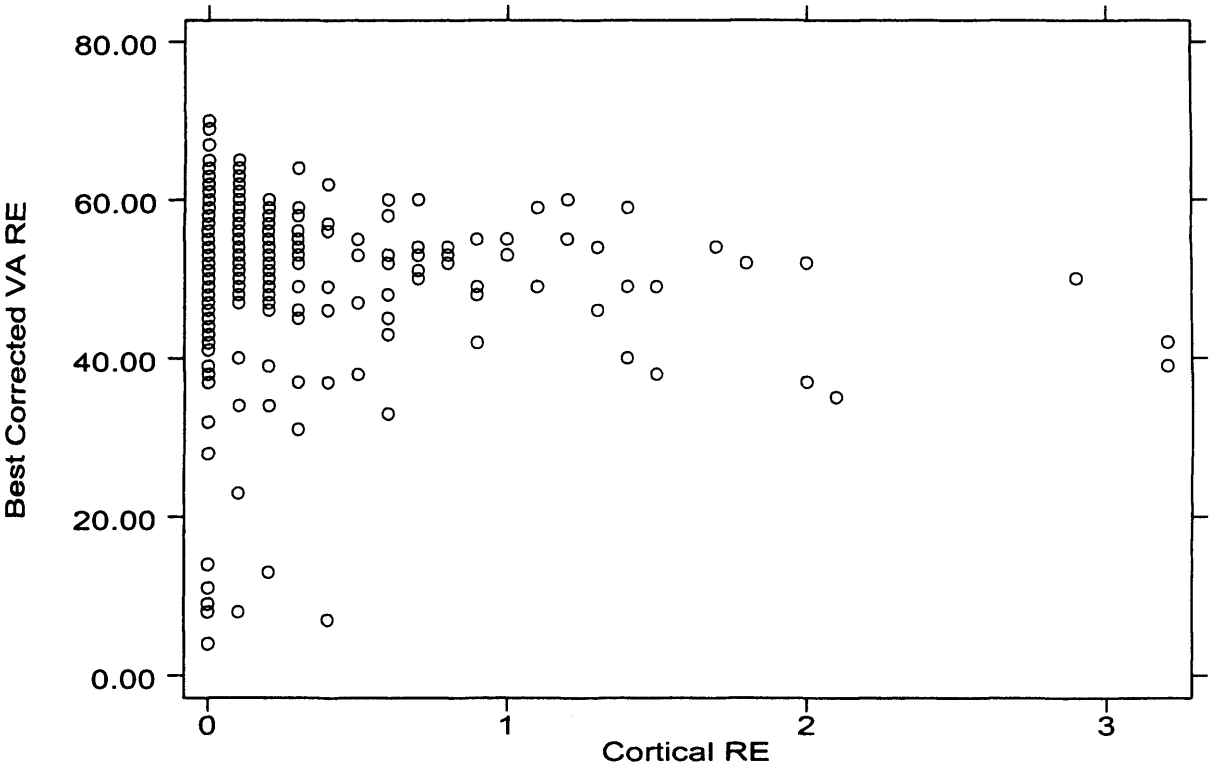


Figure VA7. Visual acuity and Oxford posterior subcapsular cataract– Right eye.

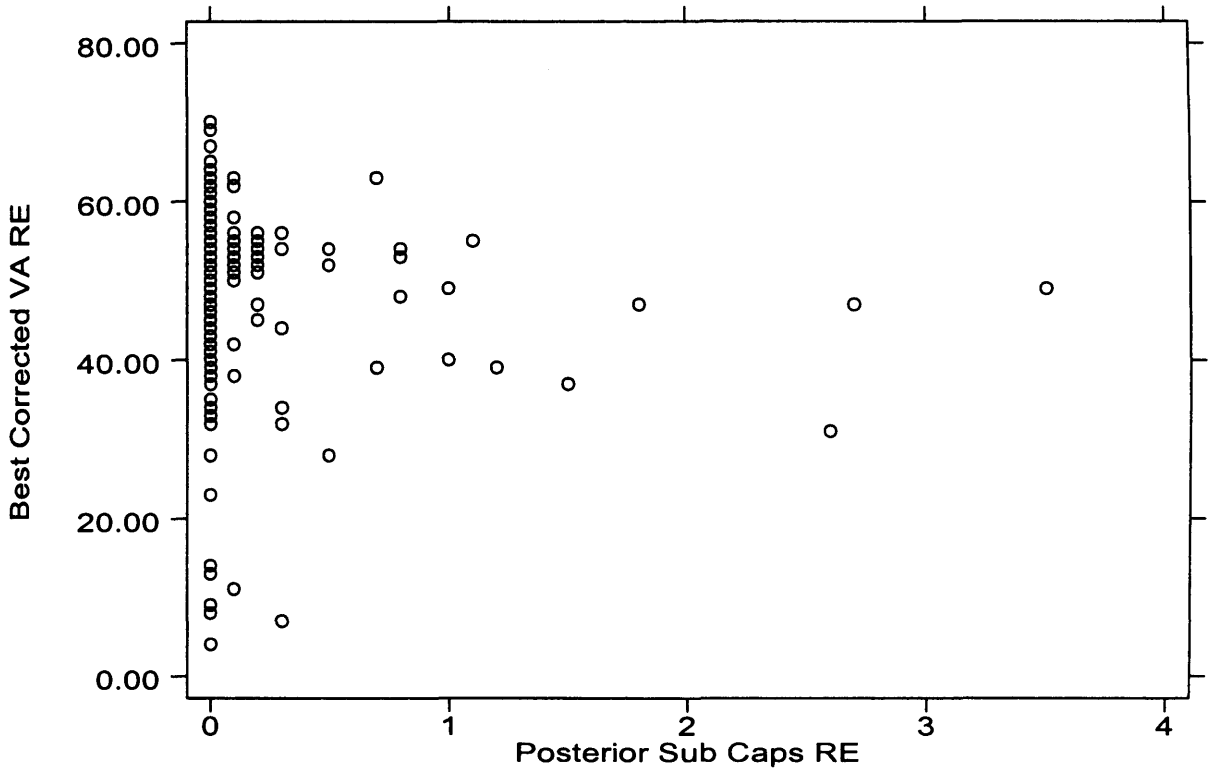


Table VA11. Estimated coefficients: best corrected visual acuity for Right Eyes and cataract* Univariate analysis- Each cataract sub-type analysed separately (correcting for age, sex and grader)

Best Corrected VA RE	Coef.	Std.Err	P>|t|	(95% Conf.Interval)	
Oxford White Scatter RE	-3.406824	.5839175	0.000	-4.553095	-2.260553
Oxford Brunescence RE	-1.964602	.5899855	0.001	-3.122784	-.806419
Oxford Retro dots RE	-1.559321	.5313097	0.003	-2.602321	-.516321
Oxford Cortical Cataract RE	-3.50347	.7602463	0.000	-4.99589	-2.011051
Oxford posterior subcapsular cataract RE	-4.893337	1.069515	0.000	-6.99287	-2.793803

*(after excluding non cataract reasons for reduced VA)

Table VA12. Estimated coefficients: best corrected visual acuity for Right Eyes and cataract* all cataract subtypes included in analysis at the same time

Best Corrected VA RE	Coef.	Std.Err	t	P>|t|	(95% Conf.Interval)	
Age at examination	-.1447372	.0492506	-2.939	0.003	(-.2414204	-.0480539)
Sex	2.075875	.4743578	4.376	0.000	(1.144668	3.007082)
Grader	1.581807	.5205812	3.039	0.002	(.5598592	2.603755)
Oxford White Scatter RE	**-2.724652**	**.6275961**	**-4.341**	**0.000**	**(-3.95668**	**-1.492624)**
Oxford Brunescence RE	-.8752956	.6129787	-1.428	0.154	(-2.078628	.3280369)
Oxford Retro dots RE	-.9837254	.5181782	-1.898	0.058	(-2.000956	.0335051)
Oxford Cortical Cataract RE	**-3.103435**	**.7526748**	**-4.123**	**0.000**	**(-4.581004**	**-1.625867)**
Oxford posterior subcapsular cataract RE	**-3.083533**	**1.071278**	**-2.878**	**0.004**	**(-5.186548**	**-.9805182)**
cons	66.87931	2.943219	22.723	0.000	(61.10151	72.65712)

*(after excluding non cataract reasons for reduced VA)

5.5 Discussion

Prevalence of visual impairment

The Melton Study had previously examined people over the age of 75 years in Melton Mowbray (Gibson, Lavery et al. 1986). The exclusion of this age group from the current study meant that the total prevalence of blindness and visual impairment was going to be lower than in other population-based studies which included those over the age of 75 years. For instance in the North London Study (Reidy, Minassian et al. 1998) found a prevalence of mild visual impairment in both eyes was 30.2% in a population aged over 65 years. In the Beaver Dam Eye Study the prevalence of mild impairment in the age groups 55- 64 and 65-74 was 0.5 and 4.3 % respectively (Klein, Klein et al. 1991) Moderate impairment (WHO visual impairment <6/18) was 0.2 and 0.4 % respectively. This correlates well with the results from the Melton Eye Study, where 0.36% of subjects in these age groups had visual impairment according to WHO criteria. Gibson et al found that in the age group 75 years and over, 25.7% had corrected vision of less than 6/18 in their better eye. 4% had corrected vision less than 6/60 (Gibson, Lavery et al. 1986) Both these figures are worse than the Beaver Dam Eye Study figures for this age group where the figures were 4% and 2% respectively (Klein, Klein et al. 1991) The Blue Mountains Eye Study is a population-based study which examined an Australian population 49 years of age and older (Attebo, Mitchell et al. 1996) Levels of visual impairment were not described according to World Health Organisation criteria but were divided into mild, moderate and severe or blind in the same manner as the Beaver Dam Eye Study. Moderate visual impairment (20/80 to 20/160 in the better eye) was found in 0.6% of Blue Mountains Eye Study. Both the Beaver Dam Eye Study and the Blue Mountains Eye Study found that levels of visual impairment increase with age and female sex. In our study the mean score for number of letters seen is statistically significant different with women seeing fewer letters than men. However this difference does not translate into a difference in levels of visual impairment. The number of visually impaired in this relatively young population is low and demonstrates no difference between men and women. The difference in number of letters seen may be due to the greater susceptibility of women to conditions that lead to a mild decrease in vision, such as mild age related macular degeneration or early cataract. For example, women have a trend to a higher prevalence of White Scatter than men do. White Scatter is associated with a reduction in vision while Brunescence is not. Alternatively, men with poor vision may have been less likely to participate in the study.

Improvement with refraction

When describing the prevalence of visual impairment the visual function of subjects is presented as the visual acuity in the better eye after an up-to-date refraction. However, it is just as important to know how people are functioning visually on a daily basis. In the Melton Eye Study, 10 subjects had severe visual impairment (<6/60) before refraction. Seven of these were improved to better than 6/60. i.e. 70% of subjects with severe visual impairment could have their vision improved by simple refraction. Refractive error is one of the priorities for reducing World blindness (Pararajasegaram 1999) Uncorrected refractive error is a significant cause of visual impairment even in the developed world. Refraction improved visual acuity by one or more lines in 45% of MES participants and by three or more lines in 13% in the Blue Mountains Eye Study (Attebo, Mitchell et al. 1996) This compared with 23.49% improvement of one or more lines in vision (one line = five letters), while 4.84% improvement by 3 lines or more in the MES study.

Associations of visual acuity with lens opacity

We are unaware of any population-based study that assess the effect of cataract on vision using a decimalised version of a cataract grading system and analysing the cataract data as a continuous variable. Maraini et al (Maraini, Rosmini et al. 1994) examined 1076 eyes examined as part of the Italian–American study of the Natural History of Age Related Cataract and found that increasing severity of nuclear cataract along the LOCS II scale was associated with the greatest increase in logMAR VA whilst increasing severity of cortical cataract was associated with the least. This greater effect of nuclear cataract on vision is confirmed by our population-based study. Our study further highlights that it is the white scatter component that leads to visual loss. It is interesting to note that the mean scores for visual acuity are lower in women and that women tend to have a higher prevalence of white scatter than men do. Both our study and Maraini et al's study were limited in the study of posterior subcapsular cataract in that the numbers of posterior subcapsular cataracts was low. Prevalence of cataract types was compared between Maryland watermen and patients presenting for surgery (Adamsons, Munoz et al. 1991) The comparison revealed that, of lenses with opacities, posterior subcapsular cataracts were present in a far greater percentage of surgery cases (60.6%) than in general population cases (5.3%). Adamson suggested that the disproportionate representation of posterior subcapsular opacities in the surgical population was because they cause more significant visual disability than do other types of cataracts. This observation was confirmed by Klein when describing the incidence of cataract in the Beaver Dam Eye Study (Klein, Klein et al.

1997); he noted that the visual acuity was worse in subjects with posterior subcapsular cataract and best in those with cortical cataract. However, our data suggests that because of the greater prevalence of nuclear cataract and its significant effect on vision, nuclear cataract is likely to be more of a public health problem.

5.6 Conclusion

Visual acuity levels in this population are similar to those in other developed countries. Mean scores for numbers of letters read are significantly lower in women although levels of visual impairment are not significantly different. There is significant, uncorrected refractive error contributing to levels of visual impairment in the population that are not apparent when best-corrected vision is used.

The visual degradation associated with nuclear cataract is due mainly to white scatter with a possible added effect from Retro-dots. Brunescence does not seem to have a significant effect on vision. Posterior subcapsular cataract and cortical cataract also have significant effects on vision. The size of the effect of white scatter on the regression is greater than either cortical or posterior subcapsular cataract. In part this reflects the greater prevalence of white scatter.

5.7 Public health implications

Significant improvement can be made in the vision of the elderly by the simple measure of up-to-date refraction. Older people may be less likely to complain, and lack the mobility and financial resources for regular review of their refraction. Regular optometric review will significantly reduce visual impairment, as well as screen for sight threatening eye diseases such as glaucoma and cataract.

The significant effect of nuclear opalescence on vision is compounded by the high prevalence in older people. Using a definition of >LOCS standard 3 (Oxford 1.85) for a significant opalescence, then over 14% of 65- to 70-year-olds had significant nuclear opacity and over 31% of those between the ages of 70 and 75 had significant visually degrading opacity. The prevalence of white scatter is also greater amongst women than amongst men, (26.74 % vs. 20 % in those over the age of 70). The incidence of nuclear cataract is also greater than the other subtypes; Klein (Klein, Klein et al. 1998) found a rate of incident nuclear cataract of 13.1% compared with only 8.0% in cortical and 3.4% in posterior subcapsular cataract. The cumulative incidence of nuclear cataract increased from 2.9% in persons aged 43 to 54 years at baseline, to 40.0% in those aged 75 years or older. Frost (Frost and Sparrow 2000) noted that 35% of UK ophthalmology consultants are prepared to consider surgery at levels better than 6/9. These data can be used to estimate the demand for cataract surgery in the United Kingdom.

6. Contrast Sensitivity and Nuclear Cataract

6.1 Introduction

Visual acuity (VA) measurements have been the gold standard for assessing visual function in patients with cataract (Maraini, Rosmini et al. 1994). However, cataracts imperfectly refract incoming light causing intra-ocular scatter and, therefore, a reduction in the contrast of the retinal image (Lasa, Datiles et al. 1992; Brown 1993). The development of clinical contrast sensitivity (CS) tests (Pelli 1988), has lead to the call, by some, for these to be used in the routine assessment of cataract patients because they provide more information than visual acuity alone and may be a more reliable guide to the likely benefits of cataract surgery (Weatherill 1993). The Pelli-Robson chart explores CS at low spatial frequencies. Inter test (test/retest) repeatability is reported to be excellent (Rubin 1988). Limited data are available on the associations of contrast sensitivity tests with cataract type and severity.

6.2 Purpose

The aims of this chapter are:

- to assess the value of contrast sensitivity testing at low spatial frequency using the Pelli-Robson chart in early cataract. In particular, to see if it adds anything to VA testing;
- to test the associations of different cataract types with contrast sensitivity.

6.3 Methods

Contrast sensitivity was measured using Pelli-Robson (Pelli 1988), contrast sensitivity charts. These charts consist of 16 groups of three letters at 1-2 cycles/degree, near peak sensitivity. The letters within each triplet each have the same contrast, the contrast decreases from one triplet to the next by a factor of $1/\sqrt{2}$. The first triplet is of maximal contrast (0.05 log units) and the following triplets reduce by 0.15 log units for a total of 2.30 log units, below the threshold for normal observers. Testing took place under standard lighting conditions using the subject's usual correction at a distance of 1 metre to minimise the effects of visual acuity on contrast sensitivity. Each letter subtends an angle of 1.5 degrees at this distance. A triplet was scored as correct if the subject identified two out of the three letters, as instructed by Pelli. Subjects were encouraged to persist for 20 seconds to identify a given character even if uncertain of its identity, as it takes some time to perceive the letter when the subject approaches threshold. The chart was changed

between eyes and again for binocular testing. The subject's score was the log contrast sensitivity corresponding to the last group of letters in which two letters were correctly named.

Statistical methods

The distribution of CS with different lens opacities was outlined graphically by scatter plots. Multiple regression analyses were done with the data from cataract grading and CS examined as continuous variables. Data on CS were examined in a number of ways. Firstly, the CS was examined as a continuous variable in a regression analysis that included age, sex and grader. Age was analysed as a continuous variable and sex and grader were analysed as indicator variables. STATA automatically drops an indicator (dummy) variable from the regression. This allows the coefficients to have the interpretation of changes from a base group. Each cataract subtype was initially included in the above regression independently, to determine the association of cataract subtype with CS. All the cataract subtypes were then examined together. Finally, the multiple regression analysis was extended by adding VA to determine whether CS is associated with cataract after adjusting for VA (Table CS7).

6.4 Results

Population means for contrast sensitivity

The mean log contrast sensitivities (LCS) are presented in Table CS1 by age and sex. Table CS2 shows the mean scores and 95% confidence intervals of LCS by sex while Table CS3 summarises the mean scores and 95% confidence intervals of LCS by age category. The correlation between VA and CS is presented graphically in Figure CS4. .

Table CS1. Mean log contrast sensitivity by age and sex Right eye.

	Observations	Mean	Std.Dev.	Min	Max
Females					
Age 55-59	103	1.73	0.18	1.10	2.15
Age 60-64	123	1.69	0.18	0.65	2.15
Age 65-69	113	1.69	0.20	0.95	2.00
Age 70-75	90	1.59	0.24	0.20	2.00
Males					
Age 55-59	111	1.74	0.17	1.25	2.15
Age 60-64	98	1.76	0.16	1.25	2.45
Age 65-69	82	1.65	0.23	0.35	2.15
Age 70-75	93	1.61	0.26	0.35	2.00
Total Male and Female	814	1.69	0.21	0.20	2.45

Table CS2. Mean scores and 95% confidence intervals of Contrast Sensitivity by sex– Right eye.

Log Contrast Sensitivity RE	Observations	Mean	Standard Error.	(95% Conf. Interval)	
Females	429	1.68	0.01	1.66	1.70
Males	385	1.69	0.01	1.67	1.72

Table CS3. Mean scores and 95% confidence intervals of Log Contrast Sensitivity by age category– Right eye.

Log Contrast Sensitivity RE	Observations	Mean	Standard Error.	(95% Conf. Interval)	
Age 55-59	215	1.74	0.01	1.71	1.76
Age 60-64	221	1.72	0.01	1.70	1.74
Age 65-69	195	1.68	0.02	1.65	1.71
Age 70-75	183	1.60	0.02	1.56	1.64

The correlations of CS with the subtypes of Oxford nuclear cataract grades are presented graphically by scatter plots in Figures CS1–4. The results of the regression analyses are presented in Tables CS4–7.

Nuclear cataract

Of the nuclear features, neither Brunescence nor White Scatter is associated with CS, at the univariate level (before correcting for VA and other lens features) (p = 0.164 and 0.388 respectively). However, Retro-dots are associated at this level of analysis (p = 0.018). **(Table CS4)** The significance of the association disappears once the effect of visual acuity is taken into account (p = 0.174) if all the subjects are considered. **(Table CS5)** However the number of subjects with Retro-dots (non-zero values) is low (61). If the analysis is repeated for Retro-dots using non-zero values only, then Retro-dots are significantly associated with LCS (p = 0.013) even after correcting for Visual Acuity and other lens opacities. **(Table CS6)**

Table CS4. Estimated coefficients: Log Contrast Sensitivity for Right Eyes and cataract
Univariate analysis (correcting for age, sex and grader, non cataract reasons for reduced VA-excluded) - Each cataract sub-type analysed separately

Log Contrast Sensitivity RE	Coef.	Std. Err.	P>|t|	(95% Conf. Interval)	
Oxford White Scatter RE	-.0139293	.0161414	0.388	-.0456163	.0177576
Oxford Brunescence RE	-.0224399	.0161016	0.164	-.0540487	.0091688
Oxford Retro dots RE	-.0341157	.0144023	0.018	-.0623887	-.0058427
Oxford Cortical Cataract RE	-.0718073	.020718	0.001	-.1124787	-.0311359
Oxford posterior subcapsular cataract RE	-.0680642	.0293805	0.021	-.1257406	-.0103879

Table CS5. Estimated coefficients: Log contrast sensitivity for Right Eyes
Multivariate analysis (correcting for age, sex, grader, each cataract subtype and best corrected VA, after excluding non cataract reasons for reduced VA)

Log Contrast Sensitivity RE	Coef.	Std. Err.	P>|t|	(95% Conf. Interval)	
Age at examination	-.0033927	.0012505	0.007	-.0058476	-.0009377
Sex	.0130134	.012159	0.285	-.0108563	.0368831
Grader	.0416745	.0132707	0.002	.0156225	.0677266
Oxford White Scatter RE	.0283534	.0160693	0.078	-.0031927	.0598995
Oxford Brunescence RE	-.0085841	.0155186	0.580	-.0390489	.0218808
Oxford Retro dots RE	-.017835	.013098	0.174	-.043548	.0078779
Oxford Cortical Cataract RE	-.0340293	.0192437	0.077	-.071807	.0037484
Oxford posterior subcapsular cataract RE	-.0184845	.027275	0.498	-.0720287	.0350597
Best Corrected VA RE	.0097291	.0009199	0.000	.0079232	.011535
_cons	1.346671	.0965287	0.000	1.157174	1.536169

Table CS6. Estimated coefficients: Log contrast sensitivity for Right Eyes and Retro-dots
Multivariate analysis (correcting for age, sex, grader, each cataract subtype and best corrected VA, after excluding non cataract reasons for reduced VA)
Subjects with non-zero values for Retro-dots. Number of observations = 61

Log Contrast Sensitivity RE	Coef.	Std. Err.	P>|t|	(95% Conf. Interval)	
Oxford Retro dots RE	-.0645363	.0251823	0.013	-.1150918	-.0139807

Figure CS1. Contrast sensitivity and Oxford White Scatter – Right eye.

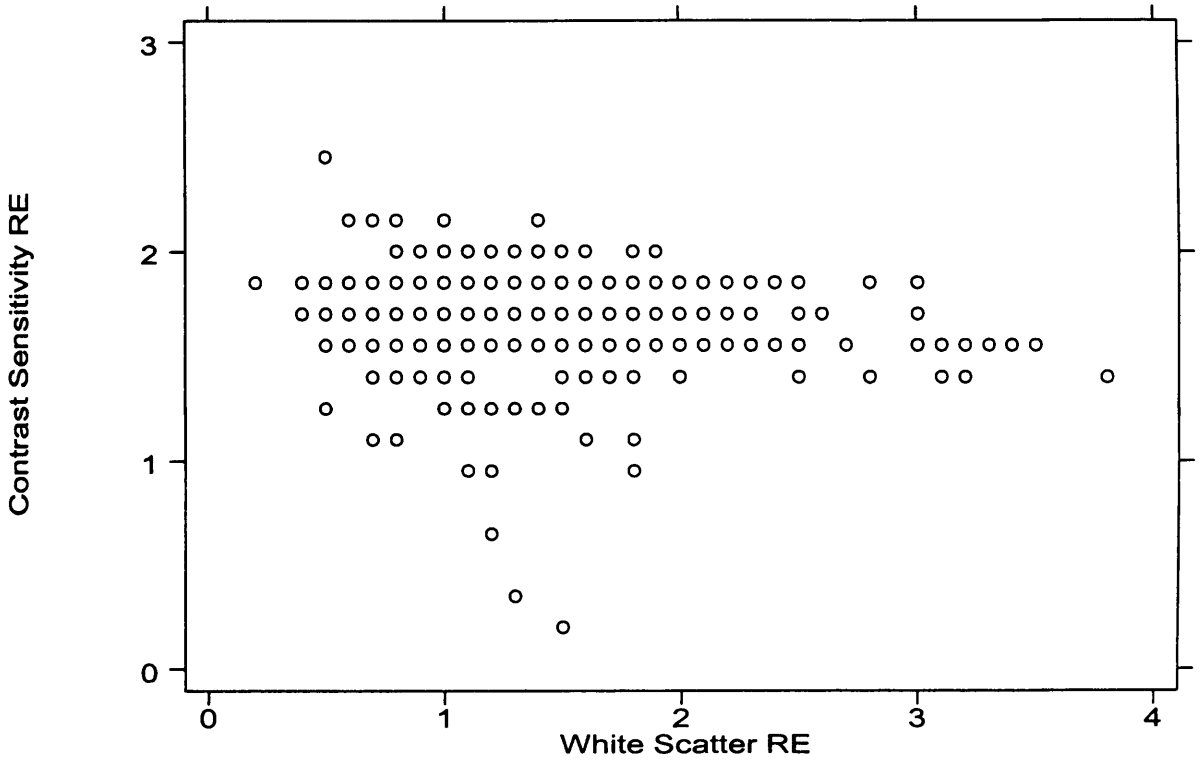


Figure CS2. Contrast sensitivity and Oxford Brunescence – Right eye.

Figure CS3. Contrast sensitivity and Oxford Retro-dots – Right eye.

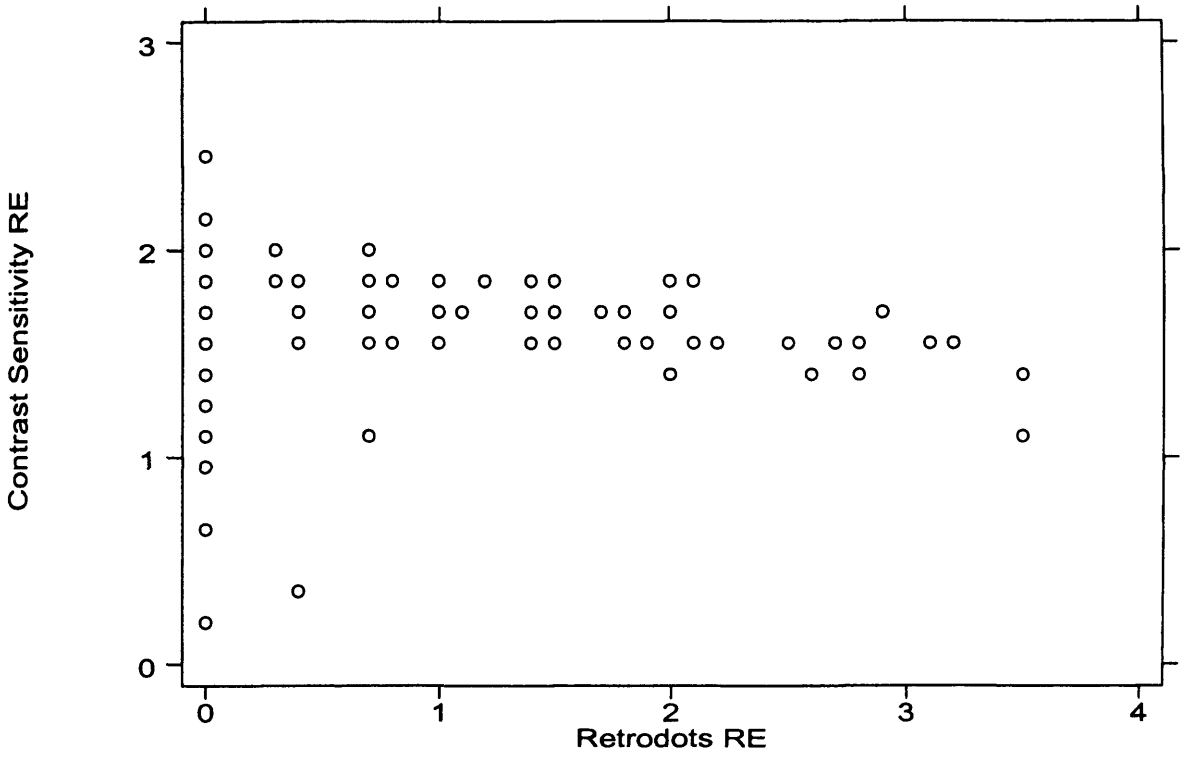
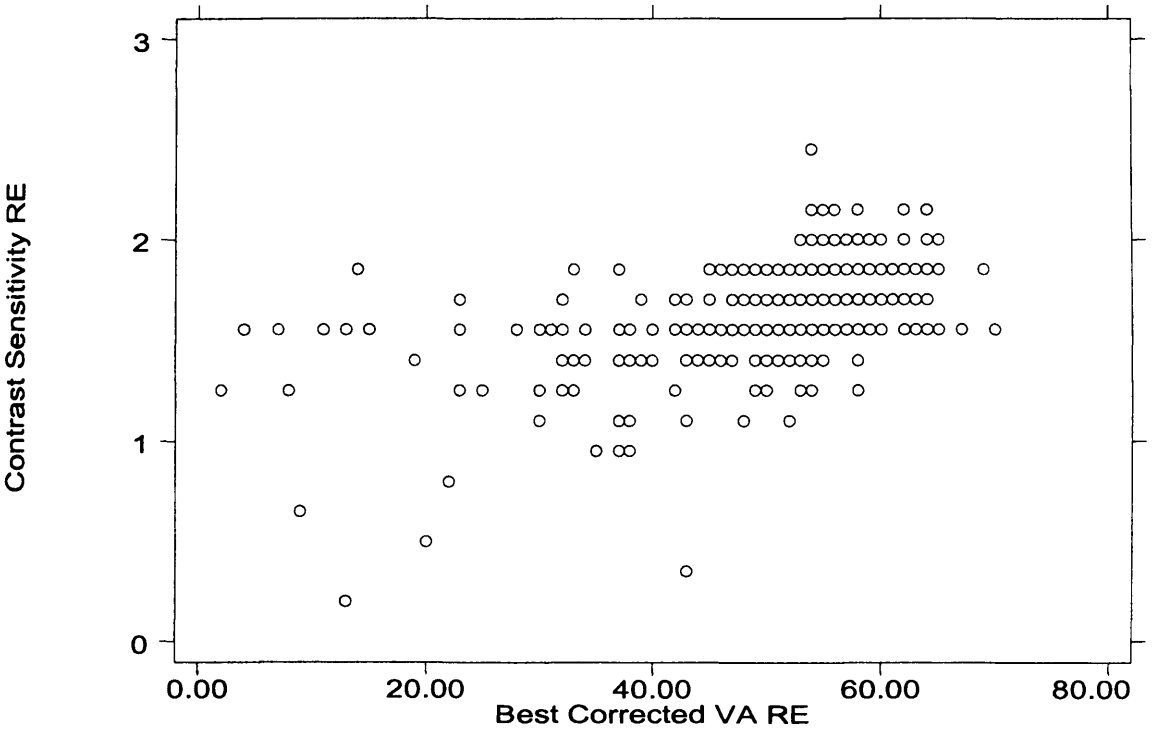


Figure CS4. Contrast sensitivity and visual acuity – Right eye.



6.5 Discussion

The population means for CS are virtually identical to those found in the Beaver Dam Eye Study in the same age groups. The author found no population-based study that analysed the effect of cataract on CS with which to compare. Retro-dots, cortical and posterior subcapsular cataract were associated with CS, but this could be explained by the strong correlation of CS with visual acuity (Fig. CS5). Once VA was corrected for, the associations were no longer significant if the whole population was considered. However if subjects with non-zero values for Retro-dots were analysed then there was a significant correlation of CS with Retro-dots. CS measurement in the low frequency range provided by the Pelli-Robson chart did not add anything to the information provided by VA. The Italian-American study examined the effect of pure forms of age-related cataract on visual acuity and contrast sensitivity. They also found that the only cataract subtype to be associated with CS was advanced cortical cataract. The Melton Eye Study was limited by only having fairly early cortical cataract. Unlike the Italian-American study (Maraini, Rosmini et al. 1994), there were insufficient pure cataract subtypes to study. Corrections for other subtypes had to be made using statistical methods. It may well be that had there been more cortical cataract for analysis, that a significant effect would have been found.

6.6 Conclusion

In this population-based study CS measurement in the low frequency range provided by the Pelli-Robson chart did not add anything to the information about cataract provided by VA.

6.7 Public Health Implications

The Melton Eye Study's population-based data would seem to be consistent with the observations of Maraini et al (Maraini, Rosmini et al. 1994), Lasa et al (Lasa, Datiles et al. 1992), and Elliot et al (Elliott, 1998) that CS testing at low spatial frequency provides no additional information once VA has been accounted for. Any additional information seems to be in the advanced cataracts, where the decision on whether surgery would be beneficial is relatively easy, as the visual function changes are documented by the changes in Snellen acuity. There seems to be no association of nuclear cataract and CS. In populations where nuclear cataract may predominate (West, Munoz et al. 1998), and surgeons are operating at lower levels of visual impairment (McCarty, Keeffe et al. 1999; Frost and Sparrow 2000), then questionnaires exploring vision related quality of life (Frost, Sparrow et al. 1998), may be a more useful tool for assessing the impact of surgery on quality of vision.

7. Refractive Errors and Nuclear Cataract

7.1 Purpose

The aims of this chapter are:

- to describe the prevalence of refractive error in the Melton population aged 55 to 75 years;
- to attempt to document mean age and spherical equivalent at first use of distance glasses
- to describe the association of current refractive error and nuclear lens opacities.
- to describe the association of early (age less than 40) refractive error (particularly myopia) and nuclear lens opacities.

7.2 Introduction

Many studies have suggested that low myopia may be an important risk factor for cataract (Weale 1980; Harding and van Heyningen 1987; Harding, Harding et al. 1989). This relationship has been disputed on the grounds that nuclear sclerotic cataract itself causes a change towards myopia, occurring independently of whether the eye was myopic or hypermetropic (Brown and Hill 1987; Brown 1993).

A number of large studies used a history of use of distance glasses as a proxy for myopia but did not differentiate those people who might have used glasses before the age of 20 because of significant hypermetropia.

In the Blue Mountains Eye Study (Lim, Mitchell et al. 1999), subjects were assumed to have myopia if they gave a history of wearing distance glasses, but excluding eyes with a current hypermetropic refraction. With regard to nuclear cataract, as expected, they found an association between any current myopia and nuclear cataract. However, the relationship was only significant for individuals who began wearing glasses after the age of 40 years. They felt that this confirmed the previous observations by Brown and Hill (Brown and Hill 1987), that it is the myopic shift caused by the nuclear sclerosis that leads to the need for distance glasses correction. Detailed descriptions of these and other studies examining the association of cataract and myopia may be found in the Literature Review.

No population-based study has yet found an association between early myopia and nuclear cataract.

7.3 Methods

Only the methods relevant to refractive errors are summarised here. In brief: the subject's current spectacle prescription was measured on a Topcon LM6 focimeter. The

visual acuity was assessed using their current refractive correction on retro-illuminated Early Treatment of Diabetic Retinopathy (ETDRS) letter 4 metre charts, which are based on the Bailie-Lovie LogMAR charts (Ferris FL 1982). An initial chart was used to determine the best corrected visual acuity, using auto refraction and subjective refinement as necessary. Once best correction was achieved, two further charts were used to record the final visual acuities. The visual acuity was recorded in LogMAR notation as the line on which at least four of five letters were identified correctly.

If the visual acuity fell below 54 letters (LogMAR 0.0 or 6/6 Snellen) in either eye, then an auto refraction using a Nidek AR-1100 auto refractor was performed and the visual acuity reassessed using that correction placed in a trial frame. If the acuity remained below LogMAR 0.0, a subjective refractive correction was performed before a final best-corrected visual acuity was accepted. If the subject was unable to read any letters on the top line (1.0 or 6/60) at 4 metres then the test was repeated at 1 metre. If this was unsuccessful then the subject's ability to count fingers, detect hand movement, or to perceive and project light was assessed.

Statistical methods

Data from cataract grading was examined as a continuous variable. Data on refractive status was examined in a number of ways. Regression analysis was used to examine the association of cataract with the presence of myopia, the presence of hyperopia and a subject's spherical equivalent. The spherical equivalent was examined as a continuous variable. Myopia (defined as –1.0 D) was analysed firstly as an indicator variable, and then used to allow a separate analysis of myopic subjects. Each nuclear feature was analysed, firstly in a univariate analysis, looking at myopia, hyperopia and spherical equivalent one at a time. Each of these factors was then included in a regression analysis, which included age, sex, grader and nuclear lens opacity. The latter was included because of its established association with index myopia. Any positive association in this analysis was then included in the final model of all risk factors. Because myopia is eye specific, a final model for myopia has to be included in this chapter, however , the cataract gradings data presented in the chapter on insulin resistance syndrome are the average of the grading from both eyes. Age was analysed as a continuous variable and sex and grader were analysed as indicator variables. The history of glasses use was then used to analyse the data according to the age category in which subjects first used glasses. STATA was also used to generate age categories for first distance glasses use and to calculate the prevalence of different refractive errors.

7.4 Results

Characteristics of subjects with reference to refractive status

Age of first distance glasses

A previous history of cataract surgery was obtained in 12 (1.45%) right eyes and 8 (0.97%) left eyes. These eyes were excluded from the analysis of the association of refractive status with nuclear cataract. There was no data on the use of distance glasses in two further subjects. Data on a history of the use of distance correction was available in 99.76% of subjects. Table R1 summarises the ages at which distance glasses were first worn. 17.71% of subjects (105) wore glasses before the age of 20 years. A further 16.36 % wore glasses for the first time between the ages of 20 and 40. The majority of subjects (53.12 %) obtained their glasses between the ages of 40 and 60. Table R2 gives the mean age and mean spherical correction in each category of age for first spectacle use. The mean current spherical equivalent for subjects whose first distance glasses were obtained under the age of 10 is +1.7 D. Whereas the mean spherical equivalent for subjects getting their first glasses between the ages of 10 and 20 was – 1.4 D. Figure R1 summarises the data on age at which distance glasses were first worn for hypermetropes and myopes.

Further analysis shows that 58.7 % of subjects who had distance glasses by the age of 10 were currently significantly (over +1.0 D) hypermetropic. This dropped to 23 .7% for those that had distance glasses by the age of 20. The corresponding prevalence of myopic corrections rose from 21.7% to 55.9%.

Table R1. Age at first use of distance glasses.

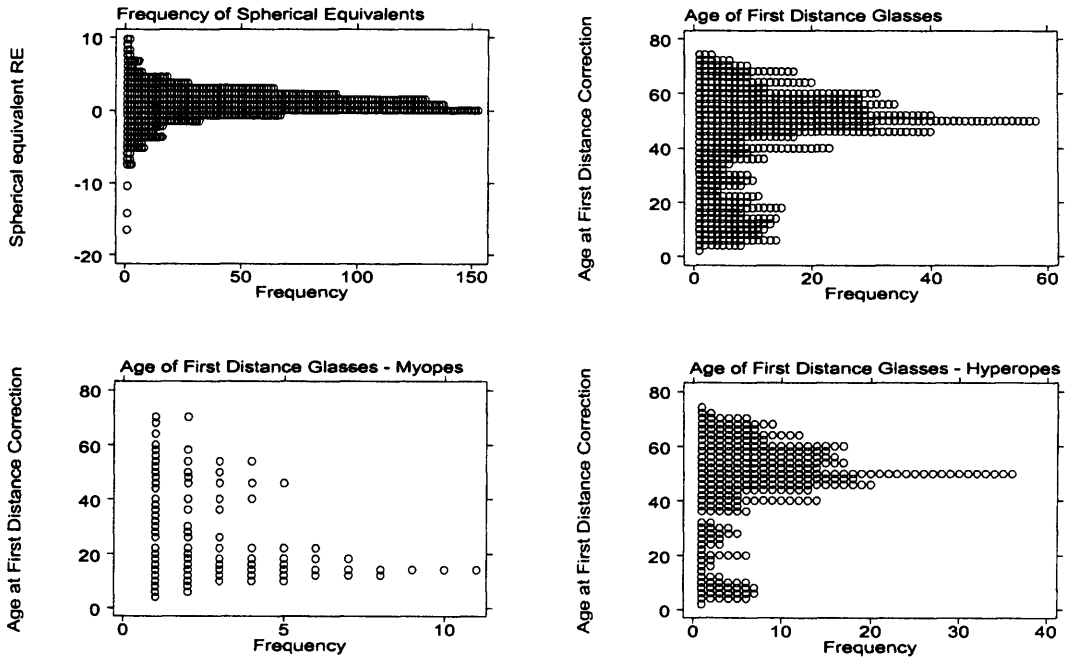
Age First Distance Glasses	Frequency	Percent	Cumulative
10 or under	46	7.76	7.76
11 to 20	59	9.95	17.71
21 to 40	97	16.36	34.06
41 to 60	315	53.12	87.18
61 to 70	76	12.82	100.00

Prevalence of refractive errors

The same definition for myopia has been used as in the Blue Mountains Eye Study (Lim, Mitchell et al. 1999). i.e. myopia less than –1.0 D and hyperopia more than +1.0 D. Similarly myopia was divided into 3 groups of mild (–1.0D to > -3.5 D) moderate (–3.5 or less to >–6 D) and high myopia (–6 D or less).

13% of subjects (116) were myopic. Of eyes with myopia, 67 had low myopia, 30 had moderate myopia and only 9 had high myopia. 325 (40.0%) of subjects were emmetropic and the remainder 381 (46.9 %) were hypermetropic. See Table R3 for 95 % confidence intervals. Table R3 also summarises the refractive status of the Melton Eye Study subjects according to the spherical equivalent (sphere plus half the astigmatic correction).

Figure R1. Summary of age at first distance correction.



Summary of Age at First Distance Correction

Table R2. Mean age and spherical equivalent at first use of distance glasses.

Age of First Distance Glasses	Obs	Mean	Std. Dev.	Min	Max
10 or less	46	6.45	2.42	2	10
Spherical Equivalent Right Eye*	46	1.75	3.89	-7.37	+9.5
above 10 to 20	59	15.36	2.80	11	20
Spherical Equivalent Right Eye	59	-1.50	4.31	-16.5	+9.5
Above 20 to 40	97	32.10	6.45	21	40
Spherical Equivalent Right Eye	95	.55	2.69	-6.87	+6
Above 40 to 60	315	51.28	5.02	41	60
Spherical Equivalent Right Eye	312	1.15	1.70	-6.25	+6.75
Above 60	76	65.96	3.37	61	73
Spherical Equivalent Right Eye	75	1.17	1.59	-3.75	+8.25

The number of observations differs where data on spectacles and therefore spherical equivalent is not available.

Table R3. Distribution of spherical equivalents for right eyes by spherical category.

Spherical category		Frequency.	Percent	Cum.	95% Conf. Interval
Myopia:	<-6	9	1.11	1.11	0.51 to 2.10
	-6 to -3.5	30	3.69	4.80	2.51 to 5.23
	-3.4 to -1	67	8.25	13.05	6.45 to 10.36
Emmetropia	>-1 to < +1	325	40.02	53.08	36.63 to 43.48
hyperopia	>1	381	46.92	100.00	43.44 to 50.42

Results of regression analyses

Details of the regression analyses are found for each cataract subtype in Tables R4–R8. These include the regression coefficients and 95% confidence intervals for White Scatter, Brunescence, and Retro-dots. Where there was no significant association amongst myopes, the regression is given for spherical equivalent without any categorisation. Each regression is accompanied by two graphs showing the spherical equivalent plotted against the relevant lens feature, one plotted according to the age distance glasses were first worn, the other depicting the plots grouped in age groups. The former, to allow the graphic depiction of any effect of early myopia, and the latter to illustrate the effect of spherical equivalent on lens opacities while dealing with the effect of age on lens opacities.

Univariate Analysis (Table R4)

Brunescence (Fig. R3).

In the univariate analysis, Brunescence was associated with myopia if distance glasses were worn for the first time after the age of 40. There is a negative association of Brunescence with spherical equivalent in those myopes who started wearing glasses aged younger than 40 years and also in those who started wearing glasses after the age of 40. In other words as the myopia (negative sphere) increases, the amount of White Scatter also increases.

White Scatter (Fig. R2)

White Scatter is also associated with myopia if distance glasses were worn for the first time after the age of 40. White Scatter is negatively associated with spherical equivalent in those myopes who started wearing glasses aged younger than 40 years but not in those who started wearing glasses after the age of 40. However, White Scatter is positively associated with spherical equivalent in hypermetropes who started to wear glasses after the age of 40.

Retro-dots (Fig. R4)

Retro-dots are associated with myopia in those who first wore glasses after the age of 40.

Table R4 Estimated Co-efficients Nuclear Cataract features against Myopia and Spherical Equivalent-Univariate Analysis

Brunescence RE	**Coef.**	**Std. Err.**	**P>|t**	**(95% Conf. Interval)**	
Myopia	.1172078	.053171	0.028	.0128376	.2215779
Myopia:1ST Glasses < 20	-.1206112	.0868027	0.166	-.2918039	.0505815
Myopia 1ST Glasses > 40	**.2650429**	**.0801132**	**0.001**	**.1077107**	**.4223751**
Spherical Equiv.	.0044094	.0073808	0.550	-.0100789	.0188978
Spherical Equiv. If 1ST Glasses < 20	-.0049905	.0104684	0.634	-.0256377	.0156567
Spherical Equiv. If 1ST Glasses < 20 &Myopia	**-.0688104**	**.0235253**	**0.005**	**-.1158523**	**-.0217686**
Spherical Equiv. If 1ST Glasses < 20 & Hyperopia	-.030305	.0307335	0.327	-.0914666	.0308565
Spherical Equiv. If 1ST Glasses > 40	**.0293809**	**.0114897**	**0.011**	**.0068158**	**.051946**
Spherical Equiv. If 1ST Glasses > 40 & Myopia	-.0316217	.0528204	0.554	-.1392133	.07597
Spherical Equiv. If 1ST Glasses > 40 & Hyperopia	.0460889	.0241803	0.058	-.001522	.0936997

White Scatter RE	**Coef.**	**Std. Err.**	**P>|t**	**(95% Conf. Interval)**	
Myopia	.0984071	.0554656	0.076	-.0104672	.2072815
Myopia:1ST Glasses < 20	-.1350983	.0930278	0.148	-.318568	.0483714
Myopia 1ST Glasses > 40	**.3124796**	**.0829404**	**0.000**	**.1495952**	**.475364**
Spherical Equiv.	.0023026	.0077086	0.765	-.012829	.0174343
Spherical Equiv. If 1ST Glasses < 20	-.0042009	.0113069	0.711	-.026502	.0181001
Spherical Equiv. If 1ST Glasses < 20 &Myopia	**-.1079035**	**.0217977**	**0.000**	**-.1514908**	**-.0643162**
Spherical Equiv. If 1ST Glasses < 20 & Hyperopia	.0052023	.032545	0.873	-.0595644	.069969
Spherical Equiv. If 1ST Glasses > 40	.0189506	.011954	0.113	-.0045264	.0424275
Spherical Equiv. If 1ST Glasses > 40 & Myopia	-.0439948	.0729338	0.551	-.1925561	.1045664
Spherical Equiv. If 1ST Glasses > 40 & Hyperopia	**.0721254**	**.0252839**	**0.005**	**.0223417**	**.1219091**

Table R4 Continued

Retro-dots RE	Coef.	Std. Err.	P>|t	(95% Conf. Interval)	
Myopia	.0680903	.0542842	0.210	-.0384653	.174646
Myopia:1ST Glasses < 40	-.0687121	.0945476	0.468	-.2551914	.1177672
Myopia 1ST Glasses > 40	**.1944547**	**.0801884**	**0.016**	**.0369748**	**.3519345**
Spherical Equiv.	-.0133852	.0076345	0.080	-.0283714	.0016011
Spherical Equiv. If 1ST Glasses < 40	-.0088493	.0119151	0.459	-.0323505	.0146519
Spherical Equiv. If 1ST Glasses < 40 &Myopia	-.018535	.0247247	0.456	-.0679918	.0309218
Spherical Equiv. If 1ST Glasses < 40 & Hyperopia	-.0293865	.0283339	0.303	-.0857727	.0269998
Spherical Equiv. If 1ST Glasses > 40	-.0180168	.0115168	0.118	-.0406351	.0046016
Spherical Equiv. If 1ST Glasses > 40 & Myopia	-.0766927	.0663946	0.257	-.211934	.0585486
Spherical Equiv. If 1ST Glasses > 40 & Hyperopia	-.0136651	.0242755	0.574	-.0614633	.0341331

Regression correcting for age, sex, grader and nuclear cataract. (Table R5)

Brunescence

Brunescence is strongly associated with White Scatter. After adjusting for White Scatter, the only relationship that remains marginally significant is that of myopia if distance glasses were worn for the first time after the age of 40 ($p = 0.05$)

White scatter.

The expected relationship between nuclear lens opacity and myopia for people who first wore distance glasses after 40 was confirmed ($p = 0.006$). The relationship between spherical equivalent and White Scatter remains highly significant ($p < 0.0001$) for myopes who started wearing glasses aged younger than 40 years. There is now also an association with spherical equivalent and hypermetropia in those aged over 40 years.

Retro-dots

Retro-dots have a significant negative association with spherical equivalent ($p = 0.031$). This remains after correcting for White Scatter and is evident graphically in Figure R5; it can be seen that some mild hypermetropes have Retro-dots, but no high hypermetropes. The prevalence and severity of Retro-dots then increases with increasing myopia. However, when the association of the category myopia, with Retro-dots was analysed, no association with myopia was found.

Table R5 Estimated Co-efficients Nuclear Cataract features against Myopia and Spherical Equivalent-Correcting for age, sex, and grader and nuclear cataract.

Brunescence RE	**Coef.**	**Std. Err.**	**P>|t|**	**(95% Conf. Interval)**	
Myopia	.062872	.0429151	0.143	-.0213677	.1471117
Myopia:1ST Glasses < 40	-.0533365	.0670298	0.427	-.1855502	.0788772
Myopia 1ST Glasses > 40	**.1308609**	**.0667224**	**0.050**	**-.0001761**	**.2618979**
Spherical Equiv.	-.000662	.0059719	0.912	-.0123847	.0110607
Spherical Equiv. If 1ST Glasses < 40	-.0022268	.0081812	0.786	-.0183649	.0139114
Spherical Equiv. If 1ST Glasses < 40 &Myopia	-.0253399	.0228883	0.273	-.0711728	.0204931
Spherical Equiv. If 1ST Glasses < 40 & Hyperopia	-.0273006	.0265885	0.308	-.0802562	.0256549
Spherical Equiv. If 1ST Glasses > 40	.0101661	.0095406	0.287	-.0085714	.0289037
Spherical Equiv. If 1ST Glasses > 40 & Myopia	.0323638	.0393786	0.418	-.0482996	.1130273
Spherical Equiv. If 1ST Glasses > 40 & Hyperopia	.02469	.0214013	0.250	-.0174526	.0668326

White Scatter RE	**Coef.**	**Std. Err.**	**P>|t|**	**(95% Conf. Interval)**	
Myopia	.0338185	.0448685	0.451	-.0542555	.1218925
Myopia:1ST Glasses < 40	-.068595	.0724857	0.345	-.2115702	.0743803
Myopia 1ST Glasses > 40	**.1923334**	**.0690812**	**0.006**	**.056664**	**.3280028**
Spherical Equiv.	-.0040372	.0062546	0.519	-.0163149	.0082405
Spherical Equiv. If 1ST Glasses < 40	-.0013668	.0089717	0.879	-.0190644	.0163308
Spherical Equiv. If 1ST Glasses < 40 &Myopia	**-.0871056**	**.0220395**	**0.000**	**-.131239**	**-.0429722**
Spherical Equiv. If 1ST Glasses < 40 & Hyperopia	.0359222	.0253989	0.161	-.0146641	.0865085
Spherical Equiv. If 1ST Glasses > 40	-.0047795	.0099643	0.632	-.0243492	.0147902
Spherical Equiv. If 1ST Glasses > 40 & Myopia	.0015354	.0614633	0.980	-.1243664	.1274372
Spherical Equiv. If 1ST Glasses > 40 & Hyperopia	**.0498311**	**.0227704**	**0.030**	**.0049925**	**.0946698**

Retro-dots RE	**Coef.**	**Std. Err.**	**P>|t|**	**(95% Conf. Interval)**	
Myopia	.0375865	.051958	0.470	-.0644042	.1395773
Myopia:1ST Glasses < 40	-.0342887	.0903151	0.705	-.2124438	.1438663
Myopia 1ST Glasses > 40	.1306627	.0780148	0.094	-.0225516	.283877
Spherical Equiv.	-.0157586	.0072943	0.031	-.0300774	-.0014399
Spherical Equiv. If 1ST Glasses < 40	-.0069874	.0113116	0.538	-.0293014	.0153266
Spherical Equiv. If 1ST Glasses < 40 &Myopia	-.001313	.0301476	0.965	-.061706	.05908
Spherical Equiv. If 1ST Glasses < 40 & Hyperopia	-.0336255	.0285339	0.242	-.0904557	.0232046
Spherical Equiv. If 1ST Glasses > 40	**-.0296426**	**.0111422**	**0.008**	**-.0515258**	**-.0077594**
Spherical Equiv. If 1ST Glasses > 40 & Myopia	-.0410566	.052667	0.442	-.1489399	.0668268
Spherical Equiv. If 1ST Glasses > 40 & Hyperopia	-.021654	.0241009	0.370	-.0691127	.0258046

Final Model

Brunescence

In the final model, the association of Brunescence with Myopia in those receiving glasses over the age of 40 falls away.

White Scatter

The negative association of spherical equivalent and White Scatter in myopes who started wearing glasses aged younger than 40 years remains ($p = 0.002$). Similarly, the expected relationship between nuclear lens opacity and myopia for people who first wore distance glasses after 40 was confirmed ($p = 0.001$).

Retro-dots

There is a negative association between Retro-dots and spherical equivalent if the age of first glasses use is greater than 40.

Table R6 Final Model White Scatter Right Eye: Estimated Co-efficients of all risk and protective factors with Spherical Equivalent if age of first glasses less than 40 and current myopia.

White Scatter Right Eye	Coef.	Std. Err.	P>|t|	(95% Conf. Interval)	
Age at examination	.0139339	.0175402	0.433	-.0218879	.0497558
Sex	.0123928	.1877067	0.948	-.3709553	.395741
Grader	.2519498	.1435103	0.089	-.0411373	.5450368
Current and past smoking (light)	.1512457	.1528145	0.330	-.1608431	.4633345
Current and past smoking (heavy)	.065877	.3523421	0.853	-.6537016	.7854557
Less than 4 drinks per day –current	-.0788563	.1689495	0.644	-.4238972	.2661845
More than 4 drinks per day –current	.0311343	.324892	0.924	-.6323836	.6946522
Diabetic	(dropped)				
Beta Carotene	-.0704936	.3161782	0.825	-.7162156	.5752285
Vitamin A	-.2808961	.4013817	0.489	-1.100627	.5388348
Triglycerides	.0518392	.0550497	0.354	-.0605874	.1642658
Systolic BP	-.0058641	.0045346	0.206	-.0151251	.0033969
Diastolic BP	.0096474	.0082379	0.251	-.0071766	.0264715
Self report Hypertension	-.1343733	.1609037	0.410	-.4629825	.194236
Brunescence Right Eye	.3742727	.1799936	0.046	.0066767	.7418687
Spherical Equivalent RE	**-.0903622**	**.0271582**	**0.002**	**-.1458267**	**-.0348978**
_cons	-.3088399	1.003723	0.760	-2.358717	1.741037

Table R7 Final Model: White Scatter Right Eye: Estimated Co-efficients of all risk and protective factors with Myopia if age of first glasses greater than 40.

White Scatter Right Eye	Coef.	Std. Err.	P>|t|	(95% Conf. Interval)	
Age at examination	.0200617	.0038706	0.000	.0124512	.0276723
Sex	-.0238766	.0418506	0.569	-.1061658	.0584126
Grader	.2399544	.0396133	0.000	.1620643	.3178445
Current and past smoking (light)	.0348528	.0427989	0.416	-.0493009	.1190065
Current and past smoking (heavy)	.021942	.0672927	0.745	-.110373	.1542569
Less than 4 drinks per day –current	-.0091437	.041568	0.826	-.0908772	.0725899
More than 4 drinks per day –current	.0144012	.0796652	0.857	-.1422412	.1710436
Diabetic	-.1532182	.0872088	0.080	-.3246934	.0182569
Beta Carotene	.087691	.0843505	0.299	-.078164	.2535459
Vitamin A	-.0436925	.1014152	0.667	-.2431011	.1557161
Triglycerides	-.010602	.0162001	0.513	-.0424556	.0212516
Systolic BP	.0025801	.0013224	0.052	-.0000201	.0051802
Diastolic BP	.0006997	.0023006	0.761	-.0038238	.0052232
Self report Hypertension	-.0738773	.0426613	0.084	-.1577606	.010006
Brunescence Right Eye	.399616	.0521593	0.000	.2970572	.5021748
Myopia	**.2547155**	**.0787832**	**0.001**	**.0998072**	**.4096237**
_cons	-.8489421	.2667423	0.002	-1.373427	-.3244576

Table R8 Final Model: Retro-dots Right Eye: Estimated Co-efficients of all risk and protective factors with Spherical Equivalent if age of first glasses greater than 40.

Retro-dots Right Eye	Coef.	Std. Err.	P>|t|	(95% Conf. Interval)	
Age at examination	.0226362	.004707	0.000	.0133807	.0318918
Sex	-.0038315	.0515578	0.941	-.1052118	.0975489
Grader	-.017133	.0507592	0.736	-.116943	.0826771
Current and past smoking (light)	.0016446	.0523845	0.975	-.1013613	.1046505
Current and past smoking (heavy)	-.0014221	.0829554	0.986	-.1645409	.1616967
Less than 4 drinks per day –current	.0062262	.0515	0.904	-.0950405	.1074929
More than 4 drinks per day –current	.0181044	.0973808	0.853	-.1733798	.2095885
Diabetic	.4184703	.1040108	0.000	.2139492	.6229914
Beta Carotene	.0722401	.1024953	0.481	-.1293009	.2737811
Vitamin A	-.0115986	.1249817	0.926	-.2573556	.2341584
Triglycerides	.0173958	.0200604	0.386	-.0220498	.0568415
Systolic BP	-.0010009	.0016351	0.541	-.0042161	.0022142
Diastolic BP	-.0007046	.0028285	0.803	-.0062664	.0048573
Self report Hypertension	.0615569	.0522252	0.239	-.0411358	.1642496
Brunescence Right Eye	.1469569	.0578769	0.012	.0331511	.2607627
Spherical Equivalent RE	**-.0303188**	**.0147995**	**0.041**	**-.0594198**	**-.0012178**
_cons	-1.398762	.3277427	0.000	-2.043217	-.7543076

Figure R2. Oxford White Scatter and spherical equivalent.

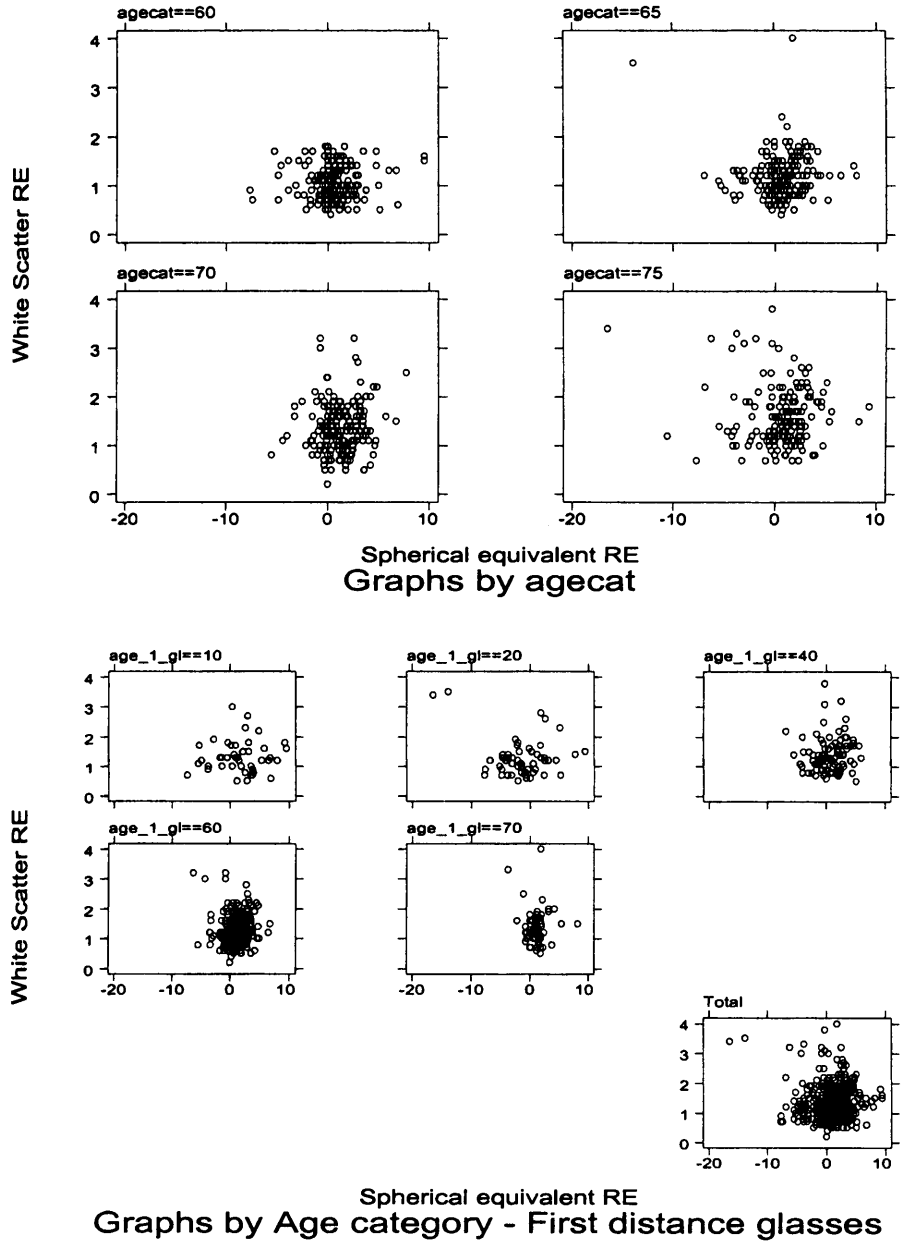


Figure R3. Oxford Brunescence and myopia

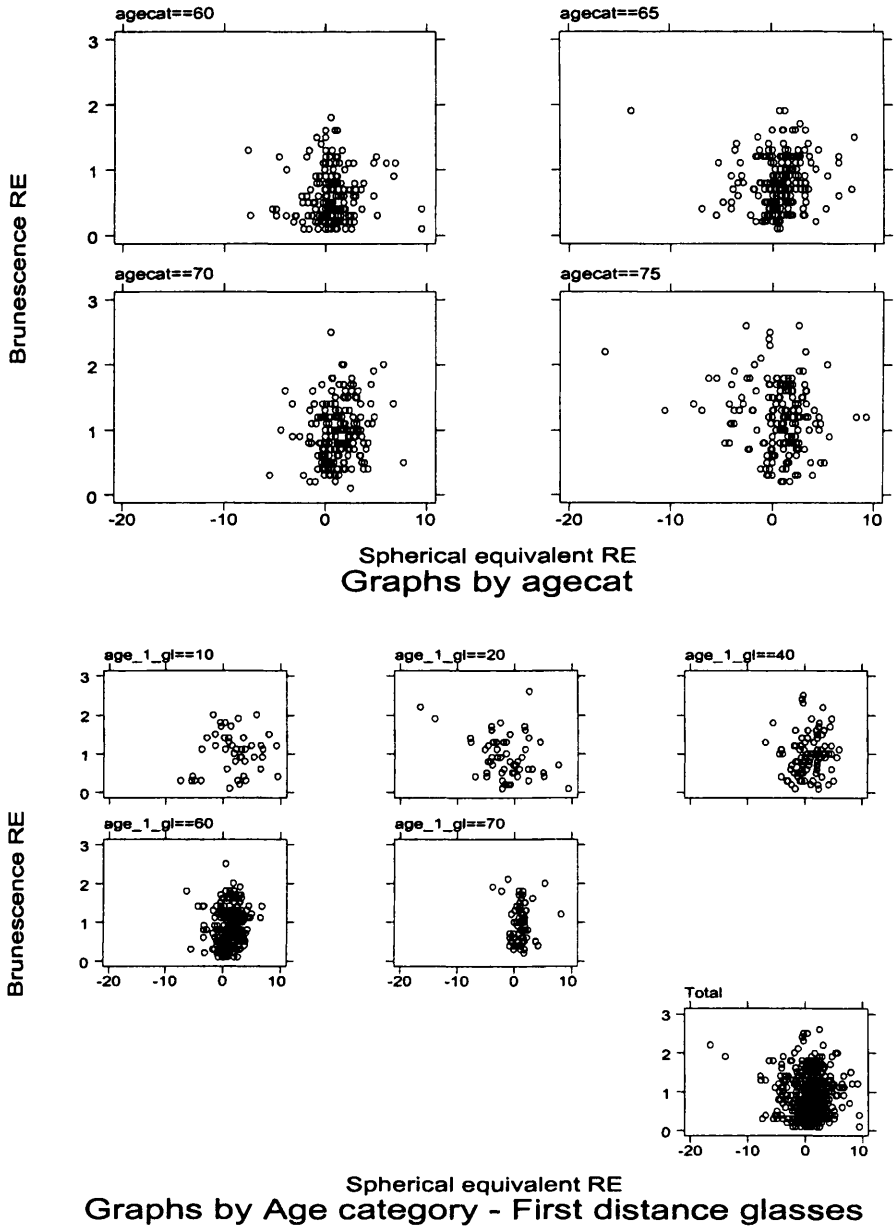
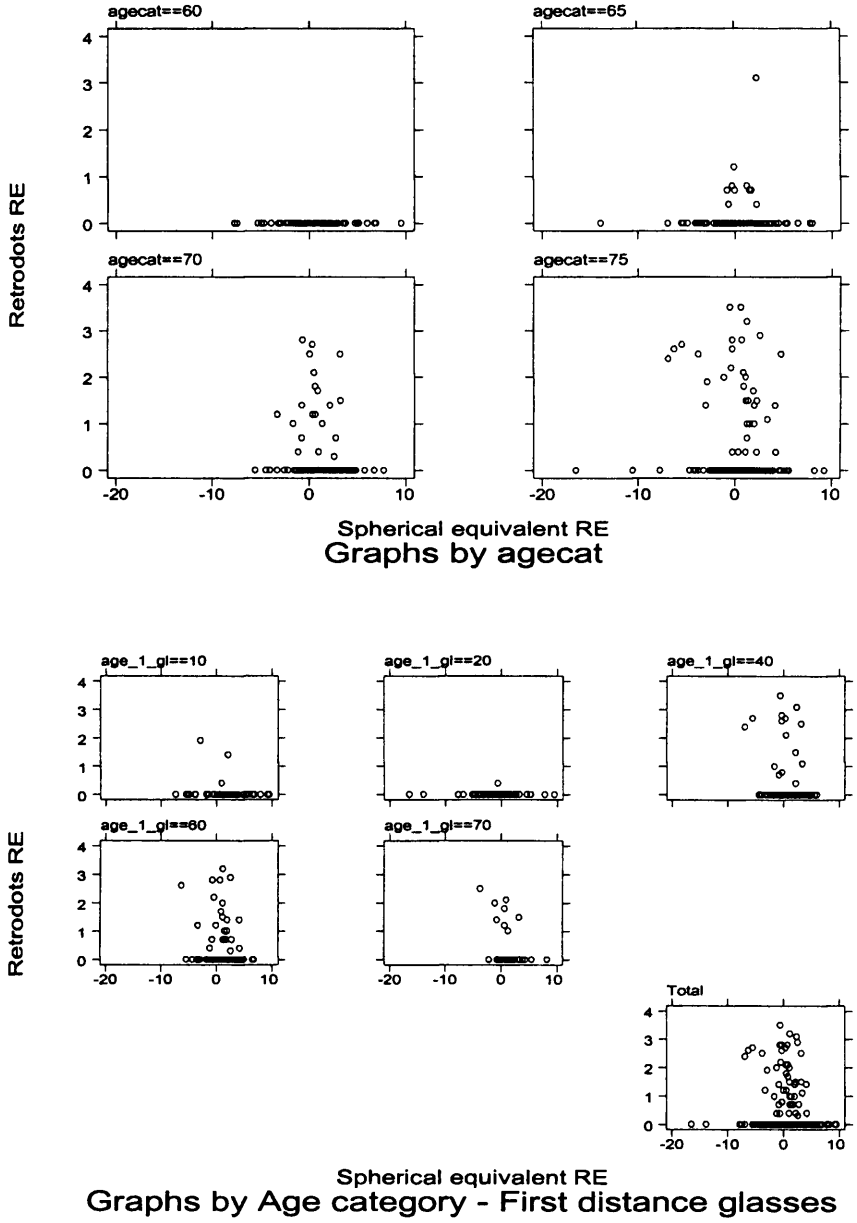


Figure R4. Retro-dots and spherical equivalent.



7.5 Discussion

This is the first population-based study to suggest that there may be an association with early onset myopia and the development of nuclear cataract..

Prevalence of refractive errors

When publishing prevalence rates of refractive error many studies have defined myopia and hypermetropia as a spherical equivalent of less than and greater than –0.5 and +0.5 dioptre (D) respectively (Wang, Klein et al. 1994; Wu, Nemesure et al. 1999). The Melton Eye Study has used the same definition for myopia as the Blue Mountains Eye Study (Lim, Mitchell et al. 1999) i.e. myopia less than –1.0 D and hyperopia more than +1.0 D.

Association of cataract with myopia

The association between current myopia and presence of nuclear cataract was expected. Lens power is increased by the increasing refractive index of the nuclear sclerosis. Unlike the Blue Mountains Eye Study, which found that this was only true for myopes who had started wearing distance glasses after the age of 40, the Melton Eye Study found a highly significant association between spherical equivalent and White Scatter in those myopes who started wearing glasses before the age of 40. This suggests that early myopia may indeed have a role in the development of nuclear sclerosis as proposed by Weale (Weale 1980) and Harding (Harding, Harding et al. 1989).

It is interesting to note that it is only the White Scatter and not Brunescence that is significantly associated with early myopia. This study is the first population-based study to use both Oxford (Sparrow, Bron et al. 1986) and LOCS III (Chylack, Wolfe et al. 1993) grading. These grading systems have the advantage of being able to grade both opalescence (White Scatter) and colour (brunescence) on similar scales. Unlike the Wilmer (West, Rosenthal et al. 1988) and Wisconsin (Klein, Klein et al. 1990) systems which have a single standard for colour. The grading of colour and White Scatter separately allows the different effects of each characteristic on the lens to be assessed.

One of the limitations of the cross-sectional study was the difficulty in clearly exploring the temporal relationship between early myopia and nuclear cataract. The use of historical and examination data used in the Melton Eye Study should correct many of the problems encountered by previous studies in exploring temporality. Harding and van Heyningen (Harding, Harding et al. 1989) asked specifically if their subjects were shortsighted as children, if they wore spectacles as children and why the spectacles were needed. In the Melton population based sample, 57% of subjects did not know if their

current distance glasses were for long or short sight. Of the 60 subjects who reported that their glasses were for short sight, nine were hypermetropes.

The Lens Opacities Case Control Study used a history of use of eyeglasses by the age of 20 as a proxy for myopia (Leske, Chylack et al. 1991). The graphs in Figure R1 depicting the spherical error at the age of first glasses and Table R2 show that in the Melton population many subjects were hypermetropic under the age of twenty. 58.7 % and 23.7% of subjects who received their distance glasses by the ages of 10 and 20 years respectively were still significantly (over +1.0 D) hypermetropic at the time of the Melton Eye Study examination. They were therefore likely to have been hypermetropic when they obtained their first glasses. The mean spherical equivalent for subjects who obtained their glasses under the age of 10 was +1.7 D. That is, young children are more likely to be getting a hypermetropic correction than a myopic one. Subjects who obtained their first glasses between the ages of 10 and 20 were more likely to have a myopic correction (mean spherical equivalent –1.4 D). Figure R1 summarises the data on age at which distance glasses were first worn for hypermetropes and myopes. Taking the use of distance glasses by 20 years of age (Leske, Chylack et al. 1991) or history of short sight as a child (Harding, Harding et al. 1989) as a proxy for myopia is therefore likely to lead to considerable confounding by those children who were hypermetropic.

To avoid this pitfall the Melton Eye Study did not rely on self-reporting of short sight, but relied instead on the current refraction, a history of glasses use before the age of 20, and the exclusion of current hypermetropes. There are no records of the individual spherical errors in childhood. It is possible that a proportion of current myopes may have been hypermetropic as children and recently become myopic because of lens-induced myopic shift. However, it is unlikely that there is any confounding in the opposite direction, i.e. that a current hypermetrope had significant (< –1.0 D) myopia as a child. While there is a slow hypermetropic shift in the normal non-cataractous population (Brown and Hill 1987; Wang, Klein et al. 1994), it is not of the order of over 2 dioptres.

While Brown's study (Brown and Hill 1987) had the advantage of being prospective, and had records from four years previously, it did not have records or enquire into childhood or early onset myopia. In addition it came from a highly select group of patients reporting to a Harley Street practice.

Most of the other studies including the Blue Mountains Eye Study (Lim, Mitchell et al. 1999), the Barbados Eye Study (Wu, Nemesure et al. 1999) and the Visual Impairment Project (McCarty, Mukesh et al. 1999) have dichotomised nuclear cataract into present or absent. This wastes a lot of information and particularly in studies that have gone to the

trouble of decimalising the grades, it is a waste of effort and time! A strength of our study is the use of decimalised information and analysis of the nuclear opacity as a continuous variable.

7.6 Conclusion

This study shows that the onset of myopia before the age of 20 years may be an independent risk factor for nuclear cataract.

7.7 Public health implications

Weale has suggested that overcorrecting young myopes will maintain their lenses in an accommodated state, reducing zonular stress and therefore mechanical stress that may predispose to cataract (Weale 1980). Although young myopes could be overcorrected, this runs contrary to the recommendation of those who believe eliminating accommodation can control myopia. Controlling zonular stress may have more impact in preventing nuclear cataract in countries with a higher prevalence of myopia, such as those in South-East Asia (Wensor, McCarty et al. 1999). In the light of recent meta-analysis suggesting that atropine and bifocals do not halt the progression of myopia it would seem that attempts to manipulate the onset of cataract or prevention of myopia should await further research

8. Cigarette Smoking Alcohol Consumption and Nuclear Cataract

8.1 Purpose

The aim of this chapter is to explore the relationship between cigarette smoking and nuclear cataract and alcohol consumption and nuclear cataract in the Melton population

8.2 Introduction

Smoking tobacco is recognised as a leading cause of death and disability (Solberg, Rosner et al. 1998). The association between cigarette smoking and the increased risk of developing age-related cataract has been reported in case-control studies (Clayton, Cuthbert et al. 1982; Harding and van Heyningen 1989; Leske, Chylack et al. 1991), cross-sectional (Klein, Klein et al. 1985; Flaye, Sullivan et al. 1989; West, Munoz et al. 1989) and prospective (Christen, Manson et al. 1992; Hankinson, Willett et al. 1992; West, Munoz et al. 1995; Hiller, Sperduto et al. 1997) epidemiological studies. The most consistent association was for nuclear lens opacities (Hiller, Sperduto et al. 1997). An association between alcohol consumption and cataract has been found in several studies: These include case-control studies (Clayton, Cuthbert et al. 1982; Harding and van Heyningen 1989; Munoz, Tajchman et al. 1993; Phillips, Clayton et al. 1996), cross sectional (Ritter, Klein et al. 1993; Cumming and Mitchell 1997) and prospective (Manson, Christen et al. 1994; Klein, Klein et al. 1999) population based studies.

8.3 Methods

Cigarette smoking in the Melton Eye Study

Full details of the study procedure are provided in the Methods chapter. In brief, subjects were asked if they had smoked more than 100 cigarettes in their life. If they had, they were asked if they still smoked, and how old they were when they started smoking. If they no longer smoked they were asked how old they were when they stopped. They were asked how many cigarettes they do/did smoke. In order to calculate a lifetime level of cigarettes consumed, subjects were asked if there had ever been a time when they smoked more heavily than they do now. If this was answered positively then the amount and duration of past heavier smoking were established.

Alcohol consumption in the Melton Eye Study

Subjects were asked on how many days of the week they drank alcohol. If the answer was one or above they were asked how much they drank on such days. In order to establish a lifetime dose subjects were asked how long they had drunk this amount for. In

order to calculate this dose more accurately, and also to include past heavy drinkers in the analysis, they were asked if there had ever been a time when they drank more heavily than they do now. If this was answered positively then the amount and duration of past heavier drinking were established. For both current and past heavier drinking the amount of weekend drinking was recorded if it differed from average daily intake during the week.

Statistical analysis

Smokers were divided into current smokers, ex-smokers and non-smokers. Any smoking heavier than the current level of smoking was also documented. The daily level of cigarette smoking was categorised by number of cigarettes smoked per day. The categories were none, 20 or less per day (light), and more than 20 per day (heavy). The categorisation was applied to both current and ex-smokers and again to those who admitted to smoking more heavily in the past. In order to assess the possibility of a dose-dependent effect of cigarette smoking on lens opacities, an estimate of "total number of cigarettes smoked" was made by multiplying the number of years of smoking by the number of cigarette packs (20 cigarettes) per day – thus providing a cumulative smoking dose.

Data on alcohol consumption was examined by categorising subjects into non drinkers, light and heavy drinkers. Heavy drinkers were defined as consuming 28 or more units per week, an average of four drinks per day. It was not possible to estimate a lifetime dose of alcohol consumption as data inspection had revealed a few errors in recording the period of drinking resulting in a number of outliers with a period of excessive drinking.

Data from cataract grading were examined as a continuous variable. Regression analysis was used to examine the association of cataract with the smoking and alcohol consumption data. The statistical method of building the model for analysis is described in the methods section. In brief the categories of cigarette smoking and alcohol consumption were first examined in a univariate analysis. The categories were then analysed one by one in a regression correcting for age, sex and the grader. Age was analysed as a continuous variable, while sex and grader were analysed as indicator variables. Finally cigarette smoking and alcohol consumption were included in the final model of all risk factors that had been found to have an association after analysis correcting for age, sex and grader.

8.4 Results

Characteristics of smokers

Table SA1 summarises the characteristics of smokers and non-smokers in the Melton Eye Study.

Table SA1. Smoking Status by age and sex.

	Current smoker		Non smoker		Ex smoker		Total	
Age Range	Male	Female	Male	Female	Male	Female	Males	Females
55 to 59	28	23	31	53	53	27	112	103
60 to 64	24	23	23	67	54	35	101	125
65 to 69	19	23	13	61	51	31	83	115
70 plus	8	10	21	51	66	31	95	92
Total	79	79	88	232	224	124	391	435

In our study, 506 (61.26%) subjects admitted to having smoked at some time. There were 158 current smokers (19.3%) of which 79 were male and 79 female. There were 320 subjects who had never smoked. 53.3% (232) of females had never smoked, whereas only 88 (22.5%) of men had never smoked. There were 348 ex-smokers. For men, the number of current smokers decreased with increasing age. In women, the number of current smokers was constant until the age of 70 and above.

Mean pack years smoked

Tables SA2 summarises the mean pack years. The mean pack years smoked is higher for men than women. Full details on previous smoking history are available on 496 smokers.

Table SA2. Mean pack years by sex (smokers only).

	Obs	Mean	Std.Dev.	Min	Max	[95% Conf. Interval
Female	201	26.00	20.94	.15	122.5	22.82 – 28.66
Male	295	37.83	36.19	.1	213.4	33.08 – 41.31

Categories of smokers

Subjects were categorised into light (20 or less cigarettes per day) or heavy (more than 20 cigarettes per day). These categories are summarised in table SA3 according to current smoking status. The table also gives details of a history of smoking more heavily in the past: This may apply to both current and ex-smokers. The history of heavier smoking may be for both light and heavy categories. A light smoker may give a history of smoking more heavily in the past but have smoked less than 20 /day even in this heavier period. An ex-smoker may have been smoking 10 per day when he stopped, but smoked 30/ day for 10 years prior to reducing to 10/day. 68 current smokers had smoked more heavily in the

past. 77 Ex- smokers had also had a period of heavier smoking during their smoking lives. (See Table SA3)

Table SA3. Categories of smokers: Light (20 or less cigarettes per day) or heavy (more than 20 cigarettes per day).

Ever Smoked N=496			
Total Light Smokers	(Current and past smoking (light)	403	
Total Heavy Smokers	(Current and past smoking (heavy)	93	
Current Smoker N=155		Ex Smoker (Past Smoking) N=341	
Light Smoker N=133	Heavy Smoker N=22	Light Smoker N=270	Heavy Smoker N=71
History of heavier smoking-light	37	History of heavier smoking-light	34
History of heavier smoking-heavy	31	History of heavier smoking-heavy	43

Characteristics of drinkers

Table SA4 summarises the numbers of drinkers in each category. 513 (62.18%) subjects reported current drinking while 312 (37.82%) were current non-drinkers. Of these, 210 or 25.45% of the total population were lifetime teetotallers. Teetotallers were more likely to be women. There were more ex-drinkers and more current drinkers amongst men than women.

Table SA4. Alcohol consumption in the Melton Eye Study.

	Current drinkers			**Non-drinkers**		
	Current- (past heavier)	Current	Total	Ex-drinkers	Lifetime Teetotallers	Total
Male	160	129	289	58	44	102
Female	65	159	224	44	166	210
Total	225	288	513 (62.18%)	102	210 (25.45%)	312 (37.82%)

In order to analyse the association of alcohol on lens opacities, drinkers were categorised into light (less than 28 units per week) and heavy (28 or more units per week).

Of the 224 women who currently drank alcohol only 7 (3.1%) admitted to drinking more than 28 units per week. If the women were categorised separately from the men using the lower limit of 21 units per week recommended for women, then 17 (7.5%) of women were classified as heavy drinkers.

A total of 289 men were current drinkers, of these 65 (22.5%) admitted to drinking 28 or more units per week. 21 women and 133 men were past heavy drinkers. Table SA5 summarises the mean units per week for current drinkers and for those who admitted past heavier drinking.

Table SA5. Mean and standard deviations for current and past heavier drinkers.

Variable	Obs	Mean	Std.Dev.	Min	Max
Current Units per week	513	12.87	14.45	.2	98
Past heavier Units per week	317	38.78	38.02	1	196

204 (24.71%) subjects reported drinking an average of four or more drinks per day currently. This was not always on every day, some subjects would, for example, drink more on weekends. The number of drinks per week for each subject were therefore calculated and divided by 7 to get the average daily consumption of units. Amongst current drinkers, 72 (8.7%) reported an average of four or more drinks per day. 154 (18.86%) subjects admitted to drinking more heavily in the past and to drinking an average of four or more drinks per day at that time.

Table SA6 summarises the numbers of heavy drinkers. The totals in each row do not add up to 100% as the categories are not mutually exclusive. For example, current moderate drinking males may also have been past heavy drinkers. The percentages refer to the total number of subjects of that sex. Over 50% of women are current non-drinkers and the totals on their row reflect this by adding up to less than 100%.

Table SA6. Number of subjects reporting current and past heavy drinking.

	Current moderate	Current heavy	Past moderate	Past heavy
Male	227 (57.3%)	65(16.6%)	81 (20.9%)	133 (34.3%)
Female	217 (50.0%)	7 (1.6%)	82 (19.16%)	21 (4.9%)
Total	444	72	163	154

Regression analysis: Brunescence, White Scatter and Retro-dots and smoking and alcohol consumption.

Univariate analysis

The results of the univariate analysis for Brunescence, White Scatter and Retro-dots are presented in Table SA7.

At the univariate level both White Scatter and Brunescence were associated with any history of light smoking (Current and past smoking (light)) or with a period of heavier smoking (light) in the past, albeit fewer than 20 cigarettes per day. See table SA3 for

explanation of smoking categories. Only Brunescence was associated with any history of drinking alcohol (Less than 4 drinks per day –past).

Regression correcting for age, sex and grader

Table SA8 reports the analysis correcting for age, sex, and grader. The details of the categories and number of subjects in each category in the analysis for smoking are summarised in Table SA3. Similarly the details for the categories used in the analysis of alcohol consumption are summarised in Table SA6.

In this analysis both Brunescence and White Scatter continue to be associated with any history of light smoking (Current and past smoking (light)). White Scatter continues to be associated with any history of smoking and with a period of heavier smoking in the past (Past heavier smoking (light)). Additionally, Brunescence is now associated with a history of heavy smoking - more than 20 cigarettes per day (Current and past smoking (heavy)) and with current heavy alcohol consumption (More than 4 drinks per day).

Table SA7. Estimated coefficients: Oxford Brunescence, White Scatter and Retro-dots against Smoking and Alcohol consumption categories:- Univariate Analysis

Brunescence	Coef.	Std. Err.	P>|t|	(95% Conf. Interval)	
Current and past smoking (light)	**.1316539**	**.0356196**	**0.000**	**.061734**	**.2015739**
Current and past smoking (heavy)	.0587356	.0570455	0.303	-.0532427	.170714
Past heavier smoking (light)	**.1397984**	**.059629**	**0.019**	**.0227484**	**.2568484**
Past heavier smoking (heavy)	.0441462	.0584948	0.451	-.0706774	.1589699
Less than 4 drinks per day -current	-.0113961	.0357796	0.750	-.0816299	.0588376
More than 4 drinks per day -current	.0118265	.0630492	0.851	-.1119361	.135589
Less than 4 drinks per day -past	**.0939469**	**.0427099**	**0.028**	**.0101079**	**.1777859**
More than 4 drinks per day -past	-.0506392	.0438872	0.249	-.1367892	.0355107
Up to 3 years Higher Education	-.1458743	.0417865	0.001	-.2279017	-.063847
More than 3 years Higher Education	-.0465395	.0738337	0.529	-.1914758	.0983968
Manual Class	.0960294	.0340803	0.005	.0291287	.1629302

White Scatter	Coef.	Std. Err.	P>|t|	(95% Conf. Interval)	
Current and past smoking (light)	**.0796878**	**.036539**	**0.029**	**.0079628**	**.1514128**
Current and past smoking (heavy)	-.0238369	.0584515	0.684	-.1385756	.0909018
Past heavier smoking (light)	.2252293	.060943	0.000	.1055995	.3448591
Past heavier smoking (heavy)	.0067652	.0593905	0.909	-.109817	.1233475
Less than 4 drinks per day -current	-.0146708	.036412	0.687	-.0861461	.0568044
More than 4 drinks per day -current	-.121299	.0645081	0.060	-.2479258	.0053277
Less than 4 drinks per day -past	.0630833	.0435954	0.148	-.0224941	.1486608
More than 4 drinks per day -past	-.0479422	.0449128	0.286	-.1361058	.0402213
Up to 3 years Higher Education	-.1395134	.0427409	0.001	-.2234144	-.0556123
More than 3 years Higher Education	-.1068083	.0755001	0.158	-.2550163	.0413998
Manual Class	.0874433	.034953	0.013	.0188291	.1560574

Retro-dots	Coef.	Std. Err.	P>|t|	(95% Conf. Interval)	
Current and past smoking (light)	.0238108	.0388288	0.540	-.0524091	.1000308
Current and past smoking (heavy)	-.0765155	.0620812	0.218	-.1983794	.0453484
Past heavier smoking (light)	.0617494	.0648579	0.341	-.0655656	.1890644
Past heavier smoking (heavy)	.0198714	.0636248	0.755	-.1050231	.1447658
Less than 4 drinks per day -current	-.0057794	.0386656	0.881	-.0816786	.0701199
More than 4 drinks per day -current	-.0451822	.068037	0.507	-.1787363	.088372
Less than 4 drinks per day -past	-.0010611	.0470946	0.982	-.0935075	.0913854
More than 4 drinks per day -past	.000768	.0485178	0.987	-.0944722	.0960081
Up to 3 years Higher Education	-.1001364	.0443131	0.024	-.1871241	-.0131488
More than 3 years Higher Education	-.0187063	.0782671	0.811	-.1723463	.1349337
Manual Class	.0242507	.0356963	0.497	-.0458227	.094324

Table SA8. Estimated coefficients: Oxford Brunescence, White Scatter and Retro-dots against smoking and Alcohol consumption categories:- correcting for Age, Sex and Grader

Brunescence	Coef.	Std. Err.	P>|t|	(95% Conf. Interval)	
Current and past smoking (light)	**.1146451**	**.0318466**	**0.000**	**.052131**	**.1771591**
Current and past smoking (heavy)	**.1041837**	**.0511511**	**0.042**	**.0037754**	**.204592**
Past heavier smoking (light)	.0859887	.0515858	0.096	-.0152734	.1872508
Past heavier smoking (heavy)	.0308153	.0511306	0.547	-.0695532	.1311839
Less than 4 drinks per day -current	.0081768	.0310896	0.793	-.0528509	.0692045
More than 4 drinks per day -current	**.1274004**	**.0571839**	**0.026**	**.0151504**	**.2396503**
Less than 4 drinks per day -past	.0634407	.0368751	0.086	-.008945	.1358265
More than 4 drinks per day -past	-.0251024	.0408375	0.539	-.1052664	.0550617
Up to 3 years Higher Education	-.0664199	.0365316	0.069	-.1381322	.0052924
More than 3 years Higher Education	.0279403	.0651938	0.668	-.1000365	.1559171
Manual Class	.054777	.0294578	0.063	-.0030501	.112604

White Scatter	Coef.	Std. Err.	P>|t|	(95% Conf. Interval)	
Current and past smoking (light)	**.0656158**	**.032369**	**0.043**	**.0020759**	**.1291556**
Current and past smoking (heavy)	.0361653	.05196	0.487	-.0658313	.138162
Past heavier smoking (light)	**.1611306**	**.0521649**	**0.002**	**.0587313**	**.2635298**
Past heavier smoking (heavy)	.0018796	.0513489	0.971	-.0989178	.1026769
Less than 4 drinks per day -current	.0100058	.0314881	0.751	-.0518045	.0718161
More than 4 drinks per day -current	.0198464	.058203	0.733	-.0944045	.1340973
Less than 4 drinks per day -past	.0365493	.0373413	0.328	-.036752	.1098506
More than 4 drinks per day -past	-.0021319	.0414456	0.959	-.0834898	.079226
Up to 3 years Higher Education	-.0519901	.0369919	0.160	-.1246064	.0206261
More than 3 years Higher Education	-.0058871	.0659999	0.929	-.1354468	.1236727
Manual Class	.0417613	.0297198	0.160	-.0165803	.1001029

Retro-dots	Coef.	Std. Err.	P>|t|	(95% Conf. Interval)	
Current and past smoking (light)	.0074862	.0391543	0.848	-.0693733	.0843456
Current and past smoking (heavy)	-.0704216	.0628286	0.263	-.1937533	.0529102
Past heavier smoking (light)	.0367906	.0629904	0.559	-.0868592	.1604403
Past heavier smoking (heavy)	.0144267	.0624414	0.817	-.1081455	.1369988
Less than 4 drinks per day -current	.0001645	.0380474	0.997	-.0745217	.0748506
More than 4 drinks per day -current	-.0047815	.0699105	0.945	-.1420141	.132451
Less than 4 drinks per day -past	-.0153547	.0460407	0.739	-.105733	.0750235
More than 4 drinks per day -past	.0129334	.0510892	0.800	-.0873551	.1132219
Up to 3 years Higher Education	-.0604966	.043342	0.163	-.1455785	.0245853
More than 3 years Higher Education	.0144918	.0773205	0.851	-.137291	.1662747
Manual Class	.008783	.0348756	0.801	-.0596797	.0772457

Regression correcting for age, sex and grader and all other associated risk and protective factors

Table SA9 gives details of the final model, which includes all the other risk and protective factors found to be significant in the univariate and age, sex and grader corrected models. In the final model all the risk and protective factors are put in the same regression model.

Table SA9a gives the regression co-efficients for Hormone Replacement Therapy in the final model. This regression included all the risk factors but examined women only. Only the HRT co-efficients are presented. The co-efficients for the different risk factors are different when men are excluded from the analysis. The full table for women can be found in the chapter on the insulin resistance syndrome.

Table SA9. Estimated coefficients: Final Model. Oxford Brunescence, White Scatter and Retro-dots against smoking and alcohol consumption categories:- corrected for Age, Sex, Grader , antioxidants, Diabetes, Hypertension and Hormone Replacement Therapy (SA9 b)

Brunescence	Coef.	Std. Err.	P>|t|	(95% Conf. Interval).	
Age at examination	**.0374937**	**.0030674**	**0.000**	**.0314673**	**.04352**
Sex	-.0589257	.0361774	0.104	-.1300014	.0121501
Grader	**.1921348**	**.0331226**	**0.000**	**.1270607**	**.2572088**
Current and past smoking (light)	**.1025201**	**.0367343**	**0.005**	**.0303503**	**.1746899**
Current and past smoking (heavy)	**.1258272**	**.0594945**	**0.035**	**.0089415**	**.2427128**
Less than 4 drinks per day -current	.0299993	.0357834	0.402	-.0403025	.100301
More than 4 drinks per day -current	**.2150109**	**.0682769**	**0.002**	**.0808711**	**.3491507**
Diabetic	**.3275524**	**.0777633**	**0.000**	**.1747752**	**.4803297**
Beta Carotene	**-.1856457**	**.0730749**	**0.011**	**-.3292119**	**-.0420795**
Vitamin A	**-.1784243**	**.0892278**	**0.046**	**-.3537252**	**-.0031233**
Triglycerides	.0101951	.0145967	0.485	-.0184822	.0388724
Systolic BP	-.000044	.001139	0.969	-.0022818	.0021938
Diastolic BP	-.0012798	.0019709	0.516	-.0051519	.0025923
Self report Hypertension	.0206477	.037132	0.578	-.0523034	.0935988
Insulin Resistance Score	**.0890622**	**.0436724**	**0.042**	**.0032598**	**.1748646**
_cons	-1.444631	.2293258	0.000	-1.895174	-.9940868

White Scatter	Coef.	Std. Err.	P>|t|	(95% Conf. Interval).	
Age at examination	**.0346939**	**.00332**	**0.000**	**.0281708**	**.0412169**
Sex	-.0593777	.0399084	0.137	-.1377888	.0190334
Grader	**.3493892**	**.0358353**	**0.000**	**.2789809**	**.4197975**
Current and past smoking (light)	**.0786133**	**.0397318**	**0.048**	**.0005491**	**.1566775**
Current and past smoking (heavy)	.0442769	.0643843	0.492	-.0822239	.1707777
Less than 4 drinks per day -current	.0204355	.0389035	0.600	-.0560013	.0968722
More than 4 drinks per day -current	.0535038	.0746293	0.474	-.0931261	.2001337
Diabetic	.0837372	.0864878	0.333	-.0861921	.2536664
Beta Carotene	-.0186443	.0796438	0.815	-.1751267	.1378381
Vitamin A	-.0687978	.0979595	0.483	-.2612664	.1236709
Triglycerides	-.0038685	.0166594	0.816	-.0366005	.0288636
Systolic BP	.0016558	.001245	0.184	-.0007903	.0041019
Diastolic BP	.0008395	.0021328	0.694	-.0033509	.0050299
Self report Hypertension	**-.082054**	**.0402984**	**0.042**	**-.1612313**	**-0028767**
Insulin Resistance Score	.02588	.0468857	0.581	-.066236	.117996
_cons	-1.329735	.2538679	0.000	-1.828529	-.8309406

Retro-dots	Coef.	Std. Err.	P>|t|	(95% Conf. Interval).	
Age at examination	**.0216729**	**.0040126**	**0.000**	**.0137892**	**.0295567**
Sex	.0523935	.0482407	0.278	-.0423883	.1471752
Grader	.0223812	.0432921	0.605	-.0626776	.1074401
Current and past smoking (light)	-.0334847	.0480285	0.486	-.1278494	.0608801
Current and past smoking (heavy)	-.0576359	.0778294	0.459	-.2105527	.0952808
Less than 4 drinks per day –current	.0303993	.0470304	0.518	-.0620046	.1228032
More than 4 drinks per day –current	.0747513	.089425	0.404	-.1009481	.2504507
Diabetic	**.2826932**	**.1045548**	**0.007**	**.0772673**	**.4881191**
Beta Carotene	.0240477	.0962787	0.803	-.1651175	.2132129
Vitamin A	-.0443137	.1180007	0.707	-.2761576	.1875303
Triglycerides	.0379291	.0201171	0.060	-.0015964	.0774546
Systolic BP	.0002776	.0014965	0.853	-.0026627	.0032178
Diastolic BP	-.0007757	.0025694	0.763	-.0058239	.0042725
Self report Hypertension	**.1005165**	**.0486805**	**0.039**	**.0048706**	**.1961623**
Insulin Resistance Score	.0727662	.0577712	0.208	-.0407357	.1862682
_cons	-1.403197	.3068591	0.000	-2.006104	-.80029

Table (SA9 b) Estimated co-efficients for Hormone replacement therapy- (women only)

	Coef.	Std. Err.	P>|t|	(95% Conf. Interval)	
Brunescence	-.0389206	.0579199	0.502	-.1530051	.0751639
White Scatter	-.0150062	.0706253	0.832	-.1541165	.1241041
Retro-dots	.0164986	.0751208	0.826	-.1314663	1644635

In the final model Brunescence has an association with both cigarette smoking and alcohol consumption. There is a positive association with any history of both light smoking ($p = 0.005$) and heavy smoking ($p = 0.035$) The association with alcohol is positive for current heavy drinking ($p = 0.002$) White Scatter is weakly associated with a history of light smoking ($p = 0.048$).

The above significant association between Brunescence and light smoking is for current and ex smokers combined. When the analysis was repeated separately for current and ex-smokers it remained significant only for ex smokers.

When the amount of smoking was examined as a continuous, rather than categorical, variable in terms of pack years, no association was found between nuclear cataract features and pack years, whether analysed for current smokers, past smokers or by light and heavy categories.

A correction for sex was made in each analysis. However, in view of the difference between men and women in smoking and drinking habits, the significant associations were reanalysed for men and women separately. Current heavy drinking had a significant association with Brunescence in men only ($p = 0.008$) (women $p = 0.297$). However, the association of a history of light smoking continued to be positive in women ($p = 0.004$). The association with smoking was significant for men only (Heavy smoking $p = 0.01$)

The association of lens opacity with alcohol in women was examined using the lower limit of 21 units per week recommended for women. 17 (7.5%) women were classified as heavy drinkers using this definition. Analysis using this lower limit showed no significant association of heavy drinking and lens opacity in women.

The association of alcohol consumption with lens opacity was examined in non-smokers. 668 of the Melton subjects were current non-smokers. There was a significant association of current heavy drinking with Brunescence ($p = 0.003$) amongst current non-smokers.

8.5 Discussion

Our results confirm the previously noted association between nuclear cataract and cigarette smoking and alcohol consumption.

If current and ex-smokers were analysed separately the relationship remained significant only for ex smokers. This probably reflects the fact that the number of current smokers is too small (n=155) to provide adequate power for the analysis. There is a trend towards a positive association (p =0.081)

Although the number of current smokers is equal amongst both men and women, it is interesting to note that fewer women ever smoked. 232 women never smoked compared with only 88 men who never smoked. This difference is reflected in the higher number of ex-smokers amongst men than women. (224 vs124 respectively) This lower number of women smokers may explain the difference in the results between men and women in terms of the association between nuclear cataract and smoking; the lack of association in women may reflect the reduced power of the lower numbers, alternatively there may be a real difference in the way men and women's lenses are affected by smoking.

There was a significant association of smoking with nuclear cataract for both White Scatter and Brunescence in the univariate analyses. However the relationship remained significant only for Brunescence in the final model.

The association of smoking with nuclear lens opacity tended to be stronger in light smokers (20 or fewer cigarettes per day) than in heavy smokers. (p=0.003 vs. p=0.022 for Brunescence for light and heavy smokers respectively and p< 0.000 and p= 0.048 for White Scatter) This is probably reflects the fact that the number of current heavy smokers (22) or ex-heavy smokers (71) was relatively low compared with current light (134) or ex-light smokers (270). The mean pack years reported by our subjects are very similar to those reported by the Beaver Dam Eye Study (Klein, Klein et al. 1993). The fact that a dose-response relationship from the data on pack years of cigarettes smoked was not demonstrated, could be due to a number of factors: the numbers of smokers studied is relatively small, and our study may not have had the statistical power required to detect an association. Alternatively, the retrospective nature of the study means that recall of the number of cigarettes smoked and the duration of smoking may, for some individuals, have been inaccurate, leading to bias.

Previous studies have tended to find an association of cataract with smoking amongst heavier smokers (Harding and van Heyningen 1989; Christen, Manson et al. 1992; Hankinson, Willett et al. 1992). The fact that the association was also found amongst

light smokers lends strength to the evidence that there is a dose-response in the way tobacco products harm the lens. The Melton Eye Study has some important limitations. The first limitation has been alluded to above – that is the limited sample size for examining the effect of heavy smoking. Another limitation includes the cross-sectional nature of this phase of the Melton Eye Study, which makes it difficult to assess the temporal relationship between exposure to tobacco smoke and development of cataract. If the planned prospective study is completed, information on smoking history will be more accurate and the temporal effect will be explored more easily.

The mechanisms by which smoking may cause cataract are discussed at length in the Literature Review. In summary, cyanide, thiocyanate and aldehydes may reach the lens to attack enzymes and lens proteins by causing aggregation and unfolding of lens proteins (Harding 1995). Cadmium appears to affect enzymes such as super oxide dismutase in the lens and may interact directly with the lens proteins leading to protein denaturation and ultimately cataract (Cekic 1998). There is also a direct oxidative challenge to the lens and a depletion of endogenous anti-oxidant pools (Solberg, Rosner et al. 1998). Low plasma levels of antioxidant vitamins C and E and Beta carotene in the blood of smokers were postulated to cause an oxidative stress to the lens, leading to increase risk of cataract (Hankinson, Willett et al. 1992).

Our population-based study found an association between current heavy alcohol consumption and nuclear opalescence. Although an adjustment was made for smokers in the initial analysis, there have been suggestions that there is an interaction between smoking and alcohol (Cumming and Mitchell 1997) which may be synergistic in cataract development or else that correcting for smoking may not correct for all the confounding that may occur. The effect of alcohol consumption in non-smokers was therefore analysed. The analysis included both current non-smokers and people who had never smoked. It was interesting to find that the association between heavy alcohol consumption and cataract was strongest amongst current non-smokers. This is in direct contrast to the Blue Mountains Eye Study which found an association between alcohol and nuclear cataract only in smokers. They postulated that this was either due to residual confounding from the effect of smoking, or else represented a real synergistic effect between alcohol and smoking (Cumming and Mitchell 1997). The fact that the Melton Eye Study found an association only in current non-smokers may be due to the small number of current smokers in our study. However, the fact that the association is found independently of smoking in both ex-smokers and those who had never smoked, lends strength to the possibility that the relationship between alcohol and increasing severity of nuclear cataract

is a causal one. An alternative explanation is that in spite of correcting for past smoking in the analysis, poor recall on the part of ex-smokers may have confounded the results. Heavier smoking in the past than a subject reported may have increased the amount of nuclear lens opacity.

The data on current amount of alcohol consumed daily is likely to be more accurate than data relying on recollection of past drinking habits. Whilst subjects are likely to have difficulty recalling the details of past drinking habits, current consumption should be easier to recall. However, there is the possibility of under-reporting current heavy drinking with people being more likely to report past heavy drinking than current heavy drinking (Ritter, Klein et al. 1993). This would have tended to reduce the observed significance of any real effect of current heavy drinking.

The Beaver Dam Study (Ritter, Klein et al. 1993) found an association between past heavy drinking and lens opacities but not for current drinking, in contrast to our findings of an association with current heavy drinkers and not with past heavy drinking. There are a number of possible reasons for this difference:

Beaver Dam analysed cataract data as ordinal scales whereas our data on lens opacity was analysed as a continuous variable;

The Beaver Dam found 126 (0.25%) current heavy drinkers and 728 (14.8%) past heavy drinkers amongst 4913 participants in the study. They comment that the lack of association could have been due to the low numbers of current heavy drinkers;

A higher number of Melton subjects reported heavy drinking than did Beaver Dam residents. This may reflect a cultural difference in what may be deemed to be a respectable amount to admit to drinking. On the other hand, it may reflect a real difference in current alcohol consumption.

Ritter et al (Ritter, Klein et al. 1993) comment that exposure to alcohol in the past may be more likely to affect cataract development than current drinking patterns. Nuclear changes were analysed as a continuous variable, allowing the use of significant early lens changes in the analysis – changes occurring as a result of current or recent drinking behaviour rather than previous exposure.

Only seven women admitted to drinking 28 or more units per week. Women may be more sensitive to the effects of alcohol by virtue of their smaller size. Lower weekly limits are therefore recommended. Women drinkers were therefore also categorised as light or heavy drinkers using the recommended 21 units per week for women. This analysis resulted in only 17 heavy drinkers. There was no association between heavy drinking and lens opacity using the lower recommended limits for women. This may represent a real

lack of association or be due to the low numbers of heavy drinkers amongst women. The Blue Mountains Eye Study (Cumming and Mitchell 1997) also suggested that there may be more of an association in men, with a strong positive association between cataract surgery and alcohol intake in men age 65 to 74 years.

The association of alcohol consumption with cataract development may be due to confounding with other risk factors. There is the suggestion that heavy drinking patterns are associated with lower socio-economic status (Ames and Janes 1987) – the latter has been established as a risk factor for cataract in many studies (Leske, Wu et al. 1997; Ughade, Zodpey et al. 1998). As for low education the association seems to be independent of various likely explanations such as poor nutrition, excessive exposure to sunlight or different job exposures, but could nevertheless be an explanatory confounder of the apparent effect of alcohol on the lens. Excessive alcohol consumption has also been linked to poor nutritional status; associations of nutritional status were not explored in all studies, (Munoz, Tajchman et al. 1993) so poor nutrition in heavy drinkers may therefore be a confounder.

8.6 Conclusion

The Melton Eye Study provides further epidemiological evidence that there is an increased risk of developing nuclear cataract amongst cigarette smokers. It also confirms an association between nuclear lens opacities and current heavy alcohol consumption. The data suggest that the association with alcohol may be independent of cigarette smoking

8.7 Public health implications

The evidence for a harmful effect of alcohol on the lens is conflicting. Some studies (Ritter, Klein et al. 1993; Cumming and Mitchell 1997) have found a protective effect of alcohol for cortical cataract. Some have reported a U- or J- shaped relationship curve. Moderate alcohol consumption need not, therefore, be discouraged. However, the chance of accelerating nuclear cataract development is yet another reason to avoid heavy alcohol consumption.

In an editorial accompanying the report on cigarette smoking and risk of cataract in men, a study involving over 22,000 male physicians in the US (Christen, Manson et al. 1992), West suggests that approximately 20% of cataract cases in the US could be attributed to smoking (West 1992). However, in a letter to the editor, Harding (Harding 1993) questions this claim on the grounds that the relative risk used to arrive at this figure applied to only a small proportion of smokers and not the full population of smokers that

had been used in the calculation. Harding has estimated that heavy smoking only accounts for 3% of cataract in Western countries (Harding 1995). Our finding of an association with light smoking suggest that the attributable risk may be higher than this.

Solberg (Solberg, Rosner et al. 1998) has pointed out that both cataract development and age-related macular degeneration, the leading causes of severe visual impairment and blindness in industrialized countries, are directly related to or accelerated by smoking. While cataract may have developed a reputation in the West of being easily cured, common vascular ocular disorders, such as anterior ischaemic optic neuropathy and retinal ischaemia, can have more devastating and permanent effects on vision and are also significantly linked to smoking. Efforts should be directed toward augmenting the campaign against tobacco smoking by adding the increased risk of blindness to the better-known arguments against smoking. Programmes directed at smoking cessation, with the aim of reducing deaths from cardiovascular disease and cancer, will have the added benefit of reducing nuclear, and other, cataract.

9. Antioxidants and Nuclear Cataract

9.1 Purpose

The aim of this chapter is to determine whether the data gathered in the Melton Eye Study can help to clarify the association antioxidants may have with nuclear cataract. Serum antioxidant levels are examined in regression analyses with nuclear cataract to determine the association.

9.2 Introduction

The lens consists almost entirely of protein. The proteins may be damaged by oxidative stress on lens enzymes, proteins and membranes. Defence systems include small molecule antioxidants (Vitamin C – ascorbic acid, Vitamin E – alpha-tocopherol and carotenoids) and antioxidant enzyme systems (superoxide dismutase, catalase, and glutathione peroxidase) (Taylor, Jacques et al. 1995; West and Valmadrid 1995).

Epidemiological research has been carried out to determine the role of antioxidants in protecting the lens against damage. The current evidence has been summarised in the Literature Review. In brief, all the major antioxidants, including Vitamin A and various carotenoids, Vitamin C, and Vitamin E have been found to be inversely associated with nuclear cataract in some studies. However, other studies including population-based, longitudinal cohort and interventional studies have not found any association.

These conflicting data suggest that further research is required before recommendations on vitamin supplementation to reduce cataract can be made.

9.3 Methods

Full details of the study procedure are provided in the Methods chapter. The aspects relevant to this chapter are summarised below.

Blood samples

Blood was taken to determine levels of antioxidants including Vitamins A, C, and E and Beta Carotene. Samples were immediately centrifuged in the clinic and the serum frozen at –20 degrees centigrade. At the end of the day the frozen samples were taken to Leicester and stored at –70 degrees centigrade. The frozen samples were processed in batches by High Pressure Liquid Chromatography (HPLC).

Statistical analysis

Antioxidants were analysed in a univariate analysis examining the association of the antioxidant factor with the various subtypes of nuclear cataract. We have made no attempt to adjust the serum anti-oxidant levels for seasonality. The analysis for Vitamin E attempted to correct for Cholesterol levels by including Cholesterol in the regression correcting for age, sex and grader.

Because of the consistent and large effect of age, sex and grader on nuclear cataract each analysis was then corrected for these variables. Age was analysed as a continuous variable and sex and grader were analysed as indicator variables. Those antioxidants that were found to be associated with nuclear cataract at this level were then included in a multivariate model comprising all of the other risk factors, which were found to be associated with nuclear cataract after correcting for age, sex and grader. Although they were not significant in the univariate analysis; years of higher education and social class were included in one model; - there was no change in the results. The model without years of higher education and social class is reported here.

Because men and women respond to the various risk factors in the insulin resistance syndrome in different ways, which may not be completely corrected for in the regression analysis, the final model was repeated by sex.

Regression analysis was used to examine the association of cataract with the serum antioxidant data. Data from cataract grading and serum antioxidant status were examined as continuous variables. Unlike refractive error and contrast sensitivity, which are eye specific, antioxidant status affects both eyes equally. The cataract data presented in this chapter is therefore the average of the grading from both eyes. If for any reason (e.g. pseudophakia) no grading is available for one eye then data from the available eye is used.

9.4 Results

Blood specimens were not available for all 826 examined subjects. 26 subjects refused to have blood taken. Difficulty was experienced taking blood due to obesity or collapsed veins in a further 39. In six other subjects there was not enough blood for all the different analyses. Subjects who did not have blood taken tended to be slightly older than those who did have blood taken and were more likely to be female. Tables AO2 and AO3 summarise the differences in mean nuclear grades, smoking status, sex and age for subjects with and without Vitamin A data.

Data were available on 722 subjects for Vitamin A, ranging down to 679 subjects for Beta Carotene. Table AO1 summarises the number of observations, mean, standard deviations and 95 % confidence intervals for each antioxidant measured.

Table AO1. Summary statistics for serum antioxidant levels.

Variable	Obs	Mean	Std. Dev.	Min	Max	(95% Conf. Interval)	
Vitamin A	722	0.62	0.18	0.10	2.00	0.60	0.63
Vitamin C	719	49.51	29.44	1.79	166.73	47.30	51.62
Vitamin E	721	14.32	5.95	1.00	46.40	13.88	14.75
Beta Carotene	679	0.51	0.22	0.40	1.70	0.49	0.53

Table AO2. Summary statistics for subjects without Vitamin A results.

Variable	Obs	Mean	Std. Dev.	Min	Max
White Scatter	97	1.30	0.53	0.50	3.50
Brunescence	97	0.94	0.55	0.10	3.00
Smoker	104	1.57	0.50	1.00	2.00
Sex	104	1.41	0.49	1.00	2.00
Age at examination	104	66.31	5.92	55.00	75.98

Table AO3. Summary statistics for subjects with Vitamin A results.

Variable	Obs	Mean	Std. Dev.	Min	Max
White Scatter	702	1.26	0.48	0.30	3.45
Brunescence	704	0.84	0.46	0.10	2.50
Smoker	720	1.62	0.49	1.00	2.00
Sex	720	1.48	0.50	1.00	2.00
Age at examination	720	64.52	5.74	55.22	75.97

Coded smoker: 1= No 2 = yes.
Coded Sex: 1 = Female 2 = Male

Regression analysis: Oxford Brunescence, White Scatter and Retro-dots and antioxidant serum levels

Univariate analysis

The results of the univariate analysis for Oxford Brunescence, White Scatter and Retro-dots are presented in Table AO4. At the univariate level only Brunescence and Beta Carotene are associated. (p = 0.013)

Table AO4. Estimated coefficients: Oxford Brunescence, White Scatter, Retro-dots, and antioxidant serum levels:- Univariate Analysis

Brunescence	Coef.	Std.Err.	P>t	(95% Conf. Interval)	
Vitamin C	-.0007703	.0005998	0.200	-.001948	.0004075
Vitamin E	-.0009312	.0029125	0.749	-.0066496	.0047871
Vitamin A	-.1308049	.0988251	0.186	-.324834	.0632242
Beta Carotene	-.1966978	.0786124	0.013	-.3510587	-.0423368

White Scatter	Coef.	Std.Err.	P>t	(95% Conf.Interval)	
Vitamin C	-.0011786	.0006275	0.061	-.0024106	.0000534
Vitamin E	.0033557	.0030086	0.265	-.0025513	.0092627
Vitamin A	-.0385282	.1026608	0.708	-.2400892	.1630327
Beta Carotene	-.0617289	.0834684	0.460	-.2256259	.1021681

Retro dots	Coef.	Std.Err.	P>t	(95% Conf. Interval)	
Vitamin C	-.0000963	.0006697	0.886	-.0014111	.0012186
Vitamin E	-.0003673	.0032854	0.911	-.0068177	.0060831
Vitamin A	-.0422682	.1112449	0.704	-.2606829	.1761464
Beta Carotene	-.0027634	.092542	0.976	-.1844771	.1789503

Regression correcting for age, sex and grader

Table AO5 reports the analysis correcting for age, sex, and grader. An attempt is made to adjust Vitamin E for cholesterol level by including cholesterol in the regression for Vitamin E. After correcting for age, sex and grader, Brunescence is the only nuclear feature to be associated with any antioxidant; it continues to be associated with Beta Carotene and now with Vitamin A as well. There was no association with Vitamin E and nuclear cataract features. This remained true whether the regression included cholesterol or not. Vitamin C was not associated with any of the nuclear features either. Figures AO1(below) and AO2(next page) depict Beta Carotene and Vitamin A plotted against Brunescence.

Figure AO1 Oxford Brunescence against Beta Carotene by gender.

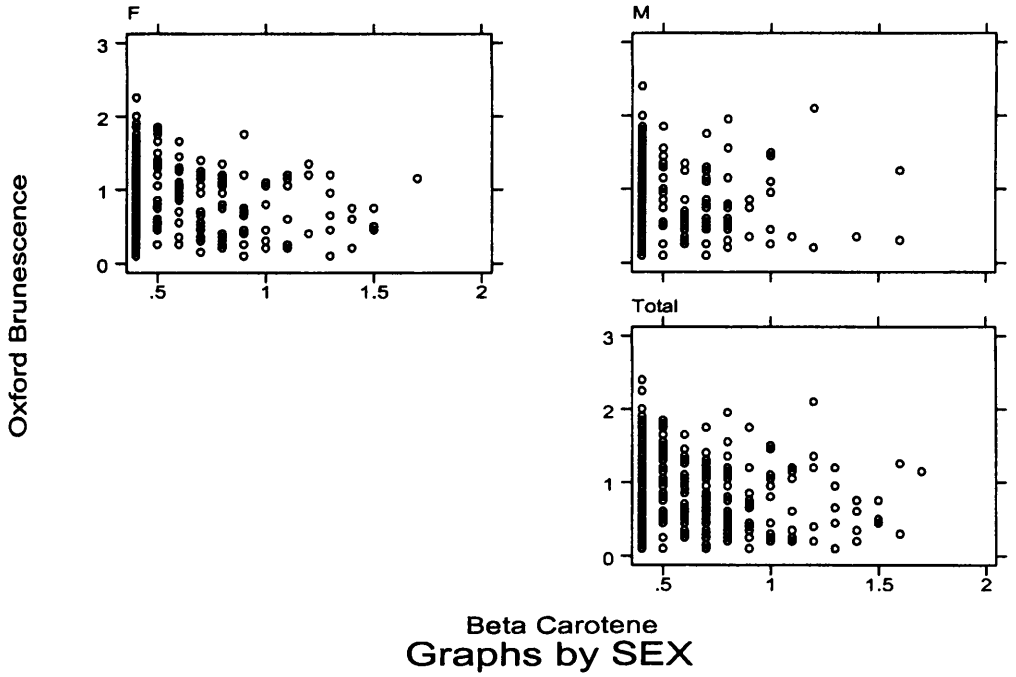


Table AO5 Estimated coefficients: Oxford Brunescence, White Scatter, Retro-dots, and antioxidant serum levels:- correcting for Age, Sex and Grader

Brunescence	Coef.	Std.Err.	P>t	(95% Conf. Interval)	
Vitamin E	-.0006634	.0025295	0.793	-.0056296	.0043029
Vitamin C	-.0002139	.0005332	0.688	-.0012607	.0008329
Vitamin A	-.1737174	.0848154	0.041	-.3402417	-.0071932
Beta Carotene	-.1566712	.0677175	0.021	-.2896405	-.023702

White Scatter	Coef.	Std.Err.	P>t	(95% Conf.Interval)	
Vitamin C	-.0008159	.000542	0.133	-.00188	.0002482
Vitamin E	.0021554	.0025497	0.398	-.0028505	.0071614
Vitamin A	-.0834273	.0861027	0.333	-.2524799	.0856252
Beta Carotene	-.0318641	.0705156	0.652	-.1703284	.1066003

Retro dots	Coef.	Std.Err.	P>t	(95% Conf. Interval)	
Vitamin C	.0003189	.000669	0.634	-.0009947	.0016325
Vitamin E	.0007222	.0031975	0.821	-.0055558	.0070002
Vitamin A	-.0575047	.1074314	0.593	-.2684336	.1534242
Beta Carotene	.0231707	.089689	0.796	-.1529423	.1992838

Regression correcting for age, sex and grader and all other associated risk and protective factors

The final model is summarised in Table AO6, which includes any variable associated with nuclear cataract features in the analysis correcting for age, sex and grader. Table AO6b gives the regression co-efficients for Hormone Replacement Therapy in the final model. This regression included all the risk factors but examined women only. Only the HRT co-efficients are presented. The co-efficients for the different risk factors are different when men are excluded from the analysis. The full table with all the co-efficients for the risk factors in women can be found in the chapter on insulin resistance syndrome.

The only nuclear feature to be associated with antioxidants was Oxford Brunescence. Brunescence was negatively associated with Beta carotene (p = 0.011) Vitamin A (p = 0.046). However when Vitamin A is examined in women only the significant negative association of Vitamin A with Brunescence is strengthened (p = 0.016).

There was no association of White Scatter or perinuclear Retro-dots with any of the serum antioxidants.

Figure AO2 Oxford Brunescence against Vitamin A

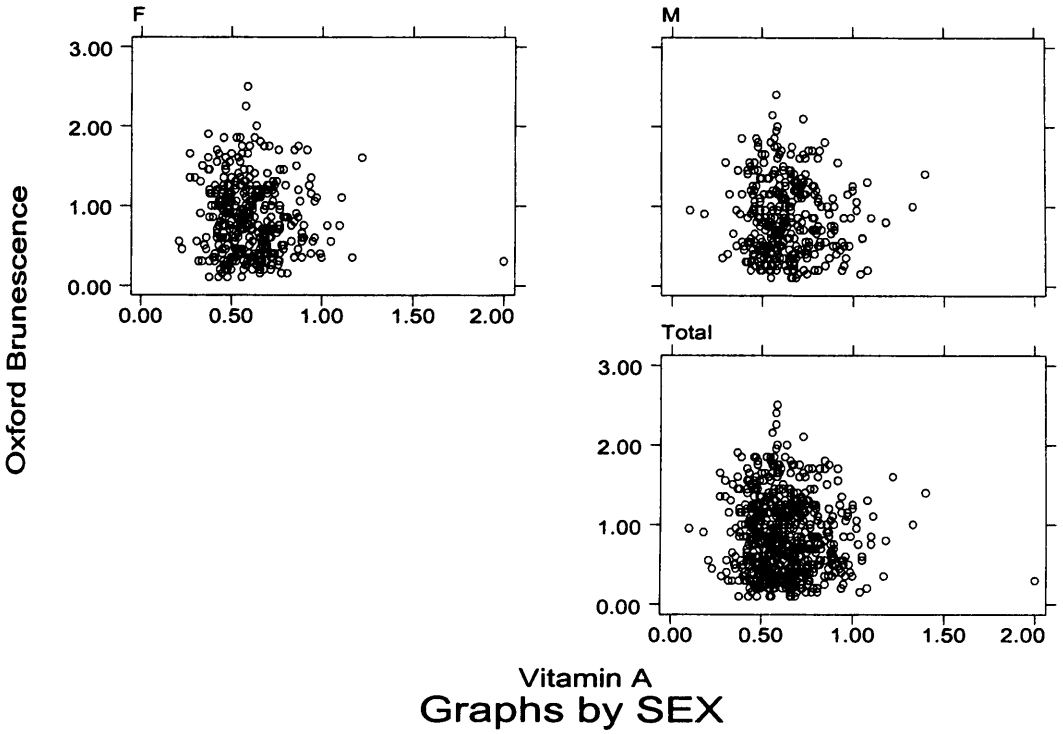


Table AO6 : Final Model. Oxford Brunescence, White Scatter and Retro-dots and antioxidants:- correcting for Age, Sex, Grader , smoking and alcohol consumption categories, Diabetes, Hypertension insulin resistance syndrome and Hormone Replacement Therapy (AO6b)

Brunescence	**Coef.**	**Std. Err.**	**P>|t|**	**(95% Conf. Interval).**	
Age at examination	**.0374937**	**.0030674**	**0.000**	**.0314673**	**.04352**
Sex	-.0589257	.0361774	0.104	-.1300014	.0121501
Grader	**.1921348**	**.0331226**	**0.000**	**.1270607**	**.2572088**
Current and past smoking (light)	**.1025201**	**.0367343**	**0.005**	**.0303503**	**.1746899**
Current and past smoking (heavy)	**.1258272**	**.0594945**	**0.035**	**.0089415**	**.2427128**
Less than 4 drinks per day -current	.0299993	.0357834	0.402	-.0403025	.100301
More than 4 drinks per day -current	**.2150109**	**.0682769**	**0.002**	**.0808711**	**.3491507**
Diabetic	**.3275524**	**.0777633**	**0.000**	**.1747752**	**.4803297**
Beta Carotene	**-.1856457**	**.0730749**	**0.011**	**-.3292119**	**-.0420795**
Vitamin A	**-.1784243**	**.0892278**	**0.046**	**-.3537252**	**-.0031233**
Triglycerides	.0101951	.0145967	0.485	-.0184822	.0388724
Systolic BP	-.000044	.001139	0.969	-.0022818	.0021938
Diastolic BP	-.0012798	.0019709	0.516	-.0051519	.0025923
Self report Hypertension	.0206477	.037132	0.578	-.0523034	.0935988
Insulin Resistance Score	**.0890622**	**.0436724**	**0.042**	**.0032598**	**.1748646**
_cons	-1.444631	.2293258	0.000	-1.895174	-.9940868

White Scatter	**Coef.**	**Std. Err.**	**P>|t|**	**(95% Conf. Interval)**	
Age at examination	**.0346939**	**.00332**	**0.000**	**.0281708**	**.0412169**
Sex	-.0593777	.0399084	0.137	-.1377888	.0190334
Grader	**.3493892**	**.0358353**	**0.000**	**.2789809**	**.4197975**
Current and past smoking (light)	**.0786133**	**.0397318**	**0.048**	**.0005491**	**.1566775**
Current and past smoking (heavy)	.0442769	.0643843	0.492	-.0822239	.1707777
Less than 4 drinks per day -current	.0204355	.0389035	0.600	-.0560013	.0968722
More than 4 drinks per day -current	.0535038	.0746293	0.474	-.0931261	.2001337
Diabetic	.0837372	.0864878	0.333	-.0861921	.2536664
Beta Carotene	-.0186443	.0796438	0.815	-.1751267	.1378381
Vitamin A	-.0687978	.0979595	0.483	-.2612664	.1236709
Triglycerides	-.0038685	.0166594	0.816	-.0366005	.0288636
Systolic BP	.0016558	.001245	0.184	-.0007903	.0041019
Diastolic BP	.0008395	.0021328	0.694	-.0033509	.0050299
Self report Hypertension	**-.082054**	**.0402984**	**0.042**	**-.1612313**	**-0028767**
Insulin Resistance Score	.02588	.0468857	0.581	-.066236	.117996
_cons	-1.329735	.2538679	0.000	-1.828529	-.8309406

Retro dots	**Coef.**	**Std. Err.**	**P>|t|**	**(95% Conf. Interval)**	
Age at examination	**.0216729**	**.0040126**	**0.000**	**.0137892**	**.0295567**
Sex	.0523935	.0482407	0.278	-.0423883	.1471752
Grader	.0223812	.0432921	0.605	-.0626776	.1074401
Current and past smoking (light)	-.0334847	.0480285	0.486	-.1278494	.0608801
Current and past smoking (heavy)	-.0576359	.0778294	0.459	-.2105527	.0952808
Less than 4 drinks per day -current	.0303993	.0470304	0.518	-.0620046	.1228032
More than 4 drinks per day -current	.0747513	.089425	0.404	-.1009481	.2504507
Diabetic	**.2826932**	**.1045548**	**0.007**	**.0772673**	**.4881191**
Beta Carotene	.0240477	.0962787	0.803	-.1651175	.2132129
Vitamin A	-.0443137	.1180007	0.707	-.2761576	.1875303
Triglycerides	.0379291	.0201171	0.060	-.0015964	.0774546
Systolic BP	.0002776	.0014965	0.853	-.0026627	.0032178
Diastolic BP	-.0007757	.0025694	0.763	-.0058239	.0042725
Self report Hypertension	**.1005165**	**.0486805**	**0.039**	**.0048706**	**.1961623**
Insulin Resistance Score	.0727662	.0577712	0.208	-.0407357	.1862682
_cons	-1.403197	.3068591	0.000	-2.006104	-.80029

Table AO6b Estimated co-efficients for Hormone replacement therapy- (women only)

	Coef.	**Std. Err.**	**P>|t|**	**(95% Conf. Interval)**	
Brunescence	-.0389206	.0579199	0.502	-.1530051	.0751639
White Scatter	-.0150062	.0706253	0.832	-.1541165	.1241041
Retro dots	.0164986	.0751208	0.826	-.1314663	1644635

Final model regression by sex .

In order to include HRT in the analysis the final model was analysed for women alone. The inverse relationship of Beta Carotene and Vitamin A with brunescent cataract remained statistically significant for women ($p = 0.002$), and ($p = 0.015$) respectively (see Table IRS 6). In view of the strengthened relationship in women, the analysis of the final model was repeated in men only. The relationship between Vitamin A, Beta Carotene and Brunescence disappeared among men; ($p = 0.710$) and ($p = 0.962$) respectively.

9.5 Discussion

The Melton Eye Study has found an inverse association between Beta carotene and brunescent nuclear cataract. In addition the Study has found an inverse relationship between Brunescence and Vitamin A in women.

Vitamin A and various carotenoids have been found to be inversely associated with nuclear cataract in some studies (Leske, Chylack et al. 1991; Mares-Perlman, Brady et al. 1995). Diets high in Vitamin A have also been associated with a reduced prevalence of nuclear cataract (Cumming, Mitchell et al. 2000). However, other studies including population-based, (Mares-Perlman, Brady et al. 1995; Lyle, Mares-Perlman et al. 1999) longitudinal cohort, (Chasan-Taber, Willett et al. 1999; Chasan-Taber, Willett et al. 1999) and interventional studies (Teikari, Virtamo et al. 1997) have not found any association. Virtually all of these studies have dichotomised nutrient data into either tertiles or quintiles; in addition many have also dichotomised nuclear cataract. A strength of this study is to examine the data on cataract and anti-oxidant status as continuous variables.

The Pathologies Oculaires Liees a l'Age (POLA) study recently found that high levels of plasma Vitamin A were associated with decreased risk of nuclear and mixed cataract (Delcourt, Cristol et al. 2000). Two previous studies assessed the association of plasma retinol with nuclear cataract (Knekt, Heliovaara et al. 1992; Vitale, West et al. 1993). Knekt et al had only 47 patients and used cataract surgery as the end point (Knekt, Heliovaara et al. 1992). Vitale and West found a non-significant negative association with plasma Vitamin A (Vitale, West et al. 1993).

A limitation of this cross-sectional stage of the study is the fact that dietary data has not yet been analysed to determine current intake of micronutrients. In addition, there has not been analysis of consumption of supplements. However, as Lyle et al point out, serum concentrations of carotenoids provide a measure that is independent of errors in dietary assessment (Lyle, Mares-Perlman et al. 1999). Furthermore, people utilise and absorb carotenoids differently (Carughi and Hooper 1994). Serum levels compensate for this

source of error. A further weakness of any cross-sectional study is the fact that data on cataract and diet are collected simultaneously.

The dietary data will be more useful in the longitudinal phase of the study, by providing accurate data on the nutritional status of individuals before cataract developed.

The difference in association between nuclear cataract and Beta Carotene and Vitamin A for men and women is interesting and could be due to a number of factors. Inspection of the graphs for Beta Carotene by sex (Fig. AO1) shows a few outliers in the graph for males, which could account for the difference. An alternative explanation is a failure to adjust for confounding variables that differ in their impact on men and women. The impact of seasonality in serum antioxidant levels has not been adjusted for; men and women may react differently to seasonal variations or be prone to fluctuations in antioxidant levels in different ways. There may be dietary differences; if men had greater homogeneity in their diets, differences between high and low levels become harder to detect (West and Valmadrid 1995). Smoking may be another confounder; although we have attempted to adjust for smoking, it is possible that the relationship between smoking and anti-oxidants is more complex than the model allows for. The alternative is that the difference is real; women are more prone to cataract and may benefit more from protective antioxidants.

No association of Vitamin E (alpha-tocopherol) with nuclear cataract was found. An inverse association has been found in a number of studies, (Leske, Chylack et al. 1991; Knekt, Heliovaara et al. 1992; Leske, Wu et al. 1995; Leske, Chylack et al. 1998) including the prospective phase of the Beaver Dam Eye Study (Lyle, Mares-Perlman et al. 1999). Of note is the fact that in the cross-sectional phase the authors found a positive association of high serum levels with increasing nuclear cataract (Mares-Perlman, Brady et al. 1995). This was attributed to temporal confounding, i.e. when older, less healthy people improve their diets to the point that their nutritional status at the time of the examination does not reflect their earlier nutritional status which may have contributed to current lens opacities. The lack of an association in our study may reflect similar temporal confounding. Alternatively, there may be a real lack of association.

9.6 Conclusion

Our study adds to the growing body of evidence that anti-oxidants may protect the lens against cataract. In this study, higher serum levels of Beta carotene and Vitamin A are inversely associated with brunescent nuclear cataract particularly in women

9.7 Public health implications

While the Melton Eye Study data and the data from various studies are supportive of a protective effect of antioxidants, it is too early to make firm recommendations that nutritional supplements should be used to prevent cataract (West and Valmadrid 1995; Leske, Chylack et al. 1998). Indeed a measure of caution is called for: Leske points out that while some observational studies suggested a protective effect of Beta carotene on lung cancer (Leske, Chylack et al. 1998) later clinical trials found that there was an opposite harmful effect (1994). Similarly Vitamin C may increase the risk of cataract by having a pro-oxidant effect in the presence of raised glucose (Podmore, Griffiths et al. 1998). These conflicting data suggest that further research is required before recommendations on vitamin supplementation to reduce cataract can be made.

10. The Insulin Resistance Syndrome, Diabetes, Oestrogens and Nuclear Cataract

10.1 Purpose

The aim of this chapter is to explore the association between the risk factors of the insulin resistance syndrome, diabetes, hormone replacement and nuclear cataract.
In addition, the chapter aims to

- Review the features of the insulin resistance syndrome.
- Develop a score for the insulin resistance syndrome.
- Describe the characteristics of the population with respect to diabetes, hypertension, use of hormone replacement, and body mass index.

10.2 Introduction

The Insulin Resistance Syndrome

The insulin resistance syndrome comprises a constellation of factors many of which have been individually implicated in the aetiology of cataract. These include obesity, central body fat distribution, glucose intolerance, elevated plasma insulin levels, increased triglycerides and decreased high-density lipoprotein cholesterol, cardiovascular disease and hypertension, nephropathy, neuropathy and retinopathy (Austin, Mykkanen et al. 1995; Hansen 1995).

Diabetes

The association of diabetes with cataract has been reported in both hospital-based and population-based studies. A detailed review of these studies is provided in the Literature Review. The majority of these studies have found an association between cortical or posterior subcapsular cataract, (Leske, Chylack et al. 1991; Klein, Klein et al. 1995), but not nuclear cataract (Leske, Chylack et al. 1998; Delcourt, Cristol et al. 2000). However, one population-based study has found that increased glycated haemoglobin levels were associated with increased risk of nuclear and cortical cataracts in those with diabetes (Klein, Klein et al. 1998).

The weight of epidemiological evidence in conjunction with laboratory evidence suggests that the relationship between diabetes and cataract is causal (Harding, Egerton et al. 1993). It has been suggested that 11% of cataract in Oxfordshire could be attributed to diabetes. The two most likely pathways are the osmotic effect of sorbitol, and the non-enzymatic glycation of lens proteins (Harding, Egerton et al. 1993).

Oestrogen

The Beaver Dam Eye Study found a protective effect in the current use of hormone replacement therapy (HRT) against more severe nuclear cataract (Klein, Klein et al. 1994). Oestrogen use was found to reduce the lens transmittance in another study (Benitez del Castillo, del Rio et al. 1997). The Blue Mountains Eye Study found no protective effect amongst all women, but amongst those aged 65 years and over there was a lower prevalence of cortical cataract amongst those using HRT (Cumming and Mitchell 1997).

10.3 Methods

Weight and height were measured to enable the calculation of body mass index. Waist and hip circumference were measured. Subjects were asked, "Have you ever been told by a doctor that you have diabetes?"

Oestrogen

Women were asked, "Are you taking Hormone Replacement Therapy?" If they were not currently taking it, they were asked if they had ever taken it in the past. They were asked for how many years they had taken HRT.

Blood samples

Blood samples were immediately centrifuged in the clinic and the serum frozen at –20 degrees centigrade. At the end of the day, the frozen samples were taken to Leicester and stored at –70 degrees centigrade. The frozen samples were processed in batches by the Leicestershire laboratory service.

In determining glucose levels subjects were not asked to fast before coming to the research clinic. The glucose levels therefore represent random glucose levels. Glycated haemoglobin levels were not performed. Blood was taken to determine serum levels of selected cardiovascular disease risk factors including cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Blood was also taken for Creatinine levels. The HDL Ratio was calculated from HDL cholesterol and LDL cholesterol.

Blood pressure

Blood pressure was measured on the left arm with the subject seated. It was measured prior to dilation since the phenylephrine drops used for dilatation may lead to an elevation in blood pressure.

Statistical analysis

Regression analysis in a univariate model was used to examine the association of nuclear cataract with the insulin resistance syndrome risk factors individually. An insulin resistance score was then created as described in the methods section. In summary the key elements of the syndrome were divided into 4 evenly distributed quartiles. The quartile with the lowest risk of being part of the insulin resistance syndrome scored 1 and the highest 4. The components included in the score were: glucose, body mass index, cholesterol, high-density lipoprotein cholesterol, and triglycerides The insulin resistance score was then analysed in the univariate regression analyses. Other risk factors that were analysed included diabetes and hormone replacement therapy. Other risk factors known to affect cataract were also analysed in the univariate model; these included social class, years of higher education, past and present smoking status, alcohol consumption. In addition, serum antioxidant levels were examined.

Data from cataract grading and anthropometric status and cardiac risk factors were examined as continuous variables. Body mass index was calculated from the weight in kilograms and height in metres (body mass index = weight in kilograms divided by the square of the height in metres). Body mass index was also examined by category. There was no association with nuclear cataract when analysed by bmi category and only the data on analysis as a continuous variable are presented here. Hypertension was assessed by examining systolic and diastolic blood pressure. A self-report of hypertension was included in the analysis in an attempt to adjust for the effect of possible treatment for hypertension. Diabetes, hormone replacement therapy, social class, years of higher education, smoking and alcohol consumption were categorised and analysed as indicator variables. Hormone replacement therapy is only give to women. Inclusion of HRT in the model was done separately for women only.

Unlike refractive error or contrast sensitivity, which are eye specific, these risk factors affect both eyes. The cataract gradings data presented in this chapter are therefore the average of the grading from both eyes. If for any reason (e.g. pseudophakia) no grading is available then data from the available eye were used.

Myopia is eye specific and so although it is a risk factor for nuclear cataract it is not included in this final model that uses the average of data from both eyes. (The chapter on myopia has a final model which examines all the risk factors against the nuclear cataract feature by age).

The risk and protective factors were then analysed one by one in a regression correcting for age, sex and the grader. Age was analysed as a continuous variable, while

sex and grader were analysed as indicator variables. A final model was built of all risk and protective factors that had been found to have an association with nuclear cataract features after analysis correcting for age, sex and grader. Each nuclear feature was analysed in turn in a regression including all the above associated factors.

Possible confounders to this analysis include previous intra-ocular surgery, and a history of blunt trauma. Three subjects gave a history of retinal detachment surgery in the right eye and two in the left eye. (Table M4). One of these had had cataract surgery in both eyes. Of the remaining four, two had higher nuclear scores in the operated eye, while the other two had only small differences. Three subjects gave a history of glaucoma surgery; there were no differences in the nuclear scores between their two eyes. A further three gave a history of possible blunt injury to the right eye while another three had a history in the left. In none of these histories was it clear that the eye was injured: Examples include- broken cheekbone, fell off bicycle, finger in the eye. None of these subjects with these possible confounders was excluded from the analysis.

10.4 Results

Characteristics of subjects

Diabetes

49 subjects (5.96%) admitted to having diabetes. Of these 20 were female and 29 were male. Seven diabetics were aged less than 60, 11 were between the ages of 60 and 64, 18 were aged 65 to 69 and 13 were 70 and older.

Seven subjects who had not been told by a doctor that they had diabetes had random blood sugars over 11.1 mmol/l. The seven subjects had a mean blood sugar of 16.99 (Std Dev 5.7) with a range of 11.2 to 24.

Oestrogen

Table IRS 1 summarises the number of women who had ever taken Hormone Replacement Therapy (HRT). Over 80% of the population had never taken HRT.

Table IRS 1 Hormone Replacement Therapy

Hormone Replacement Therapy	Frequency	Percent	Cumulative
No	351	81.82	81.82
Yes	78	18.18	100
Total	429	100	

Hypertension

262 of the subjects (32%) admitted to having hypertension. Table IRS 1b summarises the mean systolic and diastolic blood pressures on those subject who had the measurement taken. The medications subjects used to control their hypertension were not analysed.

Table IRS 1b Blood Pressure

Variable	Obs	Mean	Std. Err.	Min	Max	(95% Conf. Interval).	
Systolic Blood Pressure	814	144.06	0.74	91	230	142.6	145.50
Diastolic Blood Pressure	815	86.11	0.42	50	134	85.30	86.93

Body Mass Index

Data on body mass index was available for 810 subjects. Table IRS 2 indicates the distribution of body mass index categories, the mean Standard Deviation, minimum and maximum scores with 95% confidence intervals.

Table IRS 2 Body mass Index

Body Mass Index Category	Freq.	Percent	Cum.
BMI =21 or less	69	8.52	8.52
BMI = 24 or less	181	22.34	30.86
BMI = 27 or less	260	32.10	62.96
BMI > 27	300	37.04	100.00
Total	810	100.00	

Variable	Obs	Mean	Std. Dev.	Min	Max	(95% Conf. Interval).	
Body Mass Index	810	27.26	5.12	14.06	84.10	26.91	27.62

Regression analysis: Oxford Brunescence, White Scatter and Retro-dots: risk factors of the insulin resistance syndrome.

Univariate analysis

The results of the univariate analysis for Oxford Brunescence, White Scatter and Retro-dots are presented in Table IRS 3. It should be noted that the analysis for HRT was only performed on women (429 subjects). The analysis of the other risk factors was performed on all the subjects.

At the univariate level both Brunescence and Retro-dots are associated with diabetes ($p < 0.0001$). None of the cataract features is associated with serum glucose levels. Both Brunescence and White Scatter are negatively associated with a history of hormone replacement therapy ($p = 0.001$ and $p = 0.004$). All three nuclear features are associated with Systolic Blood Pressure, ($p = 0.015$, $p<0.0001$ and $p = 0.032$ respectively), while Retro-dots are also associated with a self-reported history of hypertension ($p = 0.011$). In serum measurements, Brunescence is associated with creatinine ($p = 0.039$) and Retro-dots with triglycerides ($p = 0.004$) (Figure IRS 1). Body mass index was not

associated with any of the nuclear features at any level of analysis. The insulin resistance syndrome score is associated with all three nuclear cataract features at this level ($p = 0.005$, 0.002 and <0001 for Brunescence, White Scatter and Retro-dots respectively.)

Figure IRS 1. Oxford perinuclear Retro-dots and triglycerides.

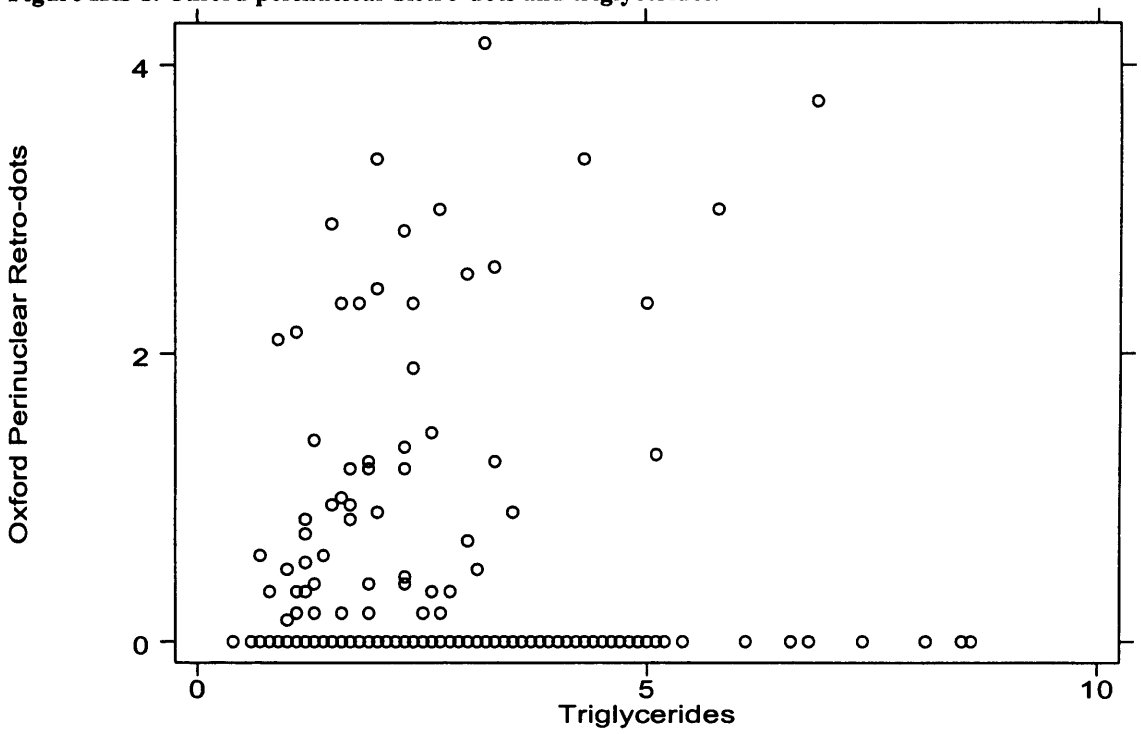


Table IRS 3 Estimated coefficients: nuclear cataract and insulin resistance syndrome: -Univariate Analysis (HRT analysed in women only)

Brunescence	Coef.	Std.Err.	P>t	(95% Conf. Interval).	
Diabetic	**.3102922**	**.0728008**	**0.000**	**.1673876**	**.4531968**
Glucose	.0103961	.009837	0.291	-.0089217	.0297138
Hormone Replacement	**-.1934424**	**.0584699**	**0.001**	**-.3083781**	**-.0785067**
Body Mass Index	.0043024	.0033131	0.194	-.0022012	.010806
Body Mass Index^2	.0000212	.0000446	0.635	-.0000664	.0001088
Waist Hip Ratio	.2205705	.1663437	0.185	-.1059651	.5471062
Systolic BP	**.0019429**	**.0007962**	**0.015**	**.0003799**	**.0035059**
Diastolic BP	-.0014076	.0014204	0.322	-.0041957	.0013806
Self report Hypertension	.0464892	.0362178	0.200	-.0246051	.1175834
Cholesterol	.0041016	.0156807	0.794	-.0266962	.0348994
HDL Cholesterol	-.0188585	.0497363	0.705	-.116558	.0788411
HDL/LDL Cholesterol Ratio	-.1943671	.1825335	0.287	-.5529268	.1641925
Triglycerides	.0198197	.01604	0.217	-.011684	.0513234
LDL Cholesterol	-.0030488	.0175833	0.862	-.0375887	.031491
Creatinine	**.0014294**	**.0006908**	**0.039**	**.0000728**	**.002786**
Insulin Resistance Score	**.0741878**	**.0262805**	**0.005**	**.0226006**	**.1257751**

White Scatter	Coef.	Std.Err.	P>t	(95% Conf.Interval).	
Diabetic	.0768566	.0749793	0.306	-.0703248	.224038
Glucose	.0075233	.0103044	0.466	-.0127124	.027759
Hormone Replacement	**-.1861221**	**.0635599**	**0.004**	**-.3110634**	**-.0611808**
Body Mass Index	.0051524	.0033575	0.125	-.0014385	.0117433
Body Mass Index^2	.000055	.0000452	0.224	-.0000337	.0001436
Waist Hip Ratio	.0737278	.1684176	0.662	-.2568803	.404336
Systolic BP	**.0031953**	**.0008082**	**0.000**	**.0016088**	**.0047818**
Diastolic BP	.0013034	.0014488	0.369	-.0015407	.0041474
Self report Hypertension	.0057592	.0369441	0.876	-.066761	.0782794
Cholesterol	.0081487	.0167035	0.626	-.0246581	.0409554
HDL Cholesterol	.0626034	.0535067	0.243	-.0425029	.1677097
HDL/LDL Cholesterol Ratio	.0959207	.1967609	0.626	-.2905882	.4824296
Triglycerides	.0052824	.0169552	0.755	-.028019	.0385839
LDL Cholesterol	-.002945	.0189509	0.877	-.0401715	.0342814
Creatinine	.0007187	.000727	0.323	-.000709	.0021463
Insulin Resistance Score	**.0847813**	**.0267935**	**0.002**	**.0321869**	**.1373756**

Retro-dots	Coef.	Std.Err.	P>t	(95% Conf. Interval).	
Diabetic	**.3662818**	**.0784029**	**0.000**	**.2123797**	**.5201839**
Glucose	.0136879	.0110898	0.218	-.0080901	.0354658
Hormone Replacement	-.083292	.065704	0.206	-.212449	.0458649
Body Mass Index	.0031187	.00361	0.388	-.0039679	.0102052
Body Mass Index^2	.000025	.0000486	0.607	-.0000703	.0001203
Waist Hip Ratio	.1989515	.1810452	0.272	-.1564456	.5543486
Systolic BP	**.0017844**	**.0008312**	**0.032**	**.0001528**	**.003416**
Diastolic BP	.0003654	.00148	0.805	-.0025399	.0032706
Self report Hypertension	**.0993013**	**.0387561**	**0.011**	**.023224**	**.1753786**
Cholesterol	.0007998	.0178542	0.964	-.034267	.0358667
HDL Cholesterol	-.0776111	.0521081	0.137	-.1799697	.0247474
HDL/LDL Cholesterol Ratio	-.2299985	.1911562	0.229	-.6054962	.1454992
Triglycerides	**.0521298**	**.0182064**	**0.004**	**.016371**	**.0878885**
LDL Cholesterol	-.0085481	.0184161	0.643	-.0447238	.0276276
Creatinine	.0008049	.0007821	0.304	-.000731	.0023408
Insulin Resistance Score	**.1123876**	**.028352**	**0.000**	**.0567339**	**.1680414**

Regression correcting for age, sex and grader

Table IRS 4 reports the analysis correcting for age, sex, and grader. Once again, the analysis for HRT was performed on women only, correcting for age and grader. All other analyses were performed on both men and women.

Both Brunescence and Retro-dots continue to be associated with diabetes ($p < 0.0001$). The association of Brunescence and White Scatter with a history of hormone

replacement therapy no longer reaches statistical significance (p = 0.637). In all three nuclear features, the statistically significant association with systolic blood pressure falls away, (p = 0.091, 0.531, 0.930) as does that of Retro-dots with a self-reported history of hypertension (p = 0.099). However there is now a weak negative association of Brunescence and diastolic blood pressure (p = 0.028). The only serum measurement that remains significant is that of Retro-dots with triglycerides (p = 0.013). White Scatter and Retro-dots continue to be associated with the insulin resistance syndrome score while Brunescence loses significance at this level. (p= 0.060).

Table IRS 4 Table of estimated coefficients: nuclear cataract and insulin resistance syndrome. Each risk factor analysed separately (correcting for age, sex and grader). (HRT analysed in women only)

Brunescence	**Coef.**	**Std.Err.**	**P>t**	**(95% Conf. Interval).**	
Diabetic	**.2314916**	**.0630717**	**0.000**	**.1076842**	**.355299**
Glucose	.0054998	.0086107	0.523	-.0114099	.0224095
Hormone Replacement	-.025136	.0532816	0.637	-.1298744	.0796024
Body Mass Index	.0025469	.0028531	0.372	-.0030537	.0081476
Body Mass Index^2	7.55e-06	.0000384	0.844	-.0000677	.0000829
Systolic BP	-.0012139	.0007177	0.091	-.0026228	.000195
Diastolic BP	**-.0026936**	**.00122**	**0.028**	**-.0050886**	**-.0002987**
Self report Hypertension	-.0275955	.0314562	0.381	-.0893432	.0341523
Cholesterol	-.0084551	.014112	0.549	-.0361723	.019262
HDL Cholesterol	-.0137624	.0446144	0.758	-.1014017	.073877
HDL/LDL Cholesterol Ratio	-.1354678	.1568346	0.388	-.4435498	.1726142
Triglycerides	.0108342	.013889	0.436	-.0164451	.0381135
LDL Cholesterol	-.0143864	.0154652	0.353	-.0447659	.0159931
Creatinine	.0003705	.0006378	0.562	-.000882	.001623
Insulin Resistance Score	.0428241	.0227578	0.060	-.0018484	.0874967

White Scatter	**Coef.**	**Std.Err.**	**P>t**	**(95% Conf.Interval).**	
Diabetic	-.0016213	.0641204	0.980	-.1274877	.1242451
Glucose	.0049513	.0087089	0.570	-.0121512	.0220539
Hormone Replacement	-.0053097	.0571082	0.926	-.1175703	.106951
Body Mass Index	.0031699	.0028677	0.269	-.0024594	.0087991
Body Mass Index^2	.000038	.0000385	0.324	-.0000376	.0001136
Systolic BP	.0004548	.0007256	0.531	-.0009696	.0018791
Diastolic BP	.0001622	.0012335	0.895	-.0022591	.0025836
Self report Hypertension	**-.0702169**	**.0315585**	**0.026**	**-.1321656**	**-.0082682**
Cholesterol	-.0106375	.0145404	0.465	-.0391962	.0179212
HDL Cholesterol	.044498	.0465397	0.339	-.0469237	.1359198
HDL/LDL Cholesterol Ratio	.1237095	.1640382	0.451	-.1985242	.4459433
Triglycerides	-.0004836	.0141795	0.973	-.0283337	.0273665
LDL Cholesterol	-.0197938	.0161888	0.222	-.0515948	.0120072
Creatinine	-.0000706	.0006466	0.913	-.0013404	.0011992
Insulin Resistance Score	**.0520492**	**.0229641**	**0.024**	**.0069716**	**.0971268**

Retro-dots	**Coef.**	**Std.Err.**	**P>t**	**(95% Conf. Interval).**	
Diabetic	**.3292916**	**.0765686**	**0.000**	**.1789893**	**.4795938**
Glucose	.0092664	.0108438	0.393	-.0120287	.0305615
Hormone Replacement	.0187956	.0661271	0.776	-.1111948	.1487861
Body Mass Index	.0023289	.0035056	0.507	-.0045527	.0092105
Body Mass Index^2	.00002	.0000471	0.671	-.0000724	.0001125
Systolic BP	.0000744	.0008449	0.930	-.001584	.0017329
Diastolic BP	-.0003555	.0014383	0.805	-.0031788	.0024678
Self report Hypertension	.0629251	.0381014	0.099	-.0118673	.1377176
Cholesterol	-.0042033	.0180536	0.816	-.0396622	.0312555
HDL Cholesterol	-.0674524	.0527848	0.202	-.1711414	.0362367
HDL/LDL Cholesterol Ratio	-.1813404	.1859706	0.330	-.5466565	.1839757
Triglycerides	**.0441682**	**.0177049**	**0.013**	**.009394**	**.0789424**
LDL Cholesterol	-.0129546	.018348	0.480	-.0489969	.0230877
Creatinine	-.0000849	.0008044	0.916	-.0016646	.0014948
Insulin Resistance Score	**.0970885**	**.027662**	**0.000**	**.0427889**	**.1513881**

Regression correcting for age, sex and grader and all other associated risk and protective factors (Final Model).

Table IRS 5 gives details of the final model which includes all the other risk and protective factors found to be significant in the univariate and age, sex and grader corrected models. In the final model, all the risk and protective factors are put in the same regression model. Table IRS 6 gives details of the final model for women only in order to give the co-efficients for HRT.

Both Brunescence and Retro-dots continue to be associated with diabetes ($p < 0.0001$ and 0.007 respectively). The relationship remained strong when examined by sex. When examined by age group it remained significant in those diabetics aged less than 60 ($p = 0.013$), aged 65 to 69 ($p = 0.005$), but was no longer significant in those aged between the age of 60 and 64 ($p = 0.146$), and those 70 and older ($p = 0.052$). There was no association of White Scatter and diabetes ($p = 0.333$).

None of the nuclear features is associated with systolic or diastolic blood pressure. However a self-reported history of hypertension is now negatively associated with White Scatter ($p = 0.042$), while Retro-dots are now positively associated ($p = 0.039$). The association of Retro-dots with triglycerides dropped from a significant level of ($p = 0.013$) to ($p = 0.060$). The association of Brunescence and White Scatter with a history of hormone replacement remains statistically insignificant. When the data are examined in women only for the model looking at HRT, most of the associations remain unchanged. However the negative association of self reported hypertension with White Scatter increases in strength ($p = 0.011$)

Table IRS 5 Estimated coefficients: Final Model. Oxford Brunescence , White Scatter and Retro-dots: correcting for Age, Sex, Grader, smoking and alcohol consumption categories, antioxidants, diabetes, Hypertension and insulin resistance syndrome.

Brunescence	Coef.	Std. Err.	P>|t|	(95% Conf. Interval).	
Age at examination	**.0374937**	**.0030674**	**0.000**	**.0314673**	**.04352**
Sex	-.0589257	.0361774	0.104	-.1300014	.0121501
Grader	**.1921348**	**.0331226**	**0.000**	**.1270607**	**.2572088**
Current and past smoking (light)	**.1025201**	**.0367343**	**0.005**	**.0303503**	**.1746899**
Current and past smoking (heavy)	**.1258272**	**.0594945**	**0.035**	**.0089415**	**.2427128**
Less than 4 drinks per day -current	.0299993	.0357834	0.402	-.0403025	.100301
More than 4 drinks per day -current	**.2150109**	**.0682769**	**0.002**	**.0808711**	**.3491507**
Diabetic	**.3275524**	**.0777633**	**0.000**	**.1747752**	**.4803297**
Beta Carotene	**-.1856457**	**.0730749**	**0.011**	**-.3292119**	**-.0420795**
Vitamin A	**-.1784243**	**.0892278**	**0.046**	**-.3537252**	**-.0031233**
Triglycerides	.0101951	.0145967	0.485	-.0184822	.0388724
Systolic BP	-.000044	.001139	0.969	-.0022818	.0021938
Diastolic BP	-.0012798	.0019709	0.516	-.0051519	.0025923
Self report Hypertension	.0206477	.037132	0.578	-.0523034	.0935988
Insulin Resistance Score	**.0890622**	**.0436724**	**0.042**	**.0032598**	**.1748646**
_cons	-1.444631	.2293258	0.000	-1.895174	-.9940868

White Scatter	Coef.	Std. Err.	P>|t|	(95% Conf. Interval).	
Age at examination	**.0346939**	**.00332**	**0.000**	**.0281708**	**.0412169**
Sex	-.0593777	.0399084	0.137	-.1377888	.0190334
Grader	**.3493892**	**.0358353**	**0.000**	**.2789809**	**.4197975**
Current and past smoking (light)	**.0786133**	**.0397318**	**0.048**	**.0005491**	**.1566775**
Current and past smoking (heavy)	.0442769	.0643843	0.492	-.0822239	.1707777
Less than 4 drinks per day -current	.0204355	.0389035	0.600	-.0560013	.0968722
More than 4 drinks per day -current	.0535038	.0746293	0.474	-.0931261	.2001337
Diabetic	.0837372	.0864878	0.333	-.0861921	.2536664
Beta Carotene	-.0186443	.0796438	0.815	-.1751267	.1378381
Vitamin A	-.0687978	.0979595	0.483	-.2612664	.1236709
Triglycerides	-.0038685	.0166594	0.816	-.0366005	.0288636
Systolic BP	.0016558	.001245	0.184	-.0007903	.0041019
Diastolic BP	.0008395	.0021328	0.694	-.0033509	.0050299
Self report Hypertension	**-.082054**	**.0402984**	**0.042**	**-.1612313**	**-0028767**
Insulin Resistance Score	.02588	.0468857	0.581	-.066236	.117996
_cons	-1.329735	.2538679	0.000	-1.828529	-.8309406

Retro-dots	Coef.	Std. Err.	P>|t|	(95% Conf. Interval).	
Age at examination	**.0216729**	**.0040126**	**0.000**	**.0137892**	**.0295567**
Sex	.0523935	.0482407	0.278	-.0423883	.1471752
Grader	.0223812	.0432921	0.605	-.0626776	.1074401
Current and past smoking (light)	-.0334847	.0480285	0.486	-.1278494	.0608801
Current and past smoking (heavy)	-.0576359	.0778294	0.459	-.2105527	.0952808
Less than 4 drinks per day –current	.0303993	.0470304	0.518	-.0620046	.1228032
More than 4 drinks per day –current	.0747513	.089425	0.404	-.1009481	.2504507
Diabetic	**.2826932**	**.1045548**	**0.007**	**.0772673**	**.4881191**
Beta Carotene	.0240477	.0962787	0.803	-.1651175	.2132129
Vitamin A	-.0443137	.1180007	0.707	-.2761576	.1875303
Triglycerides	.0379291	.0201171	0.060	-.0015964	.0774546
Systolic BP	.0002776	.0014965	0.853	-.0026627	.0032178
Diastolic BP	-.0007757	.0025694	0.763	-.0058239	.0042725
Self report Hypertension	**.1005165**	**.0486805**	**0.039**	**.0048706**	**.1961623**
Insulin Resistance Score	.0727662	.0577712	0.208	-.0407357	.1862682
_cons	-1.403197	.3068591	0.000	-2.006104	-.80029

Table IRS 6. Estimated coefficients: Final Model. Oxford Brunescence, White Scatter and Retro-dots: correcting for Age, Grader, smoking and alcohol consumption categories, antioxidants, Diabetes, Hypertension, insulin resistance syndrome and Hormone Replacement Therapy. Analysis in women only.

Brunescence	Coef.	Std. Err.	P>|t|	(95% Conf. Interval)	
Age at examination	**.0380805**	**.0043746**	**0.000**	**.0294647**	**.0466963**
Grader	**.1938358**	**.0443282**	**0.000**	**.1065315**	**.2811401**
Current and past smoking (light)	**.1306926**	**.0450191**	**0.004**	**.0420276**	**.2193575**
Current and past smoking (heavy)	.0761049	.0987407	0.442	-.1183647	.2705745
Less than 4 drinks per day -current	.0391055	.0449772	0.385	-.049477	.1276879
More than 4 drinks per day -current	.2922455	.3592292	0.417	-.4152558	.9997468
Diabetic	**.4618495**	**.110892**	**0.000**	**.243448**	**.680251**
Beta Carotene	**-.2601328**	**.0850321**	**0.002**	**-.4276033**	**-.0926622**
Vitamin A	**-.2888301**	**.1182447**	**0.015**	**-.5217129**	**-.0559473**
Triglycerides	.0044573	.0221602	0.841	-.0391871	.0481016
Systolic BP	.001019	.0015551	0.513	-.0020437	.0040817
Diastolic BP	-.0014757	.0027032	0.586	-.0067997	.0038483
Self report Hypertension	-.0182982	.0491129	0.710	-.1150261	.0784296
Hormone Replacement	-.0438958	.057361	0.445	-.1568683	.0690766
Insulin Resistance Score	.0520181	.062287	0.404	-.0706609	.1746971
_cons	-1.4091	.3525708	0.000	-2.103488	-.7147127

White Scatter	Coef.	Std. Err.	P>|t|	(95% Conf. Interval)	
Age at examination	**.0314113**	**.0054629**	**0.000**	**.020651**	**.0421716**
Grader	**.4150358**	**.055146**	**0.000**	**.3064152**	**.5236565**
Current and past smoking (light)	.0951604	.0558924	0.090	-.0149305	.2052512
Current and past smoking (heavy)	-.1596119	.1215838	0.190	-.3990948	.0798709
Less than 4 drinks per day -current	.0130104	.0556511	0.815	-.0966052	.122626
More than 4 drinks per day -current	.0629142	.4404371	0.887	-.8046119	.9304404
Diabetic	.1653471	.142879	0.248	-.1160807	.4467749
Beta Carotene	-.0012447	.1052306	0.991	-.2085168	.2060274
Vitamin A	.0159565	.1473277	0.914	-.2742339	.306147
Triglycerides	-.0024616	.0287577	0.932	-.0591056	.0541823
Systolic BP	.0016589	.0019129	0.387	-.0021089	.0054267
Diastolic BP	.0029647	.0033644	0.379	-.0036622	.0095915
Self report Hypertension	**-.154507**	**.0604801**	**0.011**	**-.2736342**	**-.0353797**
Hormone Replacement	-.0150062	.0706253	0.832	-.1541165	.1241041
Insulin Resistance Score	-.004281	.0757653	0.955	-.1535065	.1449445
_cons	-1.358382	.3926153	0.001	-2.131714	-.5850497

Retro dots	Coef.	Std. Err.	P>|t|	(95% Conf. Interval)	
Age at examination	**.0155338**	**.0058107**	**0.008**	**.0040886**	**.026979**
Grader	.0213146	.0586561	0.717	-.09422	.1368492
Current and past smoking (light)	-.0310605	.05945	0.602	-.1481589	.0860378
Current and past smoking (heavy)	.0300794	.1293228	0.816	-.2246469	.2848058
Less than 4 drinks per day -current	.0090513	.0591934	0.879	-.1075415	.1256442
More than 4 drinks per day -current	-.0741597	.4684717	0.874	-.9969055	.8485861
Diabetic	**.4369287**	**.1519735**	**0.004**	**.1375875**	**.7362699**
Beta Carotene	.0165818	.1119287	0.882	-.2038836	.2370471
Vitamin A	-.099515	.1567054	0.526	-.4081766	.2091466
Triglycerides	.0438441	.0305882	0.153	-.0164054	.1040935
Systolic BP	.002504	.0020346	0.220	-.0015036	.0065116
Diastolic BP	-.0018894	.0035786	0.598	-.008938	.0051593
Self report Hypertension	.0815886	.0643297	0.206	-.0451213	.2082985
Hormone Replacement	.0164986	.0751208	0.826	-.1314663	.1644635
Insulin Resistance Score	.0805955	.0800835	0.315	-.077135	.2383261
_cons	-1.246577	.417606	0.003	-2.069133	-.4240208

10.5 Interpreting the co-efficients for the major risk factors

The co-efficient represents the amount of change in nuclear cataract per unit of a risk factor. For example for each year of change in age, there is a 0.0375 change in Brunescence. Rather than presenting a table of co-efficients and each unit of change, data that can be read off the tables, the co-efficients will be interpreted in terms of the proportion of the ageing effect. Table IRS 7 summarises the ageing effect of each co-efficient.

Brunescence

- Age: For every year of age there is a 0.0375 increase in Brunescence. This means that for each decade of ageing one can expect a change in Brunescence score of 0.375.
- History of diabetes: A history of diabetes results in a change of 0.327 in Brunescence score. This is equivalent to an ageing effect of 0.872 of a decade i.e. nearly nine years of ageing. In women, the ageing effect of diabetes increases to over 12 years.
- Smoking: A history of light smoking results in a 0.103 increase in Brunescence. This is equivalent to an ageing effect of 0.275 of a decade i.e. around two and ¾ years of ageing.

  A history of heavy smoking results in an increase of 0.126 in Brunescence. This is equivalent to an ageing effect of 0.336 of a decade or around three and 1/3 years of ageing.
- Alcohol: A history of drinking more than four drinks per day results in a change of 0.215 in Brunescence score. This is equivalent to an ageing effect of 0.573 of a decade or nearly five and ¾ years of ageing.
- Insulin Resistance Syndrome: For each unit change in the insulin resistance syndrome score (range 1-4) there is a 0.089 increase in Brunescence. This is equivalent to an ageing effect of 0.237 of a decade or over two and 1/3 years of ageing.
- Beta Carotene: Beta Carotene is a protective factor. For each unit of change in Beta Carotene (range 0.40 to 1.70), there is 0.186 less Brunescence. This is equivalent to an ageing effect of 0.496 of a decade or nearly five years less ageing. In women, the protective effect of Beta Carotene increases to nearly seven years.
- Vitamin A: Vitamin A is a protective factor. For each unit of change in Vitamin A (range 0.10 to 2.00) there is 0.178 less Brunescence. This is equivalent to 0.475 of a decade or around four and ¾ years less ageing. In women, the protective effect of Vitamin A increases to over seven years.

White Scatter

- Age: For every year of age there is a 0.0347 increase in White Scatter. This means that for each decade of ageing one can expect a change in White Scatter score of 0.375.
- Smoking: A history of light smoking results in a 0.079 increase in White Scatter. This is equivalent to an ageing effect of 0.22 of a decade i.e. over 2 years of ageing.
- Self-Report of Hypertension: Self-reporting a history of hypertension resulted in a reduction in White Scatter equivalent to 0.236 of a decade less or around two and 2/3 years less ageing.

How much of the variance in the model can be explained by all these risk factors? The variance is given by the figure R squared in the ANOVA table of the regression output. In the final model for all subjects for Brunescence, R squared is 0.3429. In the model for HRT, (women only) R squared is 0.4145. This means that the proportion of variance explained by the risk factors in the models are accounting for 34 % and 41 % of the change in Brunescent nuclear cataract respectively. The values for White Scatter are 33% and 35 % respectively. For Brunescence, if age is analysed alone it accounts for 22 %, while if the unique environmental factors are analysed are analysed these account for 12 % of the variance. These figures compare with those of Hammond, (Hammond, Snieder et al. 2000) who found that age and unique environmental factors accounted for 38 % and 14 % of the variance respectively.

These are respectable percentages for models examining environmental factors.

Table IRS 7 Co-efficients for risk factors interpreted in terms of ageing effect.

Brunescence	Coef.	Change in Brunescence over 10years	Equivalent proportion of a decade	Equivalent years of ageing
Age at examination	0.0375	0.375		
Current and past smoking (light)	0.103		0.275	2.75
Current and past smoking (heavy)	0.126		0.336	3.36
More than 4 drinks per day -current	0.215		0.573	5.73
Diabetic	0.328		0.872	8.72
Insulin Resistance Score	0.089		0.237	2.37
Beta Carotene	-0.186		- 0.496	- 4.96
Vitamin A	-0.178		- 0.475	- 4.75

White Scatter	Coef.	Change in White Scatter over 10years	Equivalent proportion of a decade	Equivalent years of ageing
Age at examination	0.0347	0.347		
Current and past smoking (light)	0.079		0.22	2.2
Self report Hypertension	-0.082		-0.236	- 2.36

10.6 Discussion

Cardiovascular component of the insulin resistance syndrome

The conflicting nature of the association of cataract with cardiovascular component of the insulin resistance syndrome risk factors suggests that these may not have a direct effect on cataractogenesis (Leske, Wu et al. 1999). The Melton Eye Study has not found any strong associations of cataract with cardiovascular disease or its risk factors. This could be interpreted as a lack of real association, on the other hand the possibility that a real association was missed because of the limitations in the way the risk factors were examined cannot be ruled out.

Some of the cardiovascular elements of the insulin resistance syndrome were measured in serum. Relying on serum factors alone has advantages and disadvantages. Serum factors provide an objective assessment and minimize the potential for recall bias that may occur in taking the history of medical problems. However, lack of a temporal based measure is a significant weakness: serum levels only provide a brief "snap shot" in time.

Interpretation of the data is limited by certain confounders; the levels do not reveal the cardiovascular status of the subject at the time a cataractogenic effect may have been exerted. Recent illness or change in dietary habits may have led to findings that do not reflect past history or experience.

There may have been a selection bias in subjects who had blood samples taken. Data in the chapter on antioxidants show that subjects who did not consent to give blood tended to be older than those who did give blood are. Older subjects are more likely to have cardiovascular problems. Difficulty was experienced in taking blood from some subjects due to obesity or collapsed veins. These subjects may also have had more cardiovascular risk factors. Finally, a small number refused because they had just had blood tests for other illnesses.

Systolic or diastolic blood pressure was not categorised in the analysis. If there is a contribution to the development of cataract that only begins at a certain level, then analysing blood pressure as a continuous variable would have missed this association. An attempt was made to correct for a history of hypertension by including this as a category in the analysis. The effect of hypertensive medications was not assessed in any other way. However, a protective effect of the medications on nuclear cataract might explain the negative association of White Scatter with a self reported history of hypertension and cannot be ruled out.

An analysis of medications for cardiovascular disease has not been included at this stage in the study. Blood pressure may be a marker for the cataractogenic effects of various anti-hypertensive medications such as thiazide diuretics (West and Valmadrid 1995). However, as no association with raised blood pressure has been demonstrated in the Melton Eye Study, the relationship has not been explored further. The data will be more useful when exploring the temporal effects of medications and hypertension on cataract.

Diabetes and glucose

Serum Glucose was not associated with any of the nuclear features, however our study has no measure of glycated haemoglobin to use as a gauge of long-term glycation. Neither was it possible to determine the level of insulin resistance in the community. Both of these measurements would have provided better information on the association of the insulin resistance syndrome and cataract. It is likely that random glucose measurements are not an accurate reflection of the effects of long-term glycation. Past prolonged hyperglycaemia may be missed by a random sample.

The strong association between a history of diabetes with Brunescence and not with White Scatter is interesting and may explain why many studies have not found an association with nuclear cataract in the past. Most of the grading systems used in other population-based studies have only one standard for colour and they concentrate on the opalescent component of nuclear cataract (West, Rosenthal et al. 1988; Klein, Klein et al. 1990; McCarty, Mukesh et al. 1999). The significant difference between the two subtypes of nuclear cataract suggests that there may be different causal pathways for brunescent and opalescent nuclear cataract, particularly in the way that the nuclear proteins are affected by diabetes. An alternative explanation is that Brunescence is easier to grade (this is certainly suggested by the inter-observer variation which is greater for White Scatter than for Brunescence). More accurate grading would reduce confounding and result in a greater ability to detect an association. In other words, an association with diabetes and White Scatter as well cannot be ruled out.

The effect of diabetes on cataract did not fit the normal pattern when analysed by age group. This may be due to the relatively small number of diabetics in each group. An insignificant effect on nuclear cataract was found in a relatively young group (60 to 64). There was a low prevalence (less than 1%) of undiagnosed diabetes, when assessed by random blood sugar, in this community. Undiagnosed diabetes is unlikely to have affected the relationship of diabetes and cataract.

The size of the effect of diabetes on nuclear cataract is equivalent to nearly a decade of ageing in the population as a whole and over a decade in women.

Body mass index

Body mass index was not associated with any of the nuclear features whether examined as a continuous or a categorical variable. There was no significant association between any of the body mass index categories and cataract and there was no association between nuclear cataract and the other markers of obesity such as waist hip ratio. The possibility that there may be a real association with body mass index as reported in other studies cannot be ruled out (Hankinson, Seddon et al. 1993; Glynn, Christen et al. 1995; Tavani, Negri et al. 1995).(Caulfield, West et al. 1999). It may be that in this relatively young population with early lens opacities that a temporal association between body mass index and cataract is not yet apparent. Longitudinal data on this population would help clarify this relationship.

Hormone Replacement Therapy

The association of a history of ever having taken hormone replacement therapy with nuclear cataract only occurred at the univariate level. Further exploration of this relationship, using data on duration of therapy and menstrual history, is warranted. Any temporal effect could be examined in a longitudinal phase of the Melton Eye Study.

Insulin Resistance Syndrome

Although the individual components comprising the insulin resistance syndrome do not have a significant association with nuclear cataract when measured individually, when they are combined in the insulin resistance syndrome score they are significantly associated with Brunescence. The size of the effect of the insulin resistance syndrome score is about a quarter of a decade per unit of insulin resistance syndrome score or about a quarter of the effect of diabetes. Subjects with the highest insulin resistance syndrome scores could have an effect approaching that of diabetes.

10.7 Conclusion

Diabetes

Data from the Melton Eye Study confirms the association of diabetes with the increased risk of cortical cataract. A new finding is the strong association of diabetes with brunescent cataract and Retro-dots ($p < 0.0001$). A strong association of nuclear cataract with anthropometric status was not found.

Insulin Resistance Syndrome

Key elements of the insulin resistance syndrome, namely glucose, body mass index, cholesterol, low levels of high-density lipoprotein cholesterol, and Triglycerides, were used to create an insulin resistance syndrome score. This score was associated with all the components of nuclear cataract in the univariate and age, sex and grader corrected models. In the final model of all risk factors, only Brunescence was associated with the insulin resistance syndrome score. When the risk factors that comprise the insulin resistance syndrome, are analysed individually there is not an association with nuclear cataract. Although the insulin resistance syndrome score is a relatively crude measure of insulin resistance, the association does suggest that insulin resistance could have a role to play in the development of nuclear cataract. With increasing concerns about the growing problem of obesity in the population, including concerns about children, the contribution made by the insulin resistance syndrome on nuclear cataract is only likely to grow. The Melton Eye Study population is relatively young, the data collected on insulin resistance, and cardiovascular risk factors at baseline would be invaluable in exploring the temporal effect of these risk factors on the development of cataract during a longitudinal phase. Including a measure of insulin resistance as a risk factor would strengthen any longitudinal study of this population.

10.8 Public health implications

Interventions to modify the development of maturity-onset diabetes will have a significant impact on the prevalence of nuclear cataract, delaying the onset of nuclear cataract by up to 10 years. In addition to prevention of diabetes, these interventions would reduce obesity, hyperlipidaemia, hypertension and other components of the insulin resistance syndrome and would therefore be likely to have a further effect in delaying the onset of nuclear cataract. In those with established diabetes, the effect of tight clinical control has not yet been established. However, in addition to the lower risk of retinopathy, the benefit of decreasing glycaemia may also be to reduce the risk of cataract substantially.

11. Discussion

11.1 Purpose

The aims of this chapter are:

- to summarise the main findings about nuclear cataract in the Melton population,
- to discuss the major public health implications of these findings,
- to discuss a common pathway for some risk factors,
- to suggest the direction of further research.

11.2 Introduction

The Melton Eye Study has examined 826 subjects of the town of Melton Mowbray. The Study has provided up-to-date prevalence data on the eye diseases responsible for much of the visual impairment and blindness in the UK. Incidence data will become available once the study progresses into the second phase of examinations. This dissertation has focused on the epidemiology of nuclear cataract. However, the size of the population used in the study is relatively small and the racial mix of the population is restricted to Caucasians. Therefore, extrapolating the findings of the Melton Eye Study to the general population needs to be done with an element of caution.

11.3 Prevalence of nuclear cataract

All subjects had a nuclear cataract grade. However, not all of these were clinically significant. Using the LOCS III grading system and defining a significant nuclear opacity as an opacity of greater than LOCS III standard 3, then 98 (12.05 %) of subjects have significant opalescence and 90 (11.07 %) have significant nuclear colour opacities. Using Oxford grading, 89 (9.33%) of subjects had significant White Scatter and 90 (11.04 %) had significant Brunescence. Different prevalences are given by the two systems because the grading systems have different ranges. The Oxford system has a greater range, and will therefore consistently give a lower prevalence than the LOCS III score.

These opacities increased significantly with age. For Oxford Brunescence the prevalence rose from 2.82% in those aged 55 to 59 years, to 29.89% in those aged 70 to 75. Similarly White Scatter prevalence rose from 0.00 % in those aged 55 to 59 years, to 23.91 % in those aged 70 to 75.

Public health significance

The significant effect of nuclear opalescence on vision is compounded by the high prevalence in older people. Using a definition of greater than LOCS standard 3 for a significant opalescence, then over 14% of 65- to 70-year-olds had significant nuclear

opacity and over 31% of those between the ages of 70 and 75 had significant visually degrading opacity. Health planners can use these data to calculate that over 10% of those over the age of 55 might need cataract surgery. McCarty has calculated that if the presence of cataract is the sole criterion for surgery, then there would be 309 cataract operations per 1000 population aged over 40 (McCarty, Keeffe et al. 1999). If a visual acuity criterion is set at 6/12, then this value drops to 48 per 1000. The level of 100 per 1000 over the age of 55 arrived at for the Melton Eye Study is based purely on the prevalence of nuclear cataract and does not include other lens opacities. In this population, nuclear cataract is the most visually disabling and the most prevalent cataract form. An estimate of 100 cases per 1000 people over the age of 55 therefore seems reasonable. Further research into why women have more cataract then men is needed.

11.4 Visual acuity and contrast sensitivity

Increasing age and female sex are significantly associated with decreasing visual acuity. ($p < 0.0001$). In females, visual acuity (VA) (mean number of letters read by the right eye) dropped from 55 letters in females aged 55 to 59 years, to 47.9 letters in those aged 70 to 75. The drop for males in the same age groups was from 56.7 letters to 50.5 letters respectively. The approximate Snellen equivalent for 55 letters is 6/6 and 45 letters, 6/9.5. Although the mean number of letters read is lower in women than in men there is no difference in prevalence of visual impairment. The difference in the number of letters seen may be due to the greater susceptibility of women to conditions that lead to a mild decrease in vision, such as mild age related macular degeneration or early cataract. For example, women have a trend to a higher prevalence of White Scatter than men do. White Scatter is associated with a reduction in vision while Brunescence is not. Alternatively, men with poor vision may have been less likely to participate in the study.

Contrast sensitivity (CS)

Neither Brunescence or White Scatter is associated with CS even before correcting for VA ($p = 0.164$ and 0.388 respectively) In this population-based study CS measurement in the low frequency range provided by the Pelli-Robson chart did not add anything to the information about cataracts effect on vision provided by VA.

Prevalence of visual impairment

If best-corrected visual acuity is considered, then only 0.49% of subjects were visually impaired according to WHO criteria (VA < 6/18). There were no bilaterally blind people (<3/60) in this population. However, there was a significant prevalence of uncorrected refractive error. Refraction improved visual acuity by one or more lines in 230

(27.85%) out of 826 participants and by three or more lines in 40 (4.84%). Seven out of 10 subjects with vision of 6/60 or worse were improved to better than 6/60. There was no difference in visual impairment between men and women.

Associations of visual acuity with lens opacity

The visual degradation associated with nuclear cataract is due mainly to White Scatter ($p < 0.0001$) with a possible added effect from Retro-dots ($p = 0.058$). Brunescence does not seem to have a significant effect on vision ($p = 0.154$). Posterior subcapsular cataract ($p = 0.004$) and cortical cataract ($p < 0.0001$) also have significant effects on vision. There were not enough pure opacities to separate pure Brunescence from pure White Scatter. Furthermore, as the 2 are so strongly associated that it would be difficult to find sufficient pure opacities even in a larger population. The separation of effect on vision has therefore been done statistically. It is therefore not possible to rule out the possibility that Brunescence has an independent effect on visual acuity.

Public health significance

It has been suggested that posterior subcapsular cataract tends to be a greater problem in surgical populations than in the community(Adamsons, Munoz et al. 1991). Our data confirms that because of the greater prevalence of nuclear cataract and its significant effect on vision, nuclear cataract is more likely to be a public health problem.

11.5 Alcohol consumption and smoking

Alcohol

The Melton Eye Study confirmed an association between nuclear lens opacities and heavy alcohol consumption. The association of Brunescence with alcohol is positive for current heavy drinking ($p = 0.002$) Previous studies have not examined the effect in non-smokers. The data suggest that the association is independent of cigarette smoking. The association of alcohol consumption with lens opacity was examined in non-smokers. There were 649 current non-smokers. There was a significant association of current heavy drinking with Brunescence ($p = 0.003$) amongst current non-smokers. The effect of past smoking was adjusted for in the regression. The relationship remained positive in the 570 subjects who had never smoked ($p = 0.028$).

Smoking

The Melton Eye Study has provided further epidemiological evidence of an increased risk of developing nuclear cataract amongst cigarette smokers. For Brunescence

there is a positive association with any history of both light smoking (p = 0.005) and heavy smoking (p = 0.035). A relationship of light smoking with White Scatter was found (p = 0.048).

Public health implications

It has been suggested that 20% of cataract cases in the US could be attributed to smoking (West 1992). However, Harding (Harding 1993), questioned this and estimated that heavy smoking only accounts for 3% of cataract in Western countries (Harding 1995). The Melton study finding of an association even with light smoking suggests that the attributable risk may be higher than this.

There was a positive correlation between heavy alcohol consumption and lens opacity, even in non-smokers. Therefore, the chance of accelerating nuclear cataract development is yet another reason to avoid heavy drinking.

11.6 Antioxidants and nuclear cataract

The Melton Eye Study has found a negative association of brunescent nuclear cataract with Beta carotene (p = 0.011), and Vitamin A (p = 0.046) (Table AO6). The significant negative association of Vitamin A with Brunescence is strengthened if it is examined in women alone (p = 0.016).

This study adds to the growing body of evidence that antioxidants may protect the lens against cataract.

Public health implications

The results show a protective effect of high levels of Beta carotene. However, they do not imply that the same effect can be achieved through supplementation. Until the results of clinical trials are known it is premature to recommend routine supplementation of diet to prevent cataract.

11.7 Myopia

An association between myopia and cataract has been suspected for some time. The Melton Eye Study is the first population-based study to find an association between early myopia and nuclear cataract.

Thirteen percent of subjects (106) were myopic. The expected relationship between nuclear lens opacity and myopia for people who first wore distance glasses after 40 was confirmed (p = 0.001). The relationship between spherical equivalent and White Scatter remains significant (p = 0.002) for myopes who started wearing glasses aged younger than 40 years. (Fig. R2)

Previous studies have used a history of use of distance glasses in childhood as a proxy for myopia. However, they did not differentiate those people who might have used glasses before the age of 20 because of significant hypermetropia (Harding, Harding et al. 1989; Leske, Chylack et al. 1991; Wu, Nemesure et al. 1999). The Melton Eye Study did not rely on self-reporting of short sight. Instead, it relied on the current refraction, a history of glasses use before the age of 20, and exclusion of current hypermetropes.

This study shows that the onset of myopia before the age of 20 years, may be a strong and independent risk factor for nuclear cataract.

Public health implications

Weale has suggested that overcorrecting young myopes will maintain their lenses in an accommodated state, reducing zonular stress and therefore mechanical stress that may predispose to cataract (Weale 1980). Although young myopes could be overcorrected, this runs contrary to the recommendation of those who believe eliminating accommodation can control myopia. Controlling zonular stress may have more impact in preventing nuclear cataract in countries with a higher prevalence of myopia, such as those in South-East Asia (Wensor, McCarty et al. 1999). Research into the association of early myopia and cataract in these populations would provide further understanding of the underlying mechanisms.

11.8 Diabetes, anthropometric status, oestrogens and nuclear cataract

Diabetes

The association of diabetes and cataract has been reported in both hospital-based and population-based studies. The majority of these studies have found an association with diabetes and cortical or posterior subcapsular cataract (Leske, Chylack et al. 1991; Klein, Klein et al. 1995), but not with nuclear cataract (Leske, Chylack et al. 1998; Delcourt, Cristol et al. 2000). Data from the Melton Eye Study confirms the association of diabetes with the increased risk of cortical cataract. A new finding is the strong association of diabetes with brunescent cataract and Retro-dots ($p < 0.0001$). There was no association of White Scatter and diabetes ($p = 0.883$). The fact that there is a strong association of diabetes with brunescent cataract and not with White Scatter is interesting and may explain why many studies have not found an association with nuclear cataract in the past. Most of the grading systems used in other population-based studies have used only one standard for colour and have concentrated on the opalescent component of nuclear cataract (West, Rosenthal et al. 1988; Klein, Klein et al. 1990; McCarty, Mukesh et al. 1999). The significant difference between the two subtypes of nuclear cataract suggests that there may

be different causal pathways for brunescent and opalescent nuclear cataract, particularly in the way that the nuclear proteins are affected by diabetes. Alternatively, easier grading of Brunescence may reduce confounding and result in a greater ability to detect an association. In other words, an association with diabetes and White Scatter as well cannot be ruled out.

Anthropometric status

Case-control studies and prospective cohort studies have found an association between higher body mass index and cataract extraction (Hankinson, Seddon et al. 1993; Glynn, Christen et al. 1995; Tavani, Negri et al. 1995). In the Melton Eye Study body mass index was not associated with any of the nuclear features whether examined as a continuous or a categorical variable. No association was found for other markers of obesity such as waist-hip ratio. However body mass index was included in the development of the insulin resistance score.

Oestrogens

The Beaver Dam Eye Study found a protective effect of current use of hormone replacement therapy against more severe nuclear cataract (Klein, Klein et al. 1994). An association of ever having taken hormone replacement therapy and nuclear cataract only occurred at the univariate level in the Melton Eye Study. Further exploration of this relationship using data on duration of therapy and menstrual history is warranted.

Public health implications

Seven percent of the Melton Eye Study population were either known diabetics or had high random blood sugars. Both nuclear and cortical cataract was associated with diabetes. Interventions to modify the development of maturity-onset diabetes will have a significant impact on the prevalence of cataract. It would be worth studying the effect of the tight control of glycaemia on the incidence of cataract. Temporal data on the effect of hormone replacement therapy on the incidence of cataract will be useful.

Insulin Resistance Syndrome

Although the individual components comprising the insulin resistance syndrome do not have a significant association with nuclear cataract when measured individually, when they are combined in the insulin resistance syndrome score they are significantly associated with Brunescence.

11.9 Insulin resistance syndrome and cataract

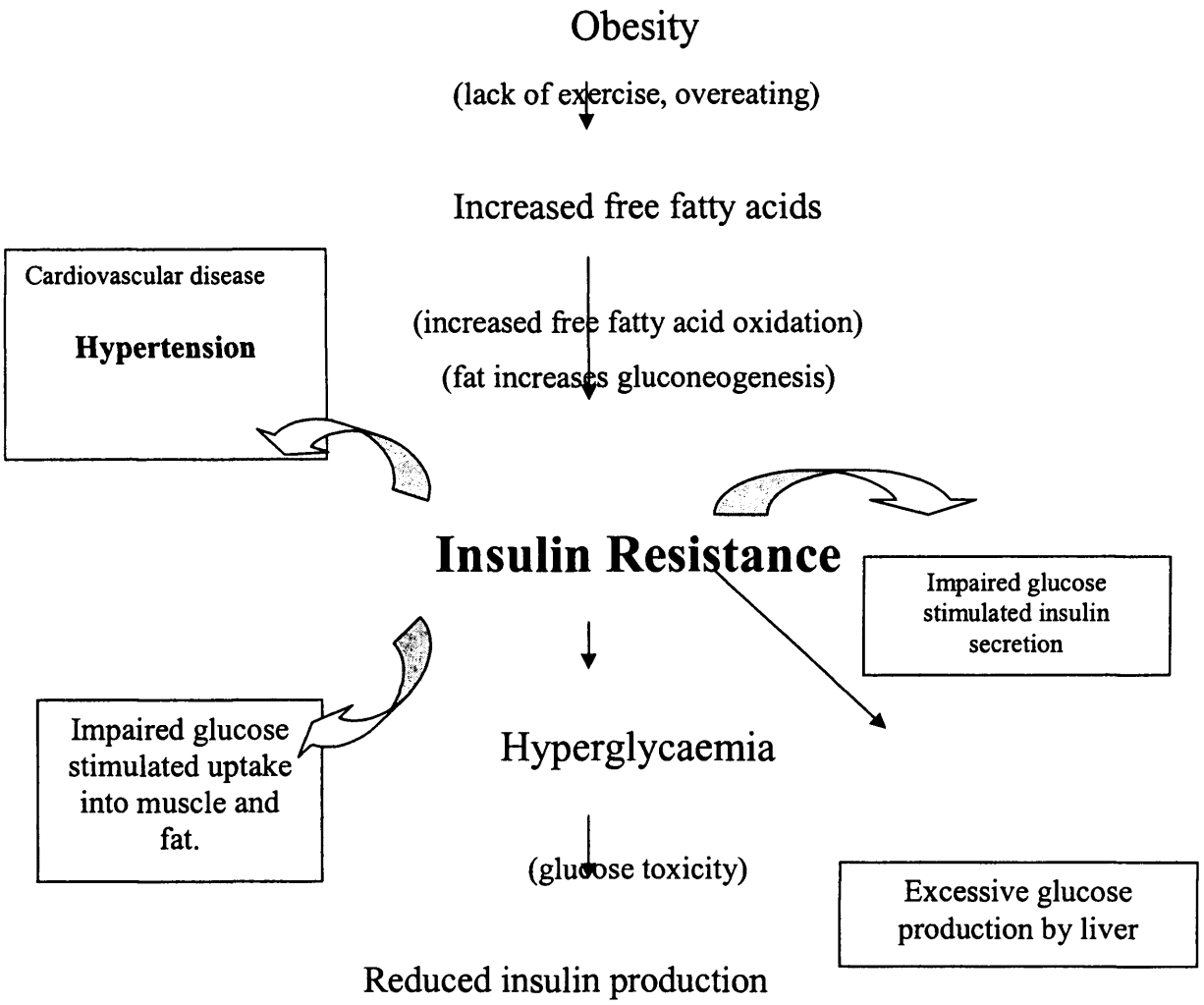
The aim of this section is to draw together evidence relating to diabetes, body mass index, oestrogens and cataract and present a theory which links them all to a final common pathway leading to cataract

Factors which need to be considered are:

- the higher prevalence of cataract in women,
- how oestrogens may protect against cataract,
- how a high body mass index may lead to cataract,
- the higher prevalence of cataract in some developing countries.

A unifying concept for the above factors is the insulin resistance syndrome. This syndrome comprises a constellation of risk factors which include, obesity, central body fat distribution, glucose intolerance, elevated plasma insulin levels, increased triglycerides and decreased high-density lipoprotein cholesterol, cardiovascular disease and hypertension, nephropathy, neuropathy and retinopathy (Austin, Mykkanen et al. 1995; Hansen 1995). Figure D1 summarises some of the components of the insulin resistance syndrome.

Figure D1. Inter-relating components of the insulin resistance syndrome.



The incidence of non-insulin dependent diabetes mellitus (NIDDM) is increasing throughout the world and is particularly high in non-Caucasian communities (Mykkanen, Laakso et al. 1990; Ramachandran, Snehalatha et al. 1994; Williams, Wareham et al. 1995). There are estimated to be over 80 million diabetics worldwide. Table D1 highlights the high hidden rates of undiagnosed NIDDM and impaired glucose tolerance (IGT) in a wide cross-section of communities (Mykkanen, Laakso et al. 1990; Ramachandran, Snehalatha et al. 1994; Mooy, Grootenhuis et al. 1995; Williams, Wareham et al. 1995).

Insulin resistance results in raised glucose levels, which may be responsible, in the long term, for glycation of lens proteins and ultimately cataract. The prevalence of insulin resistance is higher than that of diabetes. A population-based study of the prevalence of insulin resistance in Sweden found insulin resistance in 17% of the males and 18% of the females aged 25 to 64. A further 20–30 % of the population had intermediate resistance (Lindahl, Asplund et al. 1993)

Table D1. Undiagnosed NIDDM and impaired glucose tolerance.

Study population	% Impaired Glucose Tolerance		% Newly diagnosed NIDDM		% Known NIDDM		Total % Impaired Glucose Tolerance	
		F	M	F	M	F	M	F
Cambridgeshire[1] Age 40 – 65 Total = 1122	15.2	17.9	4.7	4.4	Known diabetics excluded from study		19.9	22.3
Finland[2] Age 65 – 74 Total = 1122	17.8	19.1	7.0	7.1	8.7	11.7	33.8	37.9
South Asia[3] Urban > 60 yrs Total = 873	12.8	11.9	Ratio of new to known = 1:3		29.7	19.9	42.5	31.8
South Asia[3] Rural > 60 yrs Total = 588	16.0	13.3	Ratio of new to known = 1:1		10.2	9.4	26.2	22.7
Holland[4] Age 50 – 74 Total = 2468	9.2	11.2	4.8	4.7	3.1	4.0	17.1	19.9

Key to references in table D1: 1 = (Williams, Wareham et al. 1995), 2 = (Mykkanen, Laakso et al. 1990), 3 = (Ramachandran, Snehalatha et al. 1994), 4 = (Mooy, Grootenhuis et al. 1995).

How can insulin resistance help explain the higher prevalence (Klein, Klein et al. 1992; Harding, Egerton et al. 1993; Klein, Klein et al. 1995), of cataract amongst women? Examination of Table D1 shows that impaired glucose tolerance is higher amongst women in all populations, bar the Asian example. The relative risk of cataract to women from diabetes may be two to three times that for male subjects (Harding, Egerton et al. 1993). Glycated haemoglobin has been found to be significantly associated with increased risk of nuclear cataract in women but not in men (Klein, Klein et al. 1997). Insulin resistance may therefore be the explanation for excess cataract in women. Although obesity and therefore insulin resistance and diabetes are more common in women, men are also at risk. A high BMI is a powerful predictor of NIDDM in both men and women (Haffner, Karhapaa et al. 1994; Carey, Walters et al. 1997). The association of body mass index and cataract found in the physicians health study (Glynn, Christen et al. 1995), may be explained in part by the theory of insulin resistance. There were 272 new cases of diabetes diagnosed in the follow-up period. Men with a body mass index of greater than 35 had a relative risk of developing diabetes of over 42 (Chan, Rimm et al. 1994).

Women lose the protective effect of oestrogen at the menopause. How does oestrogen exposure effect insulin resistance? The Beaver Dam Eye Study (Klein, Klein et al. 1994), found a protective effect of duration of oestrogen exposure and use of hormone replacement therapy (HRT) against cortical and nuclear lens opacities. The prevalence of nuclear lens opacities in women over the age of 70 who had taken oestrogen replacements

was 28.6% compared with 39.1% in men of the same age. Fluorophotometric examination of the nucleus showed a statistically significant difference in lens transmittance and autofluorescence, suggestive of a protective effect in women taking oestrogens (Benitez del Castillo, del Rio et al. 1997)

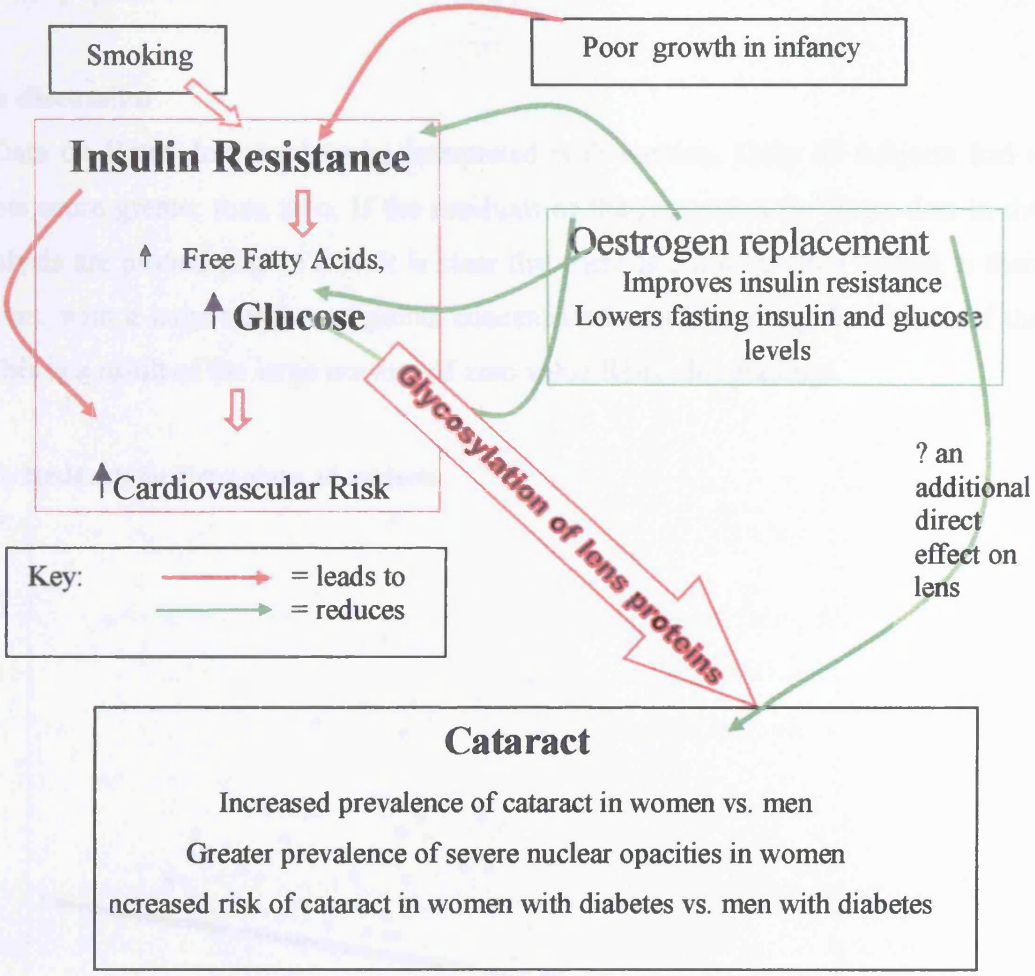
How might the apparent protective effect of oestrogens be mediated? Postmenopausal oestrogen replacement therapy reduces the risk of cardiovascular disease in women, partly because of the increase in beneficial high-density lipoproteins (Carey, Jenkins et al. 1996; Carey, Walters et al. 1997). Studies of the effect of oestrogens on insulin resistance in women suggest that oestrogens might act by reducing insulin resistance (Lindheim, Duffy et al. 1994). Lindheim found that a reduction in insulin sensitivity was observed in postmenopausal women compared to premenopausal women. A degree of insulin resistance appeared to be present in some healthy postmenopausal women. Oestrogen appeared to improve insulin sensitivity in these women (Lindheim, Buchanan et al. 1994).

This is backed up by epidemiological studies showing that oestrogen replacement therapy has been shown to reduce the levels of glucose and insulin in postmenopausal women (Fineberg 2000). The effect of sex hormones on NIDDM in men is different to women (Haffner, Katz et al. 1991; Haffner, Karhapaa et al. 1994). Women with NIDDM often have increased levels of free testosterone and low levels of sex-hormone binding globulin (Haffner, Katz et al. 1991). However, men with NIDDM are reported to have lower testosterone levels (Hansen 1995). Normal testosterone levels in men are associated with low insulin concentrations and increased glucose disposal. This may help explain why increased androgenicity is associated with increased NIDDM in women but not men.

In summary

Women are more prone to obesity than men (Poehlman, Toth et al. 1995). Women with a high BMI are predisposed to insulin resistance, IGT and NIDDM. This increases the risk of glycation of lens proteins. The prevalence of IGT and NIDDM is higher in women than men. (Table D1) Women with NIDDM have a threefold risk of developing cataract compared to men with NIDDM (Harding, Egerton et al. 1993). The loss of the protective effect of oestrogens at menopause combined with a greater prevalence of IGT results in an excess of lens opacities in women. Oestrogens protect women against nuclear cataract (Klein, Klein et al. 1994; Benitez del Castillo, del Rio et al. 1997; Cumming and Mitchell 1997). The possible interactions of insulin resistance syndrome and oestrogen on the lens are summarised in Figure D2

Figure D2. Summary of possible interactions of insulin resistance syndrome and oestrogen on the lens.



Early growth impairment and low birth weight are associated with impaired glucose tolerance and diabetes in adults (Phillips, Barker et al. 1994). People who were thin at birth but obese as adults were the most resistant to insulin. Insulin resistance may explain the findings of Evans et al, that age-related nuclear lens opacities are associated with reduced growth before 1 year of age (Evans, Rauf et al. 1998)

Part of the effect of smoking on nuclear cataract may be mediated through insulin resistance. Simon et al demonstrated that smokers have a higher waist-hip ratio than non-smokers. They felt that smoking associated differences in the waist-hip ratio may mediate, at least in part, to the higher prevalence of diabetes amongst smokers of more than 10 cigarettes per day (Simon, Seeley et al. 1997)

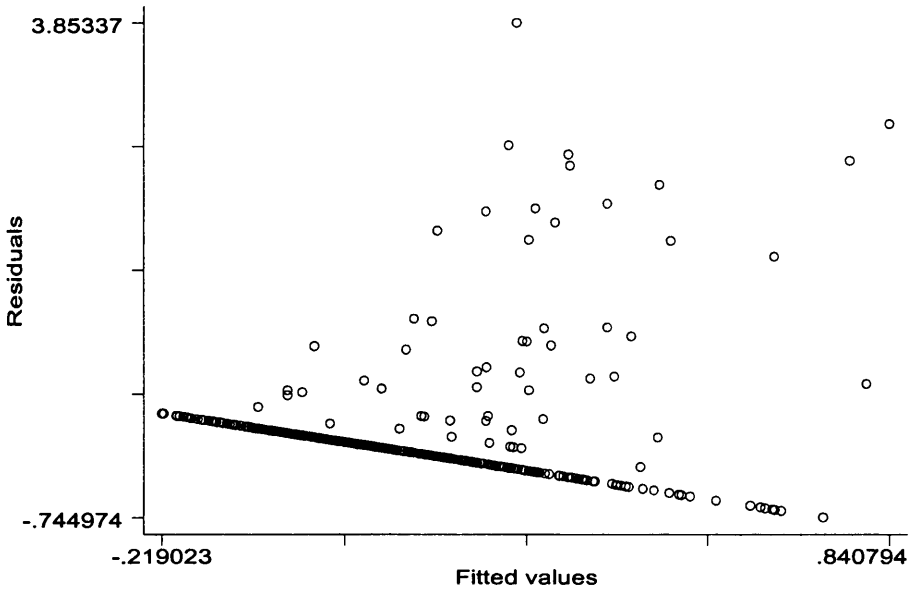
A genetic predisposition to NIDDM and obesity in non-Caucasian populations in the United Kingdom (McKeigue, Shah et al. 1991), and in the developing world

(Ramachandran, Snehalatha et al. 1994), may account for some of the excess of cataract seen in these populations.

Analysis discussion

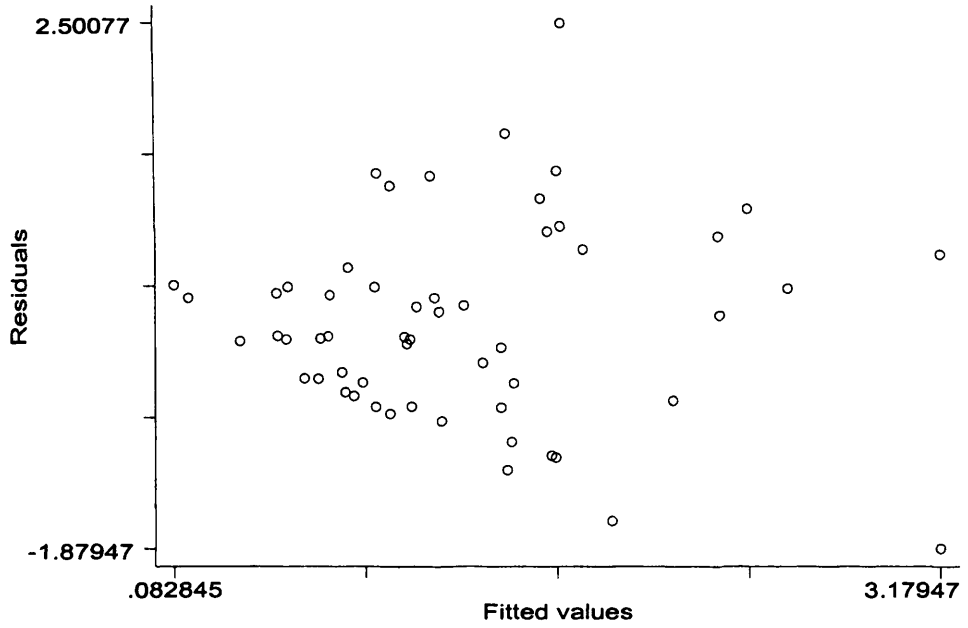
Data on Retro-dots need to be interpreted with caution. Only 83 subjects had a Retro-dots score greater than zero. If the residuals of the regression for Retro-dots in the final analysis are plotted (figure D3), it is clear that there is a non-random pattern to their distribution, with a large number of points concentrated in a line along the bottom of the graph. This is a result of the large number of zero value Retro-dot gradings.

Figure D3: Residuals for Retro-dots; all subjects



If only the non-zero values of the retro-dots are analysed in the regression than plotting the residuals results in a more random, less patterned distribution of the residuals (figure D4).

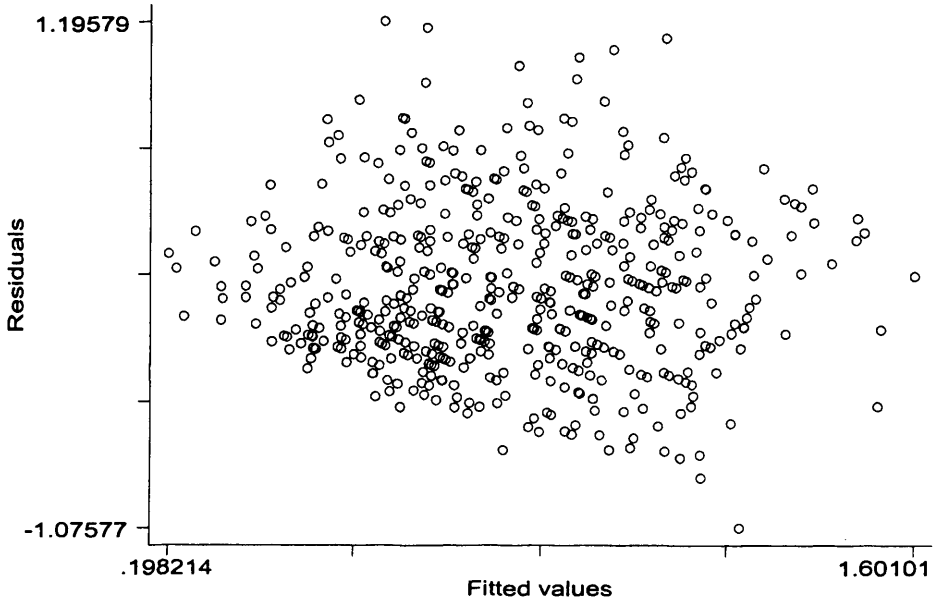
Figure D4: Residuals for Retro-dots; non zero values only.



By comparison, the pattern of the distribution of residuals found for the regression of Brunescence is a more even and random pattern (figure D4). The latter does however have a far greater number of subjects included in the regression and this is reflected in the more random distribution of points in the graph.

In summary, if all the subjects are included in the analysis, then the distribution of the residuals indicates that the results of the regression need to be interpreted with considerable caution. Similarly, if only non-zero values are included in the analysis, then it must be borne in mind that there are only 83 subjects included in the analysis.

Figure D5: Residuals for Brunescence.



In the final model the regression analyses assume that everything else in the regression is held constant. For example when regressing Brunescence against age at examination, the calculation assumes that diabetes is the same through out all the age ranges. However, people could be more likely to have diabetes as they age. Similarly, it is assumed that smoking and alcohol consumption will be held constant, however subjects may smoke and drink less as they age.

The racial composition of the population in the Melton Eye Study is almost entirely Caucasian. The results of the Study may not be generalisable to the rest of the UK population on racial grounds alone.

Although the population is relatively small, the range of uncertainty around the estimated prevalences for nuclear cataract is reasonably narrow (around 4% for both White Scatter and Brunescence). However, the size of the study means that the prevalence data might not be applicable to the whole of the UK.

11.11 Future research direction

Insulin resistance provides a common route via the sorbitol and lens glycation pathways for the association of many risk factors with cataract (Harding, Egerton et al. 1993). These include hypertension (Klein, Klein et al. 1995), increased waist-hip ratio (Leske, Wu et al. 1999), obesity and body mass index (Glynn, Christen et al. 1995; Caulfield, West et al. 1999).

Consideration of insulin resistance is important because it is one of the risk factors for cataract that can be modified (Poehlman, Toth et al. 1995).

In the Melton Eye Study, research can be directed at the relationship of insulin resistance and cataract. Serious consideration should be given to measuring insulin resistance rather than just glucose and glycated haemoglobin levels. The temporal relationship of hormone replacement therapy with cataract can be explored.

Controlled trials of hormone replacement therapy should include a component examining the lenses of women in the trial (Cumming and Mitchell 1997).

Research into the association of insulin resistance and cataract in communities with a high prevalence of diabetes and insulin resistance (McKeigue, Shah et al. 1991; Ramachandran, Snehalatha et al. 1994), would shed light on the excess burden of cataract in these communities.

Further research into the genetics of cataract (Hammond, Snieder et al. 2000), could include a component on the contribution of the genetics of insulin resistance (Austin and Selby 1995)

With regard to some of the practical aspects of the methods used, some improvements could be made. In particular, the difficulties with the soft ware for analysing nuclear cataract would need to be resolved. This would allow an objective measure of drift in grading as well as a more accurate measure of different components of the nucleus. The nuclear images remain archived and would be available for future research.

Appendices

STUDY NUMBER |_|_|_|_|_|_|_|

CONFIDENTIAL

QUESTIONNAIRE

This booklet is the property of
Department of Ophthalmology
Clinical Sciences Building
Leicester Royal Infirmary
Leicester LE2 7LX
0116 2523147

Preliminary Checks

- Introduce yourself
- Check that informed consent has been given
- Thank the person for coming for the interview
- Explain that the eye examination will follow the questionnaire
- Ask them if they have any questions before you start

Date (dd-mmm-yy) ☐☐ ☐☐☐ ☐☐ **Interviewer** ☐☐

PERSONAL DETAILS

Surname _____ **Forename** _____

Address _____

_____

Postcode ☐☐☐☐☐☐☐

Date of Birth (dd-mmm-yy) ☐☐ ☐☐☐ ☐☐ **Sex** (M/F) ☐

Age ☐☐

Are you married ? (prompt) ☐

1: Single
2: Married/Co-habiting
3: Separated
4: Divorced
5: Widowed

Do you live alone ? (y/n/dk) ☐

If YES, **How long have you lived alone ?** (years) ☐☐

Assess the subject's ethnic origin ☐

1: White Caucasian
2: South Asian
3: Black
4: Oriental
5: Other (specify)

_____

OPHTHALMIC MEDICAL HISTORY

OM1 **Have you ever been examined by a hospital eye doctor ?** (y/n/dk) ☐

If YES or UNSURE ask for diagnosis/symptoms hospital **CODE**

1: _____ ☐

2: _____ ☐

3: _____ ☐

4: _____ ☐

If NO go to OM5

OM2 **Have you ever had laser treatment to your eye ?** (y/n/dk) ☐

***If YES,* what condition was it for ?** **RE** ☐ **LE** ☐

1: Diabetic problem
2: Vein block
3: Glaucoma
4: Retial tear
5: Unsure
6: Other Specify _____

OM3 **Have you ever had surgery on your eye ?** (y/n/dk) ☐

***If YES,* what was it for ?** (tick all)

	RE	LE
Cataract	☐	☐
Glaucoma	☐	☐
Retinal Detachment	☐	☐
Unsure	☐	☐
Other	☐	☐

Specify _____

OM4 **Have you ever had an eye injury examined by a hospital doctor ?** (y/n/dk) ☐

***If YES,* what type of injury was it ?** **RE** ☐ **LE** ☐

1: sharp injury, eg glass or metal splinter
2: chemical injury, eg acid or alkali burn, wet cement
3: blunt injury, eg blow from a fist or a ball
4: Unsure
5: Other (specify)

_____

OM5 **Do you wear glasses for reading ?** (y/n/dk) ☐

If YES, **How old were you when you first wore them ?** ☐☐

OM6 **Have you ever worn glasses or contact lenses to see clearly in the distance ?** (y/n/dk) ☐

If YES, **How old were you when you first wore them ?** ☐☐

Do you still wear them ? (y/n) ☐

If NO, **at what age did you stop ?** ☐☐

are/were the glasses for long or short sight ?(l/s/dk) ☐

OM7 **Have you ever had your eyes examined by an optician ?** (y/n/dk) ☐

If YES, **How long ago was the last time ?** (months) ☐☐☐

VISION PROBLEMS

VP1 **When wearing your glasses do you have difficulty with .....**
never (1), sometimes (2) or often(3)
(not applicable 4, Don't know 5)

Reading newspaper print ☐

Reading a telephone directory ☐

Identifying people you know across the street ☐

Driving at night ☐

GENERAL MEDICAL HISTORY

GM1 **Have you ever been told by a doctor that you have high blood pressure ?** (y/n/dk) ☐

If YES, **how old were you when first told ?** ☐☐

GM2 **Have you ever been told by a doctor that you have a heart problem ?** (y/n/dk) ☐

If YES, **how old were you when first told ?** ☐☐

What sort of heart problem do you have ? (tick all)

Angina ☐

Heart attack ☐

Unsure ☐

Other (specify) _____ ☐

Have you ever had heart surgery ? (y/n/dk) ☐

Specify _____

GM3 **Have you ever had a stroke, transient ischaemic attack, or brain haemorrhage ?** (y/n/dk) ☐

Specify _____

GM4 **Do you suffer from migraine headaches ?** (y/n/dk) ☐

If NO, **have you suffered from them in the past ?** (y/n/dk) ☐

If YES to current or past migraines

How many times per month ? ☐☐

GM5 **Have you ever been told by a doctor that you had cancer ?** (y/n/dk) ☐

If YES, **what type of cancer was it ?** ☐☐

1: Prostate
2: Lung
3: Breast
4: Cervix
5: Skin (unspecified)
6: Skin - Rodent ulcer/Basal cell
7: Skin - Squamous cell
8: Skin - malignant melanoma
9: Unsure
10: other (specify)

GM6 **Have you ever been told by a doctor that you have diabetes ?** (y/n/dk) ☐

If YES, **How old were you when first told ?** ☐☐

What treatment are you on ? ☐

1: None
2: Diet only
3: Tablets
4: Insulin injection

Have you been told that the diabetes has affected your kidneys ? (y/n/dk) ☐

GM7 **Have you ever had an x-ray of your head other than by a dentist ?**(y/n/dk) ☐

GM8 **Have you ever had a CT** (computerised tomography) **scan of your head?**(y/n/dk) ☐

GM9 **Have you ever had diarrhoea severe enough to keep you in bed for 3 days or more?** (y/n/dk) ☐

If YES, **How many such episodes have you had ?** ☐☐

GM10 **Have you ever had heat stroke severe enough to keep you in bed for 3 days or more ?** (y/n/dk) ☐

If YES, **How many such episodes have you had ?** ☐☐

GM11 Have you ever had a blood transfusion ? (y/n/dk) ☐

If YES, What was it for ? (code each reason) ☐☐☐

2: Trauma
3: Bowel/Ulcer
4: Pregnancy
6: Unsure
7: Other (specify)

_____

How many transfusions have you had ? ☐☐

GM12 Have you had any other medical problems that required hospital treatment or prolonged treatment by your GP? (y/n/dk) ☐

If YES, ask for diagnosis/symptoms hospital

CODE

1: _____ ☐

2: _____ ☐

3: _____ ☐

4: _____ ☐

HORMONAL HISTORY (women only)

HH1 Have you ever taken the oral contraceptive pill ? (y/n/dk) ☐

If YES, How old were you when you started ? ☐☐

For how many years did you take it ? ☐☐

HH2 Are you taking Hormone Replacement Therapy (HRT) ? (y/n/dk) ☐

If NO, Have you ever taken it in the past ? (y/n/dk) ☐

If YES to current or past use

For how many years did/have you taken HRT? ☐

HH3 How many completed pregnancies have you had ? ☐☐

HH4 How old were you when your periods began ? ☐☐

HH5 **How old were you when your menopause started ?** ☐☐

VITAMINS, SUPPLEMENTS AND DIETS

VT1 **Do you regularly take vitamins or mineral supplements ?** (y/n/dk) ☐

If NO, **have you ever taken them in the past ?** (y/n/dk) ☐

If still NO, prompt women for when pregnant & go to VT2

Prompt for any CURRENT SUPPLEMENTS *enter name & duration of use*

	CODE	DURATION -MTHS
1:		
2:		
3:		
4:		
5:		

Prompt for any PAST SUPPLEMENTS *enter name & duration of use*

	CODE	DURATION -MTHS
1:		
2:		
3:		
4:		
5:		

VT2 **Do you eat meat or fish at least once a week ?** (y/n/dk) ☐

VT3 **Have you been on a diet to lose weight in the last year ?** (y/n/dk) ☐

VT4 **Have you been on any other special diet in the last year ?** (y/n/dk) ☐

If YES, Specify _____

DRUGS AND MEDICATIONS

DM1 **Are you currently taking any medicines prescribed by a doctor?** (y/n/dk) ☐

If YES, Prompt for any CURRENT DRUGS enter name & duration of use

	CODE	DURATION -MTHS
1:		
2:		
3:		
4:		
5:		
6:		

DM2 **Have you taken any other prescribed medicines for more than 3 months in the past ?** (y/n/dk) ☐

If YES, Prompt for PAST DRUGS enter name & duration of use

	CODE	DURATION -MTHS
1:		
2:		
3:		
4:		

DM3 **Have you ever been prescribed oral steroids such as Cortisone or Prednisone ?** (y/n/dk) ☐

DM4 **Have you ever been prescribed steroid eye drops ?** (y/n/dk) ☐

DM5 **Do you take aspirin regularly ?** (y/n/dk) ☐

If NO, **Did you ever take aspirin regularly in the past?**(y/n/dk) ☐

If YES to current or past use

How many do/did you take a day ? ☐☐.☐

For how long did/have you take them?(mth) ☐☐☐

Why do/did you take them ? ☐

1: Headaches 4: Unsure
2: Arthritis 5: Other (specify) _____
3: Thin blood (prevent stroke or heart attack)

DM10 Do you take any other pain killers regularly ? (y/n/dk) ☐

If NO, **Did you ever take them regularly in the past?**(y/n/dk) ☐

If YES to current or past use

SPECIFY _____

How many do/did you take a day ? ☐☐.☐

For how long did/have you take them?(mth) ☐☐☐

SMOKING

SM1 **Have you smoked more than 100 cigarettes in your life ?** (y/n/dk) ☐

If NO, go to SM7

SM2 **How old were you when you started smoking cigarettes regularly ?** ☐☐

SM3 **Do you still smoke cigarettes?** (y/n/dk) ☐

If NO, **How old were you when you last stopped ?** ☐☐

SM4 **How many cigarettes do/did you smoke each day ?** ☐☐☐

SM5 **Was there ever a time when you smoked more heavily than this?** (y/n/dk) ☐

If YES, **How many did you smoke each day ?** ☐☐☐

For how long were you smoking this heavily ?(years) ☐☐

SM6 **Do/did you inhale ?** ☐

SM7 **Have you ever regularly smoked cigars or a pipe ?** (c/p/b/n) ☐

ALCOHOL

AL1 **In a typical week, on how many days do you drink alcohol?** ☐

If any, **Typically how much do you drink on such days ?**

Specify type & amount

_____

_____

_____

_____

_____

units ☐☐.☐

weekend, if different ☐☐.☐

For how long have you been drinking this amount ? (yrs) ☐☐

AL2 **Has there ever been a time when you drank more heavily than you do now ?** (y/n) ☐

If YES,

In a typical week, on how many days did you drink then ? ☐

Typically how much did you drink in a day at that time ?

Specify type & amount

_____

_____

_____

_____

_____

units ☐☐.☐

weekend, if different ☐☐.☐

How long did that period last ? (years) ☐☐

How long ago did it end ? (years) ☐☐

Ordinary beer/lager	1 pint	2
	1 can	1½
Export beer	1 pint	2½
	1 can	3
Strong beer/lager	1 pint	4
	1 can	3

Cider	1 pint	3
Strong Cider	1 pint	4
Spirits	1 measure	1
	bottle	30
Wine	glass	1
	bottle	10

AL3 *If subject has ever been a drinker ask,*

We should like to ask about your attitudes to your past or current drinking

Have you ever felt that you ought to cut down on your drinking ? (y/n) ☐

Have people ever annoyed you by criticising your drinking ? (y/n) ☐

Have you ever felt bad or guilty about your drinking ? (y/n) ☐

Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover ? (y/n) ☐

EARLY YEARS

EY1 **Were you born prematurely ?** (y/n/dk) ☐

EY2 **What were your parents' occupations ?**

title/grade/industry

Mother _____ ☐

_____

Father _____ ☐

_____

EY3 **At what age did you leave school ?** ☐☐

EY4 **How many years of higher education have you had?**(full time equivalent) ☐☐

ULTRA VIOLET LIGHT

UV1 **What countries have you lived in ?** (for at least 6 months)

COUNTRY	CODE	AGES FROM	AGES TO
1:(birth)		0	
2:			
3:			
4:			
5:			
6:			

UV2 *Starting at age when they left school take each country in turn and prompt for a full job history (minimum time in the job of 6 months)*

List the jobs and then for each ask..... would you say you worked
mainly indoors, (1)
about equally indoors and outdoors (2)
mainly outdoors (3)

JOB	CODE	AGE FROM	AGE TO	WORK

UV2 In the summer how much leisure time do you spend outdoors between 10 am and 4 pm eg gardening, walking or playing golf ? (hrs per week) ☐☐☐

WEEKDAY _____ x5 WEEKEND _____ x2

UV3 Have you ever been abroad on holiday ? (y/n) ☐

If YES, How many times have you been on holiday to hotter countries ? ☐☐

UV4 When out in the sun do you wear a hat to shade your eyes
usually (1) occasionally (2) or hardly at all (3) ? ☐

UV5 When out in the sun do you wear sunglasses
usually (1) occasionally (2) or hardly at all (3) ? ☐

UV6 Have you ever used a sun lamp without protective glasses ? (y/n/dk) ☐

CURRENT WORK

WK1 **Are you working at the moment ?** (prompt for details) ☐☐

1: Full time employee
2: Part-time employee
3: Retired
4: Home-maker
5: Self-employee with employee
6: Self-employed without employee
7: Unemployed
8: Waiting to start a job
9: Long term ill/disabled
10: Other (specify)

Please describe your current job (or last job if not working) ☐

title/grade/industry

_____

_____

WK2 *If MARRIED OR WIDOWED ask*

Does/did your husband/wife work ? (prompt & code 1-10) ☐☐

Please describe their job (or last job if not working) ☐

title/grade/industry

_____

_____

GENERAL COMMENTS

Comment on an irregularities during the interview and explain the reasons for any questions not answered

_____

_____

BLOOD SAMPLE

BS1 **Blood sample taken ?** (y/n) ☐

If NO, Specify reason _____

If YES, time blood taken (24hr clock) ☐☐☐☐

time of last meal (24hr clock) ☐☐☐☐

STUDY NUMBER | M | | | | | - | |

CONFIDENTIAL

EXAMINATION BOOKLET

This booklet is the property of
Department of Ophthalmology
Clinical Sciences Building
Leicester Royal Infirmary
Leicester LE2 7LX
0533-523153

General Examination

Height (cm)				
Weight (kg)				
waist hip ratio	waist		hips	
blood pressure	systolic		diastolic	

Eye examination

Current Rx (Focimeter)	Sphere		Sphere	
	cyl		cyl	
	axis		axis	
	Add		Add	
Forgot glasses (y/n)				
Auto refraction	Sphere		Sphere	
	cyl		cyl	
	axis		axis	
Subjective Refraction	Sphere		Sphere	
	cyl		cyl	
	axis		axis	
	add		add	

Visual Acuity (logmar) — With current correction

Reading Distance (m)

Logmar Chart R.	Right correct	logmar	Left correct
H V Z D S		1.0	
N C V K D		0.9	
C Z S H N		0.8	
O N V S R		0.7	
K D N R O		0.6	
Z K C S V		0.5	
D V O H C		0.4	
O H V C K		0.3	
H Z C K O		0.2	
N C K H D		0.1	
Z H C S R		0.0	
S Z R D N		-0.1	
H C D R O		-0.2	
R D O S N		-0.3	

Visual Acuity (logmar) **With subjective refraction**

Reading Distance (m)

Chart 1 Right eye	Right correct	logmar
N C K Z O		1.0
R H S D K		0.9
D O V H R		0.8
C Z R H S		0.7
O N H R C		0.6
D K S N V		0.5
Z S O K N		0.4
C K D N R		0.3
S R Z K D		0.2
H Z O V C		0.1
N V D O K		0.0
V H C N O		-0.1
S V H C Z		-0.2
O Z D V K		-0.3

Visual Acuity (logmar) **With subjective refraction**

Reading Distance (m)

Chart 2 Left Eye	logmar	Left correct
D S R K N	1.0	
C K Z O H	0.9	
O N R K D	0.8	
K Z V D C	0.7	
V S H Z O	0.6	
H D K C R	0.5	
C S R H N	0.4	
S V Z D K	0.3	
N C V O Z	0.2	
R H S D V	0.1	
S N R O H	0.0	
O D H K R	-0.1	
Z K C S N	-0.2	
C R H D V	-0.3	

Contrast Sensitivity Tick correct letters until 2 in a row incorrect

Right Eye		Left Eye		Both Eyes	
H S Z	D S N	V R S	K D R	H S Z	D S N
C K R	Z V R	N H C	S O K	C K R	Z V R
N D C	O S K	S C N	O Z V	N D C	O S K
O Z K	V H Z	C N H	Z O K	O Z K	V H Z
N H O	N R D	N O D	V H R	N H O	N R D
V R C	O V H	C D N	Z S V	V R C	O V H
C D S	N D C	K C H	O D K	C D S	N D C
K V Z	O H R	R T Z	H V R	K V Z	O H R

Anterior Segment

Assess features in anterior and posterior segments as follows

0. absent 1. present 2. questionable 3. can't grade

Pupils (RAPD) (Y/N) ☐ ☐

lids

blepharitis (1+ to 3+)
(posterior blepharitis)

1)lid notching ☐ ☐
2)post. displacement of ducts ☐ ☐
3)plugging of gland orifices ☐ ☐
seborrhoeic ☐ ☐
mixed ☐ ☐

other lid (describe) _____ ☐ ☐

conjunctiva

	Right	Left
pingueculum	☐	☐
other *(describe)*	_____ ☐	☐

cornea

check especially for opacities that might affect vision

pterygium	☐	☐
corneal arcus	☐	☐
climatic keratopathy	☐	☐
other	_____ ☐	☐

Anterior chamber ☐ ☐

1. deep 2. occludable 3. CG

Iris *Check standards*

colour	☐	☐
other	_____ ☐	☐

Have you had any problems with your eyes in the last week? **y/n**

1.	floaters	6.	dryness
2.	itching	7.	grittiness
3.	burning	8.	soreness
4.	redness	9.	other _____
5.	stickiness		

Near Vision

1.3 My father takes me to school every day in his big green car	0.6 My mother loves to hear the young girls sing in the morning	**MINREAD CHART E Right Eye**
1.2 Everyone wanted to go outside when the rain finally stopped	0.5 The young boy held his hand high to ask questions in school	-0.1 The teacher showed the children how to draw pretty pictures
1.1 The women met on the street and talked about their children.	0.4 My brother wanted a glass of milk with his cake after lunch	-0.2 Nothing could ever be better than a hot fire to warm you up
1.0 My father asked me to help the two men carry the box inside	0.3 I do not understand why we must leave so early for the play	-0.3 The old man caught a fish here when he went out in his boat
0.9 Three of my friends had never been to a circus before today	0.2 It is more than four hundred miles from my home to the city	-0.4 Our mother tells us that we should wear heavy coats outside
0.8 My grandfather has a large garden with fruit and vegetables	0.1 Our father wants us to wash the clothes before he gets back	-0.5 One of my brothers went with his friend to climb a mountain
0.7 He told a long story about ducks before his son went to bed	0.0 They would love to see you during your visit here this week	Number of incorrect lines ☐☐

1.3 The three elephants in the circus walked around very slowly	0.6 Put your first name on this paper if you will help tomorrow	**MINREAD CHART F Left Eye**
1.2 We could not guess what was inside the big box on the table	0.5 The father gave his children some fruit for lunch every day	-0.1 The teacher wanted the children to learn how to draw a boat
1.1 The two friends did not know what time the play would start	0.4 Please do not make noise while they are reading their books	-0.2 We like to listen to music when we are eating our breakfast
1.0 She wanted to show us the new toys she got for her birthday	0.3 We sometimes take long walks together if it is warm outside	-0.3 Three of my closest friends are going to visit him tomorrow
0.9 The mother told her son that she wanted him to go to school	0.2 The snow fell softly this morning before our family woke up	-0.4 She gave a glass of water to her mother before going to bed
0.8 An old man took a picture of my sister and her little puppy	0.1 Many people came to help us clear the place after the party	-0.5 My brother was not feeling very well so he did not go today
0.7 Ten different kinds of flowers grow by the side of the road	0.0 He could see a bird outside if he looked through his window	Number of incorrect lines ☐☐

Lens photographs(Y/N)

Scheimflug not done **reason**

Retro photos not done **reason**

Macular photographs(Y/N)

Macular photo not done **reason**

Intra ocular Pressure
(Photo lens and macula 1st)

Vitreous PVD
(0. absent 1. present 2. questionable 3. can't grade)

Other

Fundus

disc
cup disc ratio
peripapillary atrophy (0-3)
optic atrophy (0-3)
? glaucoma damage(describe)

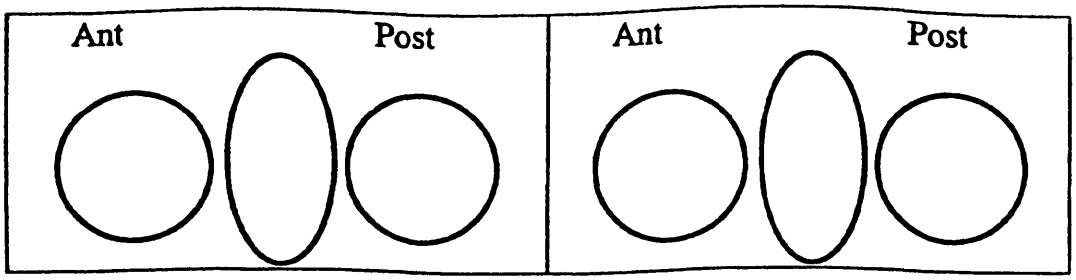
Macular Degeneration
Early Armd
(0. absent 1. present 2. questionable 3. can't grade)
1. drusen
2. Hyperpigment
3. RPE degen

Geographic atrophy
Exudative Macular degen

Diabetic Retinopathy
NVD (0-3)
NVE (0-3)
Vitreous/pre ret haem (0-3)
non-prolif. retinopathy (0-3)
(If present circle appropriate no.) 1. 2. 3. 4. 5. 6. 1. 2. 3. 4. 5. 6.
1. microaneurysms
2. retinal hemorrhages
3. exudates
4. IRMA
5. venous beading
6. cotton wool spots

Other lesions of note

OXFORD CLINICAL GRADING



Right Eye			Left Eye		
Feature		Comments	Feature		Comments
pupil size			pupil size		
asc			asc		
psc			psc		
cortical spokes			cortical spokes		
waterclefts			waterclefts		
fibre folds			fibre folds		
vacuoles			vacuoles		
retro-dots			retro-dots		
brunescence			brunescence		
white scatter			white scatter		
focal dots			focal dots		
other features			other features		
record major clock hours (cortical)			record major clock hours (cortical)		

LOCS III SLIT LAMPGRADING

opalescence			opalescence		
brunescence			brunescence		
cortical			cortical		
psc			psc		

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