

Age-related cataract

Epidemiology, pathogenesis and management



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Module 5 Part 7 of the ageing eye series

Age-related cataract is the leading cause of visual impairment worldwide, and it is estimated that globally more than 20 million people are bilaterally blind from this condition. The continued increase in life expectancy, along with the growth of the world's population, will ensure that cataract continues to be a major public health problem in years to come.

Age-related cataract involves a progressive increase in lens opacification which deteriorates the quality of the retinal image, reducing visual acuity and if untreated, leads ultimately to blindness (Figure 1).

Three main types of lens opacity have been described in age-related cataract – nuclear, cortical and sub-capsular. Pure forms of cataract (with only one type of opacity present) are found more frequently in the early stages of the disease, but as the cataract becomes more severe, several types of opacity often co-exist in the same lens producing the so-called mixed type of cataract. In terms of prevalence, cortical cataract is the most common, followed by nuclear and posterior subcapsular. Effective surgical intervention leads to a dramatic improvement in visual function, and typically 85% of eyes have a best-corrected acuity of 6/12 or better post-surgery¹. However, lens extraction is not universally available, and research continues to develop non-surgical treatments which can inhibit, or delay cataract formation.

Recently, some progress has been made towards an understanding of the molecular events involved in the process of lens opacification², and several novel reagents have been developed which have been shown to be effective cataract inhibitors in animal models. This article summarises the epidemiological features and possible risk factors in age-related cataract. Current pathogenic theories for age-onset cataractogenesis are also discussed along with current management and prevention strategies.

The normal lens

Anatomy and physiology

The primary function of the lens is to transmit visible light and sharply focus it on the retina. It contributes one third of the eye's total dioptric power and by changing its shape, it is able to fulfil the requirements of the accommodative process. The lens is a relatively simple structure, comprising regularly arranged concentric layers of elongated lens fibres which are continually formed at the equatorial germinative zone. The inner part of the lens, which contains those fibres laid down in early life, is termed the nucleus and the outer part



Figure 1
Typical nuclear cataract in an elderly patient

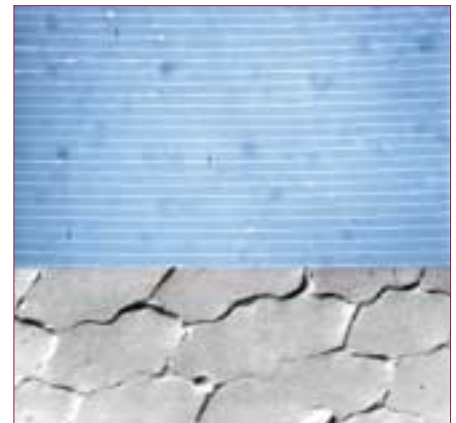


Figure 2
Lens fibres are arranged in regular arrays with thin cell membranes and minimal extracellular space

containing younger fibres is known as the cortex. This unique aspect of lens growth means that old cells are not replaced by new, and so the lens has developed strategies to minimise damage from the cumulative effects of ultraviolet radiation and other oxidative insults.

An elastic capsule synthesised by the lens epithelium, which postnatally is found only on the anterior surface and equatorial zone, encloses the lens. In keeping with its optical properties, the lens is highly transparent in the visible region of the spectrum. This is surprising for a structure containing a high concentration of protein (33%)³. Nevertheless, a young lens transmits most light between 450nm and 1400nm. The

basis of lens transparency is a series of special anatomical and physiological features which keep light scatter to a minimum:

- Lens fibres contain a high concentration of a unique series of proteins, termed crystallins (α , β and γ) which are tightly packed and demonstrate short-range order
- Lens fibres possess narrow cell membranes and are grouped in regular hexagonal arrays with minimal extracellular space (Figure 2)
- Lens fibres do not possess nuclei or cytoplasmic organelles which could act as potential scatter sources
- Changes in refractive index within the lens occur over distances less than the wavelength of light
- The electrolyte balance of the lens is tightly regulated to maintain the constant hydration level which is critical for lens transparency

Energy production is almost entirely the result of glucose metabolism⁴. Glucose enters the lens from the aqueous by a combination of diffusion and facilitated transport, and is broken down via a number of metabolic pathways – anaerobic glycolysis, hexose monophosphate shunt, aerobic glycolysis and the sorbitol pathway. However, the avascularity of the lens means that oxygen tension is always low and, therefore, anaerobic glycolysis predominates.

The ageing lens

Many changes occur in the lens with age⁵. These can be grouped under the following headings – structural, optical, metabolic, and molecular.

Structural

The lens continues to grow throughout life through the regular addition of new lens fibres. Adult lens dimensions change in a complex manner, and from the end of the second decade, the sagittal thickness shows a greater percentage increase than the equatorial diameter. This would be associated with an increased dioptric power, were it not for a compensatory change in refractive index. Increased growth also results in changes in the mechanical properties of the lens, which is a major contributor to presbyopia. With age, changes in the uniform appearance of the lens also occur. These principally affect the superficial equatorial cortex and include membrane ruptures and fluid-filled vacuoles⁵.

Optical

The young human lens transmits approximately 100% of incident light. With age, light transmission is reduced, with an associated increase in light scatter (Figure 3). Increased scatter occurs in all regions, although it is maximal in the deep cortex

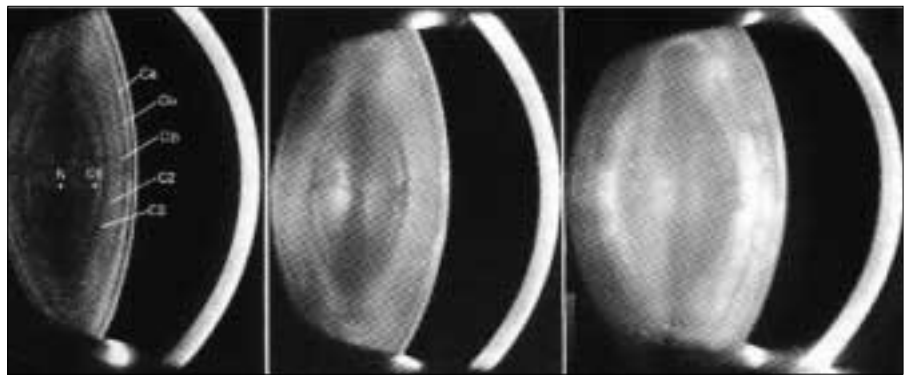


Figure 3 Schimmelpflug images of light scatter in the ageing lens (lenses at 20 years, 40 years and 80 years)

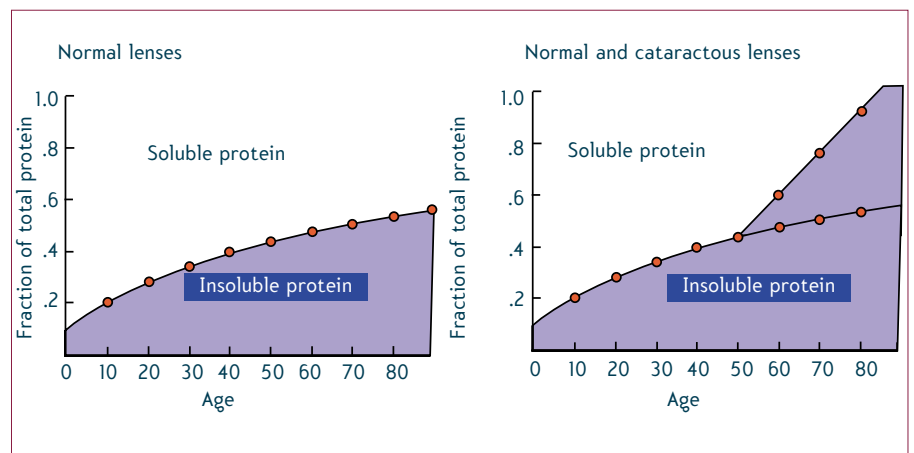


Figure 4

Graphs showing increase in insoluble protein fraction with age and in cataract

and nucleus. The intensity of back-scattered light from the lens continues to increase until physiological scatter gradually merges into the pathological scatter of nuclear cataract. Even the newborn lens is faintly yellow. With age, the post-natal accumulation of yellow chromophores leads to an increased yellow colouration⁶. These molecules also contribute to the increased 'blue fluorescence' which is a feature of the ageing lens. The increased light absorption of the lens is greatest at the blue end of the spectrum (460-470nm). This is thought to be an adaptive process to protect the retina from these potentially damaging wavelengths, although it may also contribute to the altered colour perception that occurs with age⁷.

Metabolic

Changes in the bioactivity of several anti-oxidant systems, e.g. glutathione and ascorbate, occur with age. Since these systems normally protect tissues from oxidative damage by scavenging free radicals, it is possible that their depletion may increase the susceptibility of the lens to oxidation.

Molecular

One of the most important ageing changes is the modification of lens proteins,

including crystallins and the various cytoskeletal and membrane proteins. Crystallins make up 90% of lens proteins and account for its high refractive index. They exist in the cytoplasm of lens fibres as a complex protein solution. The majority of proteins exist in a soluble phase, which favours transparency. With age, an increased number of proteins leave the soluble phase and form high molecular weight aggregates (Figure 4). The primary mechanism for protein aggregation is post-translational modification, a process involving disulphide bond formation and non-enzymatic glycation³. These changes are more pronounced in the nucleus, which contains the oldest proteins. The steady increase in insoluble protein aggregates with age is a contributing factor to increased light scatter⁵.

Epidemiology and risk factors

The goal of epidemiological research is to identify factors which are associated with a particular disease, and also to determine whether the relationship is one of cause and effect⁸. This section reviews some basic epidemiological features of cataract and summarises the known risk factors in cataractogenesis.

Most of the available data on the epidemiology of cataract comes from cross-

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» **Table 1**

Summary of the different types of epidemiological study

STUDY DESIGN	DESCRIPTION
Cross-sectional	Association between the disease and the factors under consideration is determined at one point in time
Case-controlled	In a case-controlled study, the investigator starts with a group of people with the disease (cases) and a group without the disease (controls) and looks backwards in time to analyse the role of the factors under consideration
Cohort	In this type of study, individuals are categorised according to exposure to a possible risk factor. Cohort studies can be either retrospective or prospective

sectional, case-controlled, and cohort studies (the distinction between each type of study is outlined in **Table 1**). Studies vary as to their definition of cataract. Some define cataract as opacification associated with significant visual loss, whilst others describe any opacity within the lens as cataract. Another important variable is the anatomical location of the opacity. It is becoming increasingly apparent that nuclear, cortical and posterior subcapsular cataracts cannot be treated as single entities, and may possess different aetiologies. Furthermore, each sub-type varies in its susceptibility to particular risk factors.

Although a wide range of risk factors have been reported for cataract, only those risk factors, which have been consistently identified in large-scale epidemiological studies, are described here.

Smoking

A strong association has been found between nuclear cataract and smoking using a variety of study designs¹⁰. The attributable risk is about 20%, and appears to be cumulative, although the cessation of smoking is thought to substantially reduce the risk. The precise mechanism of lens damage is not clear. However, smokers seem to have an impaired ability to cope with oxidative stress in general, and several constituents of cigarette smoke are capable of causing chemical modification of lens proteins.

Sunlight

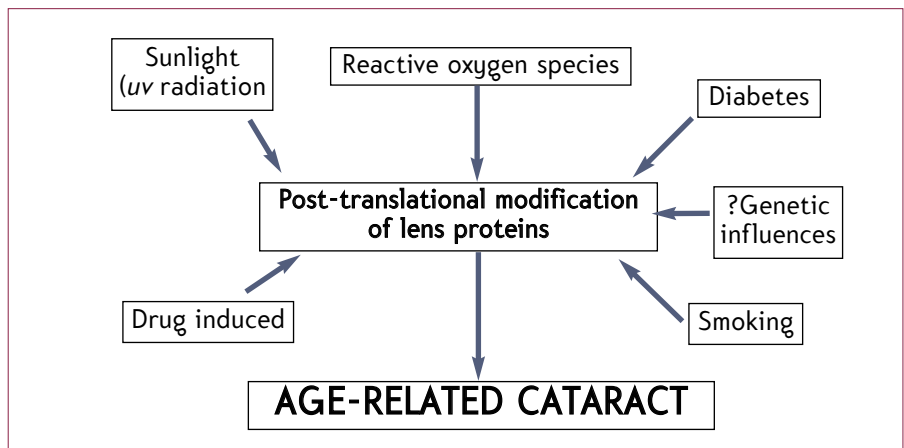
Ecological investigations of individuals living in climates with varying degrees of UVB radiation (285-315nm) indicate that a strong positive association exists between the prevalence and severity of cataract and ambient UVB exposure. Measurements of the exposure of individuals in cohort and case-controlled studies have shown that UVB light is a major risk factor for cortical cataract, and to a lesser extent, posterior sub-capsular cataract.

Alcohol use

Heavy beer drinking was found to be associated with a two-fold increase of cataract in a case-controlled study in Oxford³.

Ethnic factors

Large differences in the prevalence of age-related cataract have been reported between different racial groups. Lens opacities develop, on average, 12 years earlier in subjects living in the Indian sub-continent. The Framingham Eye Study found that the age-adjusted prevalence of cataract was three times higher for Indians than Americans. Whilst environmental factors, e.g. UV exposure and poor nutrition, must play a role, there is compelling evidence for a strong genetic influence. Indians of sub-continent descent living in the UK continue to show higher rates of lens opacity and cataract surgery than the indigenous population. Although



» **Figure 5**

Scheme showing the mechanisms involved in the pathogenesis of age-related cataract

Note: Netscape Navigator 5 and Internet Explorer 5 or more recent is recommended.

this does not rule out continued environmental differences, these data favour a genetic predisposition to cataract in this population.

Genetic factors

Population based studies have reported a two to threefold increase in cataract prevalence among subjects with affected siblings for all morphological types of cataract¹. The most direct evidence that genetic factors play a central role in the pathogenesis of cataract comes from classic twin studies^{11,12}. The genetic contribution for nuclear and cortical cataract was 48% and 59% respectively. Having established a strong genetic component, the challenge now is to identify 'cataract genes' with the future possibility of targets for intervention through gene therapy.

Pathogenesis

The pathogenesis of age-related cataract is both multifactorial and highly complex. It is also likely that aetiological differences exist between each morphological sub-type. Although most of our knowledge comes from the study of nuclear cataract, there is a consensus of opinion that post-translational modification of lens proteins plays a central role in all forms of cataract (Figure 5). These chemical changes accumulate over a number of years and are most marked in the lens nucleus, which contains the most long-lived proteins^{13,14}. Reactive oxygen species (ROS) such as peroxide, superoxide and hydroxyl radicals are thought to be a major cause of protein modification.

The healthy lens is normally well equipped with antioxidants, e.g. glutathione, ascorbate and catalase, which protect lens proteins against ROS. Glutathione is the most important antioxidant (Figure 6)¹⁵. Reduced glutathione (GSH) reacts with ROS and is converted to its oxidised form (GSSG). Restoration of GSH is achieved through the action of the enzyme glutathione reductase. Hydrogen peroxide (H_2O_2), which derives from sources both inside and outside the

lens, has been implicated as a major oxidant in the pathogenesis of experimental and human cataract. Normally, H_2O_2 is eliminated by GSH, or through the action of the enzymes – glutathione peroxidase and catalase. However, with age it appears that these protective mechanisms decrease in activity. As a result, a significant proportion of lenses from cataract patients show elevated H_2O_2 , and exposure of isolated animal lenses to the levels of H_2O_2 found in human cataract causes opacification¹³.

The lens epithelium is an initial target of H_2O_2 , inhibiting membrane lipids and transporter proteins such as $Na^+K^+ATPase$, and ultimately leading to epithelial cell death. This is quickly followed by a loss of lens transparency, caused by a number of factors such as osmotic shock, and crystallin aggregation. Although individuals may have a genetic susceptibility to ROS, the levels of exposure to environmental factors such as smoking and UVB exposure are also important variables. Another important more general variable in age-onset cataractogenesis is the presence of concomitant diseases, such as diabetes, and the intake of systemic drugs that are known to cause cataract.

Current management and prevention strategies

Surgical management

Surgical management is the mainstay of treatment for cataract in the western world, and a number of studies have shown that surgery significantly enhances the quality of patients' lives.

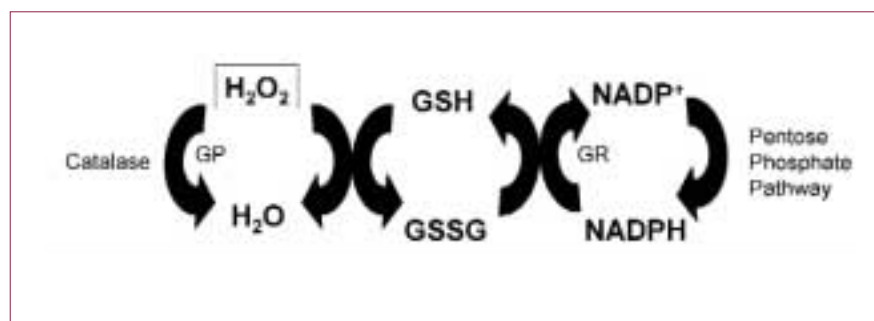
In the early stages of the disease, optimal refractive management and advice on glare reduction can lessen the impact of cataract formation. Surgery is considered when these measures are no longer adequate for the patient's visual needs. When considering surgery, both subjective and objective criteria need to be taken into account. Subjective criteria include the patient's assessment of his/own visual disability, the impact of visual disability on

their lifestyle and complaints of disabling glare. Objective criteria are generally based on the level of visual acuity, but the patient's medical and mental health must enable surgery to be performed safely.

Increasingly, the value of direct optometric referral has been recognised and several schemes are in operation using agreed protocols. The optometrist fills out a standard referral form, which provides information on visual impairment, general and ocular health, glare problems, and social factors. Most schemes also require the optometrist to discuss with the patient their willingness for surgery. A copy of the referral letter is sent to the hospital and the GP. The patient can then be listed for surgery based solely on the optometrist's report.

In most centres, small incision phacoemulsification, with the implantation of a posterior chamber IOL, is the procedure of choice in uncomplicated cataract. A short time before surgery, patients attend the eye department for biometry. Typically, this involves an ultrasound technique, but increasingly optical methods are being used. The biometer determines the IOL power for a number of refractive outcomes – it is usual practice to err slightly on the side of myopia. The phacoemulsification technique takes between 10 and 30 minutes and can be broken down into the following series of distinct steps:

1. Prior to surgery mydriatic drops are instilled, and the eye is anaesthetised: anaesthesia can be topical, sub-tenons, peribubar, retrobulbar. In rare cases, a general anaesthetic is required.
2. The main surgical incision is about 2.5mm across and is usually made in the cornea close to the limbus, using a self-sealing stepped tunnel technique. Additionally, one or more small (<1mm) incisions are made for instrument access.
3. A viscoelastic substance, such as Healon, is injected into the anterior chamber, to maintain its shape and prevent iatrogenic damage to the corneal endothelium.
4. A capsulorrhexis is then performed, which involves the production of a controlled circular tear in the anterior capsule. The dense lens nucleus is separated from the cortex by the injection of saline under the capsule.
5. The process of phacoemulsification entails the ultrasonic fragmentation and aspiration of the lens nucleus using a phaco probe.
6. After the nucleus has been removed the remnants of the cortex are aspirated. The modern generation of endocapsular IOLs are made from acrylic or silicon polymers that can be folded so they can be inserted into the capsular bag through small corneal incisions. Once the lens is in position the eye is irrigated with a topical antibiotic and a



➤ **Figure 6**

Glutathione anti-oxidant system in the lens. Hydrogen peroxide is neutralised by reduced glutathione (GSH). Oxidised glutathione (GSSG) is reformed by the enzyme glutathione reductase (GR) which uses NADPH as a co-factor. Glutathione peroxidase (GP) and catalase can also eliminate H_2O_2

- pad or transparent shield is applied.
7. For protection, the plastic shield is worn for the first 24 hours after surgery and then only at night for the next week.
 8. The patient continues to instil a combined corticosteroid/antibiotic eyedrop preparation for two to four weeks.
 9. Although in most cases refractive stability is achieved by one to two weeks, most surgeons instruct patients to wait for four to six weeks before visiting their optometrist for a final refraction.

Significant intraoperative complications of phacoemulsification in experienced hands are rare. Early post-operative complications include iris prolapse, raised IOP and infection. Cystoid macula oedema (CMO) and posterior capsular opacification (PCO) are the most common late complications. CMO can occur up to six months after surgery but is most common between four and eight weeks. Acuity is typically reduced to 6/24, and although CMO may resolve spontaneously it is usually treated by corticosteroids or non-steroidal anti-inflammatory drugs. PCO is by far the most common late complication, occurring in around 20% of patients within the first five years after surgery. However, this can be effectively treated by a Nd:YAG laser capsulotomy as an out-patient procedure.

Prevention strategies

Cataract remains a major global cause of blindness, and large sections of the world's population do not have access to cataract surgery. Therefore, the feasibility of cataract prevention by the elimination of risk factors or the development of an anti-cataract drug needs serious consideration¹⁶. Several risk factors are modifiable, e.g. heavy drinking and smoking. Furthermore, wearing appropriate protective eyewear and a hat can substantially reduce UVB exposure. The importance of diet, and particularly the anti-oxidant vitamins (A, C and E), has recently received a great deal of attention¹⁷.

Animal experiments have shown the protective benefits of anti-oxidants in experimental cataract, although the results of epidemiological studies in humans have been equivocal¹⁸. However, a reduced incidence of cataract has consistently been found in smokers who take multivitamin supplements. Anti-cataract drugs are an alternative and attractive prospect for cataract prevention and several novel agents have been shown to be effective in reducing cataract severity in animal models, but there is currently no available drug that is specifically licensed to treat or prevent cataract in humans. There is some evidence from epidemiological studies to support the beneficial effects of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen and paracetamol¹⁶. However, any beneficial effect should be offset against any potential gastrointestinal

side effects following their long-term use.

In conclusion, there is currently no promising non-surgical therapy for cataract, on the immediate horizon. However it is hoped that continued research into candidate genes for cataract together with an understanding of the precise molecular mechanism in lens opacification may generate new and exciting possibilities for future treatments.

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MCQs

**Module 5 Part 7
of the ageing eye series**

**Age-related cataract
Epidemiology, pathogenesis
and management**

**Please note there is only
ONE correct answer**

1. Which one of the following statements is incorrect regarding lens structure?
 - a. The lens represents the principal refractive component of the eye's optical system
 - b. The lens cortex contains the most recently synthesised lens fibres
 - c. The germinative zone of the lens is found within the equatorial zone
 - d. Lens fibres possess a high concentration of protein

2. What is the most important mechanism for the increased yellow colouration of the lens with age?
 - a. Short wavelength light scatter within the lens nucleus
 - b. Accumulation of yellow chromophores within the lens nucleus
 - c. Crystallin aggregation
 - d. Increased lens hydration

3. Which is the primary anti-oxidant within the lens?
 - a. Glutathione
 - b. Ascorbate
 - c. Superoxide dismutase
 - d. Catalase

4. In epidemiological research, what type of study looks at the association between risk factors and a disease at a known time point?
 - a. Case-controlled
 - b. Cohort
 - c. Cross-sectional
 - d. Descriptive

5. Which is the principal risk factor in age-related cataract?
 - a. Sunlight
 - b. Smoking
 - c. Genetics
 - d. Ethnicity

6. Which type of cataract is thought to be principally associated with UVB radiation?
 - a. Nucleus
 - b. Posterior subcapsular
 - c. Cortical
 - d. Sutural

7. Which part of the lens is thought to be affected first in oxidative stress-induced cataract?
 - a. Capsule
 - b. Epithelium
 - c. Cortex
 - d. Nucleus

8. What is the surgical procedure of choice for uncomplicated age-onset cataract?
 - a. Phacoemulsification
 - b. Intracapsular
 - c. Extracapsular
 - d. Lensectomy

9. What is the most common late post-operative complication of cataract surgery?
 - a. Macular oedema
 - b. Malposition of IOL
 - c. Infection
 - d. Posterior capsule opacification

10. What group of drugs has been suggested as potential anti-cataract agents?
 - a. Steroids
 - b. Diuretics
 - c. NSAIDs
 - d. Anti-metabolites

11. Which of the following vitamins is not an anti-oxidant?
 - a. A
 - b. C
 - c. E
 - d. D

12. Which one of the following statements regarding the heredity of age-related cataract is incorrect?
 - a. No gene defects have been identified so far in age-onset cataract
 - b. Nuclear cataract shows the greatest genetic component
 - c. Cataracts are more common in the UK amongst subjects originating from the Indian sub-continent
 - d. There is a two to threefold increase in the incidence of cataract in subjects with an affected sibling

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