AGE-RELATED MACULAR DEGENERATION

IN THE UK

Jennifer Evans

Department of Epidemiology and Population Health

London School of Hygiene and Tropical Medicine

Thesis submitted in fulfilment of the requirement for the degree of Doctor of Philosophy of London University

2003

ABSTRACT

The aim of this thesis was to investigate the prevalence and impact of age-related macular degeneration (AMD) causing visual impairment in people aged 75 years and above in the UK. A secondary objective was to investigate a small number of potential risk factors for AMD. This was an add-on study to the MRC Trial of the Assessment and Management of Older People in the Community.

The prevalence of AMD causing visual impairment was estimated at 3.7% (95% confidence interval 3.2% to 4.2%) in people aged 75 years and above. This prevalence increased sharply with age. There was a higher risk of AMD causing visual impairment in women. There were estimated to be approximately 192,000 people aged 75 years and above in the UK living in the community with visual impairment due to AMD (95% confidence interval 144,000 to 239,000) of whom 60,000 are aged 90 years or above. The prevalence of AMD causing visual impairment did not vary by socio-economic group or region.

After controlling for appropriate confounding factors, compared to people not visually impaired, people visually impaired due to AMD were more likely to have functional difficulties, report poor health and be depressed. They were more likely to be in the worst quintile for the home management and mobility dimensions of the Sickness Impact Profile (SIP). After controlling for appropriate confounding factors including binocular acuity score, compared to people visually impaired due to other causes, people visually impaired due to AMD were more likely to have functional difficulties and report poor health and less likely to be in the worst quintile for SIP body care and movement dimension or die.

There was an association between smoking status and risk of being visually impaired due to AMD. This effect was particularly strong in people aged 75-79 years of age. In these people there was a dose-response relationship between pack years of smoking and risk of AMD causing visual impairment. There were no statistically significant associations between alcohol consumption, cardiovascular disease and reproductive factors (in women) and AMD causing visual impairment.

ACKNOWLEDGEMENTS

I am greatly indebted to my supervisor, Professor Astrid Fletcher. The work in this thesis is a small patch of icing on the large cake that is the MRC Trial of Assessment and Management of Older People in the Community. Astrid and the study team have put in huge amounts of work to ensure the successful completion of the MRC Trial. This thesis would not have happened without it. Thank you Astrid and co-investigators (Professor Chris Bulpitt, Dr Dee Jones and Dr Alistair Tulloch) for allowing me to use data from the trial. Astrid has also provided much needed guidance for the add-on study reported here and direction for this thesis as a whole. Thank you.

The MRC Trial was undertaken by a large team of people (*see Appendix A*). I would particularly like to thank Susan Stirling, Elizabeth Breeze, Liam Smeeth, Edmond Ng and Gill Price at the London School of Hygiene and Tropical Medicine; Nicky Fasey at the MRC GPRF; and all the nurses and ophthalmologists who completed forms for me. Thank you too to Rakhi Kabiwala, Janbibi Mazar and Sue Prior for clerical assistance.

Richard Wormald was a co-investigator on the add-on study reported here and kindly read and commented on this manuscript. Thank you for your support.

Thanks to my family for being there. "Nana", "Grandad" and "Uncle Moo" provided timely and enthusiastic childcare. Most of all, thank you, Dave, Rosa and Sam for putting up with me while I finally finished this off.

The MRC Trial of the Assessment and Management of Older People in the Community was funded by the United Kingdom Medical Research Council, the Department of Health and the Scottish Office. Collection of data on causes of visual impairment was funded by the Gift of Thomas Pocklington.

GLOSSARY OF TERMS AND ABBREVIATIONS

Study acronyms

ARIC	Atherosclerosis Risk in Communities
NHANES	National Health and Nutrition Examination Survey
SEE	Salisbury Eye Evaluation study

Epidemiological terms and abbreviations for instruments or scales

ADL	Activities of Daily Living
ADVS	Activities of Daily Vision Scale
BMI	Body mass index
GDS	Geriatric Depression Scale
MMSE	Mini Mental State Examination
PGMS	Philadelphia Geriatric Morale Scale
SIP	Sickness Impact Profile
SMR	Standardised mortality ratio
WARMGS	Wisconsin Age-related Maculopathy Grading System

Agencies

MRC	Medical Research Council
GPRF	MRC General Practice Research Framework

CONTENTS LIST

LIST OF TABLES

Chapter 3 Prevalence

Chapter 4 Impact

LIST OF FIGURES

CHAPTER ONE BACKGROUND

1.1 INTRODUCTION

The population of the UK is ageing rapidly. By 2040, the numbers of people aged 75 years and above are projected to increase by 90% and the numbers of people aged 90 years and above by 160%.* Age-related diseases will assume increasing importance in the public health of the nation. Age-related macular degeneration (AMD) is one such disease. It is the most commonly occurring cause of prevalent visual loss in the UK. The aim of this chapter is to review the literature on the prevalence, impact and aetiology of AMD.

Most of the data presented in this thesis refer to analyses of the prevalence and impact of AMD causing visual impairment in a cohort of people aged 75 years and above taking part in the MRC trial of the assessment and management of older people in the community. There were limited data on risk factors in this cohort. In the literature review, I will give most emphasis to the areas covered in the thesis, i.e., prevalence, impact and risk factors such as smoking and alcohol consumption. For completeness, I will review briefly those areas not covered in this thesis, i.e. the role of nutrition, light exposure and genetics in the aetiology of AMD.

1.1.1 Clinical signs and definitions

AMD is a disease involving typical lesions in the macula in older people that cannot be attributed to infectious or inflammatory causes. There are two types of AMD – geographic atrophy and neovascular AMD. In geographic atrophy the retinal pigment epithelium and overlying receptors degenerate. In cases of neovascular AMD, new

---

* http://www.gad.gov.uk/population/. Accessed December 2002.

vessels grow from the choroidal circulation, leading to the destruction of the retinal pigment epithelium. If the vessels leak, the resulting haemorrhage results in further scarring and visual loss.

AMD is associated with "drusen" (yellow spots clinically observable on the retina) and pigmentary abnormalities such as hyper- and hypo-pigmentation. Drusen are commonly seen in older people, not all of whom will go onto develop visually impairing AMD. People with large, ill-defined "soft" drusen are more likely to develop AMD.

The investigators from several of the largest prevalence studies in Australia, Europe and North America have agreed a common classification for AMD in epidemiological studies. This classification is set out in table 1.1(Bird *et al.* 1995). It is the terminology that is used in this thesis. The overall term "age-related maculopathy" (ARM) covers early and late stages of the disease. Early ARM refers to signs such as large, soft drusen and pigmentary abnormalities that may, or may not develop into late stages of the disease. The term "age-related macular degeneration" (AMD) describes geographic atrophy and neovascular disease.

1.1.2 Overview of the epidemiology of AMD

AMD is the most important cause of visual loss in western industrialised countries. In the UK, approximately 30,000 people are registered blind or partially sighted every year, half of whom will have macular degeneration(Evans 1995). This pattern in the registered population is reflected in Europe, North America and Australia(Bjornsson 1981; Graf *et al.* 1999; Hansen 1981; Krumpaszky and Klauss 1992; Chan and Billson 1991). Cataract is probably more frequent as an incident cause of visual loss but, as there is safe and effective surgery for cataract, it is less common as a prevalent cause of visual loss.

AMD increased dramatically as a proportionate cause of registered visual loss in the 20th century(Evans and Wormald 1996; Maruo *et al.* 1991). In 1933, just 6% of the registered population in England and Wales had "senile macular degeneration", compared to nearly 50% in 1990(Evans and Wormald 1996). Most of this increase can be attributed to a combination of ageing population, declining importance of infectious causes of visual loss, and increasing effectiveness of ophthalmic surgery. However, age-standardised population rates indicate an excess incidence of approximately 30%. This may reflect a real increase or simply indicate changes in the detection of this condition

in parallel with its increasing importance. In section 1.2, I review the literature on the prevalence and incidence of AMD, focussing on what is known about AMD as a cause of visual loss in Britain.

Currently there is no treatment that can restore vision in AMD. There are some treatments, for example, laser photocoagulation and photodynamic therapy, that can delay the progressive loss of visual function in a small proportion of people with neovascular AMD(Fine *et al.* 2000). As the consequences of the disease are severe (visual impairment and blindness) and treatment not available for most people with the disease, there is considerable interest in possibilities for preventing AMD developing in the first place. The possible role of metabolites of molecular oxygen known as "reactive oxygen species" in the biology of ageing and age-related diseases such as AMD has provoked considerable interest(Finkel and Holbrook 2000). Increased levels of reactive oxygen species may lead to cell death by damage to proteins, lipids and DNA. Interest in the role of vascular factors in the development of AMD has lead to investigations of cardiovascular disease risk factors. As cardiovascular disease is also a disease of ageing the shared common pathway may be oxidative stress. With developments in molecular biology and genetic methods, there is increasing potential for discovery of the genetic determinants of the pathological mechanisms leading to the development of AMD. The evidence for the role of risk factors for AMD is reviewed in section 1.4.

Most research on AMD has investigated the biological, clinical and therapeutic aspects of the disease. More recently, researchers have begun to investigate the impact of the disease on the lives of people affected. Section 1.3 summarises the research in this area.

1.1.3 Identification of studies included in the literature review.

Over a period of several years, I have developed a database of references on the epidemiology of AMD. These were identified using a combination of electronic searching, searching reference lists and personal contact. In order to ensure that this database was as complete as possible, I conducted the following searches of Medline, EMBASE and the Cochrane Register in August 2002.

The following strategy was used to search MEDLINE and the Cochrane register to end May 2002

#1 "MACULAR-DEGENERATION"/ all subheadings
#2 "RETINAL-DEGENERATION"/ all subheadings
#3 "NEOVASCULARIZATION,-PATHOLOGIC"/ all subheadings

#4 "RETINAL-NEOVASCULARIZATION"/ all subheadings
#5 "CHOROIDAL-NEOVASCULARIZATION"/ all subheadings
#6 #1 or #2 or #3 or #4 or #5
#7 (MACUL* or RETINA* or CHOROID*) near (DEGENER* or NEOVASC*) in TI,AB
#8 MACULOPATHY in TI,AB
#9 (AGE or AG?ING or AGE?RELATED or SENIL*) in TI,AB
#10 (#6 or #7 or #8) and #9

The following strategy was used to search EMBASE to end May 2002.

#1 explode "RETINA-MACULA-DEGENERATION"/ all subheadings
#2 "RETINA-DEGENERATION"/ all subheadings
#3 "NEOVASCULARIZATION- (PATHOLOGY)"/ all subheadings
#4 "SUBRETINAL-NEOVASCULARIZATION"/ all subheadings
#5 ((MACUL* or RETINA* or CHOROID*) near (DEGENER* or NEOVASC*)) in TI,AB
#6 MACULOPATHY in TI,AB
#7 (AGE?RELATED or AGE RELATED OR AG?ING OR SENIL*) IN TI,AB
#8 (#1 or #2 or #3 or #4 or #5 or #6) and #7

The major ophthalmic journals were searched online for the period May to August 2002. These were: American Journal of Ophthalmology, Archives of Ophthalmology, British Journal of Ophthalmology, Ophthalmology, Ophthalmic Epidemiology, Survey of Ophthalmology.

Titles and abstract were scanned for articles of relevance to this review. Full text copy was obtained of potentially relevant references. The searches were iterative and reference lists of all studies were searched by hand.

1.2 PREVALENCE

1.2.1 Prevalence studies

Table 1.2 sets out the details of the prevalence studies on AMD. The majority of studies have been undertaken in industrialised countries – Australia/New Zealand (three studies), Europe (seven studies), and USA (seven studies). Studies enrolling purely volunteer samples or conducted in specific patient groups were excluded(Delcourt *et al.* 1998; Cruickshanks *et al.* 1997).

There have been two National Health and Nutrition Examination Surveys (NHANES) in the USA which have examined eye disease(Klein and Klein 1982; Klein *et al.* 1995b). These are large probability samples of the US noninstitutionalized civilian population.

The first survey was conducted in the early seventies, the third in the late 80's. They have been a particularly good source of information on racial differences in ARM. The Framingham Eye Study, which took place at around the same time as the first NHANES-I, was a pioneering study in the development of methods and definitions in eye disease surveys(Kahn *et al.* 1977a; Kini *et al.* 1978). Eye examinations were performed on nearly 2,500 surviving members of the Framingham Heart Study cohort, which has been examined biennially since 1948 for the purpose of identifying factors that affect the risk of cardiovascular disease. A number of subsequent population-based studies - in rural Iceland, Melton Mowbray, England and three areas in China - followed the definitions developed in the Framingham Eye Study(Jonasson and Thordarson 1987; Gibson *et al.* 1985; Wu 1987). The Copenhagen City Study was another add-on eye examination to a heart study cohort(Vinding 1995; Vinding 1990). Similar definitions to Framingham were used.

In the second half of the 1980's came the development of grading systems for classification of the disease from colour fundus photographs. Two systems were developed in the States, the Wisconsin Age-Related Maculopathy Grading System (WARMGS) which was used in the Beaver Dam Eye Study(Klein *et al.* 1991a) and the Chesapeake Bay grading system(Bressler *et al.* 1989). The Beaver Dam Eye Study was a survey of the population aged over 43 years in the community of Beaver Dam, Wisconsin(Klein *et al.* 1992a). The Chesapeake Bay study was conducted among the watermen residing in Somerset County, Maryland(Bressler *et al.* 1989). The WARMGS was taken up by investigators in a number of countries and has been used in surveys in the Netherlands(Vingerling *et al.* 1995b),Finland(Laatikainen and Hirvela 1995),Australia(Mitchell *et al.* 1995; VanNewkirk *et al.* 2000a),Barbados(Schachat *et al.* 1995),UK(Dickinson *et al.* 1997) and the third NHANES(Klein *et al.* 1995b; Klein *et al.* 1999c). It forms the basis for the International System for grading ARM (table 1.1)(Bird *et al.* 1995).

1.2.2 Methodological issues

Table 1.2 shows the response rates achieved in these prevalence studies. Response rates ranged from 46%(Klein *et al.* 1999a)to 95%(Vinding 1989). In general, response rates were higher in the studies where assessment of AMD was "clinical". When photographic grading was used, some of the people taking part did not have gradable

photographs. A couple of studies did not report response rates. In the case of the study in China, there was no discussion of a sampling frame, so it may well be that the sample was a volunteer sample(Wu 1987).

These prevalence studies can be considered in the following categories: national probability samples, probability samples of a defined area, samples drawn from general practitioner registers, samples drawn from cohorts set up for other purposes and study of an occupational cohort.

NHANES I & III in the USA were national probability samples(Klein and Klein 1982; Klein *et al.* 1995b; Klein *et al.* 1999c). The aim of the NHANES is to provide periodic national statistics on the health and nutritional status of the civilian noninstitutionalised population through household interviews and standardised physical examinations. These samples are complex multistage area probability samples carefully designed to provide an unbiased sample of the US population.

The most usual study design was a population-based study in one region, town or district using municipal registers or census records to identify everyone in eligible in the chosen area. Depending on the size of the area either everyone in the specified age range was invited to participate or a probability sample selected. In the Beaver Dam Eye Study a private census of the population of Beaver Dam, Wisconsin was used to identify eligible people who were all invited to take part in the study(Klein *et al.* 1992a). In the Rotterdam Study names and addresses of residents in one suburb of Rotterdam were drawn from the municipal register(Vingerling *et al.* 1995b). Eligible people in randomly selected clusters were invited to take part. The Oulu County Study examined everyone aged 70 years and above in three communities in Oulu County, Finland(Laatikainen and Hirvela 1995). The Barbados Eye Study selected a random sample of Barbados-born citizens, aged 40 to 84 years(Schachat *et al.* 1995). In the Blue Mountains Eye Study, the sample was identified by door-to-door census of two postcode areas west of Sydney, Australia(Mitchell *et al.* 1995). Similarly, in the Melbourne Visual Impairment Study, door-to-door census identified all eligible people in nine randomly selected pairs of adjacent census collector districts in urban Melbourne and four pairs of randomly selected adjacent census collector districts in four rural communities in Victoria(VanNewkirk *et al.* 2000a). The Melbourne Study also considered institutionalised residents of 13 randomly selected nursing homes and hostels with 5 km of the urban test sites. The Atherosclerosis Risk in Communities Study (ARIC)

comprised a probability sample of men and women aged 45 to 64 years of age in four US communities(Klein *et al.* 1999a).

For the studies conducted in the UK, the samples used were drawn from the registers of family doctors serving a particular area. In the case of Melton Mowbray, it was argued that everyone in a defined geographic area was served by one general practitioner(Gibson *et al.* 1985). In the North London Study, seven general practices were randomly selected from 17 practices in six electoral wards(Reidy *et al.* 1998). A simple random sample of people aged 65 years and above in each practice was drawn subsequently. In the Leicester Study, random samples of people aged 40 years and above were drawn from lists of patients registered with two neighbouring inner-city practices(Das *et al.* 1994).

Several studies consisted of examination of cohorts set up for other purposes. In the Framingham Eye Study, the Framingham cohort, which had originally been set up for the study of heart disease, was undergoing its twelfth biennial cycle when eye examinations began in 1973(Kahn *et al.* 1977a). Therefore only people surviving in the cohort were eligible to take part in the study. Similarly, the Copenhagen City Study was a random sample of people taking part in the Copenhagen Heart Study which had been going to five years when the eye examinations took place.

There was one occupational cohort study. In the Chesapeake Bay Study, a survey of watermen identified from fisherman licensing records at the Maryland State Department and residing in two communities in Maryland was conducted(Bressler *et al.* 1989).

In three studies, the sampling frame was not clearly described although the implication was that everyone eligible in a particular area was invited for examination(Wu 1987; Martinez *et al.* 1982; Pagliarini *et al.* 1997).

The study design providing the best national estimates is clearly the national probability samples such as the NHANES. However, given the size and national distribution these studies are more complex to undertake and are more likely to suffer poorer response rates. In addition, less eye-specific extra information, such as data collection on relevant risk factors can be undertaken. The problem with the studies conducted in one area or cluster is that between cluster variation is unknown. The smaller the area or cluster the more of a problem this will be. In the UK, particular use has been of general practice

registers to identify samples. However, these can be unreliable and not everyone in a particular locality will be registered with a general practitioner.

1.2.3 Prevalence estimates

Figures 1.1-1.3 present the results of these surveys.

The prevalence of ARM, detected by grading of retinal photographs with no visual acuity cutoff included in the definition of the disease, increases from a prevalence of between 0 and 10% at age 50 to almost 100% at age 90 (figure 1.1). If visual function is included in the definition of the disease, the observed prevalence is lower (figure 1.2). It increases from less than 10% in the 50-59 age-group to a prevalence of somewhere between 20 and 50% at ages 85 and older. In general, similar age-specific rates have been found in the different studies with the exception of the Gisborne study in New Zealand which found lower rates. Using one age-group as an example, the Melton Mowbray study in England found a rate twice as high in the age group 85 years and above as was observed in Gisborne in the 90 years and above age group(Gibson *et al.* 1985; Martinez *et al.* 1982). Calculating confidence intervals around these estimates suggest that the true prevalence for Gisborne lies somewhere between 17% and 37% whereas for Melton Mowbray it lies between 37% and 64%. The large difference between these two estimates may be due to sampling error.

AMD is less common (figure 1.3). Approximately 10% of people over 75 years have AMD. Barbados has a lower prevalence of AMD; this is discussed below in section 1.2.6.

Smith et al pooled data from three large population-based prevalence studies that had used similar classification methods(Smith *et al.* 2001). AMD diagnosis was made from masked grading of stereo macular photographs. Table 1.3 shows the results of this analysis. Overall, AMD was present in 1.63% of the combined population of 14,752 participants. The prevalence rose from 0.2% in people aged 55 to 64 years to 13% of the population older than 85 years. Neovascular AMD increased from 0.17% among subjects aged 55 to 64 years to 5.76% of those aged 85 years and above. Geographic atrophy increased from 0.04% to 4.22% for those age groups. It must be noted that, in this analysis, all the data were pooled together without taking into the account the fact that they came from different centres nor examining the data for heterogeneity.

Owen et al pooled data from six studies in order to estimate the prevalence of visual loss caused by AMD(Owen *et al.* 2002). In this analysis, correct meta-analysis techniques were used. Table 1.4 shows the prevalence of binocular visual impairment caused by AMD (in this case visual impairment was defined as 6/18 or less, rather than the more usual less than 6/18 Snellen acuity). The prevalence of visual impairment due to AMD rose from 0 in people less than 65 years of age to 15.3% (7.6% to 27.4%)* in people aged 90 years and above.

1.2.4 Gender

Women tend to live longer and people who live longer are at greater risk of AMD. The investigation as to whether there is a gender imbalance in risk of the disease must be studied bearing this fact in mind. As there may be differences between the sexes in health-seeking behaviour it is important only to consider data from population-based studies.

Figure 1.4 shows results from all the population-based studies of AMD as to the risk of the disease in men and women. The results are presented in terms of the relative risk of AMD in women compared to men. In order to take into account of the effect of age, the results have been stratified into three age-groups – 65-74, 75-84 and 85 years and above. Confidence intervals around each relative risk are plotted and an overall summary relative risk calculated for each age-group and for all studies.

It is commonly believed that women are at increased risk of developing AMD, however, the figure shows that there have been few studies that have demonstrated this increased risk unequivocally. Overall, it would appear that women are at slightly increased risk, however, we cannot be confident that we have completely excluded age effects from this estimate. Other authors have pooled data from the major population-based studies and similarly found only a small increased risk for women that could possibly be attributed to age effects(Smith *et al.* 1997; Owen *et al.* 2002).

---

* I will use the following convention regarding confidence intervals. 95% confidence intervals will be quoted unless indicated otherwise. The confidence intervals will be the form "lower to upper" confidence interval, in brackets after the estimate. If the estimate is in brackets already, the confidence intervals will come after a comma.

1.2.5 Socio-economic status

There is limited information about the social class of people with AMD. There was little relationship between education, income and employment status and ARM in the cross-sectional Beaver Dam Eye Study(Klein *et al.* 1994c). Follow-up of the cohort five years later showed that lower educational status, and being in a service-related occupation compared with a white collar professional occupation, was associated with the incidence of early ARM(Klein *et al.* 2001c). This association appeared to be independent of age, sex, smoking and vitamin supplement use. Other studies have examined the relationship between AMD and social class and education and found no relationship. In NHANES I and the Eye Disease Case-Control Study Group there was a reduced risk of AMD with increasing number of years of education. These associations were much attenuated when other factors were included in the model, such as smoking(Goldberg *et al.* 1988a; Eye Disease Case-Control Study Group 1992).

1.2.6 Ethnic group

The study of disease in different ethnic groups is controversial and difficult. The risk factor being studied is often unclear – is it a different genetic profile, or differences in lifestyle? For example, there are many genetic and cultural differences between people from different parts of Africa, however, in studies of ethnic group they are often grouped together as "black".

It is commonly believed that AMD occurs less frequently in people of African Caribbean origin or in pigmented races generally. This view has come from the clinical impression that black people form a small proportion of people presenting with the condition at hospitals. For example, only 0.08% of people enrolled in a trial of laser photocoagulation for AMD in the USA were black compared to 5-15% in other eye trials (Diabetic Retinopathy and Corneal Transplant studies) in that country(Jampol and Tielsch 1992). In the Baltimore Eye Survey, black people had twice the age-adjusted legal blindness than whites but no cases of bilateral blindness in blacks were due to AMD in contrast to 30% of blindness in whites.

Population-based studies such as NHANES-III show that early signs of ARM are common in black people(Klein *et al.* 1999c). The population-based study in Barbados, which largely comprised black people, found rates of early ARM which were similar to those found in studies of white people but lower rates of neovascular disease(Schachat

et al. 1995). It may be that later stages of the disease, particularly neovascular disease, are less common in African people.

The prevalence of AMD in different populations has been reviewed recently(Klein *et al.* 1999b). The authors concluded that the prevalence of ARM and AMD varies considerably in different places and in different ethnic groups. This variation could be due to variation in genetic and other risk factors differences, but differences in classification between studies cannot be excluded.

1.2.7 Non-industrialised countries

There is very little information on the prevalence of AMD in non-industrialised countries. The Barbados Eye Study results have been discussed above. The study in China, which used Framingham definitions, found prevalence rates of the same order of magnitude as USA studies, however it is not clear if the sample of people included in the study were population-based(Wu 1987).

In general, macular degeneration is not an important cause of blindness in national surveys conducted in non-industrialised countries, for example, Nepal and Gambia. However, not only do such countries have a younger population, but also they have an excess of avoidable blindness due to corneal disease and cataract, which may mask the existence of AMD, both physically and proportionately.

1.2.8 Incidence

Follow-up of the Beaver Dam Eye Study indicated that, in people aged 75 years and above, approximately 17% developed features of ARM such as large, soft drusen over five years(Klein *et al.* 1997b). Approximately 13% developed retinal pigment abnormalities. Late stage disease occurred in nearly 2% and occurred more commonly in people with soft drusen and retinal pigment abnormalities (7%). Similar findings were observed in the Blue Mountains Eye Study(Mitchell *et al.* 2002). 17.8% of people aged 70 years and above developed early ARM and 2.9% developed AMD over five years.

1.2.9 Summary

There are few population-based data on the prevalence of visual impairment and AMD in the British population. Estimates of the size of the problem have come from pooling

studies from other countries and continents. However, there are many difficulties with this as there are substantial differences between countries that make extrapolation of results difficult.

Current research on AMD has focussed on the prevalence of the condition and there is less information on AMD as a cause of visual loss. In part, this has occurred because population-based eye surveys are expensive and logistically difficult to undertake. This means that there is real constraint on eventual sample size. Most of the large population-based studies have had relatively few cases of advanced AMD causing visual loss and have investigated earlier signs of the disease.

The prevalence of AMD increases dramatically with increasing age; people aged 75 years and above bear a disproportionate part of the burden of the disease. However, there is a lack of data on older people. Out of approximately 55,000 people taking part in the main population-based studies approximately 7,000 have been aged 75 years and above and approximately 700 were 90 years and above (table 1.5). These figures are a little rough and ready because the published reports do not always present data disaggregated for older ages. However, it does indicate a lack of reliable information on AMD as a cause of visual loss in the older age-groups.

The distribution of AMD within different groups in the population is not well-established. Whether or not women are at increased risk of the disease is uncertain and whether there is a difference in AMD as a cause of visual loss between the two sexes has not been addressed. There appears to be little relation with socio-economic status, however, few studies have addressed this question adequately. Measures of socio-economic status have relied on educational status and the number of cases of late-stage disease has been small. No studies have been done in the British population.

1.3 IMPACT

1.3.1 Measures of the impact of disease

The aim of this section is to consider the impact of being visually impaired due to AMD on the lives of people affected. There are many potential measures of the impact of disease or the outcome of treatment. **Mortality** and **morbidity** are commonly used. The impact of disease in terms of requirements or use of services has also been measured. There are many different measurement scales aimed to measure more complex aspects

of a person's health such as functioning and well-being. The terminology in this area is not well-defined with the terms "quality of life" and "well-being" used in different ways by different researchers. I will use the conceptual framework as set out in "Measuring Health: a review of quality of life measurement scales" which is summarised below(Bowling 1997).

There are several ways of considering health status. One of the most commonly used methods is describing people's ability to perform tasks of daily living, that is, their **functional ability**. There are a number of methodological techniques for measuring function: direct physical tests of function, direct observation of behaviours and/or interviews with the person or their proxy. Most measures of functional ability or disability are self-report methods. In many studies of disability, single-item questions such as ability to read newsprint or to see faces across the road are used. One of the best known and oldest of the multi-item disability scales is the Activities of Daily Living (ADL) index developed to describe the states of elderly persons(Katz *et al.* 1963). It has been modified specifically for people with AMD(Dahlin-Ivanoff *et al.* 2001).

Measures of functional ability specific to people with vision impairment have also been developed, for example, the Activities of Daily Vision Scale (ADVS)(Mangione *et al.* 1992). This scale consists of 21 multiple-response items representing common visual activities categorised into five subscales: night driving, daytime driving, distance vision activities that do not require driving, near vision activities, and activities subject to glare. Additionally, the subscales can be combined into an overall visual function score. All scale scores range from 0 to 100, where 100 represents no difficulty and 0 means the activities are no longer performed because of visual impairment. If a person indicates that an activity is difficult because of limitations not caused by vision, the item does not contribute to the scale score. The ADVS was originally developed to evaluate the outcome of care after cataract surgery but has been used in people with a range of vision problems including glaucoma and diabetic retinopathy, and in population-based studies.

Broader measures of **health status** generally focus on people's perceptions of their health and are sometimes referred to as health-related quality of life. A popular single-item measure consists of asking respondents to rate their health as "excellent, good, fair or poor" in relation to other people of their age. This measure is linked to mortality, admission to hospital and use of health services. In some cases poor mental health will distort perceptions of health and well-being and poor physical health can also lead to

poor mental health and well-being. This can lead to difficulties in interpreting results. There are many multi-item measures reported in the literature, some of which are general, e.g., the Sickness Impact Profile (SIP)(Bergner *et al.* 1981), Nottingham Health Profile(Hunt 1984), or specific, e.g. the VF-14 aims to measure health of people with vision impairment and/or eye disease(Steinberg *et al.* 1994). There is some overlap between measures of functional ability and broader measures of health status. For example, the SIP assesses the impact of sickness on daily activities and behaviour covering the following different dimensions: work, recreation, emotion, affect, home life, sleep, rest, eating, ambulation, mobility, communication and social interaction.

There are a number of instruments designed to assess **psychological well-being** including those aimed specifically to detect psychiatric disorder such as depression, anxiety, dementia and cognitive impairment. In general these consist of a checklist of statements asking respondents to compare their recent experience to their usual state, with the answer graded according to severity. One the most commonly used in the UK is Goldberg's General Health questionnaire and in older people the Geriatric Depression Scale(Sheik and Yesavage 1986). The Mini-Mental State Examination (MMSE) is the most commonly used scale aiming to assess cognitive impairment and includes tasks such as arithmetic, memory and reading(Folstein *et al.* 1975). Again there is some overlap between measures of psychological well being and broader measures of health status, which may include components designed to assess psychological well being.

The last type of measure to be considered is measures of **emotional well being,** i.e. life satisfaction and morale. The first population survey of emotional well being asked the question "…would you say you're very happy, pretty happy or not too happy these days?" Happiness implies an affective mood or state, however, life satisfaction suggests a cognitive process and, in general, is defined as an overall assessment of one's life. It has been observed that older people often report lower levels of happiness but higher levels of life satisfaction than younger people do. This could reflect the fact that happiness reflects emotions but life satisfaction is a more cognitive concept. Morale has been less well defined but is probably best reflected as a basic sense of satisfaction with oneself. Many of the major scales of well-being correlate well, which suggests that they are directed at measuring a common underlying construct. The most commonly used scales have been LifeSatisfaction A, Bradburn Affect-Balance Scales

and Philadelphia Geriatric Center Morale Scale (PGMS)(Lawton 1975), as well as global items of happiness and life satisfaction.

To summarise, the following measures of the impact of visual impairment due to AMD will be assessed in this review:

- Morbidity
- Mortality
- Measures of functional ability
- Measures of perceived health status (health-related quality of life)
- Measures of psychological well-being
- Measures of emotional well-being (life satisfaction and morale)

As the condition "visual impairment due to AMD" consists of two parameters, having AMD and being visually impaired, I shall also consider the literature on the impact of visual impairment *per se*.

Table 1.6 summarises the studies identified.

1.3.2 Morbidity

The main type of morbidity addressed in the literature in relation to visual impairment has been that of hip fractures occurring as a result of falls.

Two studies were identified that investigated the association between visual impairment and falls in older adults. Jack et al investigated 200 consecutive patients aged 65 years and above admitted via accident and emergency to an acute geriatric medical unit (Jack *et al.* 1995). Patients admitted with falls had a higher prevalence of visual impairment (76%) than those admitted for other reasons (45%). In the cross-sectional Blue Mountains Eye Study, people with a visual acuity worse than 20/30 were twice as likely to report two or more falls(Ivers *et al.* 1998).

Four studies were identified that examined the relationship between visual impairment and hip fractures. In the Beaver Dam Eye Study, people with best-corrected acuity 20/25 or worse were twice as likely to have had two or more falls and nearly four times as likely to report having had a hip fracture(Klein *et al.* 1998a). These relationships also were found when visual function was measured by near visual acuity and current

binocular acuity. Contrast sensitivity was not associated with falls and hip fractures. In the Auckland Hip Fracture Study, having a binocular acuity worse than 20/60 was associated with increased risk of hip fracture (odds ratio 1.5, 1.1 to 2.0) with no depth perception being a marked risk factor for hip fractures (odds ratio 6.0, 3.2 to 11.1).

Similar estimates of effect were seen in the Framingham Study and EPIDOS. In the Framingham Study, 2,633 people were followed up for 10 years after the eye examination and 110 had a hip fracture (Felson *et al.* 1989). There was a "dose-response" relationship with people with good vision (20/25 or better) experiencing less hip fractures (3%) than those with moderate visual impairment (20/30 to 20/80) (8.5%) and those with poor vision (20/100 or worse) (11.3%). They also found evidence that people with different visual function in the two eyes were more likely to sustain a hip fracture. In the EPIDOS study, 7,575 women aged 75 years or older were followed up for an average of 1.9 years, 154 women experienced a first hip fracture. Reduced visual acuity (≤2/10) was associated with an increased risk of hip fracture (relative risk 2.0, 1.1 to 3.7)(Dargent-Molina *et al.* 1996).

No studies were found that investigated the different causes of visual impairment or the impact of macular degeneration on the risk of falling and hip fractures.

1.3.3 Mortality

The association between mortality and vision impairment or age-related eye disease has been examined in the Melton Mowbray Study(Thompson *et al.* 1989), Melbourne Visual Impairment Project (McCarty *et al.* 2001b; Taylor *et al.* 2000), the Beaver Dam Eye Study (Klein *et al.* 1995a), the Blue Mountains Eye Study (Wang *et al.* 2001), the North London Study (Reidy *et al.* 2002), and the National Health Interview Survey (Lee *et al.* 2002). Four of the studies were cross-sectional with repeat examination five years later at which time the number of people who had died since the first examination was assessed. In the North London Study and National Health Interview Survey participants were flagged for mortality with the relevant government agencies. In all studies, visual impairment was associated with an increased risk of death, after controlling for relevant confounding factors, such as age, sex, socio-economic status and cigarette smoking. In the Melton Mowbray study people with moderate visual impairment had a two-fold increased risk of mortality (Thompson *et al.* 1989). However, people who were blind did not. In the Blue Mountains Study the relative risk

of dying associated with visual impairment was 1.7 (1.2 to 2.3) (Wang *et al.* 2001). In the Visual Impairment Project, best corrected visual acuity of less than 6/12 was associated with a increased risk of death five years later (odds ratio 2.34) (McCarty *et al.* 2001b). In the Beaver Dam Eye Study, people with impaired vision were found to have a poorer five-year age and sex adjusted survival (87.5%) compared with those whose vision was not impaired (91.8%)(Klein *et al.* 1995a). In the North London Study and National Health Interview Survey, mortality was only associated with cataract in women (Reidy *et al.* 2002).

Appollonio et al followed up 1140 non-institutionalised elderly subjects aged 70-75 years and found that hearing impairment but not vision impairment was associated with a significant increased mortality risk in men only (Appollonio *et al.* 1995).

The Beaver Dam Eye Study was the only study to examine AMD and survival. After controlling for age and sex, ARM was not associated with survival (Klein *et al.* 1995a).

1.3.4 Functional ability

Four studies were identified which examined the relationship between visual impairment and functional ability. Three studies were cross-sectional population-based studies (Established Populations for the Epidemiologic Studies of the Elderly (Salive *et al.* 1994), Salisbury Eye Evaluation (SEE) study (Rubin *et al.* 1997), Blue Mountains Eye Study (Ivers *et al.* 2000)) and one study was conducted in nursing home residents (Marx *et al.* 1992). In addition, one qualitative study on the impact of vision impairment on functioning was identified (Keeffe *et al.* 1998).

Salive et al examined the association of visual impairment with mobility and physical function in a population-based study of older adults (Salive *et al.* 1994). Limitations in mobility, activities of daily living and physical performance were associated with worse visual function.

The SEE study was specifically designed to determine the impact of age-related eye disease and visual impairment on functional status in an elderly population and to determine the role of visual impairment on a variety of adverse outcomes, such as admission to nursing homes and falls. Salisbury is a semirural, stable community and nearly 18% of people aged 65 years and above are black. Physical function was assessed using Activities of Daily Living (ADL), which determines difficulty in the basic areas of self-care (dressing, bathing, toileting, feeding and mobility) (Katz *et al.*

1963) and the Instrumental Activities of Daily Living (IADL), which determines difficulty in more complex tasks necessary for independent living (Lawton 1975). These tasks include activities such as housework, paying bills, and shopping. The third dimension they addressed was general physical abilities and mobility, such as walking defined distances and climbing stairs. The ADL, IADL and physical mobility questions contain a five-part response scale ranging from "no difficulty" to "cannot do for health or physical reasons". To determine the level of function specific for visually orientated tasks, the ADVS questionnaire was administered. Several vision tests were performed. These included visual acuity, contrast sensitivity, glare testing, visual fields and stereo acuity. Visual impairment was defined as presenting binocular acuity worse than 20/40.

The final sample for the SEE project was 2,520 participants aged 65 years to 84 years. Visual impairment was significantly associated with all the measures of functional status assessed, i.e. ADL, IADL and ADVS. After controlling for age, sex and race, visually impaired people were more likely to report difficult with any ADL (odds ratio 1.82, 1.18 to 2.83) and with any IADL (odds ratio 2.45, 1.77 to 3.40). The mean ADVS coefficient was significantly lower in visually impaired people. For every increase in visual acuity logMAR score of 0.3 (equivalent to doubling of visual angle), there was an odds ratio of 2.39 (1.77 to 3.23) associated with being low versus high functioning as measured by the ADVS. Other measures of visual function such as contrast sensitivity, glare sensitivity, visual field and stereoacuity were independently significantly associated with ADVS score. However, the ADVS was developed for use with cataract patients in the hospital setting. In the SEE project, these associations were found to apply only to the ADVS subscales on far vision, near vision and night driving only. The day driving and glare subscales did not provide appropriate summaries in the population-based SEE project because they were limited by items not widely participated in and have weak within-subscale associations.

The Blue Mountains Eye Study was a cross-sectional census-based survey of eye disease in two postcode areas in the Blue Mountains, west of Sydney, Australia. The final sample consisted of 3,654 people. Visual acuity, contrast sensitivity, disability glare and visual fields were measured. A questionnaire on perception of visual disability was administered by an interviewer (Ivers *et al.* 2000). This included questions on trouble driving at night, difficulty recognising a friend across the street, reading a newspaper or recognising detail on television. Visual acuity and contrast sensitivity

were significantly associated with all self-reported measures of visual disability. Visual field was less strongly associated with visual disability.

Marx et al studied 103 nursing home residents (mean age 85 years) (Marx *et al.* 1992). Half of the participants were visually impaired (best corrected acuity of less than 20/70). For each resident, the degree of assistance needed to perform seven activities of daily living was assessed by the resident's charge nurse using the Maryland Appraisal of Patient Progress. The activities were toileting, transferring from bed to chair, bathing or showering, washing hands or face, dressing the upper body, dressing the lower body, and whether the resident was wheelchair-dependent. These items were rated as 1-independent/needs some assistance or 2 – completely dependent. In all the items studied, visually impaired people were more likely to be classified as completely dependent. However, these differences only reached statistical significance for toileting, transferring, washing face/hands and dressing upper body.

Keeffe et al conducted a qualitative study to investigate the impact of vision loss on people with impaired vision (Keeffe *et al.* 1998). Focus groups were formed that took into account the factors that can affect the impact of vision loss: age, gender, age of onset, cause and degree of vision loss. The following domains were explored: mobility, household and personal care, consumer and social interactions and leisure, employment and education. A fifth domain "reaction to vision loss" was added subsequently. Other issues raised were that multiple impairment, such as hearing loss, complicates matters and that men and women differ in the ways of coping with vision impairment.

Two studies were identified that specifically looked at the impact of AMD on functional ability. Both of these studies were hospital-based.

Williams et al identified 86 adults (average age 79 years, range 63 to 91) with AMD who were legally blind in at least one eye (Williams *et al.* 1998). The age, racial and gender mix of the sample was typical of people at risk for AMD. They used the IADL focussing on domains of managing medications, shopping for necessities, managing finances, using the telephone, maintaining a household and preparing meals. Responses were scored from 1 to 3 with 1 representing complete independence in these activities and 3 indicating inability to carry out any of the tasks. A composite score was created by averaging the responses to 12 items. They also used the Quality of Well-being (QWB) Scale. The QWB Scale includes functional scales for mobility, physical activity

and social activity. The scoring system applies estimates of quality of life to combinations of functioning and symptoms. The quality estimates are obtained from an independent panel of judges. The scoring system places each case on a continuum ranging form 0.0 (dead) to 1.0 (optimum function with no symptoms). The study did not have a control group but the authors compared the mean QWB score with other populations. People with macular degeneration in the sample had a mean QWB score of 0.581. This compared with 0.770 for elderly adults of a similar age. More study participants reported difficulty in carrying out instrumental activities of daily living than did a national sample of non-institutionalised adults aged 65 years and older; this applied to all the domains studied.

Mangione et al recruited 201 people with various stages of ARM from the Massachusetts Eye and Ear Infirmary (average age 71 years)(Mangione *et al.* 1999). Median corrected visual acuity for this sample was 20/25 in the better eye with all subjects having 20/200 or better in at least one eye. All participants completed an interview that included the ADVS. Although there was no control group, the authors evaluated the association between ADVS and clinical severity of AMD. There was a statistically significant linear trend across ARM severity categories for four unadjusted ADVS scores: the overall score, near vision, disability glare and daytime driving scales. Analyses were adjusted for age, sex, medical co-morbidity and presence of other eye disease. Including visual acuity in the model suggested that most, if not all, of this variation could be explained by visual acuity rather than severity of AMD *per se*.

1.3.5 Broader measures of health status (health-related quality of life)

Two cross-sectional population-based studies and one hospital-based study examined the relationship between visual impairment and health-related quality of life. Two further hospital-based studies examined patients with AMD.

Scott et al compared 86 patients with visual impairment to 51 controls and used the following questionnaires: Sickness Impact Profile, the vision-specific Sickness Impact Profile, the Community Disability Scale and the General Health Questionnaire (Scott *et al.* 1994). They found that scores of all four questionnaires and their subscales were significantly associated with visual acuity.

Wang et al examined the association between visual impairment and a single-item question on self-rated health in the population-based Blue Mountains Eye Study (Wang

et al. 2000). The question was "For someone of your age, how would you rate your overall health? Excellent, good, fair or poor". Response to this question was strongly related to visual impairment. After adjustment for potential confounding factors, for each 5 letter reduction in best-corrected visual acuity, there was a 20% increased likelihood of low self-rated health. However, this association applied only to people less than 80 years of age. In people aged 80 years and above, reduced vision had no impact on global health rating.

In the SEE project, two questions from the social interaction scales from the Sickness Impact Profile were used because the authors had identified in previous work that these were highly correlated with degree of visual impairment in a clinic-based population. People with visual impairment were more likely to report no social or religious activities compared to people without visual impairment (odds ratio 1.67, 1.17 to 2.37 for no social activities and 1.96, 1.41 to 2.74 for no religious activities), controlled for age, sex and race.

Williams et al investigated 86 elderly adults (average age 79 years) with AMD who were legally blind in at least one eye (Williams *et al.* 1998). A single-item global measure of health was used with participants being asked to rate their overall health as excellent, very good, good, fair or poor. These categories were scored from 1 (excellent) to 5 (poor). The average score was 2.5. In the absence of a comparison group it is difficult to interpret this figure and the authors did not identify another population group for comparison.

Mangione et al studied the Short Form-36 Health survey which is a generic measure of multidimensional health-related quality of life in a hospital-based sample of 201 people with various types of ARM (Mangione *et al.* 1999). There was no control group for the study but the authors found that, in contrast to the ADVS (*see section 1.3.4 above*), the SF-36 Health Survey scale was not correlated with severity of AMD. However, the sample had a good average visual acuity and few participants with severe bilateral AMD.

1.3.6 Psychological well-being

In a population-based study in northern Italy, Carabellese et al measured visual acuity in 1,191 people aged 70 to 75 years (Carabellese *et al.* 1993). Visual acuity was

significantly associated with an increased risk for clinical depression (odds ratio 2.3, 1.5 to 3.4).

Brody et al studied 151 adults aged 60 years and above with advanced macular degeneration and vision 20/60 or worse in the better eye (Brody *et al.* 2001). They found that depression, as assessed using a structured clinical interview for DSM-IV, was common - occurring in 32.5% of the sample. This was estimated to be approximately twice that in other studies of community dwelling adults, although the authors themselves had only studied people with macular degeneration.

In a hospital-based case-control study, 87 cases aged 65 years and above with mild-to-moderate Alzheimers disease were compared to 87 non-demented controls matched to the cases by age, sex and education(Uhlmann *et al.* 1991). The prevalence of visual impairment was higher in cases than in controls: unadjusted odds ratio for near-vision impairment 2.7, 1.4 to 5.2; unadjusted odds ratio for far-vision impairment 2.1, 1.02 to 4.3).

1.3.7 Emotional well-being (life satisfaction and morale)

One study was identified which examined life satisfaction, daily hassles, social support and self-esteem in 30 cases of AMD compared to age and sex-matched controls (Davis *et al.* 1995). Life satisfaction was measured using the Life Satisfaction Index of Well-being. This was scored on a five-point Likert scale. Higher summed scores on this scale indicated greater life satisfaction. Social support was measured using the Social Support Scale. Self-esteem was measured using the Revised Feelings of Inadequacy Scale. Daily hassles were measured using a revised version of the Hassles Scale. People with AMD reported significantly poorer life satisfaction and greater stress, perhaps as a result of poor social support.

Williams et al examined the Profile of Mood States which is a 65-item, self-report symptom inventory designed to assess mood state in the past week (Williams *et al.* 1998). The participants respond to each item on a five-point Likert scale, ranging from "not at all" to "extremely". There are six subscales (tension/anxiety, depression/dejection, vigour/activity, confusion/bewilderment, fatigue/inertia, and anger/hostility) and a total score. In general people with AMD had higher scores indicating more severe distress, compared with a similar aged sample.

1.3.8 Summary

There is an increasing body of literature on the impact of visual impairment on functional ability, health-related quality of life, psychological and emotional well-being. It has been shown to have a deleterious impact on many of these aspects of daily life and an increased risk of mortality and morbidity (falls and hip fractures). There is little information on the impact of AMD and nothing on the impact of AMD as a cause of visual loss in the community. Most studies in this area have been conducted in the USA and Australia; there is no information on the impact of this disease in the British population. There is also little information on older age-groups as studies have been under-powered at older ages, however, some researchers have suggested that the effect of visual impairment is different at older ages.

1.4 Risk Factors

1.4.1 Hypotheses

There are two main hypotheses for the development of AMD.

(1) Oxidative mechanisms are thought to be important in the pathogenesis of AMD (Beatty *et al.* 2000). Oxidative stress is the name given to the damage caused by metabolites of molecular oxygen known as "reactive oxygen species" (ROS). Tobacco smoking and exposure to UV and visible light increase levels of oxidative stress. Factors that reduce the level of oxidative stress include antioxidant micronutrients in the diet and blood and exposure to endogenous and exogenous oestrogen.

(2) Vascular problems leading to deficiencies in the circulation supplying the retina or increased haemodynamic resistance may lead to degeneration of the retinal pigment epithelium, either because of lack of oxygen or build up of waste products (Friedman 1997). This hypothesis has lead to the investigation of the association of cardiovascular disease and its risk factors (smoking, alcohol consumption, high blood pressure, obesity, diabetes and oestrogen levels in women) with AMD(Snow and Seddon 1999).

In practice it is difficult to disentangle these two hypotheses as oxidative stress is also a proposed mechanism in the pathogenesis of cardiovascular disease, another ageing disease.

The risk factors considered in this review are: smoking, cardiovascular disease, other shared risk factors for cardiovascular disease (high blood pressure, alcohol consumption, dietary fat intake, obesity and diabetes), antioxidant micronutrients, light exposure and oestrogen levels in women. I will conclude this section on aetiology with a brief overview of current research on the genetics of AMD.

1.4.2 Assessment of study quality

Three types of study design were considered in this review - cross-sectional studies, cohort studies and case-control studies. Table 1.7 gives an overview of study design types. There are two broad types of cohort studies: studies where the exposure is randomly allocated (randomised controlled trials) and studies where it is not (observational studies). Case-control studies can be either population or hospital-based. Population-based studies often compare the prevalence of exposure in people with AMD versus people without i.e. all the people taking part in the cross-sectional study are included in the analysis (analytic cross-sectional studies).

The following aspects of the design and execution of randomised controlled trials have been demonstrated to minimise bias in empirical studies (Juni *et al.* 2001). The allocation of treatment should be generated using a random process and concealed from people enrolling participants; the assessment of outcome should be masked to treatment status; withdrawals and dropouts should be unrelated to treatment status and an intention to treat analysis conducted. There has been less empirical research on quality of observational studies. However, two main aspects are likely to be important: ascertainment of exposure should be independent of outcome (and vice versa) and potential confounding variables should be taken into account in the analysis(Hennekens and Buring 1987). In practice, good response rates, assessment of exposure status prior to the occurrence of outcome and masking of observers to exposure / outcome status will help to reduce the occurrence of the former. Hospital-based case-control studies can be difficult to interpret because of the difficulties inherent in selecting a control group. Potential confounding variables need to be considered, measured properly and analysed appropriately.

When evaluating epidemiological evidence, it is important to take into account negative findings. Publication bias, whereby studies with statistically significant findings, are published preferentially, has been shown to be a significant problem in randomised

controlled trials (Simes 1986), and is likely to be more of a problem for observational studies. This can make obtaining an unbiased estimate of effect difficult. Authors may only report statistically significant results when presenting the results of observational studies where large numbers of exposures have been investigated. Indicators of good practice in this area are statements regarding primary and secondary outcomes and reference to a prior analysis plan.

1.4.3 Studies on risk factors for AMD

Many of the cross-sectional studies set out in table 1.8 have investigated risk factors for AMD. The usual approach has been to compare the prevalence of exposure in people with AMD compared to those people without AMD. In general these studies have been underpowered to investigate risk factors for late stage AMD with numbers of cases ranging from 9 in the Chesapeake Bay Study to 77 in the Beaver Dam Eye Study (table 1.8) (West *et al.* 1989; Klein *et al.* 1992a). The table also shows aspects of the quality of these studies with respect to investigation of risk factors. The major deficiency in these studies has been a lack of a clear analysis plan, distinguishing *a priori* and *post hoc* analyses and no clear strategy for analysis of potential confounding variables.

Table 1.9 shows the case-control studies on AMD (Maltzman *et al.* 1979; Delaney and Oates 1982; Hyman *et al.* 1983; Weiter *et al.* 1985; Blumenkranz *et al.* 1986; Eye Disease Case-Control Study Group 1992; Eye Disease Case-Control Study Group 1993; Sanders *et al.* 1993; Chaine *et al.* 1998; Hyman *et al.* 2001; AREDS 2000). The table includes some parameters of quality in the studies, for example, whether or not the assessment of exposure was masked to case status and whether appropriate confounding variables were included in the analysis.

The studies have varied in size from 26 cases (Blumenkranz *et al.* 1986) to 1844 cases in a case-control study in France (Chaine *et al.* 1998). Of the 10 case-control studies, four had sample sizes less than 100 people.

As for cross-sectional studies, a major deficiency in the case-control studies was a lack of discussion of prior analysis plans. A problem specific to case-control studies is the difficulties inherent in selecting a control group. In four studies, this problem was approached systematically with attention to avoiding bias (Eye Disease Case-Control Study Group 1992; Sanders *et al.* 1993; Hyman *et al.* 2001; AREDS 2000). In the others this issue was not adequately addressed. Similarly, not all studies specifically

stated that assessment of exposure was masked to case-control status. Most of the studies attempted to control for confounding factors other than age and sex.

Table 1.10 shows the cohort studies on AMD. There have been two types of cohort study. Examination for AMD has been added onto pre-existing cohorts, for example, the Baltimore Longitudinal Study of Aging (West *et al.* 1994a)the Physicians' Health Study (Christen *et al.* 1996) and the Nurses' Health Study (Seddon *et al.* 1996).

The second type of cohort study has been the re-examination of some of the large cross-sectional population-based surveys such as the Beaver Dam Eye Study, Rotterdam Study and the Blue Mountains Eye Study (Bressler *et al.* 1995; Cruickshanks *et al.* 2001; Klaver *et al.* 2001; Klein *et al.* 2000; Klein *et al.* 1997a; Klein *et al.* 1997b; Mitchell *et al.* 2002).

The advantage of the add-on studies is that, in general, the original cohort study or trial is large. For example, 22,071 male physicians were enrolled in the Physicians' Health Study and 31,843 registered nurses in the Nurses' Health Study. This is much larger than eye surveys which, in general, have of the order of 5,000 participants. The result is that more incident cases of AMD can be identified – 268 in the Physicians' Health Study compared to 25 in the Blue Mountains Eye Study. However, because of the size of such cohorts, a pragmatic approach has had to be taken to the assessment of AMD. In the Physicians' Health Study and Women's Health Study AMD outcome was assessed by a combination of self-report and medical record review.

Re-examination of some of the larger cross-sectional eye studies has enabled measurement of the incidence and progression of early signs of ARM such as drusen and pigmentary abnormalities. However, the number of cases of late-stage disease is very low and hence such studies lack power to investigate risk factors for visually impairing AMD.

1.4.4 Smoking

Smoking cigarettes has been established to be a major risk factor in the development of cardiovascular disease and many cancers. It is a major source of oxidative stress. Tobacco smoke contains, amongst other ingredients, nicotine, carbon monoxide and hydrogen cyanide. Nicotine is an alkaloid from the tobacco plant (Nicotiana) and is highly toxic. It is a vasoconstrictor that reduces blood flow and increases platelet adhesiveness. It is also implicated in the reduction of levels of serum antioxidants.

There are two potential mechanisms by which smoking may lead to an increased risk of macular degeneration. It may have direct effects on the choroidal circulation or it may increase the levels of oxidative stress and decrease blood plasma levels of antioxidant micronutrients.

Table 1.11 summarises the results of epidemiological studies investigating the relationship between smoking and AMD. This relationship has been investigated in eight cross-sectional studies (West *et al.* 1989; Klein *et al.* 1993b; Smith *et al.* 1996; Delcourt *et al.* 1998; Vingerling *et al.* 1996; Klaver *et al.* 1997; Hirvela *et al.* 1996; Vinding *et al.* 1992; McCarty *et al.* 2001a), three cohort studies (Christen *et al.* 1996; Seddon *et al.* 1996; Klein *et al.* 1998b), and six case-control studies (Eye Disease Case-Control Study Group 1992; Blumenkranz *et al.* 1986; Chaine *et al.* 1998; Hyman *et al.* 1983; Tamakoshi *et al.* 1997; AREDS 2000). The majority of studies have found a statistically significant association between smoking and development of AMD. Most studies found a risk of the order of 2 to 3 (range 1.6 to 4.9). Three studies did not find an association between smoking and AMD (West *et al.* 1989; Hirvela *et al.* 1996; Chaine *et al.* 1998). The French study is particularly puzzling because they had 1844 cases of AMD and found no evidence of effect with an odds ratio=1.06 (Chaine *et al.* 1998). There are several possible explanations of this: either there was some problem in the study design or execution either in the classification of smoking or AMD or in the selection of controls; the other studies may have some common bias which was somehow avoided in this study; or the effect of smoking on AMD does not apply in the French population. It has been observed in some studies that the effect of smoking is more apparent in neovascular disease (Klein *et al.* 1993b; Vingerling *et al.* 1996), however, this has not always been the case. In the Blue Mountains Eye Study, people who smoked were nearly 5 times as likely to have dry AMD compared to those who had never smoked (odds ratio for geographic atrophy in current vs. never smokers 4.94, 1.29 to 18.82) (Smith *et al.* 1996). However, this analysis included only 11 cases of disease therefore wide confidence intervals are consistent with a more moderate risk. In the Physicians Health Study the relative risk of neovascular disease with smoking was slightly lower than the relative risk for all types of AMD (Christen *et al.* 1996) and the Nurses' Health Study also found similar risks for dry and wet disease (Seddon *et al.* 1996).

More persuasive evidence for the role of smoking in the aetiology of AMD has come from the demonstration of a dose response effect. In the Physicians' Health Study, men who smoked more than 20 cigarettes a day were at increased risk compared to those who smoked less than 20 cigarettes a day (odds ratio of 2.46 versus an odds ratio of 1.26) (Christen *et al.* 1996). There was also a strong trend of increased risk with increased number of pack-years of smoking ($p<0.001$). In the Nurses' Health Study, there was a strong trend of increased risk with increasing number of cigarettes smoked per day ($p=0.004$) and pack-years ($p=0.005$) (Seddon *et al.* 1996).

The finding that smoking is implicated in the aetiology of AMD is an important one because it is a risk factor that is amenable to modification.

1.4.5 Cardiovascular disease

History of cardiovascular disease

The findings for reported history of cardiovascular disease have been inconsistent with some studies finding an association(Hyman *et al.* 1983; Chaine *et al.* 1998; Goldberg *et al.* 1988a) and others not (Maltzman *et al.* 1979; Delaney and Oates 1982; Vinding *et al.* 1992; Eye Disease Case-Control Study Group 1992; Klein *et al.* 1993a; Smith *et al.* 1998a; Delcourt *et al.* 2001). Table 1.12 summarises the results of those studies that have provided data in a form that can be extracted.

Atherosclerosis

The association between carotid atherosclerosis and AMD (geographic atrophy and neovascular disease) was investigated in the Rotterdam Study(Vingerling *et al.* 1995a). Atherosclerosis was assessed using ultrasonography with images being stored on videotape. Atherosclerotic lesions were defined as focal widening relative to adjacent segments, with protrusion into the lumen. People with plaques in the carotid bifurcation were at increased risk of AMD (odds ratio 4.5, 1.9 to 10.7). This finding has not been studied again but a study in Finland examined the relationship between retinal arteriosclerosis (defined as marked generalized narrowing of the arterioles) and AMD(Hirvela *et al.* 1996). They found that people with retinal arteriosclerosis had a higher prevalence of AMD. However, as only two people in the age group studied did not have retinal arteriosclerosis this finding cannot be considered robust. There was a higher prevalence of ARM in people with retinal arteriosclerosis but this was not statistically significant.

1.4.6 Other shared risk factors for cardiovascular disease

Blood pressure

Table 1.13 shows the results of studies that have investigated the relationship between blood pressure and AMD. Data from the Framingham Eye Study were analysed in two different ways. The mean blood pressure in people with AMD and vision of ≤ 20/30 was compared to those people without AMD (Kahn *et al.* 1977b). The data on blood pressure were collected during the Framingham Heart Study, prior to the collection of data on AMD. Only statistically significant results were reported in the paper. People with AMD in selected age-groups had a higher mean diastolic blood pressure. The Framingham Eye Study was analysed again some years later. In the repeat analysis, there were more cases of macular degeneration as vision was no longer included in the definition of the disease(Sperduto and Hiller 1986). Detailed information on hypertension, including its duration over 20 years prior to the eye examination was used. This showed that people with hypertension were more likely to have AMD and that this was related to the duration of hypertension. People who had had hypertension for longer had an increased risk of AMD. These results have been found in two other studies (Goldberg *et al.* 1988a; Chaine *et al.* 1998), but have not been replicated in a number of other studies (Maltzman *et al.* 1979; Eye Disease Case-Control Study Group 1992; Klein *et al.* 1993a; Hirvela *et al.* 1996; Smith *et al.* 1998a).

If there is a moderate increased risk of AMD with increasing blood pressure, large numbers of cases of disease will be required to detect this. This might be the reason why in some studies no statistically significant relationships were found. It is interesting to note that in most studies non-statistically significant increased odds ratios were found. However, some studies, such as the Eye Disease Case-Control Study group have been large (421 cases of neovascular disease) and have still failed to find an effect that could not be attributed to other confounding factors. In some of the cross-sectional studies, the number of cases of late stage disease has been small. However, these studies have had large numbers of early cases, and if raised blood pressure affected the incidence of the disease, it might be expected to increase the risk of early signs.

It is unlikely that raised blood pressure has a strong direct effect on the development of AMD, although there is some evidence that people with prolonged hypertension may be at increased risk of the disease.

Alcohol consumption

Alcohol has both harmful and beneficial effects on the circulation and physiology. It may increase oxidative stress or adversely affect the mechanisms that protect against oxidative damage(Cederbaum 1989). Its benefits may occur because it increases high density lipoprotein cholesterol(Gaziano *et al.* 1993) and decreases platelet aggregation(Renaud *et al.* 1992), and serum fibrinogen(Meade *et al.* 1979). All these changes may decrease the risk of cardiovascular disease in moderate drinkers. In coronary heart disease, it is thought that there is a J-shaped curve such that people who drink moderate amounts of alcohol are at reduced risk of the disease compared to those who drink none or large amounts. There have been few studies of the role of alcohol consumption in the development of AMD and these have produced conflicting results.

In NHANES 1, in an analysis of 184 individuals with AMD, moderate alcohol consumption reduced the risk of developing the disease (odds ratio 0.86, 0.73 to 0.99)(Obisesan *et al.* 1998). The authors concluded that the majority of this effect was attributable to wine consumption.

In the Copenhagen study, there was a non-significant trend of increased risk with increasing daily alcohol intake(Vinding *et al.* 1992). There was some suggestion of a J-shaped curve, with individuals consuming moderate amounts (1-2 alcoholic drinks a day) having a marginally reduced risk compared to those who drank none.

The Beaver Dam study found neither wine nor liquor consumption was related to early or late ARM. However, consumption of beer in the past year was related to a greater odds of neovascular macular degeneration (odds ratio 1.41, 1.05 to 1.88)(Ritter *et al.* 1995). In the longitudinal Beaver Dam Study, they found a higher 5-year age-adjusted incidence of various early signs of ARM in men who drank beer(Moss *et al.* 1998).

In the Eye Disease Case-Control Study, no association between alcohol consumption and risk of neovascular AMD was found(Eye Disease Case-Control Study Group 1992). In the Blue Mountains Eye Study neither alcohol intake nor intake of beer was associated with ARM, however, they did find an association between consumption of spirits and early stages of the disease(Smith and Mitchell 1996).

In the Physicians' Health Study there was no statistically significant associations but some indication of a J-shaped curve(Ajani *et al.* 1999). After adjusting for age, treatment assignment, and other potential risk factors, the relative risk for those

reporting alcohol consumption of < 1 drink/week, 1 drink/week, 2-4 drinks/week, 5-6 drinks/week, and >= 1 drink/day were 1.00 (referent), 1.00 (0.65 to 1.55), 0.68 (0.44 to 1.04), 1.32 (0.89 to 1.95), and 1.27 (0.93 to 1.73), respectively.

Cho et al analysed data from the Nurses' Health Study and the Health Professionals Follow-up Study (111,238 men and women)(Cho *et al.* 2000). ARM with vision loss of 20/30 or worse was diagnosed in 298 women (697,498 years of follow-up) and 153 men (229,180 years of follow-up). After controlling for age, smoking, high blood pressure, total energy intake, lutein/zeaxanthin intake, body mass intake, post menopausal oestrogen use and vigorous exercise, the relative risk for AMD compared with nondrinkers were 1.0 (0.7 to 1.2) for drinkers who consumed 0.1 to 4.9 g/day of alcohol; 0.9 (0.6 to 1.4) for 5 to 14.9 g/day; 1.1 (0.7 to 1.7) for 15 to 29..9 g/day; and 1.3 (0.9 to 1.8) for 30 g/day or more. They found some evidence that wine at higher levels of consumption (≥ two drinks per day) increased the risk of developing AMD (odds ratio 1.87, 1.17 to 3.00).

In summary, there are conflicting reports of the effect of alcohol intake on development of AMD. Some studies have reported an increased risk whereas others have found a decreased risk. There is no clear pattern as to which type of alcohol is important. This may reflect the consumption patterns of the communities studied, for example, beer drinking is very common in Beaver Dam but other types of alcohol are rarely consumed. This may explain why associations were only found with beer consumption in that study. In two studies, the Copenhagen Study and the Physicians' Health Study, there was some indication of a J-shaped curve but this relationship was not statistically significant.

Dietary fat intake

Dietary fat intake may influence the risk of developing AMD by two mechanisms(Mares-Perlman *et al.* 1995b). Raised levels of cholesterol in the bloodstream increase the risk of atherosclerosis which may have adverse effects on the choroidal circulation. Alternatively there may be increased deposition of fat in Bruchs membrane that would adversely affect flow supply of nutrients and removal of waste products from the retinal pigment epithelium.

Table 1.14 shows the relationship between dietary intake of fat and AMD. In the Beaver Dam Eye Study, data on the intake of food and supplements was collected using a

modification of the Health Habits and History Questionnaire developed by Block(Mares-Perlman *et al.* 1995b). There were 314 cases of early ARM and 30 cases of AMD. People with intakes of saturated fat and cholesterol in the highest quintile had a greater risk of early ARM. Similar estimates were found for AMD but these were not statistically significant due to the low number of cases.

In NHANES-III there was a non-significant association between total fat intake (expressed as a percentage of total energy intake) and ARM. After adjustment for age, race, eye colour and sedentary lifestyle, the odds ratio for early ARM was 1.4 (0.9 to 2.2) and AMD was 0.7 (0.2 to 2.6) comparing the highest against the lowest quintiles(Heuberger *et al.* 2001).

In the Eye Disease Case-Control Study, higher intakes of specific types of fat, i.e. vegetable, monounsaturated and polyunsaturated fats, rather than total fat intake was found to be associated with a greater risk of neovascular AMD(Seddon *et al.* 2001). Diets high in ω-3 fatty acids and fish were inversely associated with risk for AMD when intake of linoleic acid was low.

Cho et al reported data from the Nurses' Health Study and the Health Professionals Follow-up study. They identified prospectively 567 patients with ARM and visual loss of 20/30 or more. They found that total fat intake was associated with an increased risk of ARM. The relative risk for the highest compared with the lowest quintile of total fat intake was 1.54 (1.17 to 2.01). However, they suggest that this may have been due to intakes of individual fatty acids, such as linolenic acid rather than total intake per se. Docosahexaenoic acid had a modest inverse relation with ARM; four servings of fish per week was associated with a 35% lower risk of ARM compared with three or less servings per month (relative risk 0.65, 0.46 to 0.91).

The findings for biochemical markers of dietary fat have been inconsistent (table 1.15). Three studies have investigated this. In the Eye Disease Case-Control Study, people with high serum cholesterol (≥ 6.749 mmol/L) were at increased risk of neovascular disease compared to people with low values of serum cholesterol (≤ 4.888 mmol/L) (Eye Disease Case-Control Study Group 1992). However, this finding was not repeated in two other studies. In NHANES 1, people with high cholesterol (≥300 mg/100ml) were less likely to develop AMD compared to people with low cholesterol (<200 mg/100mml) (odds ratio 0.51, 0.26 to 1.00)(Goldberg *et al.* 1988a). Conversely, other

authors reported no association between AMD and cholesterol in NHANES-1(Klein and Klein 1982).

Body mass index

Table 1.16 shows the results of studies on body mass index.

Several studies have found that high body mass index is a risk factor for development of AMD. In the POLA study, people with a body mass index of 30 or more were at increased risk of AMD(Delcourt *et al.* 2001). In the AREDS case-control study, people in the top quintile for body mass index (≥ 31) were at increased risk of neovascular AMD compared to those in the lowest quintile (≤23.6)(AREDS 2000). This was also seen in the Eye Disease Case-Control Study Group, however, this relationship was no longer significant once other confounders were taken into account(Eye Disease Case-Control Study Group 1992). In the Oulu County Study, high body mass index (≥ 27.5) was found to be associated with ARM in men only(Hirvela *et al.* 1996).

A couple of the larger studies have found some evidence of a J-shaped curve. In the prospective Physicians Health Study, a J-shaped relationship was found such that people with normal body mass index (in this case defined as 22.0 to 24.9) were at the lowest risk of developing ARM causing visual loss(Schaumberg *et al.* 2001). A similar finding was seen in the Blue Mountains Study(Smith *et al.* 1998a). This was significant for early ARM and non-significant for AMD due to lower number of cases.

In the cross-sectional Beaver Dam Eye Study, waist-to-hip ratio was more strongly associated with risk of developing early ARM and AMD than body mass index(Klein *et al.* 2001a).

Diabetes

Hyperglycemia may affect the normal functioning and structure of the choroidal circulation, the retinal pigment epithelium or Bruch's membrane. In the cross-sectional Beaver Dam study, diabetes in men 75 years of age and older was associated with an increased risk of neovascular AMD (odds ratio 10.2, 2.4 to 43.7)(Klein *et al.* 1992b). There was little evidence for a relationship in women (odds ratio 1.1, 0.4 to 3.0

However this finding has not been repeated in any of the many studies that have examined this association(Eye Disease Case-Control Study Group 1992; Delcourt *et al.* 2001; Smith *et al.* 1998a; Hirvela *et al.* 1996; AREDS 2000).

1.4.7 Antioxidant micronutrients

There is much interest in the role of antioxidant micronutrients, largely because this, like smoking, is a potentially modifiable risk factor. If we all ate enough fruit and vegetables or took a multi-vitamin pill every day, could we avoid developing AMD in later life?

The two major antioxidant micronutrients in the retina are the carotenoids lutein and zeaxanthin. The most plausible hypothesis would be that increased levels of macular pigment would decrease the risk of AMD through its ability to reduce the effect of light induced retinal damage from the photodynamic production of free radicals(Beatty *et al.* 1999).

Unlike many of the other risk factors discussed in this paper, this is one area where there is the potential to undertake randomised controlled trials. Randomised controlled trials are considered a better source of evidence than observational studies, because the investigator, using the process of adequately concealed random allocation, can create two groups which are comparable apart from the intervention under study. I have conducted a Cochrane systematic review evaluating the effect of antioxidant vitamin and mineral supplementation on the progression of AMD(Evans 2001a). This review includes seven trials which randomised 4119 people with signs of AMD. The majority of people (88%) were randomised in one trial that was conducted in a relatively well-nourished American population. This trial found a modest beneficial effect of antioxidant and zinc supplementation on progression to advanced AMD (odds ratio 0.72, 99% confidence interval 0.52 to 0.98). People supplemented with antioxidants and zinc were less likely to lose 15 or more letters of visual acuity (equivalent to a doubling of the visual angle) (odds ratio 0.79, 99% confidence interval 0.60 to 1.04). The other six trials in this review were small and the results were inconsistent.

There is no evidence at present that people with early signs of the disease should take supplementation, however, current studies are underpowered to answer that question. The generalisability of these findings to other populations with different nutritional status is not known.

Randomised controlled trials of simple vitamin supplements may not assess the correct exposure. It may be that a few chemical supplements do not substitute for a diet rich in antioxidants. There are a number of observational studies that have examined the

association between antioxidant micronutrients in the diet and AMD(Eye Disease Case-Control Study Group 1993; Goldberg *et al.* 1988b; Mares-Perlman *et al.* 1995a; Mares-Perlman *et al.* 1996; Sanders *et al.* 1993; Seddon *et al.* 1994; VandenLangenberg *et al.* 1998; West *et al.* 1994b). Observational studies are not such a good source of evidence as to the benefits of dietary intake of antioxidant micronutrients. People who have a diet rich in antioxidant vitamins and minerals or who choose to take supplements regularly, are different in many ways from those who do not; these differences may not be adequately controlled by statistical analysis. Inconsistent results have been found(Evans 2001b). As I will not present data on antioxidant micronutrients in this thesis I will not discuss these observational studies further.

1.4.8 Light

Photoreceptors in the retina are subject to oxidative stress throughout life due to combined exposures to light and oxygen(Young 1988). The action of light on the photoreceptors generates free radicals. These are short-lived molecular fragments that have an unpaired electron in the outer orbital. This unstable structure is highly reactive and toxic. It attacks other molecules, particularly polyunsaturated fatty acids, which are an essential component of biological membranes.

It is thought that AMD might occur in individuals that have received excess light stimulation, particularly at vulnerable times, or who do not have enough protective antioxidant micronutrients in the serum or retina.

Most ultraviolet radiation (wavelength 200-400 nanometers) is absorbed by the lens and cornea. It is largely visible light (wavelength 400 to 780 nanometers) that reaches the retina. Animal studies and case reports in humans show that excessive exposure to bright light, from solar or other sources, can damage the retina. There is also some evidence that intense bright sunlight causes changes in the retinal pigment epithelium similar to those seen in ARM. Whether or not exposure to sunlight or artificial light sources is an important cause of AMD in human populations is not clear. It is difficult to measure lifetime light exposure in human populations. There is also uncertainty about when light exposure is important. Some authors have suggested that the period of exposure of interest may well be in childhood at which time the ocular media transmit more blue light and ultraviolet radiation than those of adults(Simons 1993). There is increasing absorption of short wavelength light by the lens with increasing age,

however, this is counteracted by the greater proportion of people who have cataract surgery at older ages. It has been shown that increased ambient light increases the antioxidant capability of the retina. This raises the question as to whether it is chronic high ambient light levels that are harmful or rather increases in the level of light to which the eye is accustomed that could be problematic.

It is difficult to measure lifetime light exposure directly. A number of investigators have tried to estimate the average annual exposure. They have done this by asking study participants about their activities in relation to time spent out of doors and use of hats and sunglasses and relating this to records of ambient light exposure in the region of the study. They have combined the two measures using mathematical formulae that adjust the maximum potential light exposure according to attenuating factors such as time spent indoors, use of hats and glasses. The estimates of the effects of these attenuating factors is crude as the questionnaires attempt to measure lifetime exposures, however, minute by minute exposures can vary enormously depending on the angle of the sun, the position of the head, use of hats, buildings, trees, reflective surfaces and so on. However, although such measures are necessarily crude they may be good enough to distinguish groups of people with very different exposures. In the case of cataract such instruments have been sufficient to detect an effect of ultraviolet light exposure on cortical cataract(McCarty and Taylor 2002).

There have been a number of studies that have examined the role of ultraviolet and visible light on the development of AMD(Hyman *et al.* 1983; Blumenkranz *et al.* 1986; Taylor 1989; West *et al.* 1989; Taylor *et al.* 1990; Eye Disease Case-Control Study Group 1992; Cruickshanks *et al.* 1993; Darzins *et al.* 1997; Mitchell *et al.* 1998; Cruickshanks *et al.* 2001).

In both the Chesapeake Bay study and Beaver Dam Eye Study no association was found with lifetime exposure to ultraviolet light(West *et al.* 1989; Cruickshanks *et al.* 1993). However, in a subsequent re-analysis, the Chesapeake Bay study found a borderline association with visible light(Taylor *et al.* 1990). The authors of the Beaver Dam Eye Study also argued that some of their measures indicated that visible, rather than ultraviolet, light might be the problem(Cruickshanks *et al.* 1993). Other studies have found no association with proxy measures of lifetime exposure such as time spent out doors(Darzins *et al.* 1997; Eye Disease Case-Control Study Group 1992).

1.4.9 Oestrogen

Oestrogens are female sex hormones that have well documented favourable effects on blood lipids and clotting factors and may protect against peroxidative damage of membrane lipids and low density lipoproteins. Many case-control and prospective studies have reported less coronary heart disease in women using oestrogen. Randomised controlled trials of hormone therapy have failed to confirm these beneficial effects on cardiovascular disease(Barrett-Connor and Stuenkel 1999). The role of oestrogens in the development of AMD has been investigated in several studies(Eye Disease Case-Control Study Group 1992; Vingerling *et al.* 1995c; Klein *et al.* 1994a; Smith *et al.* 1997).

The Eye Disease Case-Control Study Group was the first study to report on oestrogens(Eye Disease Case-Control Study Group 1992). They found that women currently taking oestrogen replacement were at a reduced risk of neovascular AMD compared to women who had never taken replacement therapy (odds ratio 0.3, 0.1-0.8). Women reporting former use were at an intermediate risk (odds ratio 0.6, 0.3-0.98). This association remained after controlling for smoking, education, physical activity, antioxidant intake and plasma lipids.

In the Rotterdam Study, 59 women with AMD were each matched with five controls born in the same year who did not have macular degeneration (295 controls)(Vingerling *et al.* 1995c). Women with early menopause after removal of one or both ovaries had an increased risk of macular degeneration compared to women who had their menopause at 45 years or later (relative risk 3.8, 1.1-12.6). The only confounder adjusted for in these analyses was age.

Conflicting results were produced in the Beaver Dam Study which investigated three measures of premenopausal oestrogen exposure (age at menarche, the number of years of having menstrual cycles and number of pregnancies) and two measures of exposure to exogenous oestrogens (birth control pills and oestrogen replacement therapy)(Klein *et al.* 1994a). Analysis of the relationship between these measures and various signs of early and late AMD revealed little evidence to support the hypothesis that female sex hormones are important protective factors in the development of AMD. The analyses were repeated with incidence data and similar findings obtained(Klein *et al.* 2000).

Similar findings were obtained in the Blue Mountains study(Smith *et al.* 1997). Analysis of a variety of measures of oestrogen exposure with early and late ARM only revealed one statistically significant association - women with increased time from menarche to menopause had a reduced risk of early ARM (odds ratio 0.97, 0.95-0.99).

The role of oestrogens in the development of AMD clearly warrants further study. Two studies have found effects of oestrogen replacement and early surgical menopause but two large cross-sectional studies have failed to find any strong evidence of effects with a number of factors indicating premenopausal and postmenopausal oestrogen exposure.

1.4.10 Genetic factors

Work on the genetic determinants of AMD has been slow to develop for two reasons. Firstly, as AMD is a disease of old age, surviving parents and well-established family trees are rare. Secondly, it is likely to be a complex trait, that is, its inheritance is probably controlled by more than one gene. The study of complex traits has been a relatively recent development.

The extent of heritability and the number of genes involved in AMD is unknown at present(Gorin *et al.* 1999). However, there is considerable evidence from the occurrence of AMD in families and populations to suggest that there is a genetic basis for this condition.

Several studies have shown that people reporting a family history of AMD are at increased risk of the disease(Hyman *et al.* 1983; Smith and Mitchell 1998). A number of twin studies have shown a higher concordance rate between monozygotic than dizygotic twins in features of the disease(Gottfredsdottir *et al.* 1999; Grizzard and Beck 1994; Klein *et al.* 1994b; Melrose *et al.* 1985; Dosso and Bovet 1992). Family-based studies, comparing siblings rather than twins, also provide evidence for a genetic basis for the condition(Piguet *et al.* 1993; Seddon *et al.* 1997; de Jong *et al.* 1997; Klein *et al.* 2001b). It has been estimated that siblings of an affected person have nearly a 20 times higher risk of developing the disease compared to the general population(Silvestri *et al.* 1994). Segregation analysis of siblings enrolled in the Beaver Dam Eye Study found results consistent with a major gene effect accounting for 62% and 59% of the expression of ARM in the right and left eyes respectively(Heiba *et al.* 1994).

One approach to examining the genetics of AMD has been to study the genetics of hereditary retinal dystrophies that share similar phenotypic characteristics to AMD. To

date there have been a number of autosomal genes identified for hereditary retinal dystrophies (http://www.sph.uth.tmc.edu/retnet/). Study of the biology and genetics of photoreceptor degeneration is likely to further understanding of the pathophysiology of AMD (Zack *et al.* 1999).

1.4.11 Summary

The main risk factor for AMD, apart from age and genetic factors, is smoking. This has been demonstrated in numerous studies of different design to be associated with an increased risk of AMD. The other risk factors studied such as oestrogen use, light exposure, cardiovascular disease and its risk factors and alcohol consumption have produced conflicting results. Antioxidant vitamin and mineral supplementation has been found to be associated with reduced risk of disease progression in one large trial but observational studies have produced conflicting results.

1.5 AIMS AND OBJECTIVES

The review of the literature has shown a lack of information on AMD as a cause of visual loss, no information on AMD as a cause of visual loss in Britain, and limited information for people aged 75 years and above.

Population-based studies have been limited by the numbers of people with advanced disease detected. Hospital-based studies have been limited by lack of suitable control groups and uncertainty about the representativeness of the AMD cases. There has been a lack of heterogeneity in vision status and severity of AMD.

Although people aged 75 years and above bear the burden of this disease disproportionately, previous research has not focussed on the differing needs of this group, particularly with respect to increasing age. People aged 90 years and above may have very needs compared to people aged 75-79.

The aims and objectives of this thesis are as follows:

(1) To estimate the prevalence of AMD causing visual impairment in people aged 75 years and above in UK, and to investigate how this varies by age, sex, socio-economic status and region.

(2) To investigate the impact of AMD causing visual impairment on the lives of people aged 75 years and above in the UK: specifically, its impact on:

- mortality
- morbidity
- functional ability
- health-related quality of life
- psychological well-being
- emotional well-being (life satisfaction and morale)

To investigate whether the impact of AMD causing visual impairment varies in different age and sex groups.

(3) To investigate the aetiology of visually impairing AMD in people aged 75 years and above in UK, *that is,* to test the following hypotheses:

- that smoking cigarettes and drinking alcohol are associated with an increased risk of visually impairing AMD;
- that factors indicating increased oestrogen exposure in women are protective for developing visually impairing AMD;
- that people with evidence of cardiovascular disease are at increased risk of developing visually impairing AMD.

TABLES AND FIGURES

Table 1.1 Classification of AMD

Age-group: 50 years and above *Visual acuity:* No cutoff

Detection: Grading of colour fundus transparencies

Overall term: Age-related maculopathy (ARM)

The following signs in the absence of other diseases which may cause these lesions.*

Early ARM

- Soft drusen >=63 microns
- Areas of increased pigment or hyperpigmentation (in the outer retina or choroid) associated with drusen
- Areas of depigmentation or hypopigmentation of the RPE, most often more sharply demarcated than drusen, without any visibility of choroidal vessels, associated with drusen.

Late ARM = AMD

Geographic atrophy

("dry" AMD):

- any sharply delineated roughly round or oval area of hypopigmentation or depigmentation or apparent absence of the RPE in which choroidal vessels are more visible than in surrounding areas that must be at least 175 microns in diameter.

Neovascular AMD

("disciform", "exudative" or "wet" AMD):

- RPE detachment (s) which may be associated with neurosensory retinal detachment, associated with other forms of ARM
- subretinal or sub-RPE neovascular membrane (s)
- epiretinal (with exclusion of idiopathic puckers), intraretinal, subretinal, or sub-pigment epithelial scar/glial tissue or fibrin-like deposits
- subretinal haemorrhages that may be nearly black, bright red, or whitish-yellow and that are not related to other retinal vascular disease
- hard exudates (lipids) within the macular area related to any of the above and not related to other retinal vascular disease.

---

*Other diseases:
ocular trauma, retinal detachment, high myopia, chorioretinal infection or inflammation, choroidal dystrophy

Table 1.2 Prevalence studies

Study	Where	*When	Age	Response	AMD	
					Assessment	*Definition*
NHANES I	USA	1971-74	45-75	NK	Clinical	Early & late changes, < 20/25
Framingham Eye Study	USA	1973-75	52-85	84%	Clinical	Early & late changes, ≤ 20/30
Gisborne	NZ	1980	65+	86%	Clinical	Early & late changes, ≤ 20/30
Melton Mowbray Study	UK	1982-84	76+	72%	Clinical	Early & late changes, ≤6/9
Guangzhou,Urumqi,Lhasa	China	1985/86	50-98	NK	Clinical	Early & late changes, ≤ 20/30
Chesapeake Bay Study	USA	1986	30+	65%	Photographs	Early & late changes
Copenhagen City Study	DK	1986-88	60-80	95%	Clinical	Early & late changes, ≤6/9
Baltimore Eye Study	USA	1988	40+	79%	Photographs	Early & late changes
Beaver Dam Eye Study	USA	1988-90	43-84	81%	Photographs	WARMGS
NHANES III	USA	1988-91	40+	54%	Photographs	WARMGS
Rotterdam Study	NL	1990-93	55-98	64%	Photographs	Modified WARMGS
Leicester	UK	1991	40+	61%	Clinical	Early & late changes, ≤ 20/30

Continued on next page

Table 1.2 Prevalence studies (continued)

Study	Where	*When	Age	Response	AMD	
					Assessment	*Definition*
Oulu County Study	Finland	1991	70+	85%	Photographs	Early & late changes
Salandra Study	Italy	1991	60-89	64%	Photographs	Early & late changes
Barbados Eye Study	Barbados	1992	40-84	67%	Photographs	Early & late changes
Blue Mountains Eye Study	Australia	1992-93	49+	82%	Photographs	WARMGS
Melbourne VIP Study	Australia	1992-96	40-98	78%	Photographs	WARMGS
ARIC Study	USA	1993-95	48-72	46%, 65%	Photographs	WARMGS
North London Eye Study	UK	1995-96	65+	84%	Clinical	"Age-related macular changes",<6/12
Hisayama Study	Japan	?	50+	?	Both	

NHANES: National Health and Nutrition Examination Survey WARMGS: Wisconsin Age-Related Maculopathy Grading System ARIC: Atherosclerosis Risk in Communities Study Early changes: drusen and pigmentary abnormalities Late changes: geographic atrophy, neovascular AMD International Classification: see table 1 (Bird *et al.* 1995) *If not specified, assumed two years before first publication accepted for publication.

Table 1.3 Prevalence (%) of AMD from pooled analysis of three population-based studies*

Age	N	Geographic atrophy alone	Neovascular AMD alone	Geographic atrophy and neovascular AMD	Geographic atrophy or neovascular AMD
55-64	4797	0.04	0.17	0	0.21
65-74	4799	0.29	0.54	0.02	0.85
75-84	2656	1.54	2.52	0.53	4.59
85+	521	4.22	5.76	3.07	13.05
All ages	14752	0.54	0.89	0.21	1.63

* Beaver Dam Eye Study (USA), Rotterdam Study (Netherlands), Blue Mountains Eye Study (Australia) From pooled analysis by Smith et al(Smith *et al.* 2001)

Table 1.4 Prevalence (%) of AMD causing visual impairment (binocular acuity 6/18 or less) from pooled analysis of six population-based studies

Age group	Number	Prevalence %	95% confidence intervals
65-69	3787	0.13	0.04 to 0.51
70-74	3288	0.33	0.11 to 0.88
75-79	2527	1.55	0.86 to 2.61
80-84	1422	3.58	2.13 to 5.69
85-89	570	8.07	4.74 to 12.99
90+	196	15.3	7.61 to 27.37

Beaver Dam Eye Study (USA), Blue Mountains Eye Study (Australia), Copenhagen City Study (Denmark), North London Eye Study (UK), Rotterdam Study (Netherlands), Melbourne Visual Impairment Study (Australia). From pooled analysis by Owen et al(Owen *et al.* 2002)

Table 1.5 Number of participants assessed for AMD in prevalence studies

Study	Age range	Total number examined	Number aged 75 years and above	Number aged 90 years and above
NHANES I	45-75	3056	0	0
Framingham Eye Study	52-85	2477	392	0
Gisborne	65+	481	433	56
Melton Mowbray Study	76+	484	484	92**
Chesapeake Bay Study	30+	777	119*	NK
Copenhagen City Study	60-80	924	242	0
Baltimore Eye Study	40+	5308	?	?
Beaver Dam Eye Study	43-84	4771	676	0
NHANES III	40+	4007	NK	NK
Rotterdam Study	55-98	6251	1570	326**
Leicester	40+	377	92*	NK
Oulu County Study	70+	478	478*	NK
Salandra Study	60-89	366	73	0
Barbados Eye Study	40-84	3444	780*	0
Blue Mountains Eye Study	49+	3654	788	135**
Melbourne VIP Study	40-98	4345	NK	27
ARIC Study	48-72	11532	0	0
North London Eye Study	65+	1547	743	NK
Hisayama Study	50+	1486	?	?
Total		55765	6870	636

* 70 years and above ** 85 years and above

Table 1.6 Characteristics of studies investigating impact of visual impairment and AMD

Study (country)	Author(s),year	Type of study	Setting	Classification of visual impairment/AMD	Outcome measures	Number of cases	Findings
Age-related macular degeneration progression study (USA)	Mangione et al, 1999	Cross-sectional	Hospital	AMD, no direct comparison group	ADVS, SF-36	201	Severity of AMD associated with ADVS but not SF-36
Auckland Hip Fracture Study (New Zealand)	Ivers et al, 2000	Case-control	Hospital	VI <6/18	Cases were people hospitalised with hip fracture	675 people with hip fracture	Increased risk of hip fracture in people with VI
(Brescia) (Italy)	Appollonio et al, 1995	Longitudinal	Community	VI <6/15	Mortality	32 VI	Non-significant increased risk of death with VI
	Carabellese et al, 1993	Cross-sectional			Depression ADL Social relationships	138 VI	Increased risk of depression, low social relationships and low daily living functioning in people with VI

Table 1.6 Characteristics of studies investigating impact of visual impairment and AMD (continued)

Study (country)	Author(s),year	Type of study	Setting	Classification of VI or AMD	Outcome measures	No. of cases	Findings
Beaver Dam (USA)	Klein et al, 1998	Cross-sectional	Community	VI ≤ 6/7.5	Reported falls & hip fractures	781	Increased risk of falls & hip fractures in people with VI
	Klein et al 1995	Longitudinal	Community	VI ≤ 6/12 ARM (none, early, late)	Mortality	198	Non-significant increased risk adjusted OR 1.08 (CI 0.77 to 1.51) with VI Non-significant reduced risk adjusted OR 0.89 (CI).74 to 1.07) with increased ARM
Blue Mountains (Australia)	Ivers et al, 1998	Cross-sectional	Community	VI < 6/9	Falls	813	Increased risk of falls in people with VI adjusted OR 1.9 (CI 1.2 to 2.0)
	Wang JJ et al, 2000			VI < 6/24	Self-reported health	43	Increased risk of rating health as poor or fair with decreased vision in people aged <80 but not in those aged 80+.
	Wang JJ et al, 2001	Longitudinal	Community	VI ≤ 6/12 ARM	Mortality	?	Increased risk of mortality associated with VI adjusted hazard ratio 1.5 (CI 1.2 to 1.9) ARM not associated with mortality

Table 1.6 Characteristics of studies investigating impact of visual impairment and AMD (continued)

Study (country)	Author(s),year	Type of study	Setting	Classification of VI or AMD	Outcome measures	No. of cases	Findings
EPESE (USA)	Salive 1994	Cross-sectional & longitudinal	Community	Severe VI <6/60	ADL	232	Increased risk of ADL limitations adjusted OR 4.6 (CI 3.3 to 6.4) Increased risk of incident ADL limitations adjusted OR 3.5 (CI 1.7 to 7.2)
EPIDOS (France)	Dargent-Molina et al, 1996	Longitudinal	Community	VI ≤ 6/30	Incident hip fractures	547 VI	Increased risk of hip fracture in people with VI
GAO-Cleveland (USA)	LaForge et al, 1992	Longitudinal	Community	Vision self-rated excellent/good/ fair/poor/blind	Mortality Functional decline (change in ADL/IADL)	129 "poor" vision	Increased risk of death with poor vision Increased risk of decline with poor vision
(Maryland) (USA)	Marx et al, 1992	Cross-sectional	Nursing home	VI <6/21	ADL	51	Greater proportion of residents with low vision dependent on caregivers for performing ADLs
Melbourne VIP (Australia)	McCarty et al, 2001	Longitudinal	Community	VI <6/12	Mortality	43	Increased risk of death unadjusted OR 2.3 (CI 1.03 to 5.32)
				ARM		501	Non significant increased risk of death with ARM OR 1.36 (CI 0.96 to 1.94)

Table 1.6 Characteristics of studies investigating impact of visual impairment and AMD (continued)

Study (country)	Author(s),year	Type of study	Setting	Classification of VI or AMD	Outcome measures	No. of cases	Findings
Melton Mowbray (UK)	Thompson et al, 1989	Longitudinal	Community	Snellen acuity analysed in groups	Mortality	469 (total)	Non-significant increased risk with decreased vision, except decreased risk with blindness
NHIS (USA)	Lee et al, 2002	Longitudinal	Community	Reported VI	Mortality	327	Increased risk of death in women with VI adjusted hazard ratio 2.21 (CI 1.61 to 3.02)
RCT of self-management intervention (USA)	Brody et al, 2001	Cross-sectional	Hospital	AMD, no direct comparison group	Depression, NEI-VFQ	151	Twice the rate of depression (SCID-IV criteria) compared to general population
(San Diego) (USA)	Williams et al, 1998	Cross-sectional	Hospital	VI < 6/18 due to AMD, no direct comparison group	QWB, POMS, IADL, Self-rated health status	86	Ratings for QWB & POMS significantly worse than for similarly aged community adults. More likely to need significant help with IADL
SEE (USA)	West et al, 1997	Cross-sectional	Community	VI < 6/12	ADL/IADL Social interaction	174	Increased risk of "no social interaction" adjusted OR 1.67 (CI 1.17 to 2.37) Increased risk of difficulty with any ADL adjusted OR 1.83 (CI 1.18 to 2.83)

Table 1.6 Characteristics of studies investigating impact of visual impairment and AMD (footnote)

ADL	Activities of Daily Living
ADVS	Activities of Daily Vision Scale
CI 95%	Confidence intervals
EPESE	Epidemiologic Studies of the Elderly
IADL	Instrumental Activities of Daily Living
NEI-VFQ	National Eye Institute Visual Function Questionnaire
NHIS	National Health Interview Study
POMS	Profile of Mood States
QWB	Quality of Well-being
SCID-IV	Structured Clinical Interview for DSM-IV
SF-36	Short form health survey
VI	Visual impairment
VIP	Visual impairment Project

Table 1.7 Overview of study designs

Type of study	Useful for	Advantages	Limitations
Cross-sectional study	Evaluating effect of exposures by comparing prevalence ratios (relative risk) between different groups defined by exposure		Exposure often measured retrospectively Knowledge of disease status may change measurement of risk factor Effects of confounders can be difficult to assess
Cohort study randomised controlled trial	Evaluating effect of exposures/interventions/ treatments	Random allocation removes effects of known/unknown confounding variables	Can only study exposures where ethical/practical to randomise Needs to be large
Cohort study observational study	Estimating incidence Evaluating effect of exposures	Exposure status measured before disease occurs	Relevant confounding variables need to be measured accurately and analysed appropriately Needs to be large
Population-based case-control study	Estimating effect of exposure (relative risk)	Selection of control group reasonably straightforward	Can be harder to obtain large case group Relevant confounding variables need to be measured accurately and analysed appropriately Exposure often measured retrospectively Knowledge of disease status may change measurement of exposure
Hospital-based case-control study	Estimating effect of exposure (relative risk)	Easier to obtain reasonably large case group	Selection of control group can be problematic Relevant confounding variables need to be measured accurately and analysed appropriately Exposure often measured retrospectively Knowledge of disease status may change measurement of exposure Relative risk estimated by odds ratio which can be problematic if rare disease assumption does not apply

Table 1.8 Cross-sectional studies on AMD

	AMD		Number of cases of AMD identified			Measures of study quality		
Study	*Assessment*	*Visual acuity cutoff*	*Early ARM*	*AMD (late ARM)*	*Early ARM and/or AMD*	*Masking in exposure assessment*	*Analysis plan or primary/ secondary outcomes specified*	*Some attempt to control for confounding factors other than age and sex*
NHANES I	Clinical	<20/25			178* or 184**	Not stated	No* Yes **	Yes
Framingham Eye Study	Clinical	≤20/30			163	Not stated	No	No
		None			236	Not stated	No	No
Melton Mowbray Study	Clinical	≤20/30			201	Not stated	No	No
Chesapeake Bay Study	Photographs	None	87	9		Not stated	No	No
Copenhagen City Study	Clinical	≤ 6/9			112	Not stated	No	No
Beaver Dam Eye Study	Photographs	None	739	77		Yes	No	Yes
NHANES III	Photographs	None	644	53				
Rotterdam Study	Photographs	None			101	Yes	No	No
Oulu County Study	Photographs	None	160	39	199	Not stated	No	No
Blue Mountains Eye Study	Photographs	None	240	72		Not stated	No	Yes
Melbourne VIP Study	Photographs	None	656	30				
ARIC Study	Photographs	None			16			
POLA Study	Photographs	None		41		Not stated	No	Yes

* Klein et al(Klein and Klein 1982) ** Goldberg et al(Goldberg *et al.* 1988a)

Table 1.9 Case-control studies

Study	Where	Year of publication	AMD: *Definition*	AMD: *Cases*	Measures of study quality: *Controls represent population from which cases drawn*	Measures of study quality: *Masking in exposure assessment*	Measures of study quality: *Some attempt to control for confounders other than age and sex*
Maltzman et al	USA	1979	"Senile macular degeneration" with vision <=20/30	30	Probably	Not stated	Yes
Delaney & Oates	USA	1982	Early and late changes with loss of central vision	50	Not known	No	No
Hyman et al	USA	1983	Early and late changes with some visual loss	228	Probably	Not stated	Yes
Weiter et al	USA	1985	Presence of macular drusen	650	Not known	Yes	No
Blumenkranz et al	USA	1986	NV-AMD	26	Not known	Yes	No

Continued

NV-AMD: neovascular AMD GA: geographic atrophy

Table 1.9 Case-control studies continued

Study	Where	Year of publication	AMD		Measures of study quality		
			Definition	*Cases*	*Controls represent population from which cases drawn*	*Masking in exposure assessment*	*Some attempt to control for confounders other than age and sex*
EDC-CSG	USA	1992	NV-AMD	421	Yes	Yes	Yes
Sanders et al	UK	1993	Early changes	65	Yes	Probably	Yes
Chaine et al	France	1998	Early and late changes	1844	Probably	Not stated	Yes
AMD Risk Factors Study	USA	2000	NV-AMD & "non NV-AMD"	293 (NV) 339 (non-NV)	Yes	Yes	Yes
AREDS	USA	2000	NV-AMD & GA	658 (NV) 118 (GA)	Yes	Not stated	Yes

EDC-CSG: Eye Disease Case Control Study Group AREDS: Age-related Eye Disease Study NV-AMD: neovascular AMD GA: geographic atrophy

Table 1.10 Cohort studies

			AMD			Measures of study quality	
Study	Where	Year of publication	*Assessment*	*Definition*	*Cases*	*Masking in outcome assessment*	*Some attempt to control for confounding factors other than age and sex*
Baltimore Longitudinal Study of Aging	USA	1994	Photographs	Early and late changes	226	Yes	Yes
Physicians' Health Study	USA	1996	Self-report followed by medical record review	AMD with vision loss	268	Yes	Yes
Nurses' Health Study	USA	1996	Self-report followed by medical record review	AMD with vision loss	215	Yes	Yes
Beaver Dam Eye Study	USA	1997	Photographs	AMD	Not clear	Not stated	Yes
Rotterdam Study	NL	2001	Photographs	AMD			
Blue Mountains Eye Study	Aus	2002	Photographs	AMD	25	Not stated	

Year of publication: year of first publication NL: Netherlands Aus: Australia

Table 1.11 Smoking

Study	AMD *Definition*	*Cases*	Smoking measure	Confounding variables	RR/OR	95% confidence intervals
Chesapeake	Early & late		Ever vs. never	Age	0.61	0.35 to 1.05
Beaver Dam	NV-AMD	M: 16 F: 39	Ever vs. never	Age, passive smoking, diabetes (men only)	M:2.86	0.64 to 12.7
					F:2.06	**1.01 to 6.20**
	GA	M: 9 F:18	Ever vs. never		"No relationship"	
Blue	NV-AMD	33	Current vs. never	Age and sex	**3.26**	**1.45 to 7.33**
Mountains	GA	11	Current vs. never	Age and sex	**4.94**	**1.29 to 18.82**
POLA Study	Late AMD		Current vs. never	Age and sex	**3.6**	**1.1 to 12.4**
Rotterdam Study	NV-AMD	98	Never vs. current	Age and sex	**3.5**	**1.8 to 7.0**
	GA	36	Never vs. current	Age and sex	1.5	0.6 to 3.9
Oulu County	Early & late	199	Yes vs. No		Standardized difference of 1% (95% ci –14% to 16%)	
Copenhagen Study	Early & late	112	Inhaling vs. non		**2.4**	p<0.05

Continued

Bold indicates statistically significant results (p<0.05) NV-AMD: neovascular AMD GA: geographic atrophy

Table 1.11 Smoking continued

Study	AMD *Definition*	*Cases*	Smoking measure	Confounding variables	RR/OR	95% confidence intervals
VIP	AMD	30	Smoked>40 years		**2.39**	**1.02 to 5.57**
Physicians' Health Study	AMD, ≤20/30	132	Current >20 cig/day vs. never	Age, treatment assignment	**2.57**	**1.7 to 3.9**
	NV-AMD, ≤20/30	37	Current >20 cigarettes per day vs. never	Age, treatment assignment	**2.1**	**1.01 to 4.37**
Nurses' Health Study	AMD, ≤20/30	119	Current vs. never	Age	**1.9**	**1.3 to 2.6**
EDC-CSG	NV-AMD	421	Current vs. never	Age,sex,clinic,education, physical activity,carotenoids, cholesterol,fibrinogen, tricglycerides, CD- ratio, refractive error.	**2.2**	**1.4 to 3.5**
Chaine et al	Early and late changes	1844	Present vs. non-smoking		1.06	0.84 to 1.33
Blumenkranz	NV-AMD	26	Ever vs. never		1.25	0.3 to 4.4
Hyman et al	AMD, vision loss	228	Cigarette smoking		1.2	0.8 to 1.89
Tamakoshi	NV-AMD	56	None vs. current	Age	**2.97**	**1.0 to 8.84**
AREDS	GA	118	Ever smoked for at least six months	Age,sex,BMI,education,refractive error,race,hypertension, angina,lens opacity,various medicines	**1.61**	**1.06 to 2.42**
	NV-AMD	658			**1.91**	**1.57 to 2.33**

Bold indicates statistically significant results (p<0.05) NV-AMD: neovascular AMD GA: geographic atrophy VIP: visual impairment project EDC-CSG: Eye Disease Case-Control Study Group AREDS: Age-related eye disease study

Table 1.12 History of cardiovascular disease

Study	History of:	Type of AMD	Number of cases	Odds ratio	95% c.i.	Confounders adjusted for in addition to age and sex
Beaver Dam	Myocardial infarction	NV-AMD	50	0.51	0.15 to 1.68	
	(m.i.)	GA	24	0.95	0.27 to 3.35	
	Stroke	NV-AMD	50	0.96	0.33 to 2.79	
		GA	24	0.38	0.05 to 2.91	
	Cardiovascular disease	NV-AMD	50	0.67	0.33 to 1.37	
		GA	24	0.74	0.28 to 1.90	
Blue Mountains	Stroke	AMD	72	1.54	0.74 to 3.21	Smoking, family history AMD
	Angina	AMD	72	1.22	0.65 to 2.28	
	Acute m.i.	AMD	72	1.43	0.72 to 2.85	
NHANES-I	Cardiovascular disease	ARM	178	1.22	0.15 to 9.81	Race
	Cerebrovascular disease	ARM	**178**	**4.19**	**1.08 to 16.2**	
Hyman et al	≥ 1 cardiovascular disease	ARM	**228**	**1.7**	**1.1 to 2.7**	
Copenhagen City	Myocardial infarction	ARM	112	1.2	NS	
Study	Stroke	ARM	112	0.6	NS	
Chaine et al	Coronary artery disease	NV-AMD	**672**	**1.49**	**1.03 to 2.15**	Unclear
		GA	**343**	**3.19**	**1.81 to 5.64**	

Bold indicates statistically significant results ($p<0.05$) NV-AMD: neovascular AMD GA: geographic atrophy

Table 1.13 Blood pressure

		AMD					
Study	Country	*Definition*	*Cases*	Definition of hypertension	Confounding variables	Relative risk or odds ratio	95% confidence intervals
Framingham Eye Study	USA	Early and late changes, vision <=20/30	163	Diastolic blood pressure	Mean diastolic blood pressure significantly higher in people with AMD in men aged 65-74 and women aged 52-64 and 65-74		
Framingham Eye Study	USA	Early and late changes with no vision cut off	408	>=160mmHg systolic and/or >=95 diastolic and/or use of antihypertensive medication	Age, sex	**1.2**	**1.01 to 1.44**
Maltzman et al	USA	"Senile macular degeneration" with vision <=20/30	30	Reported hypertension or blood pressure >160/95		1.31	0.42 to 4.09
NHANES 1	USA	Early and late changes, vision <20/25	178	Systolic >=170 compared to <130 mmHg	Age	**1.59**	**1.00 to 2.54**
Eye Disease Case-Control Study Group	USA	NV-AMD	421	Systolic >=155 compared to <=118	Age, sex, clinic	**1.7**	**1.02 to 2.8**
Beaver Dam Eye Study	USA	NV-AMD	59	Reported	Age,sex	0.79	0.44 to 1.42

continued

Bold indicates statistically significant results (p<0.05) NV-AMD: neovascular AMD GA: geographic atrophy

Table 1.13 Blood pressure continued

		AMD					
Study	Country	*Definition*	*Cases*	Definition of hypertension	Confounding variables	Relative risk or odds ratio	95% confidence intervals
Oulu County	Finland	GA & NV-AMD	39	>=160mmHg systolic and/or >=95 diastolic and/or use of antihypertensive medication	Restricted to analysis of 85 years and above	Greater prevalence of hypertension in people without AMD	
Chaine et al	France	Early and late changes	1844	Hypertension>= 160mmHg systolic and/or >=95 diastolic	Not clear exactly what had been adjusted	**1.28**	**1.09 to 1.5**
Blue Mountains Eye Study	Australia	GA & NV-AMD	72	Previous diagnosis or systolic >160mmHg or diastolic>95mm Hg	Age, sex, current smoking, family history AMD	1.06	0.63 to 1.79
Blue Mountains Eye Study	Australia	GA & NV-AMD	72	Diastolic >=100 compared to <80 mmHg	Age	1.26	0.79 to 2.02

Bold indicates statistically significant results (p<0.05) NV-AMD: neovascular AMD GA: geographic atrophy

Table 1.14 Dietary fat

Study	AMD *Definition*	AMD *Cases*	Measure of dietary fat (highest vs. lowest quintiles unless other specified	Confounding variables other than age	RR/OR	95% confidence intervals
Beaver Dam	AMD	30	Total fat % kJ		0.7	0.2 to 2.3
			Saturated fat % kJ		1.5	0.5 to 4.5
			Oleate % kJ		0.9	0.3 to 2.9
			Linoleate % kJ		0.5	0.1 to 2.0
			Cholesterol, mg/4200 kJ		1.4	0.4 to 4.8
			Seafood, g/4200 kJ			
NHANES-III	Early ARM	644	Total fat %	Sex, race, smoking, BMI,	1.4	0.9 to 2.2
	AMD	53	Total fat %	history CVD, eye colour, sedentary lifestyle	0.7	0.2 to 2.6
Eye Disease Case-Control Study	NV-AMD	349	Total fat	Sex, clinic, education,	1.44	0.83 to 2.47
			Animal fat	carotenoid intake,	0.97	0.53 to 1.78
			Vegetable fat	systolic bp, physical	**2.84**	**1.45 to 5.57**
			Cholesterol	activity, alcohol intake, BMI, smoking, calories	0.89	0.94 to 1.46
Nurses' & Health Professionals Studies	ARM with vision less than 20/30	567	Total fat intake		**1.54**	**1.17 to 2.01**
			Linolenic acid		**1.49**	**1.15 to 1.94**
			Docosahexaenoic acid		**0.70**	**0.52 to 0.93**

Bold indicates statistically significant results (p<0.05)

Table 1.15 Serum lipids

	AMD					
Study	*Definition*	*Cases*	Serum lipids	Confounding variables other than age	RR/OR	95% confidence intervals
Sanders et al	Early and late changes	65	Cholesterol mmol/L highest vs. lowest tertile	Age and sex-matched controls	1.00	0.4 to 2.48
EDC-CSG	Neovascular AMD	421	Cholesterol mmol/L low versus high	Sex, clinic, smoking, education, physical activity, biochemical fat/antioxidants	**4.1**	**2.3 to 7.3**
NHANES-I	Early and late changes, vision≤20/25	178	Cholesterol mg/100ml		0.51	0.26 to 1.00
BMES	Early ARM	240	Cholesterol mmol/L	Sex, current smoking, family history	0.95	0.84 to 1.09
BMES	Late AMD	72	Cholesterol mmol/L	Sex, current smoking, family history	1.08	0.92 to 1.27
Beaver Dam	Early ARM	744	Cholesterol mmol/L		F:0.89	0.80 to 0.98
Beaver Dam	NV-AMD	59	Cholesterol mmol/L		1.12	0.88 to 1.44
Beaver Dam	GA	29	Cholesterol mmol/L		1.00	0.69 to 1.46

Bold indicates statistically significant results (p<0.05) NV-AMD: neovascular AMD GA: geographic atrophy EDC-CSG: Eye Disease Case-Control Study Group

Table 1.16 Body mass index

	AMD					
Study	*Definition*	*Cases*	Body mass index kg/m^2	Confounding variables other than age	RR/OR	95% confidence intervals
Physicians	ARM with	340	<22.0	Randomised aspirin/beta carotene	**1.43**	**1.01 to 2.04**
Health Study	visual loss		22.0 to 24.9	assignments, cigarette smoking	1	
			25.0 to 29.9		**1.24**	**0.93 to 1.66**
			30 or more		**2.15**	**1.35 to 3.45**
POLA	AMD		30 or more	Sex	**2.29**	**1.0 to 5.23**
Blue	AMD	72	<20	Smoking, family history of AMD, sex	1.70	0.76 to 3.8
Mountains			20 to 25		1	
			26 to 30		1.36	0.72 to 2.57
			>30		1.91	0.86 to 4.22
AREDS	NV-AMD	658	≥ 31 vs. ≤ 23.6	Unclear	**1.43**	**1.08 to 1.91**
EDC-CS	NV-AMD	421	≥ 30 vs. ≤ 23.0	Sex, clinic	1.5	0.96 to 2.2

Figure 1.1: Prevalence of ARM by age: studies using grading of photographs

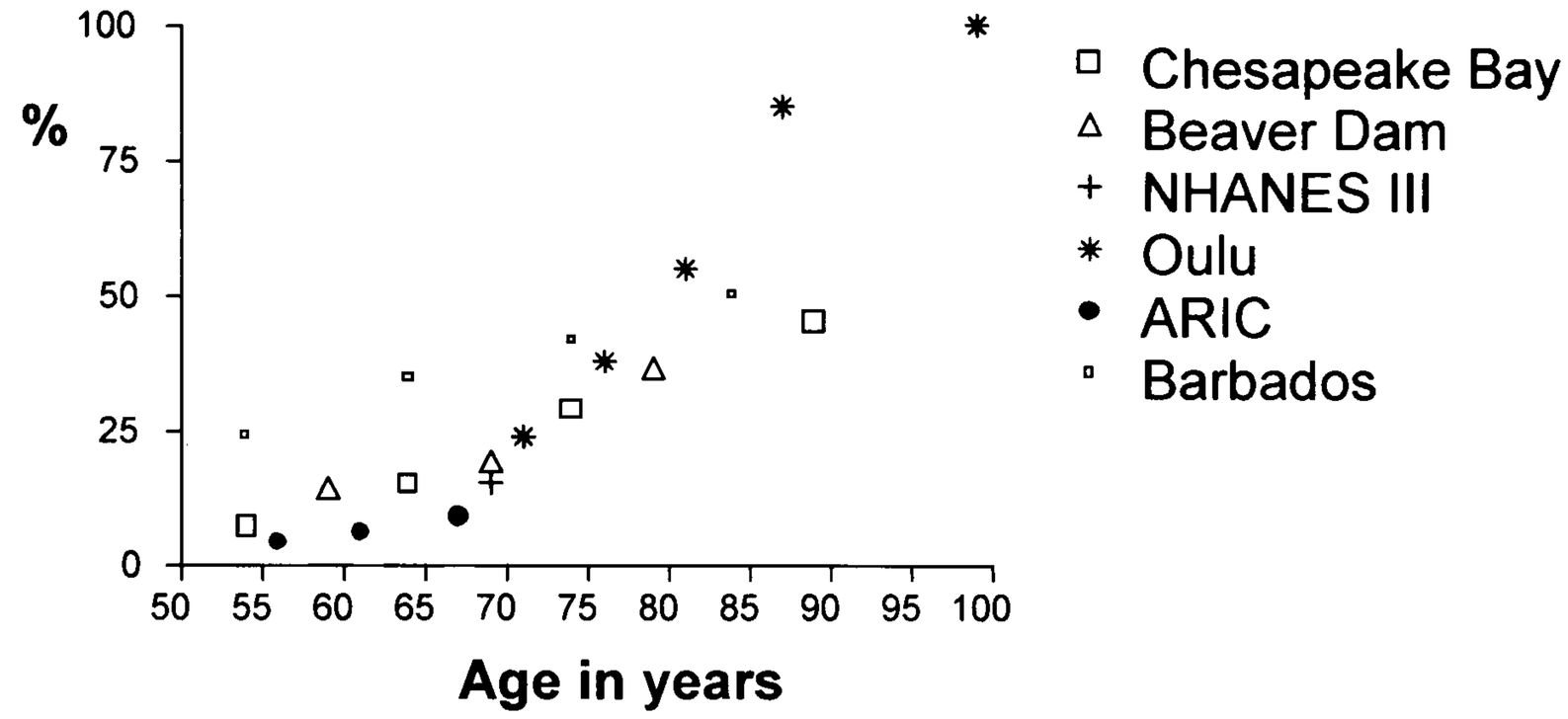


Figure 1.2: Prevalence of ARM by age: studies using clinical examination with visual acuity cutoff

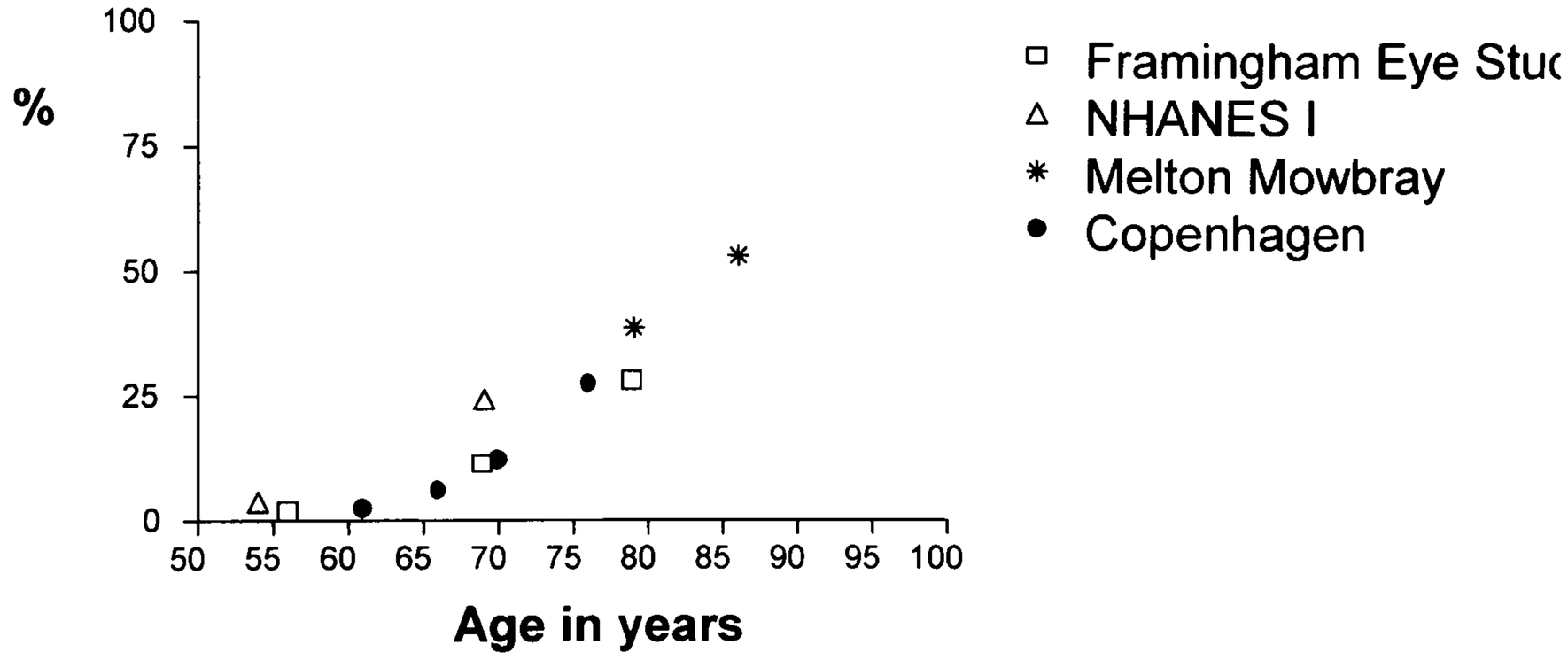


Figure 1.3: Prevalence of AMD by age: studies using grading of photographs

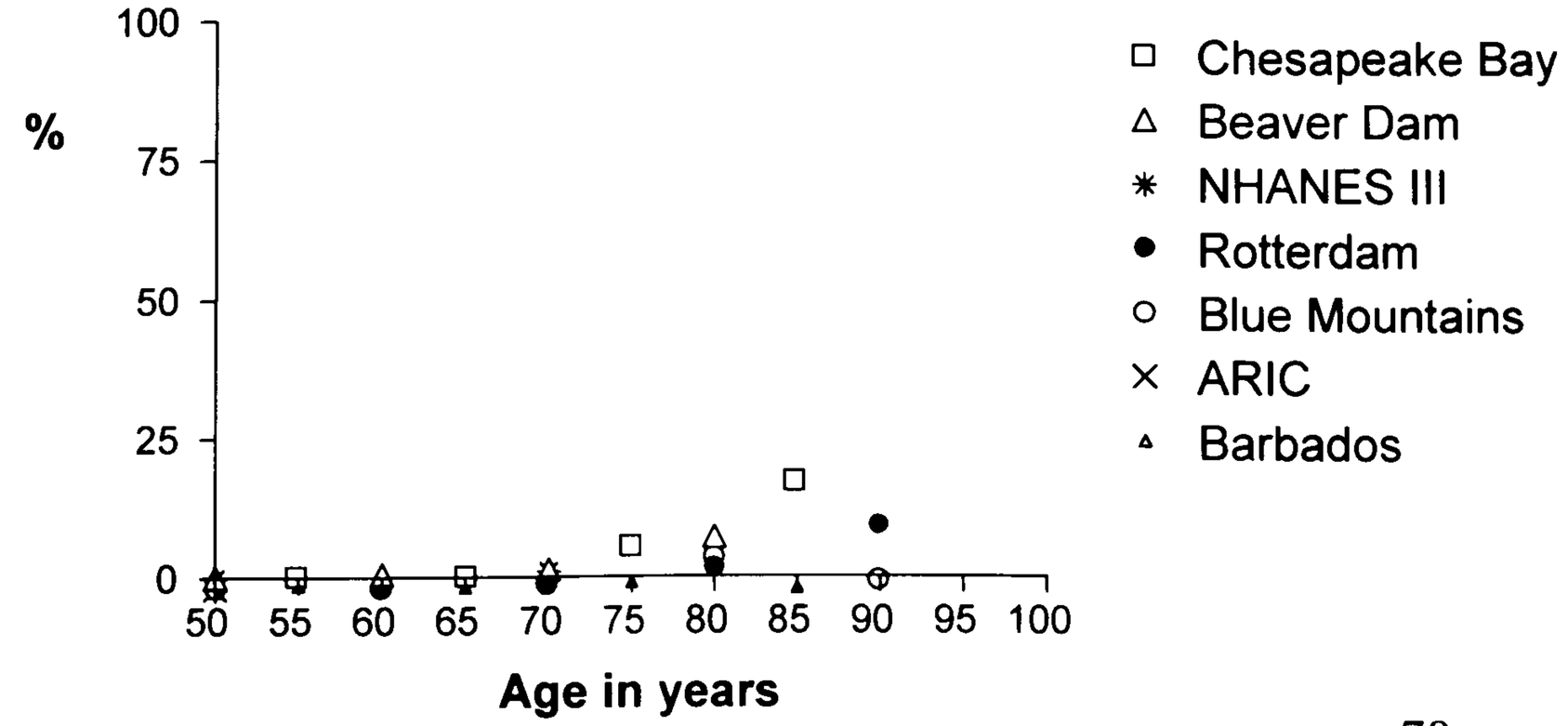
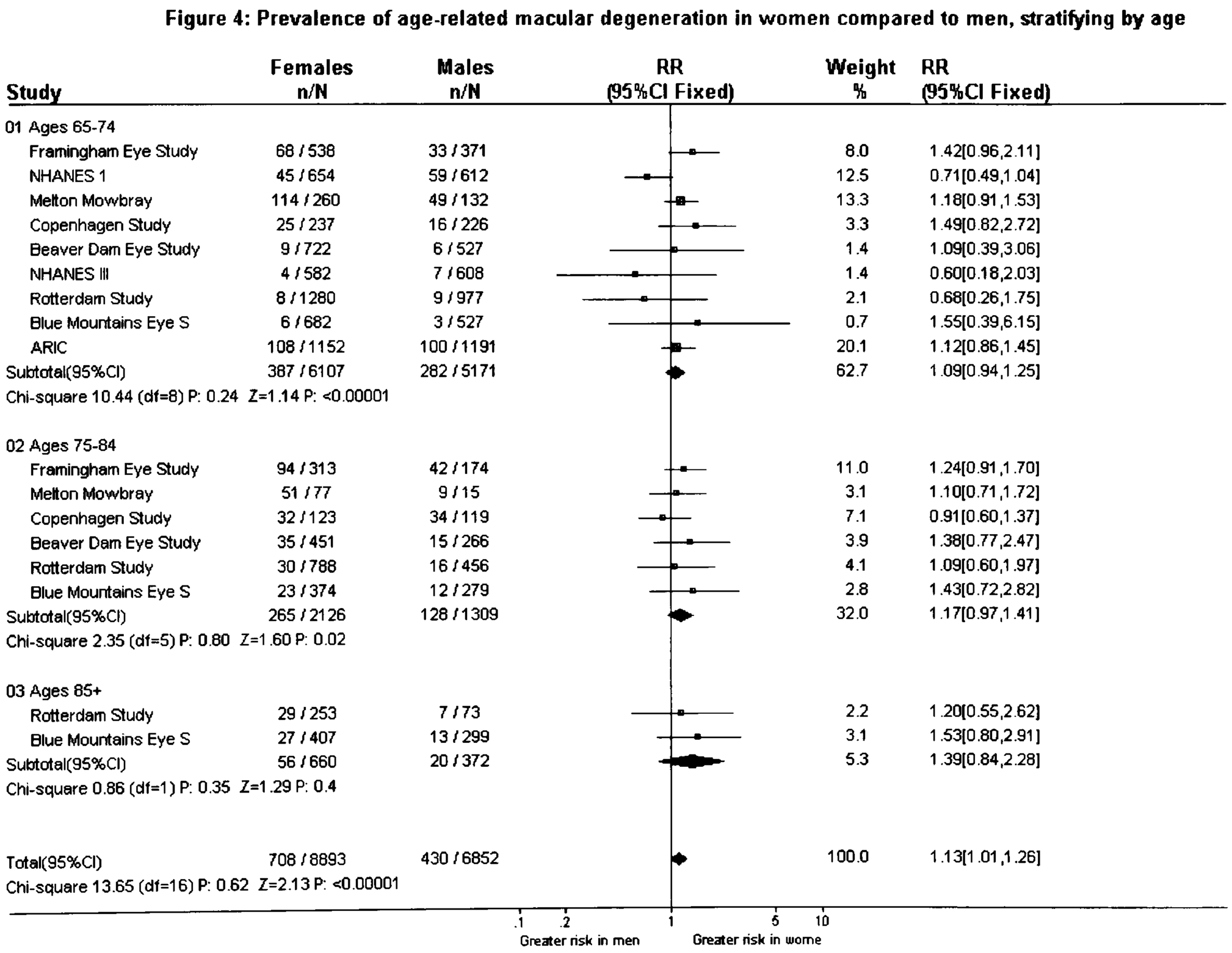


Figure 1.4: Prevalence of AMD in women compared to men, stratifying by age



2.1 MRC Trial of the Assessment and Management of Older People in the Community

2.1.1 Background to the MRC Trial

The study of visual impairment and macular degeneration reported in this thesis is an add-on study to the MRC trial of the assessment and management of older people in the community. The MRC trial is a large community-based randomised trial taking place in England, Wales and Scotland (Britain). Participating practices belong to the MRC General Practice Research Framework (GPRF) which is a network of practices interested in research, co-ordinated by the MRC GPRF Co-ordinating Centre, now based at the Clinical Trials Unit, University College, London.

The MRC Trial was undertaken because surveys in the UK population indicated that many older people have health problems that are undetected, including visual impairment. However, there was little evidence as to whether assessment of people aged 75 years and above in general practice would be effective in reducing the risk of mortality, hospital and institutional admissions, or whether it would have measurable benefits on quality of life. Despite the lack of evidence, the Department of Health Contract of Service with General Practitioners 1990 required that general practitioners should invite all patients aged 75 and over to a consultation. It was required that assessment should include sensory function, mobility, mental condition, physical condition including continence, use of medicines and social environment. There was little direction as to exactly what form the assessment should take or the best way of managing the problems identified. Different methods of initial assessment can be used –

such as postal, lay person or nurse – and screening can be universal, i.e. comprehensive, or targeted. Whether health problems identified should be dealt with by primary care professionals or using specialist geriatric assessment was also unclear.

2.1.2 Overview of MRC Trial study design

The aim of the MRC Trial was to determine the best method of assessing and managing people aged 75 years and above in primary care within the context of the 1990 Contract(Fletcher *et al.* 2002). The principal investigators were Professor Astrid Fletcher, Dr Dee Jones, Professor Chris Bulpitt and Dr Alastair Tulloch. Details of the study team are shown in Appendix A.

The study compared two different types of assessments ("targeted" versus "universal") and two different management models ("primary care team" versus "multidisciplinary geriatric evaluation team"). Figure 2.1 shows the design of the study.

General practices recruited through the GPRF were randomly allocated to the two different types of assessment. In the "targeted" arm, patients were given a brief questionnaire followed up by a detailed examination by a practice nurse if any (predetermined) responses indicated potential problems, i.e. if they "triggered". The triggers were set to allow an approximate 20% referral rate for detailed assessment. Table 2.1 shows the details of the brief assessment questionnaire questions. It covers all areas covered in the GP contract with a few extra questions on alcohol consumption, cigarette smoking and physical activity.

In the "universal arm" all patients were given both a brief assessment and a detailed examination. The detailed examination covered all the same health issues as the brief assessment but included objective measures as well. For example, in the brief assessment participants were asked "*Do you have a problem reading newsprint even while wearing glasses?*" while in the detailed examination they were given a visual acuity test. Other objective tests in the detailed examination included whispered voice test for hearing, Mini Mental State Examination (MMSE) for cognitive impairment and the Geriatric Depression Scale (GDS). Physiological measurements e.g. blood pressure, heart rate and a full biochemical screen were undertaken, with additional laboratory investigations in response to appropriate abnormal findings e.g. faecal occult testing for a positive response to blood in the stools. Functional ability and social difficulties were also assessed.

Two different methods of assessment were tested: administering a brief questionnaire versus giving a detailed examination by a nurse, with very different cost implications. Within each arm of the trial, the practices were randomly allocated to three different ways of administering the brief questionnaire: postal, lay or nurse.

In the detailed examination the practice nurse followed a standard protocol to refer the patient onto a "management team", other medical services or agencies and emergency referrals to the general practitioner. In the case of vision, if a participant had a pinhole corrected logMAR visual acuity score of 0.5 or more (equivalent to less than 6/18 Snellen acuity) in either eye the nurse was required to refer them to an ophthalmologist, if the problem had not been previously identified. If uncorrected acuity of 0.5 or more corrected to less than 0.5 with a pinhole the participant was advised to see an optician. Each practice was randomly allocated to two different types of "management team" - the primary care team or the local hospital geriatric multidisciplinary team. As the details of this stage of the trial are not relevant to the causes of visual impairment add-on study, it is not discussed further.

In the add-on study reported here, data from the 53 practices in the "universal arm" only were used as everyone had a visual acuity test in these practices.

2.1.3 MRC Trial study population

The recruitment of practices was by invitation letter to all the practices in the GPRF. Practices then volunteered to take part. For practices who agreed, in principle, to take part the "local" geriatrician was then approached and invited to participate (with a view to the second stage randomisation). The aim of the study was to recruit practices which were representative of the UK population. In order to ensure a good distribution of practices from different socio-economic areas and different health states of population, the practices were recruited according to indicators of deprivation (Jarman score (Jarman 1983)) and health (standardised mortality ratio (SMR)). The Jarman score is derived from ward percentages of the following census variables: elderly people living alone; households with children under 5 years; one parent families; unskilled manual workers; unemployed people; overcrowded households; residents who have changed address in the previous year; and head of household born in the new commonwealth. A higher score indicates more relative deprivation.

A total of 106 practices were recruited with 43,219 people aged 75 years and above eligible to take part in the study. Table 2.2 shows the distribution of the practices according to tertiles of Jarman score and SMR. Table 2.3 shows the random allocation.

All patients aged 75 years or over on the general practitioner list were included in the study, unless they were in long stay hospital or nursing homes, or were terminally ill at the time of the study.

2.1.4 Outcome measures in the MRC Trial

The main outcome measures for the trial were mortality, hospital admissions and length of stay and institutional admissions including long stay hospitals, (geriatric, or psychogeriatric), local authority residential and nursing homes and private nursing homes. Quality of life was also an outcome measure and was assessed in a randomly selected subset of practices (n=23).

Follow-up for mortality was undertaken by the Office of National Statistics, Southport, who notified the trial co-ordinators when a trial participant had died. They provided data on the date and cause of death which was coded according to International Classification of Disease Revisions 9 and 10(WHO 1977; World Health Organization 1992).

The practice nurse collected information on hospital admissions for each participant by hospital discharge letters contained in the participant's GP medical notes. Hospital admissions were recorded for two years after recruitment into the trial. Institutional admissions were collected on an ongoing basis for each patient, up until October 2000.

Quality of life interviews took place before the trial assessments (baseline) and 18 months and 36 months following the baseline interview. Quality of life was measured using three instruments – the Sickness Impact Profile(Bergner *et al.* 1981), the Philadelphia Geriatric Centre Morale Scale(Lawton 1975) and the SF-36 health survey questionnaire. The interviews were undertaken by research fieldworkers who were independent of the practice nurses.

Use of services was ascertained by cross sectional and longitudinal sampling throughout the study in order to provide a full economic evaluation.

2.1.5 Ethics approval

The MRC Trial was approved by all the relevant local research ethics committees.

2.1.6 Date of data collection

Data collection began in April 1994 and finished in November 1999, however, the majority of assessments (99.7%) were done between 1995 and 1998.

2.2 Measurement of visual impairment

2.2.1 Measurement of visual acuity at the detailed assessment

Visual acuity was measured at 3 metres with a Glasgow Acuity Chart which measures the minimal angle of resolution on a logarithmic scale (LogMAR)(McGraw and Winn 1993). This chart was originally developed for use in children but has been shown to give equivalent measurements to the Bailey-Lovie chart in adults(McGraw *et al.* 2000), and has been used in other surveys in the elderly(van der Pols *et al.* 2000). This chart was chosen because it met the requirements for a simple visual screening test to be conducted in general practice and as part of the over 75s health check. As well as applying modern scientific principles to the measurement of visual acuity, it was cheap and portable. The nurses also could use the chart on home visits.

Binocular vision was measured first, followed by vision in the right and left eyes. People with a logMAR vision of 0.5 or more in either eye (equivalent to less than 6/18 Snellen acuity) were tested again using a pinhole occluder. Everyone with a pinhole vision of 0.5 or more in either eye was referred to an ophthalmologist by the general practitioner. People whose vision improved from 0.5 or more to less than 0.5 were advised to see an optician. All vision measurements were conducted while wearing usual spectacle correction; participants were asked to bring their glasses with them. All patients were also asked about their vision and whether they were on the blind or partial sight register.

Study nurses attended a two day training session in the trial protocol which included a training session run by myself on how to use the chart. This included ensuring the measurement was taken as far as possible under standardised conditions at the correct distance and with optimum lighting. All nurses received regular quality control visits from a regional trainer who checked their performance against a checklist. In addition, I

reviewed the data periodically and gave feedback to the nurses at annual workshops and in newsletters. Sections of the training manual relating to vision screening and the regional trainer checklist are shown in Appendix B which also includes a comparison of the Snellen notation and logMAR acuity score.

2.2.2 Definitions of visual impairment and blindness

Visual acuity is measured on a continuous spectrum. There is considerable variation in the cutpoints and terminology used. The International Classification of Diseases 10th edition (ICD10)* defines *low vision* as a visual acuity of less than 6/18, but equal to or better than 3/60 in the better eye with best possible correction and *blindness* as visual acuity of less than 3/60 or corresponding visual field loss in the better eye with best possible correction. In this study, binocular presenting vision is used to describe the level of vision that the person uses in everyday life with usual spectacle correction. Although not reporting best corrected vision, the terminology of ICD10 and the same cut points for visual acuity to describe binocular low vision and blindness are used. The term visual impairment includes both low vision and blindness.

Visual impairment overall was defined as a binocular acuity of <6/18 Snellen acuity (logMAR score of 0.5 or more), *low vision* as a binocular acuity of <6/18 to 3/60 Snellen acuity (logMAR score 0.5-1.375) and *blindness* as <3/60 Snellen acuity (logMAR score of 1.4 or more, that is, could not read the Glasgow acuity chart at one metre). Visual acuity for the better eye was used if binocular visual acuity data were not available.

Some people already registered as blind or partially sighted were not given a visual acuity test. This may be because the participant was reluctant to have a test that they knew could not confer any benefit. People who reported that they were on the blind register were counted as blind. People who reported that they were on the partial sight register were counted as low vision. Registration status was cross-checked with the general practitioner medical notes.

---

* http://www.who.int/m/topics/blindness/en/index.html [accessed October 2nd 2001]

2.3 CAUSES OF VISUAL IMPAIRMENT ADD-ON STUDY

2.3.1 Procedures

All of the 53 practices taking part in the universal arm of the MRC trial were approached to take part in the causes of visual impairment study; 49 practices agreed to take part. For those who agreed to take part the following procedures took place.

First, a list of visually impaired people was compiled. For the purposes of this study, visual impairment was defined as presenting binocular acuity of less than 6/18. Overall, there were 1,742 (12.5%) people binocularly visually impaired in the 49 practices taking part. Of these, 450 (26%) achieved a pinhole acuity in either eye of 6/18 or better. In these people, the principal reason for visual loss was considered to be refractive error. There were, therefore, 1,292 people in 49 practices for whom a cause of visual loss was sought.

Each study nurse was sent a list of people with visual impairment for their practice. Each person was identified only by a unique number that enabled the study nurse to locate the general practice notes. The study nurse abstracted diagnostic information from the general practitioner notes. This diagnostic information was obtained from correspondence between the hospital ophthalmologist and general practitioner. The nurse used a form that included: date of correspondence, source of correspondence, results of any visual acuity test, diagnosis, treatment (*see appendix C*). The nurse also recorded the name and hospital of the last ophthalmologist seen. All correspondence relating to eye disease was abstracted, in addition to the correspondence resulting from the MRC Trial examination. Each form was completed at least six months after the detailed assessment in order to give time for the results of any referrals to come through. If any participant had died in the interim, their notes were obtained by the practice nurse from the appropriate Family Health Services Authority.

In order to validate the causes of visual loss derived from coding the diagnostic information obtained from the general practitioner notes, a one-page questionnaire was sent to the hospital ophthalmologist who had last seen the patient (*see appendix C*). This questionnaire was in the form of a check-list by eye that covered: age-related macular degeneration (exudative, geographic atrophy), cataract (age-related, congenital, other), glaucoma (primary open-angle, primary closed-angle, other), diabetes (diabetic retinopathy, other), myopic degeneration, other (specify). The ophthalmologist was

asked to rank, if possible, any conditions ticked in order of their contribution to cause of visual loss. In addition, they recorded which eye lost vision last and visual acuity at last examination.

If no reply was received from the ophthalmologist, one reminder letter was sent. Each ophthalmologist was offered a small payment (£20 per form) to compensate for the time involved.

2.3.2 Ethics approval

As this was additional data collection to that originally in the protocol for the MRC Trial I obtained approval from all the relevant local research ethics committees.

2.3.3 Date of data collection

Data collection took place between 1996 and 2000.

2.3.4 Coding cause of visual loss

All forms were returned to myself and coded twice in order to minimise any errors. A maximum of three diagnoses was recorded. The aim was to identify the cause of visual loss for the person. The main cause of visual impairment was taken to be the cause of visual loss in the eye that lost vision last. Appendix D sets out the coding scheme.

If there were co-existing conditions which made it difficult to assess which was the major cause of visual loss then two options were followed. If there was enough information then the condition least amenable to intervention was chosen. For example, if a person had co-existing cataract and AMD, and the hospital ophthalmologist had decided that surgery for cataract was not worthwhile because of the macular degeneration, then AMD was coded as the main cause of visual loss because the person was unlikely to have vision restored after cataract surgery. If the situation was not so clear cut, then both conditions, for example, AMD and cataract were coded as contributory causes of visual loss. In effect, there was uncertainty as to which condition was most responsible for the visual loss.

The medical notes provide a longitudinal record of visual deterioration. However, the detailed assessment of the MRC Trial was a cross-sectional study. As the ophthalmic examinations did not often coincide with the MRC Trial detailed examination the following assumptions were made when coding the general practice medical notes:

- that chronic causes of visual loss (such as AMD, cataract, glaucoma etc) recorded before the detailed examination were present at the detailed examination, unless otherwise indicated.
- that chronic causes of visual loss recorded within one year after the detailed examination were present at the detailed examination, unless otherwise indicated.
- that if the first recorded ophthalmic examination occurred more than one year after the MRC Trial, any chronic causes of visual loss reported at this ophthalmic examination was assumed to be the most likely cause of visual loss at the detailed examination.

2.4 Classification of AMD

The following coding schema was used for age-related macular degeneration.

(1) Definite AMD, type unspecified

The following terms, recorded by a hospital ophthalmologist in correspondence with the general practitioner.

- Age-related macular degeneration *or* Senile macular degeneration.

(2) Definite exudative AMD

The following terms in conjunction with a diagnosis of age-related macular degeneration

- Neovascular, Exudative, Disciform, Pigment epithelial detachment, Wet
- Any terms relating to new vessel growth and/or leakage/haemorrhage in the retina

(3) Definite geographic atrophy

- A diagnosis of age-related macular degeneration combined with any definite statement that the condition was "dry" or that there was no evidence of new vessels/leakage on fluoroscein angiography.

(4) Possible AMD

- Macular degeneration/disturbance with onset after 50 with no obvious cause but that was not directly described by the ophthalmologist as "age-related". This was also

subdivided into exudative disease and geographic atrophy according to the definitions above.

- Age-related macular degeneration or macular degeneration described by an optician or other health professional.

2.5 LINKED DATA FROM THE MRC TRIAL

The aims of the study are set out in chapter one and briefly summarised here:

(1) To estimate the prevalence of AMD causing visual impairment in people aged 75 years and above in the United Kingdom, and to investigate how this varies by **age, sex, socio-economic status and region.**

(2) to investigate the impact of AMD causing visual impairment on the lives of people aged 75 years and above in the UK: specifically, its impact on:

- **functional ability**
- **health-related quality of life**
- **psychological well-being**
- **emotional well-being (life satisfaction and morale)**
- **mortality**
- **morbidity**

(3) To investigate the aetiology of visually impairing AMD in people aged 75 years and above in the UK, *that is,* to test the following hypotheses:

- that **smoking cigarettes** and **drinking alcohol** are associated with an increased risk of visually impairing age-related macular degeneration;
- that **reproductive factors** indicating increased oestrogen exposure in women are protective for developing visually impairing age-related macular degeneration;
- that people with evidence of **cardiovascular disease** are at increased risk of developing visually impairing age-related macular degeneration;

Collection of data on visual acuity (in the MRC Trial) and cause of visual loss (by me) are described in sections 2.2 to 2.4. The other data (indicated in bold above) were all collected during the course of the MRC Trial and are described below. All data were

collected during the detailed assessment that was done by the MRC Research Nurses as part of the MRC Trial, unless otherwise indicated.

2.5.1 Age, sex and socio-economic status

Age and sex were derived from the general practice registers. They were checked at the time of the detailed assessment and cross-checked with data on cause of death from the Office of National Statistics, where available.

There were several measures of material wealth collected on all participants in the MRC Trial. The most important one was *housing tenure*. This is a commonly used indicator of socio-economic status and is particularly appropriate in the elderly as other measures depend on classification of occupation. Housing tenure was divided up into "owner occupier" and "rented" accommodation. In addition, a proportion of the population aged 75 years and above live in the MRC Trial were living in "sheltered" accommodation.

Participants were also asked whether they had central heating, access to an indoor toilet, difficulty keeping their home warm and/or difficulty making ends meet. For each of these variables, the numbers of people responding "negatively" were small. An overall *socio-economic status score*, including housing tenure, was constructed as follows:

Question	Score
Housing tenure	Home owner=0 Rented accommodation=1
Do you have central heating?	Yes or missing=0 No=1
Do you have an indoor toilet?	Yes or missing=0 No=1
In the last year have you had difficulty keeping your home warm?	Yes or missing=1 No=0
Do you ever having difficulty making ends meet, I mean, is it difficult to find the money to pay your bills?	Yes or missing=1 No=0

The score ranged from 0 to 4 and was set to missing for people who had missing data for every question. People who were in sheltered housing were excluded as these measures are not meaningful in that context.

In the randomly selected subset of practices in which quality of life was assessed, participants were asked about their occupation, usual for "most of their working life". The quality of life interviews were administered by independent interviewers. Occupation was coded according to the Registrar General Classification of Social Class by clerical officers at LSHTM. This divided the study sample into *social class* groups. For married and widowed women, the husband's occupation was used. This gives a measure of socio-economic status during lifetime rather than current status.

2.5.2 Impact

Functional ability

Two single-item measures of functional ability were used. Participants were asked *"Do you have difficulty in seeing newsprint, even when you are wearing your glasses?"* and *"Do you have difficulty managing your finances, I mean paying bills, working out change etc?"*

One multi-item measure of functional ability was used: the Activities of Daily Living (ADL) scale(Katz *et al.* 1963). In the MRC Trial eight questions were asked regarding Activities of Daily Living and Instrumental Activities of Daily Living. Participants are required to indicate the level of difficulty (No difficulty/Some difficulty/Unable to do) that they have performing basic tasks. The following activities were assessed.

Activity	Coding
Activities of Daily Living	0=No data
Cut your own toenails	1= No difficulty
Dress yourself including zips or buttons	2=Some difficulty
Go up and down stairs and steps (if necessary using a frame, tripod or stick)	3=Unable to do alone
Wash all over (including bathing or showering)	
Walk 50 yards down the road (if necessary using a frame, tripod or stick)	
Instrumental Activities of Daily Living	
Cook a hot meal	
Do light housework or simple repairs	
Do shopping	

A composite score was created by adding the scores for each variable. The resultant score ranged from 0 to 24. People who scored 0 i.e. had no data for all categories were set to missing. People who had some data for each category, some of which indicated difficulties were counted as missing. People who had some data, all of which indicated no difficulty were included. The score was divided up into quintiles. People in the worst quintile for ADL score had some difficulty, or were unable to do alone, the following tasks: do shopping (99.9%), cut their own nails (98.6%), go up and down stairs (96.0%), do light housework (95.9%), walk 50 yds (93.0%), wash all over (91.0%), cook a hot meal (84.3%), dress themselves (66.3%). This pattern of disability reflects that seen in longitudinal studies where it has been observed that tasks requiring lower-extremity strength such as walking and washing are lost before those requiring upper-extremity strength, such as cooking and dressing (Dunlop *et al.* 1997),(Jagger *et al.* 2001).

Psychological well-being

Cognitive ability was measured using the MMSE(Folstein *et al.* 1975). This consists of a series of tasks testing recall (remembering three words); mental arithmetic (subtracting from 100); spelling backwards; naming everyday objects; repeating a sentence; following a 3-stage command; reading a simple instruction and following it correctly; writing a sentence; copying a drawing. The resulting score ranges from 0 to 30 with higher scores indicating better cognitive ability. The score was divided to create a dichotomous variable to indicate people with poor cognitive ability.

There are two sections: a verbal section with a maximum score of 21 and a performance section (that involves, for example, copying a drawing) with a maximum score of nine. For physical or educational reasons not all people are able to complete the performance section. In the MRC Trial this was decided by the nurse administering the questionnaire. Separate cut-off points are used depending on whether or not the performance section was completed. The cut off points of less than 17 for the whole test or less than 12 if the performance section was not completed were used. In order to remove any potential effects of poor vision on ability to complete the test, independent of cognitive ability, only the verbal section was used.

Depression was assessed using the GDS-15. This is a set of 15 short questions (with yes/no answers) about feelings over the last week(Sheik and Yesavage 1986; Yesavage *et al.* 1982). The total possible score is 15 with higher scores indicating worse depression. The cutoff point used to define depression was <6/6+ as this has been used in other studies in the MRC Trial(Osborn *et al.* 2002). It was chosen for the cutpoint because it gives a higher specificity for depression (between 74% and 82%) than other thresholds such as <3/3+ and <5/5+ which have been used by other authors.

Health-related quality of life and morale

One global item was used: *"Compared to other people of your own age would you say that your health is generally: excellent, good, fair or poor?"*

Health-related quality of life was also measured using the Sickness Impact Profile (SIP) in a randomly selected subset of practices. The quality of life interviews were administered by independent interviewers. The SIP was developed to provide a measure of perceived health status, broadly applicable across different illnesses(Bergner *et al.* 1981). It is similar to the ADL scale in that it aims to measure the actual performance of

activities, however, it is much broader in scope. In its full form it consists of 136 statements about health-related function in 12 different areas: sleep and rest, eating , work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness behaviour, emotional behaviour and communication. In the MRC Trial, four of these areas were assessed: home management, mobility, body care and movement and social interaction. A full description of the questions asked is in appendix E.

People could choose one of three responses in the SIP: "yes, and due to health"; "yes, and not due to health"; and "no". The scores used in this thesis include any "yes" answers, whether due to health or not. The item answers were weighted using British weights from the Lambeth Disability Study and the total converted into a percentage of the maximum. Higher scores mean lower quality of life.

Emotional well-being (life satisfaction and morale) was assessed using the Philadelphia Geriatric Morale Scale (PGMS). The PGMS is a series of questions, all in a dichotomous format, that aim to measure the morale of older people (Lawton 1975). See appendix E for the list of questions. The resultant score ranges from 0 to 17 with higher scores reflecting a worse morale.

Other authors have examined the characteristics of people in the worst quintile for PGMS score in the MRC Trial cohort (Breeze 2002). People in the worst quintile for PGMS score reported that "things kept getting worse as they got older" (91%), that they "took things to heart" (90%), did not have as much energy as they did last year (88%), that they felt less useful as they got older (88%), that they were not as happy now as when younger (81%) and got upset easily (80%). 75% reported that as they got older things were not better than expected and 73% that "little things bothered them more" this year.

Mortality

Follow-up for mortality was undertaken by the Office of National Statistics, Southport, who notified the trial co-ordinators when a trial participant had died. They provided data on the date and cause of death.

Morbidity

The participants were asked "*In the last six months, how many falls have you had at home*?" They were also asked "*Has a doctor ever told you that you had a fractured hip*?"

Potential confounding factors

There were several variables indicating the living circumstances of the participants in the MRC Trial, *that is*, whether they *live alone, care for someone else, have access to help,* and *frequency of seeing friends/neighbours or relatives*.

Other sensory impairments include *hearing loss*. This was measured using the "whispered voice test" (Swan and Browning 1985). The nurse stood behind the patient at a distance of 15 centimetres and whispered three words, after having exhaled. If the participant was unable to repeat these items, the test was done again. In the case of people who failed the test twice, the ears were examined for wax and syringed if necessary, after which time the test was repeated again. The whispered voice test has been found to have sensitivity of between 80% and 100% and specificity of between 80 and 89% when compared to hearing loss in the range 30 to 40 decibels measured by pure tone audiometry (Smeeth *et al.* 2002b). The test was performed with any hearing aids worn at the time of testing, thus testing the participants' everyday hearing.

Other potentially confounding factors are discussed in the next section.

2.5.3 Risk factors

Cigarette smoking

Smoking history was ascertained using an interviewer-administered questionnaire. The questions used came from the Whitehall study (de Mheen *et al.* 2001). Participants were asked whether they smoked currently. For people who responded no, they were asked whether they had ever smoked cigarettes. Age smoking started and stopped was also elicited and the number of cigarettes (ozs tobacco) smoked a day. One ounce of tobacco was assumed to correspond to 30 cigarettes.

The following variables were created:

- Smoking status 1=Never smoked 2=Ex-smoker 3=Current smoker

- Pack-years were calculated from the number of years participants had smoked, multiplied by the usual daily cigarette-equivalent intake, and divided by 20. This gives a measure of the lifetime exposure dose received.
- The number of years since stopping smoking was calculated from the current age minus the age stopped smoking. People who were still smoking had a value of 0; people who had never smoked were excluded from this variable.

Alcohol consumption

Alcohol consumption was ascertained using an interviewer-administered questionnaire. Each participant was asked whether they had had an alcoholic drink during the past year. For those responding yes, they were asked to quantify their consumption in the past week. The number of drinks of spirits (single), wine (glass) or beer (half pint) was recorded. Each of these measures corresponds approximately to one unit of alcohol equivalent to 8g of ethanol. The total number of units of alcohol consumed in the previous week was calculated.

In order to assess whether patterns of alcohol consumption had changed, each participant was asked whether or not they drank more, less or about the same today compared with five years ago. People who were non-drinkers were asked whether they had always been a non-drinker, and, if they had stopped drinking why they had stopped.

Cardiovascular disease

Participants were also asked about a history of cardiovascular disease. *"Has a doctor ever told you that you had any of the following? If yes, was that in the last year?" High blood pressure and/or heart attack and/or stroke.*

The Rose Chest Pain Questionnaire was used to identify people with definite or probable angina (Rose *et al.* 1977; Bulpitt *et al.* 1990).

Systolic blood pressure was measured using a random zero sphygmanometer after the participant had rested for at least three minutes. The sitting blood pressure was repeated after another three minutes rest, followed by standing blood pressure after three minutes rest. It was recorded to the nearest 2mmHg. If the pressure was greater or equal to 180mmHg, the test was repeated one week later.

Body mass index

Weight and height were measured and body mass index calculated as weight (kg)/height (metres)^2. Body mass index was grouped into the following groups: less than 20 (underweight), 20 to less than 25 (normal), 25 to less than 30 (overweight), 30 and above (obese).

Reproductive factors (in women)

Women were asked about their menstrual history, that is, age at menarche and menopause. *"How old were you when you had your first menstrual period?"* and *"How old were you when you had your last menstrual period?"* and *"Did your periods stop naturally, because of surgery or for some other reason?"* They were also asked about number of pregnancies and children. *"Have you ever been pregnant (including miscarriages and stillbirths)? How many children, including stillbirths, have you had?"*

Years of menstruation was analysed as a continuous measure and also sub-divided into quartiles. A cut-off point to define the 10 % of women with early menopause (40 years or less) was also used. In order to compare with previous studies, women with menopause at less than 45 years due to surgery were identified.

2.6 STATISTICAL METHODS

2.6.1 Data entry and cleaning

The data from the main MRC Trial were collected on specially designed forms that were scanned directly onto computer. Range checks were conducted by Edmond Ng and Elizabeth Breeze and clerical officers (*see Appendix A for details of MRC study team*). For the visual acuity data, I did further range checks and basic consistency checks (for example, checking that visual acuity scores were compatible with the distance at which the measurement was done). Clerical officers at LSHTM checked any odd values by looking at the original data forms.

The data from the cause of visual impairment questionnaire and hospital ophthalmologist form were entered onto a customised Access database with range and consistency checks built into the program. Both sets of data were entered twice and errors checked. Prior to analysis, range and consistency checks were done and raw data checked.

2.6.2 Variable format

Some variables were in a binary format *e.g., reported fractured hip/not reported fracture hip*; many were in the form of a score or scale. The distribution of the scale was examined. If it was normally distributed, or could be transformed to a normal distribution, it was analysed as a continuous variable. If it was skewed it was divided up into quintiles, and a binary variable derived whereby 0=not in worst quintile 1 = in worst quintile ("worst" quintile indicates most severely affected or poorest outcome). In some cases an *a priori* cutpoint was used as identified in the literature review, *e.g., for the Geriatric Depression Scale a score of 6+ was used to define depression* (Sheik and Yesavage 1986).

2.6.3 Taking into account the cluster design of the study

Classical statistical techniques and regression models share a common assumption that individual observations are statistically independent of each other. In the MRC Trial, treatments were assigned at the general practice level, therefore general practices, rather than individual patients, were selected to take part in the study. Observations on individuals within the same general practice may be correlated. Therefore, the assumption of statistical independence does not hold for the data presented in this thesis. Ignoring the extra variation introduced by clustering may lead to an incorrect interpretation as confidence intervals, in general, will be narrower and p-values smaller than they should be (Skinner *et al.* 1989).

A simple way round this problem is to calculate a single summary measure for each cluster (i.e. each practice). This would be feasible for simple analyses, for example, in presenting the overall prevalence of visual impairment, however, it is difficult to take into account the effects of factors that occur at the individual level, such as age and sex, using this method.

There are three possible options for analysing clustered data at the individual level. Calculating "robust" standard errors, using population average models (generalised estimating equations) or random effects models (multilevel models). Random effects models are theoretically preferable because they specify a full probability model, however, they have problems when dealing with binary outcomes, as is the case for most of the analyses in this thesis. All regression analyses took account of the cluster design of the study using the "svy" commands in Stata (StataCorp 2001). These

commands calculate semi-robust confidence intervals, allowing for clustering within practices (Eltinge and Sribney 1996).

Associations between categorical variables were tested using the chi-square test adjusted for the clustered design of the study (Rao and Thomas 1989).

All data were analysed at the individual person level or the practice level. There was therefore no need to take into account correlation between eyes.

All analyses were done using Stata version 7.0.

2.6.4 Analysis strategy

The majority of the data reported in this thesis are cross-sectional, i.e. outcomes and exposures were collected at the same point in time.

The analysis strategy varied according to the different research questions.

(1) Prevalence study (*chapter three*).

The overall strategy for analysis was to estimate the prevalence of AMD causing visual impairment, including confidence intervals taking into account the cluster design (*see above*). The prevalence of AMD was estimated in different socio-economic groups and by region. Age and sex were considered as potential confounding factors. The main methodological issues were the possible effects of missing data on the prevalence estimates.

The effect of missing data (non-response)

In this study of AMD causing visual impairment, there were two steps. Firstly, I estimated the prevalence of visual impairment. Secondly, I considered how much of the visual impairment identified was due to AMD.

The prevalence of visual impairment in people who were eligible to take part in the study, but who were not examined for whatever reason, is unknown. The implicit assumption in the figures presented in this chapter is that the prevalence of visual impairment in non-responders was similar to that in people examined. I calculated the prevalence of visual impairment as n/N where n=number of people visually impaired and N=number of people with data on vision in the MRC Trial.

I investigated the cause of visual loss for everyone who was visually impaired in the MRC Trial. For some of these people, I could not find out why they had a measured

binocular acuity of less than 6/18 at the detailed examination in the MRC Trial. A conventional approach would be to assume (as for visual impairment above) that missing data were similar to the non-missing data. However, during data collection I was aware that the people for whom I could not identify the cause were likely to be different to those for whom I could. For example, the medical notes of people who had died since the detailed examination were less likely to be available as they leave the practice and were not always returned upon request. People who had a longstanding eye complaint and who had been registered blind or partially sighted were more likely to have data on cause of visual loss in their medical notes. I therefore felt it unwise to make any assumptions about people for whom I could not identify the cause of visual loss. I calculated the prevalence of AMD causing visual impairment as follows: n_a/N where n_a=number of people visually impaired due to AMD and N=number of people with data on vision in the MRC Trial. This assumes that none of the people whom I knew to be visually impaired but for whom I could not find out the cause of the visual loss were visually impaired due to AMD. In section 3.4 I also present alternative prevalence figures calculated with less conservative assumptions.

Coding cause of visual loss

In this study, the aim was to identify the cause of visual loss for the person. For each person identified as visually impaired the cause of visual loss in the last eye to lose sight was identified, where possible. If there were co-existing conditions which made it difficult to assess which was the major cause of visual loss then two options were followed. If there was enough information then the condition least amenable to intervention was chosen. For example, if a person had co-existing cataract and AMD, and the hospital ophthalmologist had decided that surgery for cataract was not worthwhile because of the macular degeneration, then AMD was coded as the main cause of visual loss because the person was unlikely to have vision restored after cataract surgery. If the situation was not so clear cut, then both conditions, for example, AMD and cataract were coded as contributory causes of visual loss. In effect, there was uncertainty as to which condition was most responsible for the visual loss.

The medical notes provide a longitudinal record of visual deterioration. However, the detailed assessment of the MRC Trial was a cross-sectional study. As the ophthalmic examinations did not often coincide with the MRC Trial detailed examination the following assumptions were made when coding the general practice medical notes:

- that chronic causes of visual loss (such as AMD, cataract, glaucoma etc) recorded before the detailed examination were present at the detailed examination, unless otherwise indicated.
- that chronic causes of visual loss recorded within one year after the detailed examination were present at the detailed examination, unless otherwise indicated.
- that if the first recorded ophthalmic examination occurred more than one year after the MRC Trial, any chronic cause of visual loss reported at this ophthalmic examination was assumed to be the most likely cause of visual loss at the detailed examination.

Choice of a comparison group when investigating associations with age, sex, socio-economic status and region

Most of the analyses in this chapter are simple presentations of prevalence figures. However, when investigating the independent effects of age, sex and socio-economic status, I constructed logistic regression models. These require a dependant variable in the format 0=comparison group 1=AMD causing visual impairment. There were several options for a comparison group: (i) people with good vision only, (ii) people not visually impaired, (iii) people not visually impaired or visually impaired due to other causes. I chose (iii) because this model most closely corresponds to the prevalence figures with <u>all</u> the population included in the analyses.

Analysis strategy

The overall strategy for analysis was to estimate the prevalence of AMD causing visual impairment, including confidence intervals taking into account the cluster design (*see section 2.6.3*).

This prevalence was estimated for the population as a whole, and within different subgroups in the population defined by age (four groups, 75-79, 80-84, 85-89 and 90+) and sex. In order to assess the independent effects of age and sex, a logistic regression model was developed with AMD causing visual impairment as the outcome (binary 0=not visually impaired/visually impaired due to other causes, 1=AMD causing visual impairment), and terms for age and sex.

The prevalence of AMD causing visual impairment was estimated in the different socio-economic groups. There were three different measures of socio-economic status (*see*

section 2.5.1): housing tenure (owner occupier, rented, sheltered accommodation), socio-economic status score which included housing tenure (score=0, score=1 and score≥2); and social class as indicated by lifetime occupation (five groups). The latter measure was available in a sub-sample of 11 practices only. Housing tenure and socio-economic score are current measures of socio-economic status. People in sheltered accommodation were excluded from the socio-economic status score as measures such as having an indoor toilet or keeping the house warm do not apply to people in sheltered housing. Social class assessed from occupation is a lifetime measure.

Age and sex were considered as potential confounding variables, using logistic regression models as described above.

Regional variation was assessed by grouping the 53 practices according to area: Scotland, North, Midlands and South. The one Welsh practice was included in the Midlands group.

<u>(2) Cross-sectional analytical study investigating the association between visual impairment and AMD and functioning and quality of life and longitudinal analyses of the association between visual impairment and mortality (*chapter four*)</u>

In these analyses, the variables on functioning, quality of life, morbidity and mortality were considered as "outcome" variables with visual impairment due to AMD as the "exposure". Possible confounding factors associated both with the outcome and exposure were identified and controlled for in logistic regression models. For the mortality analyses, Cox proportional hazards models were used.

The condition "AMD causing visual impairment" has two parameters that might have an impact on people's lives: "AMD" and "visual impairment". For that reason the analysis consisted of three stages: firstly, visually impaired people were compared to non-visually impaired people; secondly, people visually impaired due to AMD, and people visually impaired due to other causes were compared to non-visually impaired people; lastly, people visually impaired due to AMD were compared directly to people visually impaired due to other causes, and binocular acuity score included in the model. Interactions by age and sex were investigated.

AMD and visual impairment

The condition "AMD causing visual impairment" has two parameters that might have an impact on the lives of people affected: "AMD" and "visual impairment". People with AMD had worse acuity than people visually impaired due to other causes (*see chapter three section 3.4*). Controlling for the effects of visual acuity is problematic because non-visually impaired people all have binocular acuity 6/18 or better and visually impaired people all have acuity of less than 6/18. When considering the effects of visual acuity, only visually impaired people were examined.

"Impact" variables

Data on impact were drawn from three sources. (1) Data on most of the variables were collected by the practice nurse at the time of the brief assessment or detailed examination. These were available on almost all the study population. These variables were: self-reported health and physical activity, self-reported difficulties seeing, activities of daily living, difficulty managing finances, depression, cognitive function, falls and hip fractures. (2) More detailed information on health-related quality of life - Sickness Impact Profile (SIP) - and morale - Philadelphia Geriatric Morale Scale (PGMS) - were collected by independent fieldworkers in a randomly selected subset of 11 practices only. (3) Data on mortality was collected prospectively by flagging the records with the Office of National Statistics.

The variables indicating "impact" were considered to be the outcome or dependent variables. These variables were in different formats. Some were in a binary forma*t e.g., reported fractured hip/did not reported fracture hip*; many were in the form of a score or scale. The distribution of the scale was examined. If it was normally distributed, or could be transformed to a normal distribution, it was analysed as a continuous variable. If it was skewed it was divided up into quintiles, and a binary variable derived whereby 0=not in worst quintile 1 = in worst quintile ("worst" quintile indicates most severely affected or poorest outcome). In some cases an *a priori* cutpoint was used as identified in the literature review, *e.g., for the Geriatric Depression Scale a score of 6+ was used to define depression* (Sheik and Yesavage 1986).

Identification of potential confounding factors

Confounding factors were considered to have the following attributes:(Rothman 1986). (i) A confounding variable must be a risk factor for the disease (ii) a confounding variable must be associated with the exposure under study in the population from which

the cases derive (iii) a confounding variable must not be an intermediate step in the causal path between the exposure and the disease.

Potential confounding factors were identified from review of the literature, (*see section 1.4*) (Rubin *et al.* 2001; Rubin *et al.* 1997; Valbuena *et al.* 1999; Ivers *et al.* 1998; Ivers *et al.* 2000; Wang *et al.* 2001; Wang *et al.* 2000; Appollonio *et al.* 1996; Appollonio *et al.* 1995; Carabellese *et al.* 1993; Brody *et al.* 2001; Williams *et al.* 1998; Keeffe *et al.* 1998), and previous analyses of the MRC Trial(Osborn *et al.* 2002; Breeze *et al.* 2001). They were as follows:

Socio-economic and demographic factors

- Age and sex
- Socio-economic status
- Social support

Lifestyle factors

- Smoking and alcohol consumption
- Body mass index (BMI)

Other diseases and impairments

- Hearing impairment
- History of arthritis
- History of asthma
- History of cardiovascular disease
- Angina
- Diabetes
- Urinary incontinence
- Lower legs swollen in morning
- Severe shortness of breath
- Three or more prescribed medicines

In addition, the following "impact" outcomes could possibly be considered as confounders for others.

- Depression
- Falls and hip fractures
- Cognitive impairment

However, as these confounders are considered as an effect of visual impairment, they might be considered to be on the “causal pathway”. The analyses were done with, and without, these variables as recommended by Rothman (*see figures 4.1 to 4.4*)(Rothman 1986).

Analysis strategy

The overall analysis strategy was to determine which of the confounding factors were likely to be important by examining whether they were associated with the outcome ("impact") and with the exposure ("visual impairment by cause"). The association between exposure and outcome controlling for confounding variables was assessed using logistic (or Cox proportional hazard) models. Having identified which confounders were likely to be important, three sets of analyses were done for each outcome. Firstly, visually impaired people were compared to non-visually impaired people; secondly, visually impaired people were separated into those visually impaired due to AMD and those visually impaired due to other causes and the analyses repeated. Thirdly, direct comparison was made between people visually impaired due to other causes and those visually impaired due to AMD, controlling for visual acuity.

The following steps were taken in the analysis of each "impact" variable.

- Potential confounding factors were identified from the literature review (*see above*). Only variables that were significantly associated with visual impairment by cause (not visually impaired, visually impaired due to other causes, visually impaired due to AMD) (design-based $\chi 2$ test, $p<0.05$), were considered further as potentially confounding factors. These factors were: housing tenure, smoking, drinking, BMI less than 20, hearing impairment, reported stroke, reported diabetes, urinary incontinence, lower legs swollen in morning, severe shortness of breath and three or more prescribed medicines.
- The following "outcomes" were also considered as potentially confounding factors for other outcomes: depression, cognitive impairment, falls and hip fractures. As these could theoretically be considered to be on the causal pathway, analyses were done with, and without, these factors.
- The association between the potential confounding factor and the "impact" variable was assessed by constructing a series of logistic regression models with the "impact" variable as the outcome and including terms for age (75-79, 80-84,85-89,90+) sex and the confounding factor. Only confounding factors significantly associated with the "impact" variable in question were included in further models of that variable (*see table 4.1*).

- Estimates of odds ratios and confidence intervals of visual impairment associated with outcome, controlled for appropriate confounding factors, were derived from separate models for each "impact" variable. These models included terms for age, sex and potential confounding factors.

- In order to control for the effects of differing levels of visual impairment, further models were constructed including only visually impaired people, including a term for distance visual acuity – binocular acuity score grouped into five equal groups (quintiles) and comparing people visually impaired due to AMD with people visually impaired due to other causes (referent group).

- In order to assess whether the effect of visual impairment on outcome was different between men and women and at different ages, interaction terms for age*"visual impairment" and sex*"visual impairment" were entered into each of the above models. The significance of these terms was assessed using the adjusted Wald test. Interactions with other potential confounding factors were assessed if there was an *a priori* reason to do so.

- For the two measures collected on a subset of practices only (SIP and PGMS) as numbers of people over 90 years of age was small, age was grouped in three groups (75-79, 80-84 and 85 years and above). In addition, analyses of these outcomes required a different strategy as the data were derived from only 11 practices. It was impossible to include all potential confounding factors in the model at the same time. The strategy was as follows: each potential confounding factor was introduced into a model with age, sex and visual impairment by cause only. If the factor changed the effect estimate by 10% or more it was retained as a confounder. Otherwise it was dropped.

- Mortality data were collected prospectively. The incidence rate (number died/person years at risk) of mortality was calculated. The person years at risk was estimated from the start date of the MRC Trial as that was the date of diagnosis of visual impairment for the purposes of this study. The 31st of December 2001 was taken as the censoring date if still alive. Analyses were similar as for other "impact" variables however the data were modelled using Cox proportional hazard model. Log-log plots were examined to verify that the proportional hazard rule applied (Cox 1972).

- All hypothesis tests and models took into account the cluster design of the MRC Trial (*see section 2.6.3*).

(3) Case-control study investigating possible risk factors for AMD, including smoking, alcohol consumption, reproductive factors and cardiovascular disease (*chapter five*).

In this chapter, the outcome under study was case/control status with cases being people with AMD causing visual impairment and controls being people with good vision (binocular acuity of 6/6 or better). The risk factors (exposures) studied were smoking, alcohol consumption, cardiovascular disease and reproductive factors. Logistic regression models were used to control for potential confounding factors and interactions by age and sex investigated.

Control selection

People with AMD causing visual impairment were considered as "cases" and compared to a "control" group. There were two different options for selection of the control group. Firstly, to compare people visually impaired due to AMD with the rest of the MRC Trial study population. This control group would include people visually impaired due to other causes and people not visually impaired. The second option considered was to compare people visually impaired due to AMD with people with good vision (i.e. visual acuity of 6/6 or better).

The signs and symptoms of AMD form a continuous spectrum. Dichotomising the disease, as in many other conditions, is essentially arbitrary. In this study, relatively severe AMD cases were selected because a cut-point of visual acuity worse than 6/18 was used to identify them. It is likely that a small proportion of people with vision worse than 6/6 and better than, or equal to, 6/18 will have AMD and a larger proportion will have early age-related maculopathy (ARM) i.e. drusen and pigmentary changes putting them at increased risk of developing AMD(Bird *et al.* 1995). For this reason, in order to minimise the number of controls who have AMD or ARM, a control group of people with good vision, i.e. binocular visual acuity of 6/6 or better, was selected.

Controlling for the effects of age

Visual acuity decreases with increasing age. The control group of people with good vision will have a different age structure to the visually impaired cases. Table 5.1 shows the number of cases and controls by age and sex.

Age is likely to be an important confounding factor in many analyses. There are two ways of dealing with this different age structure, either in the design, by matching cases to controls based on age, or in the analysis. As matching makes the analysis more complicated (requiring conditional logistic regression) I decided to control for the effects of age (and sex) in the analysis using logistic regression models.

Concurrent versus historical data

In common with all case-control studies there are differences in strength of evidence in concurrent data versus historical data. For example, there were two different measures of hypertension in the MRC Trial. Participants were asked whether a doctor had ever told them that they had high blood pressure. Blood pressure was also measured at the detailed examination. The latter measure is not a good indicator of cardiovascular disease in older people as many people take anti-hypertensive medication. In addition, as the measurement of outcome and exposure are concurrent, it is not clear which came first.

Identification of potential confounding factors

Confounding factors were considered to have the following attributes:(Rothman 1986). (i) A confounding variable must be a risk factor for the disease (ii) a confounding variable must be associated with the exposure under study in the population from which the cases derive (iii) a confounding variable must not be an intermediate step in the causal path between the exposure and the disease.

All exposures were considered as potential confounding factors for each other. Other potential confounding factors were identified from review of the literature. They were as follows:

- Socio-economic status
- Antioxidant micro-nutrient intake
- Exposure to sunlight
- Family history of AMD
- Postmenopausal oestrogen use (in women)
- Physical activity

Data were not available on antioxidant micro-nutrient intake, exposure to sunlight, family history of AMD or postmenopausal oestrogen use. Data were available on socio-economic status and physical activity and these were considered as possible confounders in addition to age, sex and the other exposures under study.

Power of the study

The size of the study was set by the size of the MRC Trial. The add-on study on causes of visual impairment generated approximately 500 cases of visual impairment due to age-related macular degeneration.

Although *post hoc* power calculations are not to be encouraged, in this specific situation, where the number of cases is fixed by factors outside the control of the investigator, it is of interest to know what level of risk is detectable for the different risk factors studied.

Table 5.2 (*chapter five*) shows the power of the study to detect various odds ratios, given the prevalence of exposure in the control group. For most of the risk factors examined the study, has good power (>90%) to detect odds ratios of 2 or more. For some of the risk factors that occur more commonly in this age-group such as systolic blood pressure over 140mmHg and alcohol consumption the study has good power to detect odds ratios of 1.5. For none of the risk factors is the study powerful enough to detect odds ratios in the order of 1.2.

For smoking, odds ratios in the order of 2-3 have been reported in the literature (*see chapter one table 1.11*). One study on menopause before 45 years of age due to surgery found an odds ratio of 5. In these two cases, the study is adequately powered to test these hypotheses.

Information on the other risk factors is more inconsistent. However, given the distribution of exposures in the control group in this study, there is reasonable power for most risk factors to detect odds ratios of the order of 2 or more.

Analysis strategy

The following steps were undertaken in the analysis.

- The association between exposure (or confounders) and AMD causing visual impairment was assessed using a logistic regression model. This model had case/control status as the dependent variable (control=0, case=1) and included terms

for age (75-79,80-84,85-89,90+), sex and the variable in question. This was termed a "univariate" screen.

- All variables that were significantly associated ($p<0.05$) with AMD causing visual impairment on the univariate screen were included in a final model. Any variables that did not contribute to the fit of the model as assessed using an adjusted Wald test ($p<0.05$) were dropped from the model to produce a final model.
- Estimates of odds ratios and confidence intervals of exposure associated with outcome, controlled for appropriate confounding factors, were derived from this model.
- All models took into account the cluster design of the MRC Trial (*see chapter two section 2.6.3*).
- Exposures that were significantly associated with AMD causing visual impairment, after controlling for potential confounders, were analysed in more detail as follows
    - Effect modification by age and sex was examined. Other potential effect modifiers were examined if indicated from literature review or *a priori* hypothesis. To assess effect modifiers, interaction terms of the format *age*exposure* were entered into the model and their significance assessed using the adjusted Wald test.
    - Duration or dose of exposure was examined by constructing relevant logistic regression models.
- As reproductive factors only apply to women, they were analysed separately. The above analysis steps were repeated.

2.6.5 Missing data

Prevalence data: various assumptions were made for the missing data to derive more accurate levels of prevalence of AMD. The rates were calculated assuming that the prevalence of visual impairment in the 31% of people who were invited for examination but either did not attend, or who attended and did not have vision measured, was similar to those that attended and had vision measured/were registered. There was also a group of people who were known to be visually impaired but for whom no cause of visual loss was established. The prevalence rates assume that none of these people had visual loss

due to AMD. This gives a conservative measure of prevalence. In order to determine how important this assumption was the prevalence rates were recalculated assuming that the proportion of people with AMD in cases where no cause of visual loss was identified were similar to those were it was.

In general no other assumptions were made about missing data, other than that any associations observed also applied in the people for whom data were missing.

Table 2.1 Brief assessment questionnaire

Areas specified in the GP contract	Questions
Social Environment	
	<u>Social support</u>
	Living circumstances
	Carer for someone else at home
	Someone to call on for help
	Frequency of social contacts
	<u>Self care</u>
	Wash all over
	Get dressed
	Cut toe nails
	Cook hot meal
	Do light housework or simple repairs
	<u>Financial problems</u>
	Difficulty keeping home warm
	Problems in making ends meet
Sensory impairment	Difficulty hearing
	Difficulty seeing newsprint
Mental condition	Feeling sad, depressed or miserable
	Problems with everyday memory
	Difficulty managing finances
	Problems remembering medication
Physical condition	Vomited blood
	Coughed up blood
	Severe shortness of breath sitting
	Severe swollen legs
	Unexpected weight loss
	Falls in last six months
Incontinence	Urinary
	Faecal
Use of medicines	Number of prescribed medicines
Mobility	Walk 50 yards
	Go up and down stairs and steps
	Do shopping
Lifestyle	Use of alcohol in previous week
(not part of GP contract)	Current smoker (amount daily)
	Physical activity

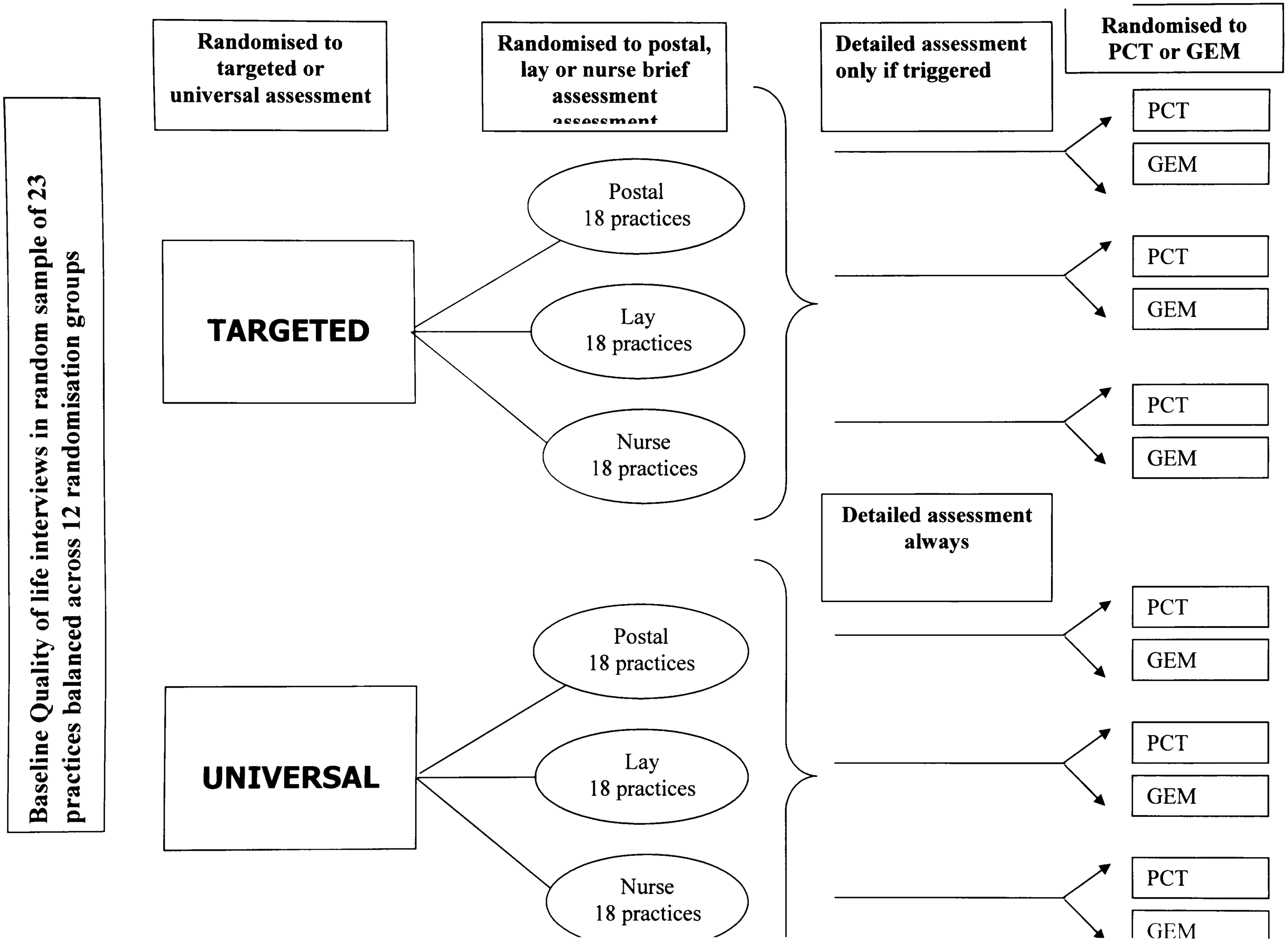
Table 2.2 Distribution of practices according to Jarman score and SMR

Number of practices	Low SMR	Medium SMR	High SMR	Total
Low Jarman	12	11	12	35
Medium Jarman	7	13	13	33
High Jarman	14	11	13	38
Total	33	35	38	106

Table 2.3 Allocation of practices in the MRC Trial

Method of administration of questionnaire	"Targeted" Detailed examination by nurse if indicated by the questionnaire	"Universal" Detailed examination by nurse irrespective of the results of the questionnaire
Postal questionnaire	17	19
Lay person interview	18	17
Nurse interview	18	17
Total	53	53

Figure 2.1 Design of MRC Trial of assessment and management of older people in the community



CHAPTER THREE PREVALENCE OF VISUAL IMPAIRMENT DUE TO AMD

3.1 INTRODUCTION

3.1.1 Research questions

There were three main research objectives:

- To estimate the prevalence of AMD causing visual impairment in people aged 75 years and above in the UK.
- To investigate how this varies by age, sex and socio-economic status.
- To investigate regional variation in the prevalence of AMD as a cause of visual impairment in people aged 75 years and above in the UK.

In order to set the data on AMD in context, the prevalence of visual impairment is described (*see section 3.2*), followed by analysis of the causes of visual loss (*see section 3.3*). Data on the research objectives are presented in the sections 3.4 to 3.6.

3.1.2 A note on cutpoints

- People with AMD who were not visually impaired were not counted

This thesis examined the prevalence of AMD causing visual impairment. There will be people with AMD who did not have binocular acuity less than 6/18 (or who improved to

6/18 or better with pinhole). This will mean that the prevalence estimates presented in this chapter underestimate the prevalence of AMD. The choice of the cutpoint of less than 6/18 was dictated by the design of the MRC Trial. People with visual acuity of less than 6/18 in either eye were referred for ophthalmic investigation. This point is considered in the discussion *(see section 6.1.2)*.

3.2 VISUAL IMPAIRMENT IN THE MRC TRIAL

Figure 3.1 shows the location of all the 106 practices taking part in the trial. The distribution of the study practices reflects the population density of Britain with the majority of practices located in the major conurbations. However, there are a good number of rural practices and a spread of practices from north to south and east to west of the three countries of Britain

3.2.1 Response

Figure 3.2 shows a profile of the study. There were 42,278 eligible people in the 106 practices enrolled in the study. In the universal arm of the study, there were 21,241 eligible people in 53 general practices. Of these, 15,126 (71%) had a detailed assessment. People taking part in the study were of a similar age (median age 80.3 interquartile range 77.2-84.2) to those not taking part (median age 81.0 interquartile range 77.7-85.2). Women were less likely to take part than men – 68% of the non-responders were women, compared to 62% of the responders ($p<0.001$).

Not everyone given a detailed assessment participated in a visual acuity test. Out of 15,126 detailed assessments 699 people did not have a vision test; 173 of these were registered blind or partially sighted and are therefore counted in our measure of visual impairment. A total of 526 (3.5%) people therefore did not have any information on their vision, even though they had been seen by the nurse and had received some of the detailed assessment. These people were older (median age 83.3 interquartile range 79.1-87.9) and were more likely to be women (69% vs. 62%, $p<0.001$). In addition, they were more likely to require a person to help with the interview – 22% of people with missing vision required a totally or partly proxy interview compared to 3% of people with a visual acuity test ($p<0.001$).

3.2.2 Prevalence of visual impairment and blindness

Table 3.1 shows the prevalence of visual impairment, low vision and blindness by age and sex. A total of 1803 (12.4%) of people were counted as visually impaired. Of these, 229 people were counted as visually impaired on the basis of self-reported registration status alone. The visual status of these people was checked from examining the general practitioner notes, hospital consultant form and detailed assessment carried out by the nurse: 172 were confirmed to be registered from general practitioner notes; 15 were confirmed to be visually impaired from general practitioner notes or from hospital questionnaire; 25 had other comments from nurse at the detailed assessment indicating that they could not see; 16 reported glaucoma; and one person was unclear but on balance was considered to be visually impaired.

The prevalence of low vision increased sharply between the ages 75-79 and 90 years and above. At ages 75-79, 5.6% (4.5% to 6.6%)* of the cohort had low vision. At ages 90 and over, 30.0% (25.8% to 34.1%) had low vision. Women had a higher prevalence of low vision than men in all age groups.

The prevalence of blindness also showed a dramatic increased risk with increasing age. At ages 75-79, 0.6% (0.3% to 0.9%) of the cohort was blind. At ages 90 and over 6.6% (3.1% to 10.1%) were blind. Women had a marginally increased risk at all ages.

Table 3.2 gives the results of logistic regression models showing the association between age, and sex with visual impairment. People in the 90 years and above age-group had markedly increased odds of being visually impaired (odds ratio 8.34, 6.67 to 10.43) compared to people aged 75-79. Women were at a 67% increased risk compared to men which was only slightly attenuated after controlling for age. In models looking at blindness alone, the association with sex was not as marked and no longer remained statistically significant after controlling for age.

---

* As for chapter one, I will use the following convention regarding confidence intervals. 95% confidence intervals will be quoted unless indicated otherwise. The confidence intervals will be the form "lower to upper" confidence interval, in brackets after the estimate. If the estimate is in brackets already, the confidence intervals will come after a comma.

3.2.3 Using other definitions of visual impairment

Figure 3.3 shows the results using three different ways of defining visual impairment. (i) visual acuity of less than 6/18 in the better eye pinhole corrected; (ii) binocular visual acuity of less than 6/18; and (iii) binocular acuity of less than 6/12.

The graph shows that the definition of binocular visual acuity less than 6/18 as a measure of visual impairment is a conservative one. If we had defined visual impairment as binocular visual acuity of less than 6/12, over half of our population in the older age-groups would have been visually impaired.

The MRC Trial protocol required that everyone with visual acuity less than 6/18 receive a pinhole test. However, use of the pinhole was not straightforward in this elderly population and only 62% of people with visual acuity less than 6/18 in either eye completed a pinhole test satisfactorily. The graph shows that using the pinhole removed some of the refractive error as a cause of visual impairment in our population. The prevalence of pinhole corrected acuity of less than 6/18 in the better eye was 10.2%. Using the pinhole resulted therefore in an approximate 18% reduction in prevalence of visual impairment (10.2% compared to 12.4%).

3.3 CAUSES OF VISUAL IMPAIRMENT

3.3.1 Collecting data on cause of visual loss from the general practice notes

Response

I approached all 53 practices in the universal arm of the MRC Trial and asked if they wished to take part in the add-on study on the causes of visual impairment. 49 practices agreed to take part. These practices had a similar age and sex distribution and prevalence of visual impairment compared to the four practices that declined to take part (table 3.3). The practices that declined to take part appeared to be smaller in size with an average of 181 participants in the MRC Trial compared to 294 in the practices that agreed to take part. However, this difference was not statistically significant (ttest $t=1.395$, $p=0.183$).

In these 49 practices, there were 1742 people who had a binocular acuity of less than 6/18. Of these 450 (26%) achieved a pinhole acuity of better than or equal to 6/18 in the better eye. In these people the principle cause of visual impairment was considered to be

refractive error. For the remainder (n=1292) I tried to find out the cause of visual loss using the methods as set out in section 2.3.

Out of 1292 visually impaired people, I obtained the cause of visual loss for 976 (76%). There were 316 people for whom I could not identify the cause of visual loss. The reasons why are set out in table 3.4. In 43% of these missing cases the practice nurse was unable to locate the medical notes, either because the patient had moved practice or died (and the Family Health Services Authority refused to supply the notes), or the notes were lost. In a further 42% of cases, the practice nurse was able to obtain the medical notes but there was no record of the patient having an eye examination. In 5% it was not clear from the notes what the cause of visual loss was.

People for whom data on the cause of visual loss were available were similar in terms of age and sex to those for whom data were not available (table 3.5). However, they had worse visual acuity – 25.5% had a visual acuity of less than 3/60 compared to 13.0% of people for whom cause of visual loss was not available.

3.3.2 Verifying the cause of visual loss with the consultant ophthalmologist

The aim behind collecting data both from the general practice notes and the hospital consultant was to verify that the data collection on cause of visual loss from medical record review had been reasonably accurate.

I sent a questionnaire to all consultant ophthalmologists most recently involved in the care of the 976 people for whom there was a cause of visual loss identified from the general practice medical notes (*see Appendix C)*. A total of 470 (48%) forms were completed by consultant ophthalmologists. Of these, three people appeared to have a mistaken identity and were excluded leaving a total of 467 forms.

The main difference between the two sources of data was that the hospital ophthalmologist recorded fewer potential causes of visual loss. In 46% of cases s/he recorded only one condition. In the review of the general practice medical records only one condition was recorded in 32% of cases.

In addition to recording fewer potential causes of visual loss, the hospital consultant was more likely to attribute a main cause in cases where several conditions co-existed. S/he attributed a main cause in 86% of cases where several conditions co-existed, in

contrast to review of the general practice medical notes where a main cause was attributed in 65% of cases with multiple conditions.

Table 3.6 compares the results of the hospital questionnaire with the coding of general practice correspondence. In 335/467 cases (72%), both the medical record review and hospital consultant questionnaire attributed a main cause of visual loss. In 295 (88%) of these 335 cases, the two sources of data agreed as to what was the main cause of visual loss (kappa = 0.81).

Taking the table as a whole, the overall agreement is 64%. This corresponds to a kappa of 0.51. However, this underestimates the level of agreement for two reasons: firstly, cases where joint causes were assigned, such as AMD/Cataract, are taken as being "disagreements" when compared to cases where, for example, AMD only was assigned. Secondly, kappa is dependent on the number of categories. In a table such as this with many categories kappa will be lower irrespective of the actual agreement(Maclure and Willett 1987).

In order to deal with the first problem a weighted kappa was calculated, assuming that cases such as AMD/cataract "agreed" with coding of "AMD" or AMD or cataract with another cause. This gave a kappa of 0.79.

For AMD, in a total of 239 cases the hospital and general practice agreed that AMD was the main or contributory cause; in 156 cases they agreed that AMD was not a main or contributory cause. In 39 cases the general practice notes suggested that AMD was a main or contributory cause but the hospital consultant disagreed whereas in 33 cases the opposite was true. This gives a percentage agreement of 395/467=85% (kappa = 0.68).

3.3.3 Causes of visual loss

Table 3.7 shows the main causes of visual impairment for the 976 people for whom data were available. The data are drawn from the hospital questionnaire, where available, and from the coding of general practice notes otherwise. "Joint" causes are assumed to contribute 50% each to the cause of visual loss.

The table shows the causes of visual loss in two categories of people: firstly, in people with a binocular acuity of less than 6/18; and, secondly, in people with a binocular acuity of less than 6/18, but excluding people who achieved a pinhole acuity in the right

of left eye of 6/18 or better. In these people the principal cause of visual loss was assumed to be refractive error.

In addition, the percentages are calculated including and excluding people for whom the cause of visual loss was unknown.

In all cases, the main cause of visual loss was AMD, followed by (refractive error), cataract, glaucoma, myopic degeneration, diabetic eye disease and vascular occlusions.

AMD

The proportion of binocularly visually impaired people affected by AMD is likely to lie somewhere between 27% and 33%. The lower estimate of 27% assumes none of the cause unknown had AMD (a conservative assumption), the higher estimate of 33% assumes that people whose cause was unknown had a similar prevalence of AMD. If people with refractive error are excluded, the proportion of people affected by AMD increases and probably lies between 36% and 48%.

Other causes

Table 3.8 shows details of the other causes of visual loss.

The most common "other" cause of visual loss was corneal opacity which affected 17 people. In seven of these people this was considered the main cause of visual loss, in the rest it was a contributory cause with AMD (1 person), cataract (8 people) and retinal detachment (1 person). 10 of these 17 people had Fuchs endothelial dystrophy. 15 people had some form of retinal degeneration. There were three cases of retinitis pigmentosa and eight macular holes. 12 people were visually impaired due to disease of the visual cortex or optic pathways. In the majority of cases (7) this was optic nerve disease. Seven people had retinal detachments. In most of these cases this was considered to be the main cause of visual loss. There were a small number of people (5) who had visual symptoms such as diplopia or who had systemic disease causing tremor which affected their vision. Herpes zoster, uveitis and trauma accounted for a further six cases.

Cataract

Nearly 30% of visually impaired people had cataract as the main or contributory cause of visual loss. Table 3.9 sets out further details of the cataract cases. In the majority of cases (281, 80%) there was record in the medical notes prior to the MRC Trial detailed

examination that the person had a cataract. 36 people were on the waiting list and 8 people were in the process of being referred. 50 people had already had a cataract operation in one or both eyes but still failed the visual acuity test at the detailed examination. Three of these people took part in the MRC Trial shortly after their cataract operation and their vision probably had not settled down; a further 14 had record of surgical complications, high astigmatism or posterior subcapsular opacity that could account for the visual loss. In most cases, however, there was no obvious reason why the person should not have achieved good vision after cataract surgery.

In 187 people, cataract had been identified prior to the MRC Trial, however, an operation had not been performed. 28 of these people had refused the operation and for 56 there was record that a decision had been taken not to do the operation for health reasons. In the remaining 103, the record of ophthalmic examinations prior to the MRC Trial had indicated that the lens opacity had been mild. In the majority of these cases no further follow-up took place (62). In 31, they were referred again within one year of the MRC Trial, and in 10 after one year after the MRC Trial examination.

Figure 3.4 shows the causes of visual loss by age and sex. In men, AMD was the most important cause of visual loss at all ages. In women, at the younger age-groups, 75-79, cataract was the most important cause of visual loss. With increasing age, AMD became the predominant cause. Figure 3.5 shows the causes of visual loss by binocular visual acuity score. This shows that cataract and AMD predominate as causes of moderate visual loss but as vision becomes poorer AMD becomes increasingly important. Over 60% of people with a binocular acuity of less than 3/60 (blind) lost their sight because of AMD. Both figures 3.4 and 3.5 emphasise the dominance of AMD and cataract in causing visual impairment in this age-group.

3.4 AMD AS A CAUSE OF VISUAL IMPAIRMENT IN THE MRC TRIAL

Table 3.10 shows the distribution of AMD. In total there were 976 visually impaired people for whom a cause of visual loss was identified. Of these, 516 were identified as having AMD as a cause of visual loss. Of these 516 people, 428 (83%) were definite AMD and a further 88 people had "possible" AMD (*see section 2.4 for definitions of definite and possible AMD).*

Table 3.11 shows the different subtypes of AMD identified. In 26% it was not possible to identify a subtype. In 34% neovascular AMD was identified and in 40% geographic

atrophy was identified. Out of 467 people with a hospital questionnaire returned, 103 had neovascular disease and 158 had geographic atrophy. This suggests that for every two cases of neovascular disease there were three cases of geographic atrophy in this visually impaired population.

Table 3.12 shows the characteristics of people with AMD as a cause of visual loss compared to people who had another cause of visual loss. People with AMD as a cause of visual loss were older than people with other causes of visual loss (design-based $\chi 2$ $p<0.001$). There was no difference between men and women ($p=0.475$). They were more likely to be registered blind or partially sighted ($p<0.001$) and to have a worse visual acuity ($p<0.001$).

Table 3.13 compares people with the different subtypes of the disease. They had a similar age-distribution ($p=0.424$). People with type unspecified were more likely to be women but this could have been due to chance ($p=0.138$). People with neovascular disease were more likely to be registered blind or partially sighted, compared to people with type unspecified or geographic atrophy ($p=0.003$) and had a worse visual function ($p= 0.052$).

Table 3.14 shows the age-specific prevalence rates of AMD causing visual impairment. Overall, 3.7% (3.2% to 4.2%) of the population of people aged 75 years and above were visually impaired due to AMD. There was a higher rate in women (4.4%) than men (2.6%). There was a strong relationship with age, 1.2% of the 75-79 year age-group were visually impaired due to AMD compared to 14.4% of people aged 90 years and above. Women had a higher rate than men at all ages. Table 3.15 shows the results of logistic regression models showing the association between age, and sex with visual impairment due to AMD.

These rates are calculated assuming that the prevalence of visual impairment in the 31% of people who were invited for examination but either did not attend, or who attended and did not have vision measured, was similar to those that attended and had vision measured/were registered. There was also a group of people who were known to be visually impaired but for whom no cause of visual loss was established. I have calculated the prevalence rates assuming that <u>none</u> of these people had visual loss due to AMD. This gives a conservative measure of prevalence.

Excluding people with unknown cause of visual loss from the denominator gives an estimate of prevalence of AMD causing visual impairment that assumes that the proportion of people with cause of visual loss unknown affected by AMD was similar to the proportion of people with cause of visual loss known affected by AMD (table 3.14). These results give a less conservative estimate of the prevalence of AMD causing visual impairment and are shown on the table. These figures indicate that as many as 1 in 5 women aged 90 years and above may be visually impaired due to AMD.

Table 3.16 shows the effect of applying these figures to the UK population in 2001. There are estimated to be approximately 192,000 people aged 75 years and above visually impaired due to AMD (144,000 to 239,000) living in the UK. The majority of the burden of visual impairment due to AMD in this age-group is borne by women. Out of the estimated 192,000 people visually impaired due to AMD, 146,000 (76%) are women.

3.5 AMD AND SOCIO-ECONOMIC STATUS

3.5.1 Housing tenure

In this population of people aged 75 years and above, 64% owned their own homes, 28% rented their accommodation and 9% lived in sheltered housing. The majority of the rental population was council accommodation. Home ownership declined with increasing age, especially in women, who had lower levels of home ownership at all ages. The proportion of the population in sheltered housing increased with age, particularly in the 90 years and above age-group. In each age-group, women are more likely to be in sheltered accommodation than men.

Table 3.17 shows the prevalence of AMD causing visual impairment by housing tenure. There was a similar prevalence in people who owned their own homes and people living in rented accommodation (3.3% and 3.7% respectively). People living in sheltered accommodation had a higher prevalence of AMD causing visual impairment (6.2%). Table 3.18 shows the results of a logistic regression model with AMD causing visual impairment as the dependent variable (0=not visually impaired/visually impaired due to other causes, 1=AMD causing visual impairment) and including terms for housing tenure, age and sex. There was no statistically significant association between AMD

causing visual impairment and living in sheltered accommodation, after taking into account age and sex.

3.5.2 Socio-economic status

A socio-economic score was constructed from variables on housing tenure, central heating, access to an indoor toilet, difficulty keeping their home warm and/or difficulty making ends meet (*see section 2.5.1).* A higher score indicated a worse socio-economic status. People living in sheltered housing were excluded from the score.

The majority (56%) of the population scored 0 on this variable i.e. they owned their own homes, had central heating, an indoor toilet, did not have difficulty keeping their home warm and did not report any difficulty making ends meet. A further 34% scored 1 and 10% scored 2 or more. In general, women had a worse score than men; there was no clear pattern with age.

Table 3.19 shows the prevalence of AMD causing visual impairment by socio-economic score and table 3.20 shows the results of a logistic regression model including terms for age, sex and socio-economic status score. There was little evidence of any relationship between AMD causing visual impairment and socio-economic score.

3.5.3 Social class from lifetime occupation

Social class was graded from lifetime occupation using the Registrar General's Classification of Occupation (*see section 2.5.1*). For married or widowed women, the husband's occupation was used.

35% of the population were in groups I/II, 11% in IIINM, 35% in IIIM and 19% in groups IV/V. An increasing proportion of the population were in groups IV/V with increasing age and decreasing proportion in groups I/II with increasing age. Men were more likely to be in social class group I/II than women.

Table 3.21 shows the prevalence of AMD causing visual impairment by social class group. People in groups I to IIIM had a similar prevalence of visual impairment due to AMD of approximately 2.5% to 3%. People in social class group IV/V had an increased risk of AMD causing visual impairment (3.9%). However, the confidence intervals for these estimates overlap. Table 3.22 shows a logistic regression model including terms for age, sex and social class group. There was little evidence of any association with social class. People in social class group IV/V had a non-significant

increased odds ratio (1.15, 0.34 to 2.11), however, there was no overall trend with social class.

3.6 Regional variation in AMD causing visual impairment

Practices taking part in the MRC Trial were divided into the following regions: South, Midlands, North and Scotland. 38% of participants were in the south, 28% in the Midlands, 24% in the north and 10% in Scotland.

Table 3.23 shows the prevalence of AMD causing visual impairment by region. There was little evidence for any regional differences in the prevalence of AMD causing visual impairment (design-based χ^2 p=0.119).

3.7 KEY POINTS

- 3.7% (3.2% to 4.2%) of this population aged 75 years and above had AMD causing visual impairment.
- There was a strong relationship with age: 1.2% of the 75-79 age-group were visually impaired due to AMD compared to 14.4% of people aged 90 years and above.
- Women were at greater risk of AMD causing visual impairment than men at all ages.
- There were an estimated 192,000 (144,000 to 239,000) people aged 75 years and above visually impaired due to AMD in the UK in 2001.
- AMD causing visual impairment was not associated with housing tenure, socio-economic status score nor an occupational classification of social class.
- There was no evidence of any regional variation in AMD causing visual impairment.

TABLES AND FIGURES

Table 3.1 Prevalence of visual impairment, low vision and blindness

		All visual impairment Binocular acuity <6/18		Low vision Binocular acuity <6/18 - 3/60		Blindness Binocular acuity <3/60	
	N	Prevalence	95% confidence interval	Prevalence	95% confidence interval	Prevalence	95% confidence interval
All ages							
Total	14600	12.4	10.8 to 13.9	10.3	8.7 to 11.8	2.1	1.8 to2.4
Men	5620	9.1	7.9 to 10.4	7.5	6.2 to 8.7	1.7	1.3 to2.0
Women	8980	14.4	12.6 to16.2	12.1	10.2 to 13.9	2.3	1.9 to2.8
Men and women							
75-79	6898	6.2	5.1 to 7.3	5.6	4.5 to 6.6	0.6	0.4 to 0.8
80-84	4602	11.9	9.9 to 13.8	9.6	7.6 to 11.5	2.3	1.8 to 2.8
85-89	2319	23.4	20.5 to 26.4	19.2	16.2 to 22.1	4.3	3.4 to 5.2
90+	781	36.9	32.5 to 41.2	30.0	25.8 to 34.1	6.9	4.8 to 9.0
Men							
75-79	2961	4.8	3.6 to 5.9	4.2	3.1 to 5.2	0.6	0.3 to 0.9
80-84	1695	10.0	8.4 to 11.7	7.7	6.0 to 9.4	2.3	1.5 to 3.1
85-89	782	19.2	15.5 to 22.9	16.0	12.4 to 19.6	3.2	2.0 to 4.4
90+	182	28.6	21.6 to 35.5	22.0	15.6 to 28.4	6.6	3.1 to 10.1
Women							
75-79	3937	7.3	6.0 to 8.5	6.6	5.4 to 7.9	0.6	0.3 to 1.0
80-84	2907	12.9	10.4 to 15.5	10.6	8.1 to 13.1	2.3	1.6 to 3.0
85-89	1537	25.6	22.3 to 28.9	20.8	17.6 to 24.0	4.8	3.6 to 6.0
90+	599	39.4	34.5 to 44.3	32.4	27.4 to 37.4	7.0	4.7 to 9.3

Data from the 53 practices in the universal arm of the MRC Trial. Confidence intervals adjusted for the clustered design of the study

Table 3.2 Risk of visual impairment and blindness by age and sex

		Odds ratio	95% confidence interval
Visual impairment: binocular acuity <6/18			
Independent associations			
Age	75-79	1	
	80-84	2.05	1.80 to 2.33
	85-89	4.65	3.88 to 5.56
	90+	8.88	7.11 to 11.07
Men		1	
Women		1.67	1.51 to 1.85
With both factors in the model			
Age	75-79	1	
	80-84	2.00	1.76 to 2.28
	85-89	4.52	3.76 to 5.42
	90+	8.34	6.67 to 10.43
Men		1	
Women		1.46	1.32 to 1.61
Blindness: binocular acuity <3/60			
Independent associations			
Age	75-79	1	
	80-84	3.76	2.63 to 5.37
	85-89	7.11	4.95 to 10.20
	90+	11.84	7.88 to 17.8
Men		1	
Women		1.39	1.09 to 1.78
With both factors in the model			
Age	75-79	1	
	80-84	3.73	2.61 to 5.32
	85-89	7.02	4.89 to 10.06
	90+	11.51	7.64 to 17.35
Men			
Women		1.16	0.91 to 1.49

Data from the 53 practices in the universal arm of the MRC Trial. Odds ratios derived from logistic regression models taking into account cluster sample design. They represent the increased odds of developing visual impairment or blindness associated with age (compared to age-group 75-79) and being female.

Table 3.3 Comparing practices taking part and not taking part in causes of visual impairment study

	Number of people in practice taking part in MRC Trial	Male %	Age			Prevalence of visual impairment %
			Minimum	Maximum	Mean	
Practices taking part in causes study (n=49)	294	39	75.2	97.0	81.2	12.2
Practices not taking part in causes study (n=4)	181	37	75.5	96.2	81.8	11.6

Data from the 53 practices in the universal arm of the MRC Trial. All the figures in this table are mean figures for practices in each of the two groups (taking part in causes of visual impairment study, not taking part in causes of visual impairment study).

Table 3.4 Reasons for no cause of visual loss

Reason for no cause of visual loss	N	%
Notes unavailable	137	43
- moved GP practice (87) - notes not supplied by FHSA (31) - notes lost (17) - no consent from patient (2)		
Patient never had an ophthalmic examination	134	42
- Refused referral (26) - No assessment, unclear why (108)		
Cause not clear	15	5
Form not completed	30	10
Total with no cause of visual loss	316	100

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 3.5 Comparing people with data on cause of visual impairment with those with missing data on cause of visual impairment

	Male %	Age			Binocular acuity <3/60 (blind) %
		Minimum	Maximum	Mean	
People with data on cause of visual loss (n=1292)	28	75	108	84.7	25.5
People with no data on cause of visual loss (n=316))	28	75	102	85.5	13.0

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 3.6 Comparing hospital and general practice

	AMD	CAT	GLA	DIAB	VO	MYO	OTH	AMD/ CAT	AMD/ GLA	AMD/ DIAB	AMD/ VO	AMD/ MYO	AMD/ OTH	CAT/ GLA	CAT/ DIAB	CAT/ MYO	CAT/ OTH	GLA/D IAB	GLA/ MYO	GLA/ OTH	TOTAL
AMD	174	7	2	2	1	2	2	36	6	2	1	1	2	2	0	0	2	1	0	1	244
CAT	4	69	3	1	0	0	1	17	0	0	0	1	0	2	2	0	2	0	0	0	102
GLA	1	0	24	0	1	0	0	1	4	0	0	0	0	6	0	0	0	0	0	0	37
DIAB	1	0	0	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9
VO	1	0	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	4
MYO	0	0	0	0	0	13	1	1	0	0	0	0	0	1	0	0	0	0	0	0	16
OTH	5	2	0	0	0	2	6	1	0	0	0	0	0	0	0	0	3	0	0	0	19
AMD/CAT	11	3	0	0	0	0	0	4	0	0	0	0	1	1	0	1	0	0	0	0	21
AMD/GLA	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2
AMD/DIAB	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
AMD/MYO	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3
AMD/OTH	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
CAT/GLA	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
CAT/OTH	0	2	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	4
GLA/DIAB	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
GLA/OTH	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
TOTAL	198	84	34	11	3	20	10	62	10	2	1	2	3	12	2	2	8	1	1	1	467

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.
AMD: Age-related macular degeneration CAT: Cataract GLA: Glaucoma DIAB: Diabetic Eye Disease VO: Vascular occlusions MYO: myopic degeneration

Table 3.7 Causes of visual impairment

	Binocular visual impairment less than 6/18				Binocular visual impairment less than 6/18, excluding people with pinhole corrected vision in right or left eye of 6/18 or better			
	Including cause unknown		Excluding cause unknown		Including cause unknown		Excluding cause unknown	
Cause	N	%	N	%	N	%	N	%
*Refractive error	450	25.8	450	31.6	-	-	-	-
AMD	464.5	26.7	464.5	32.6	464.5	36.0	464.5	47.6
Cataract	291.5	16.7	291.5	20.4	291.5	22.6	291.5	29.9
Glaucoma	91.5	5.3	91.5	6.4	91.5	7.1	91.5	9.4
Diabetic eye disease	30.5	1.8	30.5	2.1	30.5	2.4	30.5	3.1
Vascular occlusions	8	0.5	8	0.6	8	0.6	8	0.8
Myopic degeneration	36.5	2.1	36.5	2.6	36.5	2.8	36.5	3.7
Other	53.5	3.1	53.5	3.8	53.5	4.1	53.5	5.5
Cause unknown	316	18.1	-	-	316	24.5	-	-
Total	1742	100	1426	100	1292	100	976	100

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Causes of visual loss from hospital consultant questionnaire where available, from general practitioner notes otherwise. Causes where more than one coexisting eye disease and main cause not clear, each of first two causes contribute 0.5 to final total count. *People with pinhole corrected vision in right or left eye of 6/18 or better

Table 3.8 Other causes of visual impairment

	N	Main or contributory cause
Corneal opacity	17	Main cause-7 *With AMD -1 *With cataract -8 *With retinal detachment -1
Retinal degeneration	15	Main cause-12 *With cataract – 3
Diseases of visual cortex and optic pathways	12	Main cause – 5 *With AMD – 4 *With cataract –2 *With myopic degeneration – 1
Retinal detachment	7	Main cause – 6 *With corneal opacity – 1
Visual symptoms without obvious cause/ systemic cause	5	Main cause – 4 *With cataract – 1
Amblyopia	5	*With AMD – 2 *With cataract – 2 *With glaucoma – 1
Herpes zoster	3	Main cause – 3
Uveitis	2	*With cataract – 2
Trauma	2	Main cause – 2

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Visual impairment: binocular acuity less than 6/18 with usual spectacle correction. People achieving 6/18 or better with pinhole in either eye were excluded. Other causes of visual loss from hospital consultant questionnaire where available, from general practitioner notes otherwise.
*Causes where more than one coexisting eye disease and main cause not clear, each of first two causes contribute 0.5 to final total count (*see table 3.7*).

Table 3.9 Cataract as a cause of visual loss

(a)	N	%
Being assessed at time of MRC Trial detailed examination		
• On waiting list	36	10.3
• Referral in process at time of MRC Trial detailed examination	8	2.3
Cataract identified prior to MRC Trial		
• Operation performed*	50	14.3
• Operation not performed**	187	53.4
Cataract newly identified after MRC Trial examination		
• Within one year	43	12.3
• More than one year after	11	3.1
Not enough information	15	4.3
Total number with cataract as a cause of visual loss	350	100
(b)		
*Probable reason for visual impairment at time of MRC Trial examination		
Immediately post-op	3	6.0
Surgical complications / Astigmatism /PCO	14	28.0
No obvious reason for visual loss	33	66.0
Total number with operation performed	50	100
(c)		
** Probable reason why operation not performed		
Refused operation	28	15.0
Operation not indicated for health/comorbidity reasons	56	29.9
Cataract mild previously no further follow-up	62	33.2
Cataract mild previously, referred within one year of MRC Trial	31	16.6
Cataract mild previously, referred more than one year after MRC Trial	10	5.3
Total number with operation not performed	187	100

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 3.10 AMD

	N	%
Non-AMD cause	460	47.1
Possible AMD	88	9.0
Definite AMD	428	43.9
Total number of visually impaired people with cause of visual loss identified	976	100

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 3.11 Subtypes of AMD

	N	%
Type unspecified	112	26.2
Neovascular AMD	144	33.6
Geographic atrophy	172	40.2
Total number of visually impaired people with definite AMD identified as a cause of visual loss	428	100

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 3.12 Characteristics of people with AMD as a main cause of visual loss

	AMD as a main cause of visual loss (n = 516)		Other cause of visual loss (n=460)	
	N	%	N	%
Age in years				
75-79	74	14.3	128	27.8
80-84	159	30.8	140	30.4
85-89	176	34.1	141	30.7
90+	107	20.7	51	11.1
Male	138	26.7	132	28.7
Female	378	73.3	328	71.3
Registered blind	122	23.6	54	11.7
Registered partially sighted	176	34.1	88	19.1
Not registered	202	39.2	288	62.6
Data missing	16	3.1	30	6.5
Binocular visual acuity logMAR score				
0.5-0.675	126	24.4	221	48.0
0.7-0.875	89	17.3	83	18.0
0.9-1.375	71	13.8	34	7.4
Blind	90	17.4	28	6.1
Data missing	140	27.1	94	20.4

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 3.13 Characteristics of people with different subtypes of AMD as a main cause of visual loss

	Type unspecified (n=112)		Neovascular disease (n=144)		Geographic atrophy (n=172)	
	N	%	N	%	N	%
Age in years						
75-79	20	17.9	20	13.9	25	14.5
80-84	31	27.7	54	37.5	46	26.7
85-89	40	35.7	45	31.3	65	37.8
90+	21	18.7	25	17.4	36	20.9
Male	20	17.8	44	30.6	46	26.7
Female	92	82.1	100	69.4	126	73.3
Registered blind	23	20.5	40	27.8	30	17.4
Registered partially sighted	34	30.4	64	44.4	62	36.1
Not registered	53	47.3	37	25.7	74	43.0
Data missing	2	1.8	3	2.1	6	3.5
Binocular visual acuity logMAR						
0.5-0.675	34	30.4	26	18.1	47	27.3
0.7-0.875	18	16.1	20	13.9	35	20.4
0.9-1.375	14	12.5	20	13.9	21	12.2
Blind	17	15.2	27	18.8	29	16.9
Data missing	29	25.9	51	35.4	40	23.3

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 3.14 Age-specific prevalence (%) of AMD causing visual impairment

		Minimum prevalence		Prevalence excluding people with no information on cause of visual impairment from denominator	
		% Prevalence	95% c.i.	% Prevalence	95% c.i.
All ages					
Total	13900	3.7	3.2 to 4.2	3.9	3.4 to 4.5
Men	5357	2.6	2.1 to 3.1	2.7	2.2 to 3.2
Women	8543	4.4	3.8 to 5.0	4.7	4.1 to 5.4
Men and women					
75-79	6582	1.1	0.9 to 1.4	1.2	0.9 to 1.4
80-84	4388	3.6	3.0 to 4.3	3.8	3.1 to 4.5
85-89	2186	8.1	6.4 to 9.7	8.9	7.0 to 10.7
90+	744	14.4	11.6 to 17.2	17.1	13.7 to 20.5
Men					
75-79	2831	0.9	0.5 to 1.3	0.9	0.6 to 1.3
80-84	1623	2.9	2.2 to 3.6	3.0	2.3 to 3.8
85-89	729	6.2	4.4 to 8.0	6.8	4.8 to 8.7
90+	174	11.5	6.9 to 16.1	13.2	7.8 to 18.7
Women					
75-79	3751	1.3	0.9 to 1.7	1.3	0.9 to 1.7
80-84	2765	4.1	3.2 to 4.9	4.3	3.3 to 5.3
85-89	1457	9.1	7.0 to 10.9	9.9	7.7 to 12.1
90+	570	15.3	12.0 to 18.6	18.4	14.4 to 22.3

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Confidence intervals adjusted for clustered design of study

Table 3.15 Risk of visual impairment due to AMD by age and sex

		Odds ratio	95% confidence interval
Independent associations			
Age	75-79	1	
	80-84	3.31	2.66 to 4.11
	85-89	7.70	5.95 to 9.97
	90+	14.77	10.75 to 20.29
Men		1	
Women		1.75	1.49 to 2.06
With both factors in the model			
Age	75-79	1	
	80-84	3.24	2.60 to 4.04
	85-89	7.46	5.71 to 9.75
	90+	13.86	10.03 to 19.15
Men		1	
Women		1.44	1.22 to 1.69

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Odds ratios derived from logistic regression models taking into account cluster sample design. They represent the increased odds of developing visual impairment due to AMD associated with age (compared to age-group 75-79) and being female.

Table 3.16 Estimated number of people aged 75 years and above with AMD causing visual impairment in the UK in 2001

	*Number of people aged 75 years and above in the UK in 2001 (000's)	**Prevalence of AMD causing visual impairment			***Number of people aged 75 years and above in the UK in 2001 with AMD causing visual impairment		
		Prevalence %	Lower c.i.	Upper c.i.	Estimate	Lower c.i	Upper c.i.
Men							
75-79	817	0.9	0.5	1.3	7353	4085	10621
80-84	480	2.9	2.2	3.6	13920	10560	17280
85-89	230	6.2	4.4	8.0	14260	10120	18400
90+	90	11.5	6.9	16.1	10350	6210	14490
Women							
75-79	1137	1.3	0.9	1.7	14781	10233	19329
80-84	830	4.1	3.2	4.9	34030	26560	40670
85-89	523	9.1	7.0	10.9	47593	36610	57007
90+	327	15.3	12.0	18.6	50031	39240	60822
Total					192318	143618	238619

Population data from http://www.gad.gov.uk **Prevalence data from table 3.14
***calculated by multiplying prevalence by number of people in each age and sex group.

Table 3.17 AMD causing visual impairment and housing tenure

Housing tenure	Number of people with data on vision	People with AMD causing visual impairment		
		N	%	95% confidence intervals
Home owner	8803	292	3.3	2.8 to 3.9
Rented accommodation	3796	140	3.7	2.8 to 4.6
Sheltered accommodation	1202	75	6.2	4.7 to 7.8

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Confidence intervals adjusted for clustered design of study. 99 people had missing data on housing tenure

Table 3.18 Association between AMD causing visual impairment and housing tenure, controlling for age and sex.

Housing tenure	Odds ratio	95% confidence intervals
Home owner	1	
Rented accommodation	1.06	0.80 to 1.41
Sheltered accommodation	1.12	0.83 to 1.50

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Derived from a logistic regression model with AMD causing visual impairment as the dependant variable (0=not visually impaired/visually impaired due to other causes, 1=AMD causing visual impairment) and including terms for age (four groups), sex and housing tenure. Confidence intervals adjusted for the clustered design of the study. 99 people had missing data on housing tenure

Table 3.19 AMD causing visual impairment and socio-economic status score

		People with AMD causing visual impairment		
Socio-economic status score	Number of people	N	%	95% confidence intervals
Score = 0	7410	214	2.9	2.4 to 3.4
Score = 1	4506	181	4.0	3.1 to 4.9
Score ≥ 2	1332	37	2.8	2.0 to 3.6

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Confidence intervals adjusted for clustered design of study. 1352 people had missing data on socio-economic status score of whom 1251 were in sheltered accommodation

Table 3.20 Association between AMD causing visual impairment and socio-economic status score, controlling for age and sex

Socio-economic status score	Odds ratio	95% confidence intervals
Score = 0	1	
Score = 1	1.22	0.98 to 1.52
Score ≥ 2	0.94	0.69 to 1.27

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Odds ratios derived from a logistic regression model with AMD causing visual impairment as the dependant variable (0=not visually impaired/visually impaired due to other causes, 1=AMD causing visual impairment) and including terms for age (four groups), sex and socio-economic score. Confidence intervals adjusted for the clustered design of the study. 1352 people had missing data on socio-economic status score of whom 1251 were in sheltered accommodation

Table 3.21 AMD causing visual impairment and social class group

*Social class group	Number of people	People with AMD causing visual impairment		
		N	%	95% confidence intervals
I/II	1044	30	2.9	1.4 to 4.3
IIINM	304	8	2.6	0 to 5.4
IIIM	958	24	2.5	1.3 to 3.7
IV/V	514	20	3.9	2.2 to 5.6

Data from the 11 practices in which quality of life interviews done and which also in universal arm of MRC Trial and causes of visual impairment study (23 practices in whole MRC Trial randomly selected for quality of life interviews). In these 11 practices, 229 people had missing data on social class group. Social class group is derived from occupation. For widowed and married women, husband's occupation was used. Confidence intervals adjusted for the clustered design of the study.

Table 3.22 Association between AMD causing visual impairment and social class group, controlling for age and sex

	Odds ratio	95% confidence intervals
I/II	1	
IIINM	0.88	0.29 to 2.62
IIIM	0.86	0.42 to 1.78
IV/V	1.15	0.63 to 2.11

Data from the 11 practices in which quality of life interviews done and which also in universal arm of MRC Trial and causes of visual impairment study (23 practices in whole MRC Trial randomly selected for quality of life interviews). 229 people had missing data on social class group. Social class group is derived from occupation. For widowed and married women, husband's occupation was used. Odds ratios derived from a logistic regression model with AMD causing visual impairment as the dependant variable (0=not visually impaired/visually impaired due to other causes, 1=AMD causing visual impairment) and including terms for age (four groups), sex and social class group. Confidence intervals adjusted for the clustered design of the study.

Table 3.23 AMD causing visual impairment by region

	Number of people	People with AMD causing visual impairment		
		N	%	95% confidence intervals
South	5092	192	3.8	3.0 to 4.5
Midlands	4066	150	3.7	2.5 to 4.8
North	3297	116	3.5	2.7 to 4.4
Scotland	1445	58	4.0	3.0 to 5.1

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Confidence intervals are adjusted for clustered design of study

Figure 3.1 Location of practices participating in the MRC Trial of the Assessment and Management of Older People in the Community

Figure 3.2 Study profile

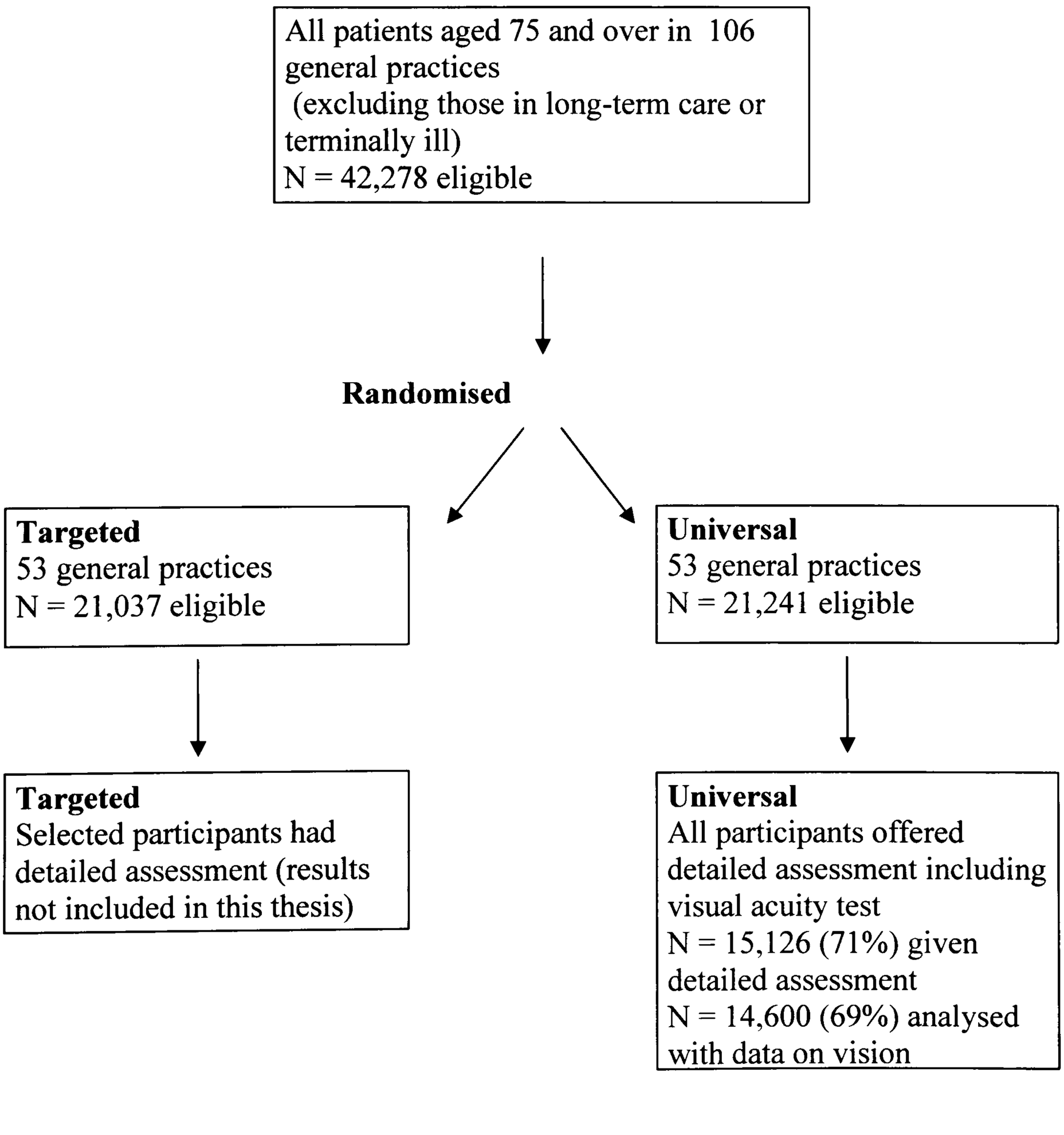


Figure 3.3 Comparison of different measures of visual impairment

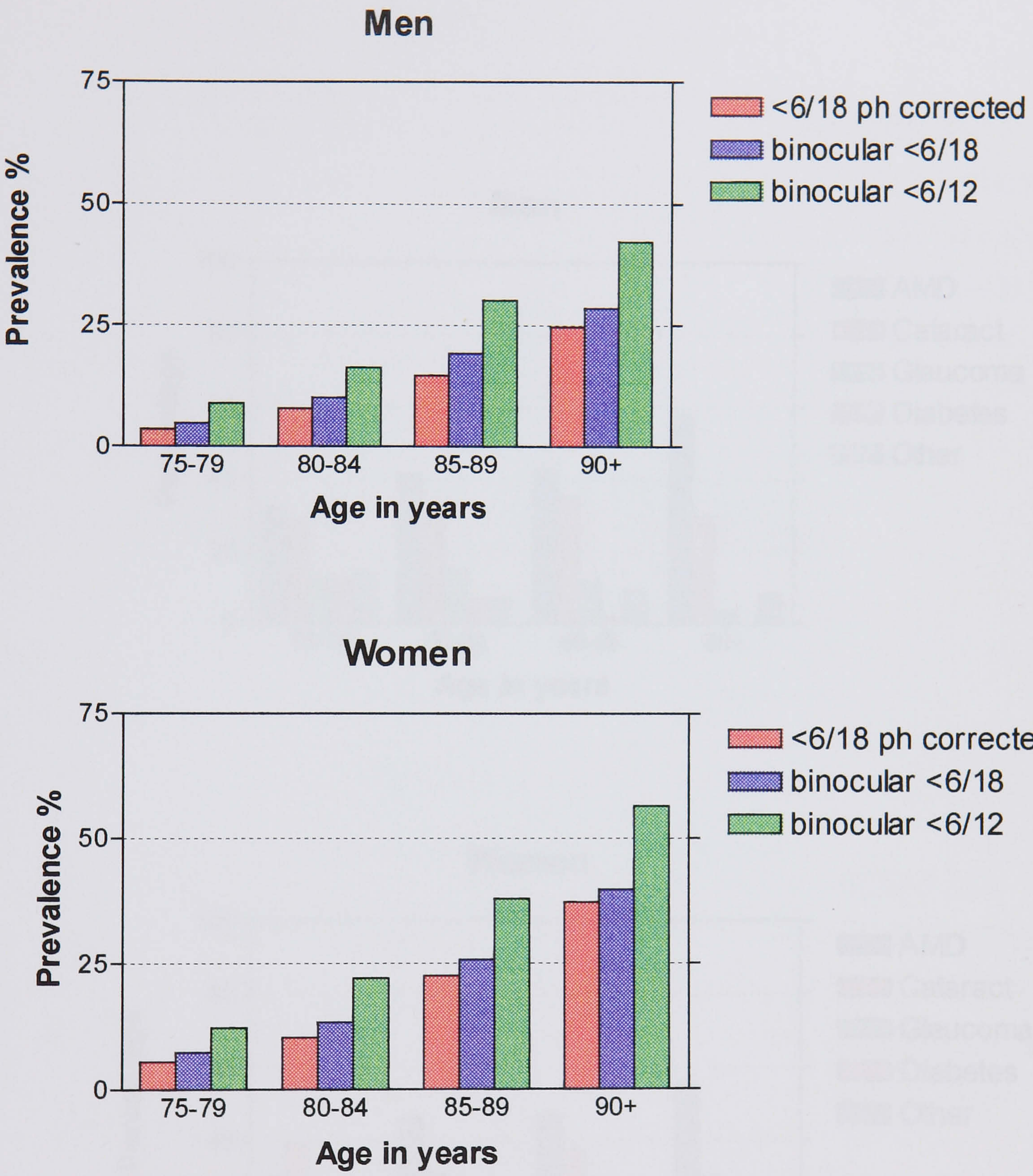


Figure 3.4 Causes of visual impairment by age and sex

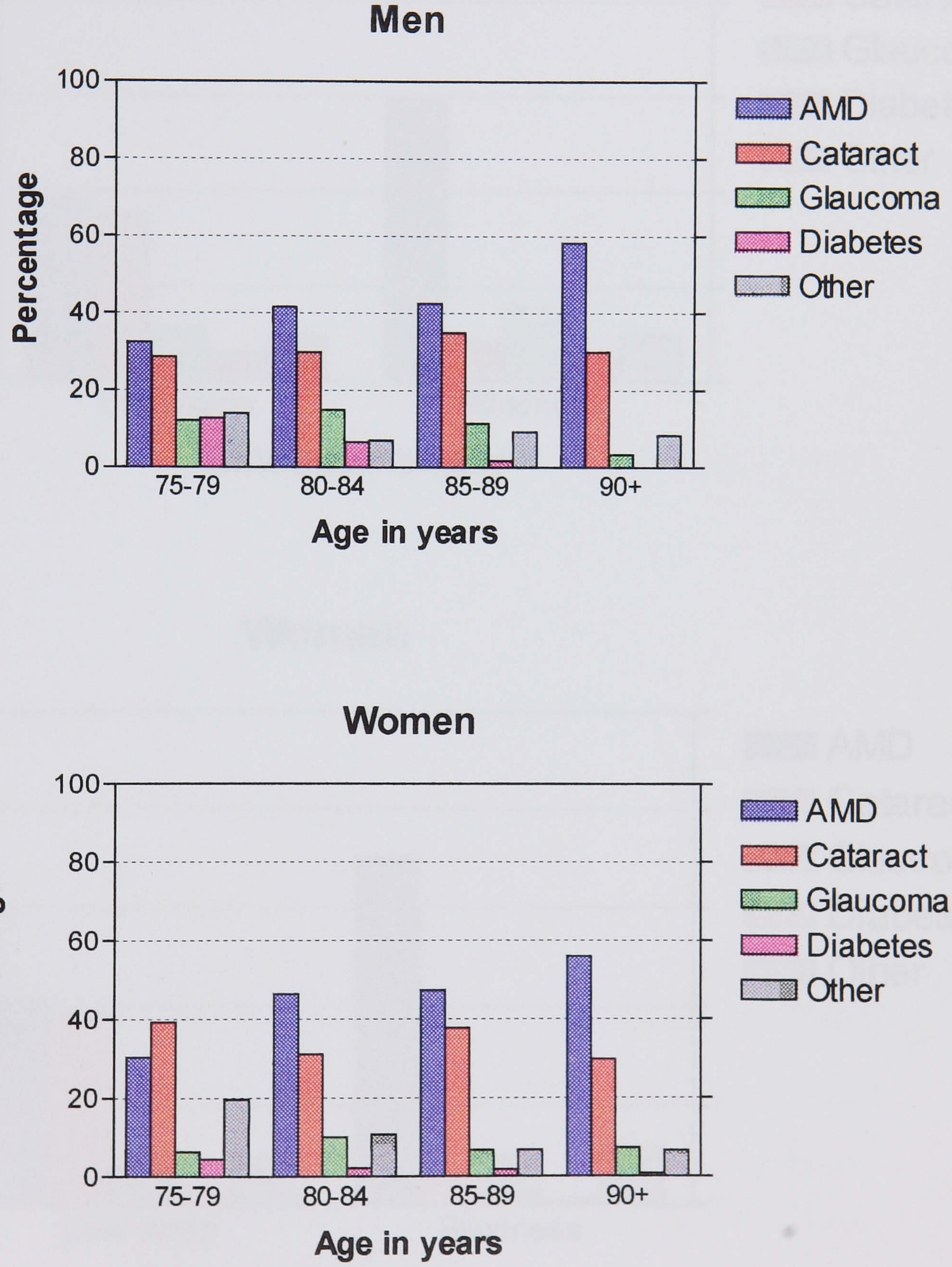
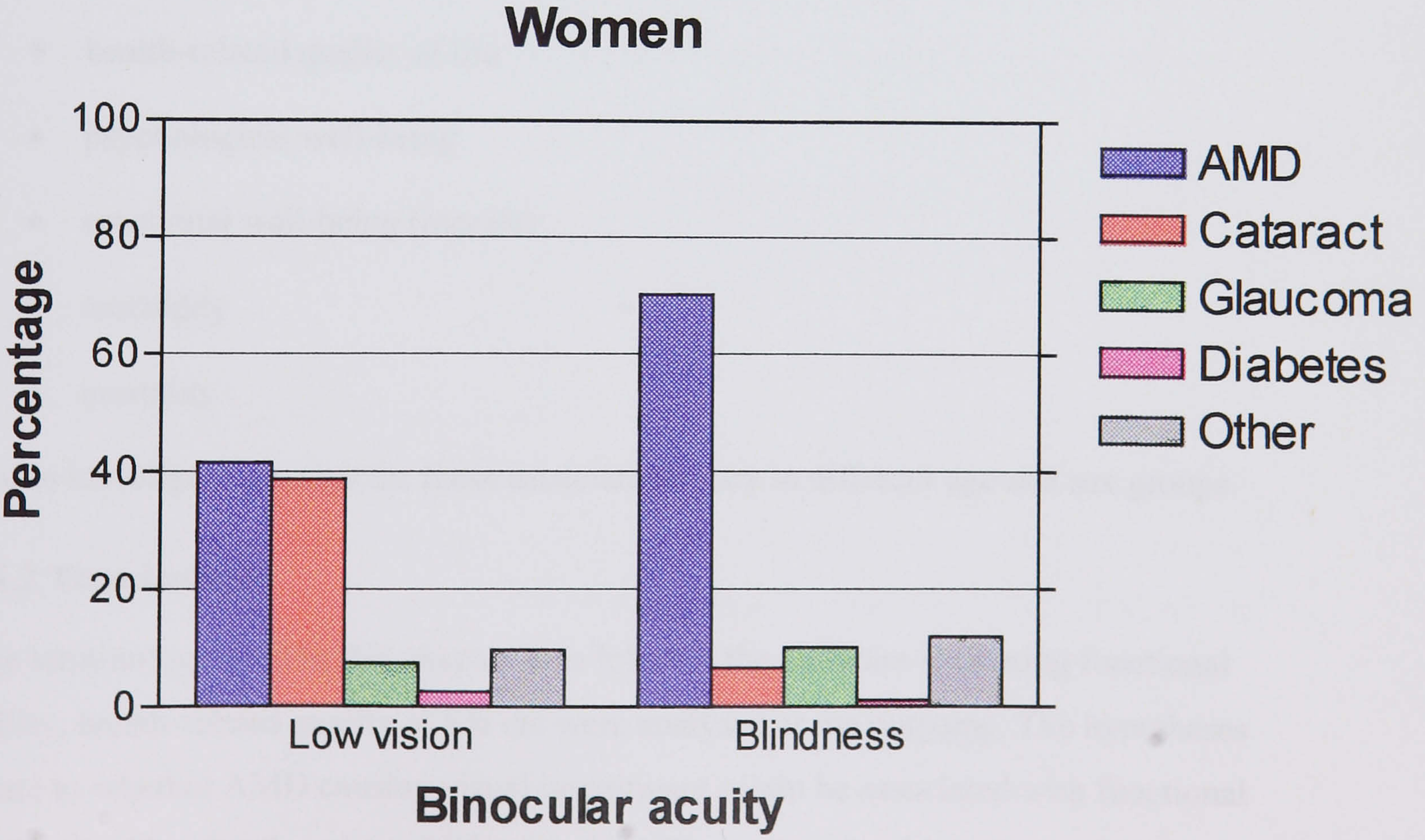


Figure 3.5 Causes of low vision and blindness



CHAPTER FOUR IMPACT

4.1 INTRODUCTION

4.1.1 Research questions

The aim of this chapter is to investigate the association between AMD causing visual impairment and :

- functional ability
- health-related quality of life
- psychological well-being
- emotional well-being (morale)
- morbidity
- mortality

and to investigate whether the these associations vary in different age and sex groups.

4.1.2 Terminology

The terminology used in this chapter is as follows: the variables indicating functional ability, health-related quality of life etc were analysed as the outcome. The hypotheses relate to whether AMD causing visual impairment might be associated with functional ability, health-related quality of life etc… "AMD causing visual impairment" is therefore considered as the exposure in these analyses. Potential confounding factors

associated with both outcome and exposure were identified from review of the literature.

Confidence intervals and statistical significance

As for previous chapters, 95% confidence intervals are reported in brackets (lower to upper) after the effect estimates (odds ratios or hazard ratios). If the effect estimate is already in brackets the 95% confidence intervals are quoted after a comma. Statistical significance ($p<0.05$) is assumed whenever the confidence intervals do not cross unity.

4.2 FUNCTIONAL ABILITY

4.2.1 Distribution in study population

There were three variables that reflected functional ability: difficulty reading newsprint, difficulty managing finances and activities of daily living (ADL). Table 4.2 shows the distribution of these outcomes in the study population.

Overall, 9.9% of the study population reported a lot of difficulty reading newsprint and 3.4% had difficulty managing their own finances. Older people experienced more difficulties. The proportion of people reporting a lot of difficulty reading newsprint increased from 5% in the 75-79 age-group to 27.7% in those 90 years and above. Similarly, those reporting difficulty managing their own finances increased with age (1.9% to 9.4%).

Women also reported more difficulties. 7.7% of men had difficulty reading newsprint compared to 11.2% of women. 2.8% of men had difficulty managing finances compared to 3.8% of women.

The ADL score ranged from 5 to 24 with a median value of 10 and mean of 12.1. Graphical plots and tests of normality indicated that the variable was highly skewed, it was therefore divided into five equal groups (quintiles) and the proportion of people in the worst quintile (i.e. experiencing most difficulties with activities of daily living) was analysed.

The proportion of people in the worst quintile increased with increasing age, from 9.3% in the 75-79 age-group to 54.6% in the 90 and above age-group. Women were more likely to be in the worst quintile than men (22.0% compared to 13.7%).

4.2.2 Association with confounding factors

Table 4.1 (and table F.1 in Appendix F) shows the association between these three functional ability variables and potential confounding factors. Difficulty reading newsprint was associated with all the potential confounding variables with the exception of smoking and reported hip fractures. Difficulty managing finances was associated with all variables except smoking, reported hip fracture and body mass index. Being in the worst quintile for ADL score was associated with all confounding variables.

4.2.3 Association with visual impairment and AMD, controlling confounders

This section discusses tables 4.3 to 4.6. Each table contains results for three models. In all three models the outcome was the impact variable (for example, "a lot of difficulty" reading newsprint). Model 1 included a term for visual impairment (0=not visually impaired 1=visually impaired); Model 2 included a term for visual impairment by cause (0=not visually impaired, 1=visually impaired due to other causes, 2=visually impaired due to AMD); Model 3 included only visually impaired people and included a term for visual impairment by cause (0=visually impaired due to other causes, 1=visually impaired due to AMD). These three models were repeated with different confounders. (a) age and sex alone; (b) age, sex and all other potentially confounding factors, except those potentially on the causal pathway (*see table 4.1*); and (c) age, sex, and all other potentially confounding factors. The discussion of these tables is restricted to the models including all potential confounders, i.e. (c). Only where there are interesting differences between the results are these discussed in more depth.

<u>Reported difficulty reading newsprint</u>

Visually impaired people were more likely to report "a lot of difficulty" reading newsprint compared to those not visually impaired (odds ratio 13.34, 10.56 to 16.85) (table 4.3).

People visually impaired due to AMD were also more likely to report difficulties reading newsprint compared to people not visually impaired, with a large increased relative odds (odds ratio 48.97, 34.93 to 68.65). This was in contrast to people visually impaired due to other causes who had a more modest increased odds of reporting "a lot of difficulty" reading newsprint compared to people not visually impaired (odds ratio 7.68, 5.98 to 9.87).

People visually impaired due to AMD were more likely to report difficulty reading newsprint, compared to people visually impaired due to other causes, and controlling for binocular acuity score in addition to other confounders (odds ratio 3.96, 2.66 to 5.90).

Reported difficulty managing finances

Visually impaired people were more likely to report difficulty managing their own finances compared to those not visually impaired (odds ratio 2.52, 1.98 to 3.21) (table 4.4).

As for reading newsprint, there was some evidence that people visually impaired due to AMD were worse affected. People visually impaired due to AMD had an odds ratio of 4.12 (2.95 to 5.76) of reporting difficulties compared to non visually impaired people. People visually impaired due to other causes had an odds ratio of 1.89 (1.42 to 2.52) compared to non visually impaired people.

People visually impaired due to AMD were more likely to report difficulty managing their finances, compared to people visually impaired due to other causes, and controlling for binocular acuity score in addition to other confounders (odds ratio 1.66, 1.03 to 2.67).

Being in worst quintile for ADL score

Visually impaired people were more likely to be in the worst quintile for ADL score compared to people not visually impaired (odds ratio 1.86, 1.47 to 2.36) (table 4.5).

As for reading newsprint and managing finances above, there was some evidence that people visually impaired due to AMD were worse affected than people visually impaired due to other causes. People visually impaired due to AMD had an odds ratio of 2.72 (1.98 to 3.73) for being in the worst quintile for ADL score compared to people not visually impaired. People visually impaired due to other causes had an odds ratio of 1.55 (1.16 to 2.06) compared to non visually impaired people. Comparing people visually impaired due to AMD directly to those visually impaired due to other causes, and controlling for binocular acuity score in addition to other confounders, gave an odds ratio of 1.65 (1.07 to 2.55).

Repeating these analyses without the confounding factors potentially on the causal pathway (depression, cognitive impairment, falls and hip fractures) gave a slightly

different result. People with AMD were at increased risk of being in the worst quintile for ADL score (odds ratio 1.44, 0.96 to 2.16) however this was of borderline statistical significance (p=0.079).

4.2.4 Effect modification by age and sex

Models 1 and 2 (including all confounding factors) were repeated including interaction terms for "visual impairment term*sex" and "visual impairment term*age". There was little evidence of any effect modification by age and sex.

4.3 SELF-REPORTED HEALTH AND PHYSICAL ACTIVITY

4.3.1 Distribution in study population

Participants were asked to grade their health compared to people their own age. Table 4.6 shows the distribution of this variable in the study population. Self-reported health was graded as excellent, very good, good, fair or poor. As only 3% fell into the poor category, fair and poor were grouped together. Overall, 16.1% reported that their health was "fair/poor". There was no particular trend with age and a slightly higher reported "fair/poor" health in women (17.2% vs. 14.4%). Participants were asked how physically active they felt that they were. This was graded as very, fairly, not very and not at all. Overall, 4.8% reported being "not at all" physically active. This increased with age and was higher in women.

4.3.2 Association with confounding factors

Self-reported health was strongly associated ($p<0.001$) with all the confounders, i.e. housing tenure, smoking, alcohol consumption, body mass index, hearing impairment, reported stroke, diabetes, urinary incontinence, lower legs swollen in the morning, severe shortness of breath, three or more prescribed medicines, depression, cognitive impairment, falls and hip fractures (table 4.1). Self-reported physical activity was associated with most of the potential confounders, with the exception of body mass index and hearing impairment.

4.3.3 Association with visual impairment and AMD, controlling confounders

Reporting "fair/poor" health

Visually impaired people were more likely to report having "fair/poor" health compared to people not visually impaired, however, this effect was modest and not statistically significant (odds ratio 1.20, 0.98 to 1.47) (table 4.7).

In contrast to all visually impaired people, people visually impaired due to AMD were more likely to report "fair/poor" health than people not visually impaired (odds ratio 1.54, 1.15 to 2.06). People visually impaired due to other causes had an odds ratio of 1.07 (0.85 to 1.36) compared to non visually impaired people.

Comparing people visually impaired due to AMD directly to those visually impaired due to other causes, and controlling for binocular acuity score in addition to other confounders, gave an odds ratio of 1.86 (1.26 to 2.74).

Reporting being "not at all" physically active

Visually impaired people were more likely to report being "not at all" physically active compared to people not visually impaired, however, as for self-reported health, this effect was not statistically significant (odds ratio 1.32, 0.99 to 1.76) (table 4.8).

Similar size effects were seen in people visually impaired due to other causes and people visually impaired due to AMD. Comparing people visually impaired due to AMD directly to those visually impaired due to other causes, and controlling for binocular acuity score in addition to other confounders, indicated little difference between people visually impaired due to AMD and those visually impaired due to other causes.

4.3.4 Effect modification by age and sex

Models 1 and 2 (including all confounding factors) were repeated including interaction terms for "visual impairment term*sex" and "visual impairment term*age". There was little evidence of any effect modification by age and sex.

4.4 Sickness Impact Profile (SIP) and Philadelphia Geriatric Morale Scale (PGMS)

4.4.1 Distribution in study population

Four dimensions of the SIP were assessed in a subset of 11 randomly selected practices. These were: home management, mobility, body care and movement and social interaction. All four SIP scales were highly skewed and were therefore grouped into quintiles and the worst quintile analysed. In all four dimensions there was a marked trend with age such that older people experienced more difficulties and had a higher probability of being in the "worst" quintile (table 4.9). Women also reported more problems in all four dimensions.

The PGMS is a series of 17 questions. One point is scored for each question answered "negatively", thus higher scores reflect a worse morale. In this population, the PGMS ranged from 0 to 17 with a median value of 4 and mean of 5.1. The variable was highly skewed and therefore analysed in quintiles. The proportion of people in the "worst" quintile increased with increasing age. At ages 75-79, 20.4% were in the worst quintile, at ages 85 and above, 27.7%. Women had a worse morale (27.7%) than men (15.8%).

4.4.2 Association with confounding factors

Table 4.1 shows the association between the SIP dimensions and PGMS score with potential confounding factors. In general, being in the worst quintile for SIP score was associated with most of the potential confounding factors.

In the case of the SIP and PGMS analyses, as described in the analysis strategy, the confounders had to be restricted because of the relatively small number of practices in which the data were collected, and hence degrees of freedom in the model. Most of the confounders in table 4.1 did not change the odds ratios by 10% or more. The following confounders were used for each model in addition to age and sex: home management, mobility and PGMS – housing tenure; body care and movement – three or more prescribed medicines and depression; social interaction – BMI and depression.

4.4.3 Association with visual impairment and AMD, controlling confounders

SIP: Home management score

Visually impaired people were more likely to be in the worst quintile for home management score compared with people not visually impaired (odds ratio 1.99, 1.51 to 2.63) (table 4.10).

People visually impaired due to AMD were more likely to be in the worst quintile for home management score compared with people not visually impaired (odds ratio 1.85, 1.03 to 3.34). There was little evidence of any difference between people visually impaired due AMD and those visually impaired due to other causes. Comparing people visually impaired due to AMD directly to those visually impaired due to other causes, and controlling for binocular acuity score in addition to other confounders, gave an odds ratio of 0.64 (0.23 to 1.76).

SIP: Mobility score

Visually impaired people were more likely to be in the worst quintile for mobility score compared with people not visually impaired (odds ratio 1.95, 1.28 to 2.98) (table 4.11).

People visually impaired due to AMD were more likely to be in the worst quintile for mobility score compared with people not visually impaired (odds ratio 1.85, 1.21 to 2.84). As for home management, there was little evidence of any difference between people visually impaired due AMD and those visually impaired due to other causes. Comparing people visually impaired due to AMD with those visually impaired due to other causes and controlling for binocular acuity score in addition to other confounding factors gave an odds ratio of 0.86 (0.43 to 1.71).

SIP: Body care and movement score

Visually impaired people were more likely to be in the worst quintile for body care and movement score compared with people not visually impaired (odds ratio 1.56, 1.08 to 2.25) (table 4.12).

In contrast to all visually impaired people, people visually impaired due to AMD were not more likely to be in the worst quintile for mobility score compared with people not visually impaired (odds ratio 0.94, 0.55 to 1.63).

People with AMD appeared to fare better than people visually impaired due to other causes. Comparing people visually impaired due to AMD with those visually impaired

due to other causes and controlling for binocular acuity score in addition to other confounding factors gave an odds ratio of 0.42 (0.23 to 0.79).

SIP: Social interaction score

Visually impaired people were more likely to be in the worst quintile for social interaction score compared to people not visually impaired, however, this effect was not statistically significant (odds ratio 1.32, 0.89 to 1.97) (table 4.13).

Similar size effects were seen in people visually impaired due to other causes and people visually impaired due to AMD. Comparing people visually impaired due to AMD directly with those visually impaired due to other causes, controlling for binocular acuity score in addition to other confounding factors, suggested little difference between AMD and other causes in social interaction (odds ratio 1.02, 0.42 to 2.45).

PGMS

Visually impaired people were more likely to be in the worst quintile for PGMS score compared to people not visually impaired, however, this effect was modest and not statistically significant (odds ratio 1.23, 0.84 to 1.81) (table 4.14).

People visually impaired due to AMD were more likely to be in the worst quintile for PGMS score compared to people not visually impaired, however, as for visually impaired people as a whole, this effect was not statistically significant (odds ratio 1.44, 0.86 to 2.40). There was little evidence for any differences between AMD and other causes in terms of their association with morale. Comparing people visually impaired due to AMD with those visually impaired due to other causes and controlling for binocular acuity score in addition to other confounding factors gave an odds ratio of 1.01 (0.53 to 1.93).

4.4.4 Effect modification by age and sex

There was weak evidence that the association between visual impairment and home management score varied in men and women (interaction visual impairment*sex p=0.035) and stronger evidence that the association between visual impairment and the body care and movement score was different in men and women (interaction visual impairment*sex p=0.005). Repeating the analyses for men and women separately gave the following results.

In men, the odds ratio for being in the worst quintile for home management score in people visually impaired compared to those not visually impaired was 3.64 (2.37 to 5.58). In women, the equivalent odds ratio was 1.46 (0.90 to 2.36).

In men, the odds ratio for being in the worst quintile for home management score in people visually impaired due to AMD compared to those not visually impaired was 5.17 (2.65 to 10.07). In women, the equivalent odds ratio was 1.12 (0.54 to 2.35).

Similarly in the case of body care and movement score, visual impairment was associated with body care and movement in men but not in women. In men, the odds ratio for being in the worst quintile for body care and movement score in people visually impaired compared to those not visually impaired was 2.22 (1.64 to 2.99). In women, the equivalent odds ratio was 1.32 (0.88 to 2.00).

In men, the odds ratio for being in the worst quintile for body care and movement score in people visually impaired due to AMD compared to those not visually impaired was 1.74 (0.57 to 5.35). In women, the equivalent odds ratio was 1.01 (0.73 to 1.39).

In men, the odds ratio for being in the worst quintile for body care and movement score in people visually impaired due to other causes compared to those not visually impaired was 2.42 (1.88 to 3.12). In women, the equivalent odds ratio was 1.47 (0.89 to 2.44).

4.5 COGNITIVE IMPAIRMENT AND DEPRESSION

4.5.1 Distribution in study population

There were two measures of psychological well-being – cognitive ability as measured by the Mini Mental State Examination (MMSE) and depression as measured by the Geriatric Depression Scale (GDS). The MMSE was restricted to the "verbal" section only in order to avoid vision-dependant tasks. Both measures were converted to binary format using cut-points derived from the literature. The MMSE was dichotomised with a cutoff of less than 12 indicating poor cognitive ability. For GDS a cutpoint of six and above was used to indicate depression.

Table 4.15 shows the distribution of these variables in the study population.

Overall, 7.7% of the population was depressed as indicated by a GDS score of six or more. The prevalence of depression increased with increasing age from 6.5% in the 75-

79 age-group to 10.7% in people aged 90 years and above. Women had a marginally higher prevalence of depression than men (8.5% versus 6.5%).

Overall, 5.4% of the population had cognitive impairment as defined by an MMSE (verbal section) of less than 12. The proportion of people with poor cognitive ability increased with increasing age from 2.6% in the 75-79 age-group to 19.6% in the 90 years and above age-group. A greater proportion of women had poor cognitive ability than men (6.5% versus 3.5%).

4.5.2 Association with confounding factors

Table 4.1 shows the association of the variables indicating psychological well-being and potential confounding factors. Depression was strongly associated with all the potential confounding factors with the exception of alcohol consumption and cognitive impairment. Cognitive impairment was associated with fewer confounding factors.

4.5.3 Association with visual impairment and AMD, controlling confounders

<u>Depression</u>

Visually impaired people were more likely to be depressed compared to people not visually impaired (odds ratio 1.46, 1.22 to 1.76) (table 4.16).

Similar size effects were seen in people visually impaired due to other causes and people visually impaired due to AMD. After controlling for visual acuity, there was little evidence for any difference between visual impairment due to AMD and visual impairment due to other causes - comparing people visually impaired due to AMD with those visually impaired due to other causes and controlling for binocular acuity score in addition to other confounding factors gave an odds ratio of 0.86 (0.58 to 1.27).

<u>Cognitive impairment</u>

Visually impaired people were more likely to be cognitively impaired compared with people not visually impaired (odds ratio 1.67, 1.28 to 2.19) (table 4.17).

People visually impaired due to AMD were more likely to be cognitively impaired compared to people not visually impaired, however, this effect was not statistically significant (odds ratio 1.36, 0.87 to 2.13).

Comparing people visually impaired due to AMD with those visually impaired due to other causes and controlling for binocular acuity score in addition to other confounding

factors gave an odds ratio of 0.59 (0.32 to 1.06). This result suggests that people with visual impairment due to AMD may be less likely to be cognitively impaired compared to people with visual impairment due to other causes, taking visual acuity into account. The upper confidence interval for this result crosses 1 however and therefore this finding is not statistically significant and could have arisen by chance.

4.5.4 Effect modification by age and sex

Models 1 and 2 (including all confounding factors) were repeated including interaction terms for "visual impairment term*sex" and "visual impairment term*age". There was no evidence of any effect modification by age and sex.

4.6 FALLS AND HIP FRACTURES

4.6.1 Distribution in study population

There were two aspects of morbidity that were considered – falls and hip fractures. Table 4.18 shows the distribution of these in the study population.

20% of the population reported having one or more falls at home in the last six months. 12.5% had had one fall, 4.5% two falls, 2.0% three falls, and 1.9% four of more falls. The cut-point of two or more falls was chosen as this represented a group of people significantly affected by falls. 8.4% of the population reported two or more falls in the last six months. This proportion increased with increasing age from 5.9% in the 75-79 age-group to 15.4% in the 90 years and above age-group. Women had a slightly higher risk of reporting two or more falls than men (9.0% vs. 7.5%). Overall 3.8% of the population reported having had a fractured hip. Women were much more likely to report fractured hip (5.0%) than men (1.9%). There was an increasing risk of hip fracture with age from 2.3% in the 75-79 age-group to 7.7% in the 90 years and above age-group.

4.6.2 Association with confounding factors

Table 4.1 shows the association of potential confounding factors with reported falls and hip fractures.

Two or more falls at home was associated with most of the confounders, with the exception of smoking. Reported hip fracture was associated with fewer potential confounding factors.

4.6.3 Association with visual impairment and AMD, controlling confounders

Falls

Visually impaired people were more likely to report two or more falls at home in the last six months compared to not visually impaired people, however, this effect was modest and not statistically significant (odds ratio 1.18, 0.95 to 1.47) (table 4.19).

Similar size effects were observed in people visually impaired due to AMD and people visually impaired due to other causes. Comparing people visually impaired due to AMD with those visually impaired due to other causes and controlling for binocular acuity score in addition to other confounding factors gave an odds ratio of 0.89 (0.51 to 1.54).

Hip fractures

Visually impaired people were more likely to report a fractured hip compared to people not visually impaired, however, this effect was modest and not statistically significant (odds ratio 1.23, 0.94 to 1.61) (table 4.20).

As for falls there was little evidence of any difference between people visually impaired due to AMD and those visually impaired due to other causes. Comparing people visually impaired due to AMD with those visually impaired due to other causes and controlling for binocular acuity score in addition to other confounding factors gave an odds ratio of 0.86 (0.49 to 1.51).

4.6.4 Effect modification by age and sex

The association between visual impairment and reported hip fracture appeared to be different at different ages (p=0.045). Repeating the analyses in each age-group gave the following results: ages 75-79 the odds ratio of reporting hip fracture if visually impaired was 1.86 (0.97 to 3.56); ages 80-84 it was 1.22 (0.75 to 1.99); ages 85-89 it was 0.66 (0.43 to 1.03); ages 90 years and above it was 2.21 (1.04 to 4.71). For AMD causing visual impairment the corresponding odds ratios were: ages 75-79, 0.87 (0.11 to 7.17); ages 80-84 0.60 (0.21 to 1.74); ages 85-89 0.48 (0.20 to 1.15); ages 90 years and above 3.75 (1.61 to 8.74). These figures suggest that the main difference occurs at ages 90 years and above. At ages 75-89 the odds ratio of reporting hip fracture if visually impaired was 1.30 (0.96 to 1.76). At ages 90 years and above it was 2.21 (1.04 to 4.71). For AMD causing visual impairment the corresponding odds ratios were: ages 75-89 0.78 (0.43 to 1.42); ages 90 years and above 3.75 (1.61 to 8.74).

4.7 MORTALITY

4.7.1 Crude incidence rates and rate ratios

Table 4.21 shows the incidence rates of mortality in the three groups. Non visually impaired people had an incidence rate of 0.072/person year at risk. There was an increased mortality rate in visually impaired compared to non-visually impaired people.

People visually impaired due to AMD were nearly twice as likely to die following the detailed assessment, compared to people who were not visually impaired (rate ratio 1.84, 1.61 to 2.11).

Similar size effects were observed in people visually impaired due to AMD and people visually impaired due to other causes.

4.7.2 Association with confounding factors

Mortality was strongly associated with all the potential confounding variables identified (table 4.1).

4.7.3 Association with visual impairment and AMD, controlling confounders

Three Cox proportional hazard models were constructed with deaths as the outcome and time since the detailed assessment as the person time at risk. December 31st was taken as the censoring date if still alive. Age, sex and all the potential confounding factors as set out in table 4.1 were included in these models.

After controlling for all the potential confounders, visually impaired people had a hazard ratio of 1.32 (1.22 to 1.43) compared to people not visually impaired. People visually impaired due to AMD had a lower risk (hazard ratio 1.21, 1.07 to 1.37). Comparing people visually impaired due to AMD with those visually impaired due to other causes, including a term for binocular acuity score in the model, gave a hazard ratio of 0.76 (0.63 to 0.90). This indicates that mortality in people visually impaired due to AMD is significantly lower than in people visually impaired due to other causes, after taking into account obvious confounders, including visual acuity.

4.7.4 Effect modification by age and sex

There was no evidence for any effect modification by age and sex.

4.8 KEY POINTS

After controlling for appropriate confounding factors, compared to people not visually impaired, visually impaired people were more likely to:

- report "a lot of difficulty" reading newsprint
- report difficulty managing finances
- be in the worst quintile for ADL score
- be in the worst quintile for the following dimensions of the SIP: home management, mobility and body care and movement
- be cognitively impaired
- be depressed
- die

After controlling for appropriate confounding factors, compared to people not visually impaired, people visually impaired due to AMD were more likely to:

- report "a lot of difficulty" reading newsprint
- report difficulty managing finances
- be in the worst quintile for ADL score
- report "fair/poor" health
- be in the worst quintile for the following dimensions of the SIP: home management, mobility
- be depressed
- die

After controlling for appropriate confounding factors including binocular acuity score, compared to people visually impaired due to other causes, people visually impaired due to AMD were more likely to:

- report "a lot of difficulty" reading newsprint
- report difficulty managing finances
- be in the worst quintile for ADL score
- report "fair/poor" health

and less likely to:

- be in the worst quintile for SIP body care and movement dimension
- die.

TABLES AND FIGURES

Table 4.1 Association between outcomes and potential confounding factors

Outcomes	Functional ability			Reported health & physical activity		SIP & PGMS					Depression & cognitive impairment		Falls & hip fractures		Mortality
Potential confounding factors	Reading news print	Managing finances	ADL	Reported health	Physical activity	SIP:Home	SIP:Mobil	SIP:Body care	SIP:Social	PGMS	Depression	Cognitive	Falls	Hip fractures	Mortality
Housing tenure (owner,rented,sheltered)	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔	✔		✔
Smoking (Never,ex,current)			✔	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔
Drink in last year	✔	✔	✔	✔	✔	✔	✔	✔	✔			✔	✔		✔
BMI (≥20,<20)	✔		✔	✔		✔			✔		✔	✔	✔	✔	✔
Hearing impairment	✔	✔	✔	✔					✔	✔	✔	✔	✔	✔	✔
Reported stroke	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔
Diabetes	✔		✔	✔	✔	✔	✔	✔			✔		✔		✔
Urinary incontinence	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔
Lower legs swollen in morning	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔
Severe shortness of breath	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔		✔
3+ prescribed medicines	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔
Depression	✔	✔	✔	✔	✔	✔	✔	✔	✔	NA	NA		✔	✔	✔
Cognitive impairment	✔	✔	✔	✔	✔	✔	✔		✔			N/A	✔		✔
Two or more falls	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	NA	NA	✔
Reported hip fracture			✔	✔	✔	✔	✔	✔			✔		NA	NA	✔
Continued															

Table 4.1 Association between outcomes and potential confounding factors continued

Tick indicates that variables are associated $p<0.05$. P values (Wald test) derived from logistic regression model including outcome as dependant variable with terms for age (75-79,80-84,85-89,90+), sex and potential confounding factor. NA indicates that factor was not considered as a confounder on theoretical grounds. Variables were binary format unless other wise indicated on the table and were included in the models as 0=No and 1=Yes. Confounders considered as potentially on causal pathway are indicated in italics. Tables showing results in more detail are in appendix F. Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 4.2 Percentage with "a lot of difficulty" reading newsprint, difficulty managing finances or in worst quintile for ADL score by age and sex

Outcome	% with "outcome"	% with "outcome" in each age-group				% with "outcome" in men and women	
		75-79	80-84	85-89	90+	Men	Women
A lot of difficulty reading newsprint	9.9	5.0	10.7	16.2	27.7	7.7	11.2
Difficulty managing own finances	3.4	1.9	3.4	6.0	9.4	2.8	3.8
Activities of daily living – worst quintile	18.9	9.3	18.8	34.0	54.6	13.7	22.0

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 4.3 "A lot of difficulty" reading newsprint: logistic regression models assessing the associations with visual impairment, visual impairment due to other causes and visual impairment due to AMD

Values in the table are odds ratios (95% c.i.)	Model 1	Model 2		Model 3
	Comparing VI with not VI	Comparing VI other causes with not VI	Comparing VI due AMD with not VI	Comparing VI due AMD with VI other causes
(a) Controlled age & sex	12.99 (10.60 to 15.91)	8.47 (6.83 to 10.50)	37.88 (29.60 to 48.48)	3.13 (2.39 to 4.11)
(b) Controlled for all confounders except those potentially on causal pathway	13.22 (10.53 to 16.59)	7.72 (6.06 to 9.83)	46.84 (33.32 to 65.83)	3.84 (2.63 to 5.62)
(c) Controlled age, sex, & all confounders	13.34 (10.56 to 16.85)	7.68 (5.98 to 9.87)	48.97 (34.93 to 68.65)	3.96 (2.66 to 5.90)

VI = visual impairment

(a) Models 1 to 3 were constructed as follows: the outcome/dependant variable was 0=none/little difficulty reading newsprint 1=a lot of difficulty reading newsprint. Terms for age (75-79,80-84,85-89,90+), sex and visual impairment were included. Binocular visual acuity score (quintiles) was included in model 3.
(b) As for (a) including terms for all potential confounding factors (*see table 4.1*) but not including terms for confounders potentially on causal pathway
(c) As for (a) including terms for all potential confounding factors (*see table 4.1*).

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Confidence intervals adjusted for clustered design of the study.

Table 4.4 Difficulty managing finances: logistic regression models assessing associations with of visual impairment, visual impairment due to other causes and visual impairment due to AMD

Values in the table are odds ratios (95% c.i.)	Model 1	Model 2		Model 3
	Comparing VI with not VI	Comparing VI other causes with not VI	Comparing VI due AMD with not VI	Comparing VI due AMD with VI other causes
(a) Controlled age & sex	3.01 (2.40 to 3.78)	2.56 (2.02 to 3.24)	4.08 (3.00 to 5.54)	1.47 (1.04 to 2.09)
(b) Controlled for all confounders except those potentially on causal pathway	2.81 (2.27 to 3.48)	2.20 (1.72 to 2.80)	4.33 (3.16 to 5.93)	1.57 (1.00 to 2.48)
(c) Controlled age, sex, & all confounders	2.52 (1.98 to 3.21)	1.89 (1.42 to 2.52)	4.12 (2.95 to 5.76)	1.66 (1.03 to 2.67)

VI = visual impairment

(a) Models 1 to 3 were constructed as follows: the outcome/dependant variable was 0=no difficulty 1=difficulty managing finances. Terms for age (75-79, 80-84, 85-89, 90+), sex and visual impairment were included. Binocular visual acuity score (quintiles) was included in model 3.
(b) As for (a) including terms for all potential confounding factors (*see table 4.1*) but not including terms for confounders potentially on causal pathway
(c) As for (a) including terms for all potential confounding factors (*see table 4.1*).

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Confidence intervals adjusted for clustered design of the study.

Table 4.5 Worst quintile for ADL score: logistic regression models assessing associations with of visual impairment, visual impairment due to other causes and visual impairment due to AMD

Values in the table are odds ratios (95% c.i.)	Model 1	Model 2		Model 3
	Comparing VI with not VI	Comparing VI other causes with not VI	Comparing VI due AMD with not VI	Comparing VI due AMD with VI other causes
(a) Controlled age & sex	2.39 (2.01 to 2.83)	2.31 (1.88 to 2.84)	2.57 (2.06 to 3.21)	1.09 (0.82 to 1.44)
(b) Controlled for all confounders except those potentially on causal pathway	2.00 (1.58 to 2.52)	1.71 (1.31 to 2.23)	2.76 (2.01 to 3.79)	1.44 (0.96 to 2.16)
(c) Controlled age, sex, & all confounders	1.86 (1.47 to 2.36)	1.55 (1.16 to 2.06)	2.72 (1.98 to 3.73)	1.65 (1.07 to 2.55)

VI = visual impairment

(a) Models 1 to 3 were constructed as follows: the outcome/dependant variable was 0=not in worst quintile 1=in worst quintile for ADL score. Terms for age (75-79, 80-84, 85-89, 90+), sex and visual impairment were included. Binocular visual acuity score (quintiles) was included in model 3.
(b) As for (a) including terms for all potential confounding factors (*see table 4.1*) but not including terms for confounders potentially on causal pathway
(c) As for (a) including terms for all potential confounding factors (*see table 4.1*).

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Confidence intervals adjusted for clustered design of the study.

Table 4.6 Percentage reporting "fair/poor" health or "not at all" physically active by age and sex

Outcome	% with "outcome"	% with "outcome" in each age-group				% with"outcome" in men & women	
		75-79	80-84	85-89	90+	Men	Women
Self-reported "fair/poor" health	16.1	14.7	16.8	18.8	16.7	14.4	17.2
Reported being "not at all" physically active	4.8	3.1	4.6	7.8	12.0	4.2	5.2

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 4.7 "Fair/poor" self-reported health: logistic regression models assessing associations with of visual impairment, visual impairment due to other causes and visual impairment due to AMD

Values in the table are odds ratios (95% c.i.)	Model 1	Model 2		Model 3
	Comparing VI with not VI	Comparing VI other causes with not VI	Comparing VI due AMD with not VI	Comparing VI due AMD with VI other causes
(a) Controlled age & sex	1.73 (1.51 to 1.98)	1.73 (1.49 to 2.01)	1.73 (1.38 to 2.15)	1.12 (0.85 to 1.48)
(b) Controlled for all confounders except those potentially on causal pathway	1.29 (1.07 to 1.56)	1.17 (0.94 to 1.45)	1.63 (1.24 to 2.13)	1.67 (1.16 to 2.39)
(c) Controlled age, sex, & all confounders	1.20 (0.98 to 1.47)	1.07 (0.85 to 1.36)	1.54 (1.15 to 2.06)	1.86 (1.26 to 2.74)

VI = visual impairment

(a) Models 1 to 3 were constructed as follows: the outcome/dependant variable was 0="excellent/very good/good" health 1="fair/poor" health. Terms for age (75-79, 80-84, 85-89, 90+), sex and visual impairment were included. Binocular visual acuity score (quintiles) was included in model 3.
(b) As for (a) including terms for all potential confounding factors (*see table 4.1*) but not including terms for confounders potentially on causal pathway
(c) As for (a) including terms for all potential confounding factors (*see table 4.1*).

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Confidence intervals adjusted for clustered design of the study.

Table 4.8 "Not at all" physically active: logistic regression models assessing associations with of visual impairment, visual impairment due to other causes and visual impairment due to AMD

Values in the table are odds ratios (95% c.i.)	Model 1	Model 2		Model 3
	Comparing VI with not VI	Comparing VI other causes with not VI	Comparing VI due AMD with not VI	Comparing VI due AMD with VI other causes
(a) Controlled age & sex	2.14 (1.71 to 2.66)	2.21 (1.73 to 2.81)	1.98 (1.42 to 2.77)	1.03 (0.67 to 1.58)
(b) Controlled for all confounders except those potentially on causal pathway	1.52 (1.16 to 2.00)	1.51 (1.10 to 2.06)	1.55 (1.03 to 2.35)	1.16 (0.68 to 1.95)
(c) Controlled age, sex, & all confounders	1.32 (0.99 to 1.76)	1.32 (0.95 to 1.84)	1.32 (0.82 to 2.10)	1.19 (0.68 to 2.10)

VI = visual impairment

(a) Models 1 to 3 were constructed as follows: the outcome/dependant variable was 0="very/fairly/not very" 1="not at all" physically active. Terms for age (75-79, 80-84, 85-89, 90+), sex and visual impairment were included. Binocular visual acuity score (quintiles) was included in model 3.
(b) As for (a) including terms for all potential confounding factors (*see table 4.1*) but not including terms for confounders potentially on causal pathway
(c) As for (a) including terms for all potential confounding factors (*see table 4.1*).

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Confidence intervals adjusted for clustered design of the study.

Table 4.9 Sickness Impact Profile and Philadelphia Geriatric Morale Scale: percentage of people in the worst quintile by age and sex*

	% in worst quintile	% in worst quintile in each age-group			% in worst quintile in men and women	
		75-79	80-84	85+	Men	Women
Sickness Impact Profile						
Home management	20.2	10.9	21.6	40.1	17.3	22.2
Mobility	20.0	11.6	21.2	38.0	13.9	24.0
Body care and movement	20.0	12.4	20.7	36.8	14.6	23.5
Social interaction	19.5	13.7	21.0	31.0	17.1	21.1
Philadelphia Geriatric Morale Scale						
PGMS	22.8	20.4	23.9	27.7	15.6	27.5

Data from the 11 practices in which quality of life interviews done and which also in universal arm of MRC Trial and causes of visual impairment study (23 practices in whole MRC Trial randomly selected for quality of life interviews).

Table 4.10 Worst quintile for SIP home management score: logistic regression models assessing associations with visual impairment, visual impairment due to other causes and visual impairment due to AMD

Values in the table are odds ratios (95% c.i.)	Model 1	Model 2		Model 3
	Comparing VI with not VI	Comparing VI other causes with not VI	Comparing VI due AMD with not VI	Comparing VI due AMD with VI other causes
(a) Controlled age & sex	2.26 (1.74 to 2.95)	2.30 (1.71 to 3.10)	2.17 (1.34 to 3.51)	0.63 (0.26 to 1.56)
(b) Controlled age, sex & housing tenure	1.99 (1.51 to 2.63)	2.05 (1.41 to 2.99)	1.85 (1.03 to 3.34)	0.63 (0.23 to 1.76)

VI = visual impairment

(a) Models 1 to 3 were constructed as follows: the outcome/dependant variable was 0=not in worst quintile 1=in worst quintile for SIP home management score. Terms for age (75-79,80-84,85-89,90+), sex and visual impairment were included. Binocular visual acuity score (quintiles) was included in model 3.
(b) As for (a) including terms for all potential confounding factors (*see section 4.4.2*)

Data from the 11 practices in which quality of life interviews done and which also in universal arm of MRC Trial and causes of visual impairment study (23 practices in whole MRC Trial randomly selected for quality of life interviews). Confidence intervals adjusted for clustered design of the study.

Table 4.11 Worst quintile for SIP mobility score: logistic regression models assessing associations with visual impairment, visual impairment due to other causes and visual impairment due to AMD

Values in the table are odds ratios (95% c.i.)	Model 1	Model 2		Model 3
	Comparing VI with not VI	Comparing VI other causes with not VI	Comparing VI due AMD with not VI	Comparing VI due AMD with VI other causes
(a) Controlled age & sex	2.22 (1.52 to 3.24)	2.26 (1.51 to 3.38)	2.13 (1.34 to 3.38)	0.84 (0.43 to 1.64)
(b) Controlled age, sex & housing tenure	1.95 (1.28 to 2.98)	1.99 (1.22 to 3.25)	1.85 (1.21 to 2.84)	0.86 (0.43 to 1.71)

VI = visual impairment

(a) Models 1 to 3 were constructed as follows: the outcome/dependant variable was 0=not in worst quintile 1=in worst quintile for SIP mobility score. Terms for age (75-79, 80-84, 85+), sex and visual impairment were included. Binocular visual acuity score (quintiles) was included in model 3.
(b) As for (a) including terms for potential confounding factors (*see section 4.4.2*)

Data from the 11 practices in which quality of life interviews done and which also in universal arm of MRC Trial and causes of visual impairment study (23 practices in whole MRC Trial randomly selected for quality of life interviews). Confidence intervals adjusted for clustered design of the study.

Table 4.12 Worst quintile for SIP body care and movement score: logistic regression models assessing associations with visual impairment, visual impairment due to other causes and visual impairment due to AMD

Values in the table are odds ratios (95% c.i.)	Model 1	Model 2		Model 3
	Comparing VI with not VI	Comparing VI other causes with not VI	Comparing VI due AMD with not VI	Comparing VI due AMD with VI other causes
(a) Controlled age & sex	1.80 (1.33 to 2.43)	2.03 (1.52 to 2.71)	1.31 (0.77 to 2.23)	0.54 (0.37 to 0.79)
(b) Controlled age, sex, prescribed medicines & depression	1.56 (1.08 to 2.25)	1.89 (1.29 to 2.78)	0.94 (0.55 to 1.63)	0.42 (0.23 to 0.79)

VI = visual impairment

(a) Models 1 to 3 were constructed as follows: the outcome/dependant variable was 0=not in worst quintile 1=in worst quintile for SIP body care and movement score. Terms for age (75-79, 80-84, 85+), sex and visual impairment were included. Binocular visual acuity score (quintiles) was included in model 3.
(b) As for (a) including terms for potential confounding factors (*see section 4.4.2*)

Data from the 11 practices in which quality of life interviews done and which also in universal arm of MRC Trial and causes of visual impairment study (23 practices in whole MRC Trial randomly selected for quality of life interviews). Confidence intervals adjusted for clustered design of the study.

Table 4.13 Worst quintile for SIP social interaction score: logistic regression models assessing associations with visual impairment, visual impairment due to other causes and visual impairment due to AMD

Values in the table are odds ratios (95% c.i.)	Model 1	Model 2		Model 3
	Comparing VI with not VI	Comparing VI other causes with not VI	Comparing VI due AMD with not VI	Comparing VI due AMD with VI other causes
(a) Controlled age & sex	1.61 (1.14 to 2.28)	1.65 (1.15 to 2.38)	1.51 (0.98 to 2.35)	0.98 (0.57 to 1.69)
(b) Controlled age, sex, BMI & depression	1.32 (0.89 to 1.97)	1.30 (0.83 to 2.06)	1.37 (0.86 to 2.18)	1.02 (0.42 to 2.45)

VI = visual impairment

(a) Models 1 to 3 were constructed as follows: the outcome/dependant variable was 0=not in worst quintile 1=in worst quintile for SIP social interaction score. Terms for age (75-79, 80-84, 85+), sex and visual impairment were included. Binocular visual acuity score (quintiles) was included in model 3.
(b) As for (a) including terms for potential confounding factors (*see section 4.4.2*)

Data from the 11 practices in which quality of life interviews done and which also in universal arm of MRC Trial and causes of visual impairment study (23 practices in whole MRC Trial randomly selected for quality of life interviews). Confidence intervals adjusted for clustered design of the study.

Table 4.14 Worst quintile for PGMS: logistic regression models assessing associations with visual impairment, visual impairment due to other causes and visual impairment due to AMD

Values in the table are odds ratios (95% c.i.)	Model 1	Model 2		Model 3
	Comparing VI with not VI	Comparing VI other causes with not VI	Comparing VI due AMD with not VI	Comparing VI due AMD with VI other causes
(a) Controlled age & sex	1.37 (0.94 to 2.00)	1.31 (0.90 to 1.90)	1.56 (0.88 to 2.75)	0.96 (0.51 to 1.82)
(b) Controlled age, sex & housing tenure	1.23 (0.84 to 1.81)	1.16 (0.75 to 1.78)	1.44 (0.86 to 2.40)	1.01 (0.53 to 1.93)

VI = visual impairment

(a) Models 1 to 3 were constructed as follows: the outcome/dependant variable was 0=not in worst quintile 1=in worst quintile for PGMS. Terms for age (75-79, 80-84, 85+), sex and visual impairment were included. Binocular visual acuity score (quintiles) was included in model 3.
(b) As for (a) including terms for potential confounding factors (*see section 4.4.2*)

Data from the 11 practices in which quality of life interviews done and which also in universal arm of MRC Trial and causes of visual impairment study (23 practices in whole MRC Trial randomly selected for quality of life interviews). Confidence intervals adjusted for clustered design of the study.

Table 4.15 Percentage depressed (GDS 6+) or cognitively impaired (MMSE<12) by age and sex

Outcome	% with "outcome"	% with "outcome" in each age-group				% with "outcome" in men and women	
		75-79	80-84	85-89	90+	Men	Women
Depression (GDS 6+)	7.7	6.5	7.8	10.1	10.7	6.5	8.5
Cognitive impairment (MMSE<12)	5.4	2.6	5.1	9.0	19.6	3.5	6.5

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 4.16 Depression (GDS 6+): logistic regression models assessing associations with visual impairment, visual impairment due to other causes and visual impairment due to AMD

Values in the table are odds ratios (95% c.i.)	Model 1	Model 2		Model 3
	Comparing VI with not VI	Comparing VI other causes with not VI	Comparing VI due AMD with not VI	Comparing VI due AMD with VI other causes
(a) Controlled age & sex	1.72 (1.53 to 1.95)	1.64 (1.34 to 2.01)	1.92 (1.47 to 2.49)	1.21 (0.81 to 1.80)
(b) Controlled for all confounders except those potentially on causal pathway	1.47 (1.23 to 1.77)	1.48 (1.16 to 1.89)	1.45 (1.07 to 1.96)	0.85 (0.58 to 1.25)
(c) Controlled age, sex, & all confounders	1.46 (1.22 to 1.76)	1.46 (1.14 to 1.87)	1.47 (1.10 to 1.97)	0.86 (0.58 to 1.27)

VI = visual impairment

(a) Models 1 to 3 were constructed as follows: the outcome/dependant variable was 0=not depressed (GDS <6) 1=depressed (GDS 6+). Terms for age (75-79, 80-84, 85-89, 90+), sex and visual impairment were included. Binocular visual acuity score (quintiles) was included in model 3.
(b) As for (a) including terms for all potential confounding factors (*see table 4.1*) but not including terms for confounders potentially on causal pathway
(c) As for (a) including terms for all potential confounding factors (*see table 4.1*).

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Confidence intervals adjusted for clustered design of the study.

Table 4.17 Cognitive impairment (MMSE <12): logistic regression models assessing associations with visual impairment, visual impairment due to other causes and visual impairment due to AMD

Values in the table are odds ratios (95% c.i.)	Model 1	Model 2		Model 3
	Comparing VI with not VI	Comparing VI other causes with not VI	Comparing VI due AMD with not VI	Comparing VI due AMD with VI other causes
(a) Controlled age & sex	2.09 (1.67 to 2.61)	2.39 (1.89 to 3.03)	1.46 (0.99 to 2.17)	0.61 (0.41 to 0.92)
(b) Controlled for all confounders except those potentially on causal pathway	1.67 (1.27 to 2.18)	1.82 (1.31 to 2.51)	1.34 (0.86 to 2.10)	0.58 (0.33 to 1.05)
(c) Controlled age, sex, & all confounders	1.67 (1.28 to 2.19)	1.81 (1.31 to 2.52)	1.36 (0.87 to 2.13)	0.59 (0.32 to 1.06)

VI = visual impairment

(a) Models 1 to 3 were constructed as follows: the outcome/dependant variable was 0=not cognitively impaired (MMSE 12+) 1=cognitively impaired (MMSE<12). Terms for age (75-79, 80-84, 85-89, 90+), sex and visual impairment were included. Binocular visual acuity score (quintiles) was included in model 3.
(b) As for (a) including terms for all potential confounding factors (*see table 4.1*) but not including terms for confounders potentially on causal pathway
(c) As for (a) including terms for all potential confounding factors (*see table 4.1*).

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Confidence intervals adjusted for clustered design of the study.

Table 4.18 Percentage reporting two or more falls at home in last six months or hip fracture by age and sex

Outcome	% with "outcome"	% with "outcome" in each age-group				% with "outcome" in men and women	
		75-79	80-84	85-89	90+	Men	Women
Two or more falls at home in the last six months	8.4	5.9	9.1	12.0	15.4	7.5	9.0
Reported hip fracture	3.8	2.3	4.2	6.0	7.7	1.9	5.0

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 4.19 Two or more falls at home in last six months: logistic regression models assessing associations with visual impairment, visual impairment due to other causes and visual impairment due to AMD

Values in the table are odds ratios (95% c.i.)	Model 1	Model 2		Model 3
	Comparing VI with not VI	Comparing VI other causes with not VI	Comparing VI due AMD with not VI	Comparing VI due AMD with VI other causes
(a) Controlled age & sex	1.49 (1.28 to 1.74)	1.55 (1.29 to 1.86)	1.34 (1.04 to 1.74)	0.76 (0.51 to 1.13)
(b) Controlled for all confounders except those potentially on causal pathway	1.23 (0.98 to 1.53)	1.23 (0.98 to 1.56)	1.21 (0.81 to 1.81)	0.88 (0.51 to 1.53)
(c) Controlled age, sex, & all confounders	1.18 (0.95 to 1.47)	1.19 (0.95 to 1.50)	1.16 (0.78 to 1.72)	0.89 (0.51 to 1.54)

VI = visual impairment

(a) Models 1 to 3 were constructed as follows: the outcome/dependant variable was 0=none or one fall 1=two or more falls at home in last six months. Terms for age (75-79, 80-84, 85-89, 90+), sex and visual impairment were included. Binocular visual acuity score (quintiles) was included in model 3.
(b) As for (a) including terms for all potential confounding factors (*see table 4.1*) but not including terms for confounders potentially on causal pathway
(c) As for (a) including terms for all potential confounding factors (*see table 4.1*).

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Confidence intervals adjusted for clustered design of the study.

Table 4.20 Reported hip fracture: logistic regression models assessing associations with visual impairment, visual impairment due to other causes and visual impairment due to AMD

Values in the table are odds ratios (95% c.i.)	Model 1	Model 2		Model 3
	Comparing VI with not VI	Comparing VI other causes with not VI	Comparing VI due AMD with not VI	Comparing VI due AMD with VI other causes
(a) Controlled age & sex	1.46 (1.14 to 1.88)	1.47 (1.09 to 1.98)	1.45 (1.07 to 1.97)	1.00 (0.70 to 1.44)
(b) Controlled for all confounders except those potentially on causal pathway	1.24 (0.95 to 1.61)	1.30 (0.92 to 1.84)	1.10 (0.74 to 1.65)	0.86 (0.49 to 1.51)
(c) Controlled age, sex, & all confounders	1.23 (0.94 to 1.61)	1.30 (0.92 to 1.83)	1.10 (0.73 to 1.65)	0.86 (0.49 to 1.51)

VI = visual impairment

(a) Models 1 to 3 were constructed as follows: the outcome/dependant variable was 0=no reported hip fracture 1=reported hip fracture. Terms for age (75-79, 80-84, 85-89, 90+), sex and visual impairment were included. Binocular visual acuity score (quintiles) was included in model 3.
(b) As for (a) including terms for all potential confounding factors (*see table 4.1*) but not including terms for confounders potentially on causal pathway
(c) As for (a) including terms for all potential confounding factors (*see table 4.1*).

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Confidence intervals adjusted for clustered design of the study.

Table 4.21 Visual impairment and mortality rate

Category	Number of deaths	Person-time at risk (years)	Incidence rate	95% c.i.	Rate ratio	95% c.i.
Not visually impaired	3863	53691	0.072	0.070 to 0.074	1	
Visually impaired	909	6569	0.138	0.130 to 0.148	1.92	1.75 to 2.11
Not visually impaired	3863	53691	0.072	0.070 to 0.074	1	
Visually impaired other causes	649	4609	0.141	0.130 to 0.152	1.96	1.76 to 2.17
Visually impaired AMD	260	1960	0.133	0.117 to 0.150	1.84	1.61 to 2.11

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. Confidence intervals adjusted for clustered design of the study.

Table 4.22 Mortality: Cox proportional hazard models assessing associations with visual impairment, visual impairment due to other causes and visual impairment due to AMD

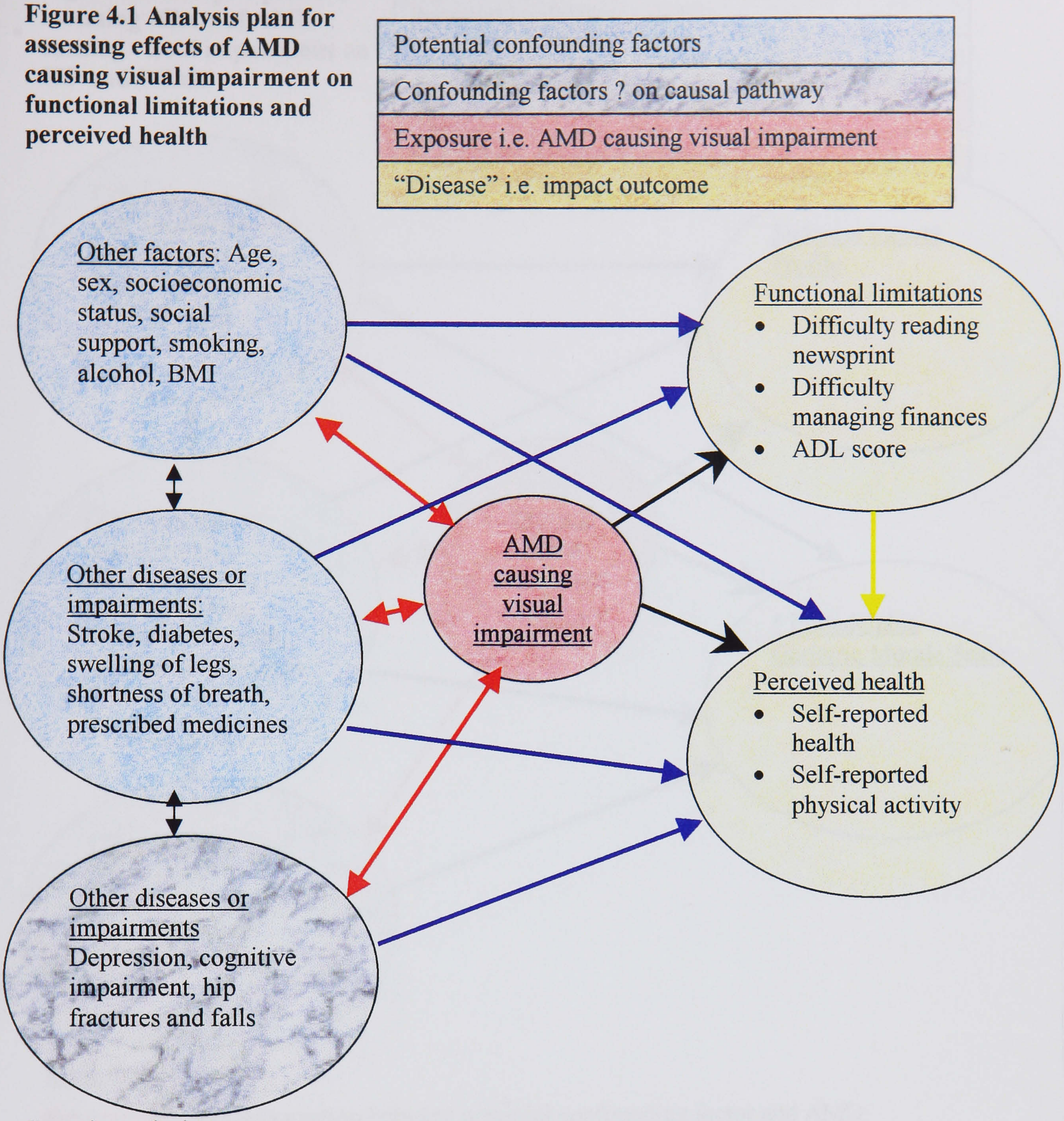
Values in the table are hazard ratios (95% c.i.)	Model 1	Model 2		Model 3
	Comparing VI with not VI	Comparing VI other causes with not VI	Comparing VI due AMD with not VI	Comparing VI due AMD with VI other causes
(a) Controlled age & sex	1.53 (1.43 to 1.63)	1.63 (1.50 to 1.76)	1.32 (1.17 to 1.49)	0.72 (0.63 to 0.83)
(b) Controlled for all confounders except those potentially on causal pathway	1.29 (1.20 to 1.39)	1.33 (1.23 to 1.45)	1.20 (1.06 to 1.36)	0.79 (0.66 to 0.94)
(c) Controlled age, sex, & all confounders	1.32 (1.22 to 1.43)	1.37 (1.26 to 1.49)	1.21 (1.07 to 1.37)	0.76 (0.63 to 0.90)

VI = visual impairment

(a) Models 1 to 3 were Cox proportional hazards models with death as the outcome. Terms for age (75-79, 80-84, 85-89, 90+), sex and visual impairment were included. Binocular visual acuity score (quintiles) was included in model 3.
(b) As for (a) including terms for all potential confounding factors (*see table 4.1*) but not including terms for confounders potentially on causal pathway
(c) As for (a) including terms for all potential confounding factors (*see table 4.1*).

Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial. 32 people not traced. Confidence intervals adjusted for clustered design of the study.

Figure 4.1 Analysis plan for assessing effects of AMD causing visual impairment on functional limitations and perceived health



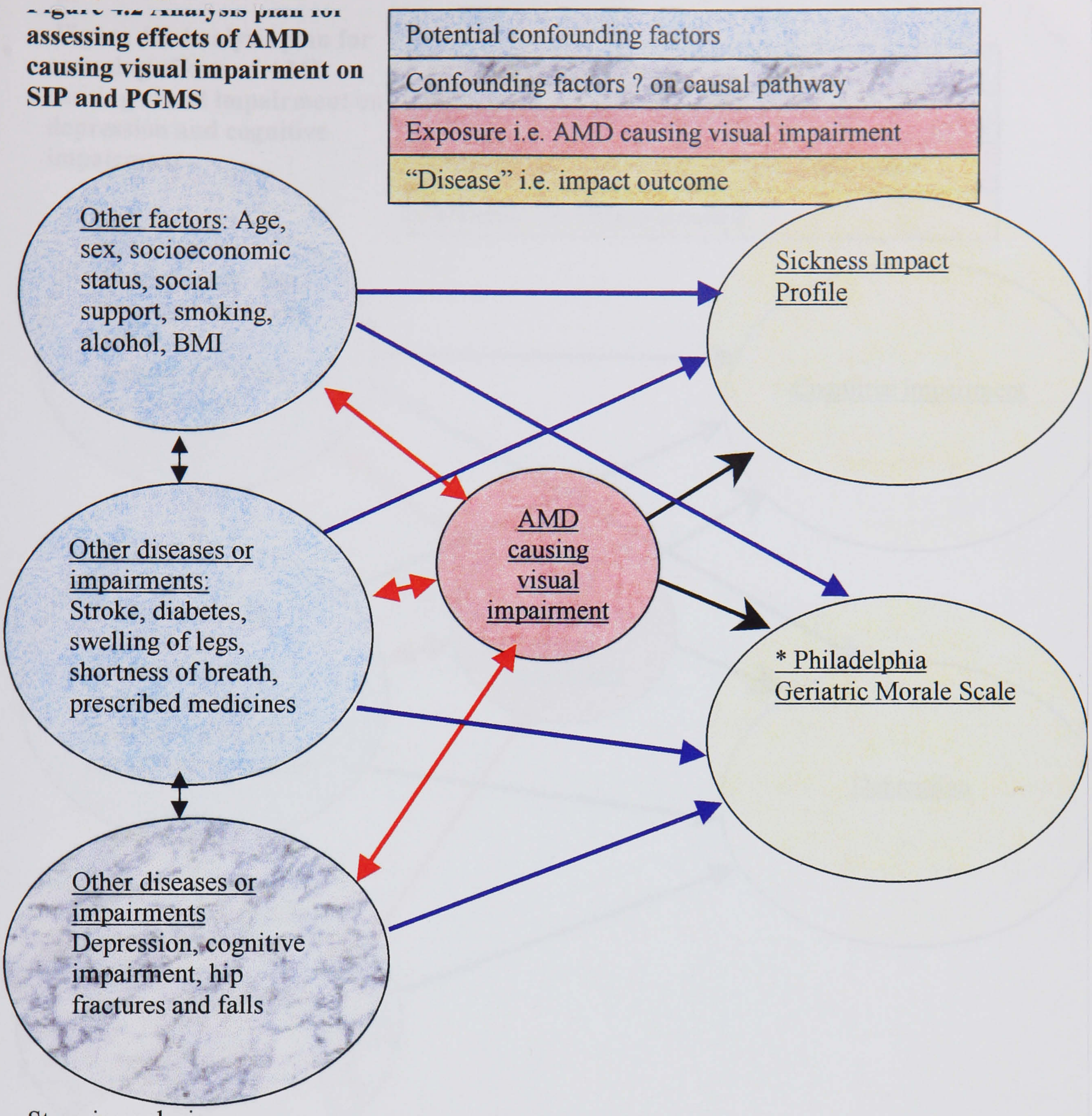
Steps in analysis

(1) Association between potential confounding factor and AMD causing visual impairment: if design-based χ^2 <0.05 included as a confounding factor in (2)

(2) Effect of confounding factor on outcome: logistic model, outcome as dependent variable, terms for age, sex and confounder, if Wald test <0.05 included as a confounding factor in (3).

(3) Effect of AMD causing visual impairment on outcome, controlling confounders identified above: logistic model, outcome as dependent variable, terms for age, sex, confounders and AMD causing visual impairment

Figure 4.2 Analysis plan for assessing effects of AMD causing visual impairment on SIP and PGMS



Steps in analysis

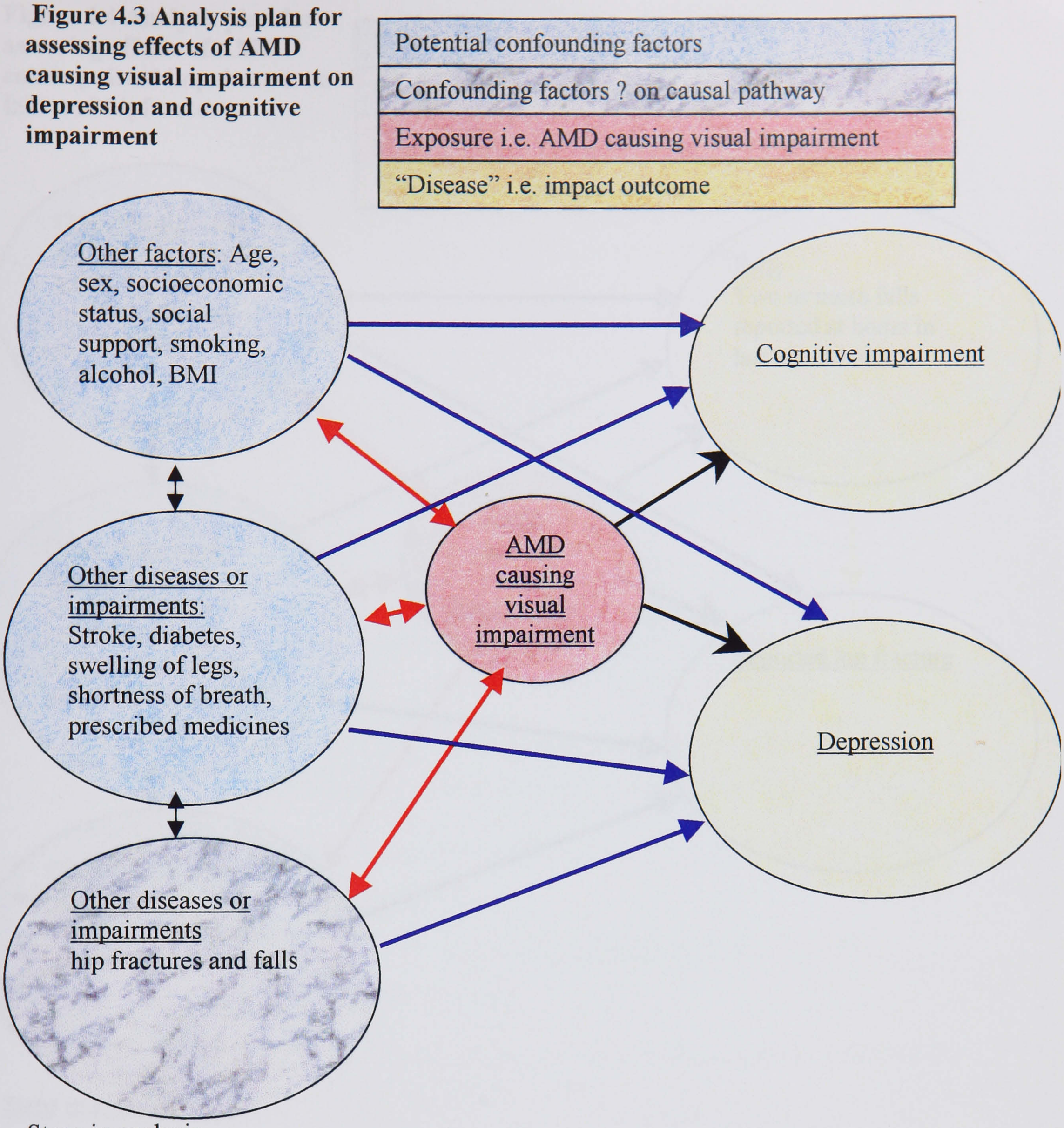
(1) Association between potential confounding factor and AMD causing visual impairment: if design-based χ^2 <0.05 included as a confounding factor in (2)

(2) Effect of confounding factor on outcome: logistic model, outcome as dependent variable, terms for age, sex and confounder, if Wald test <0.05 included as a confounding factor in (3).

(3) Effect of AMD causing visual impairment on outcome, controlling confounders identified above: logistic model, outcome as dependent variable, terms for age, sex, confounders and AMD causing visual impairment

* For PGMS depression not considered as a confounder due to conceptual overlap.

Figure 4.3 Analysis plan for assessing effects of AMD causing visual impairment on depression and cognitive impairment



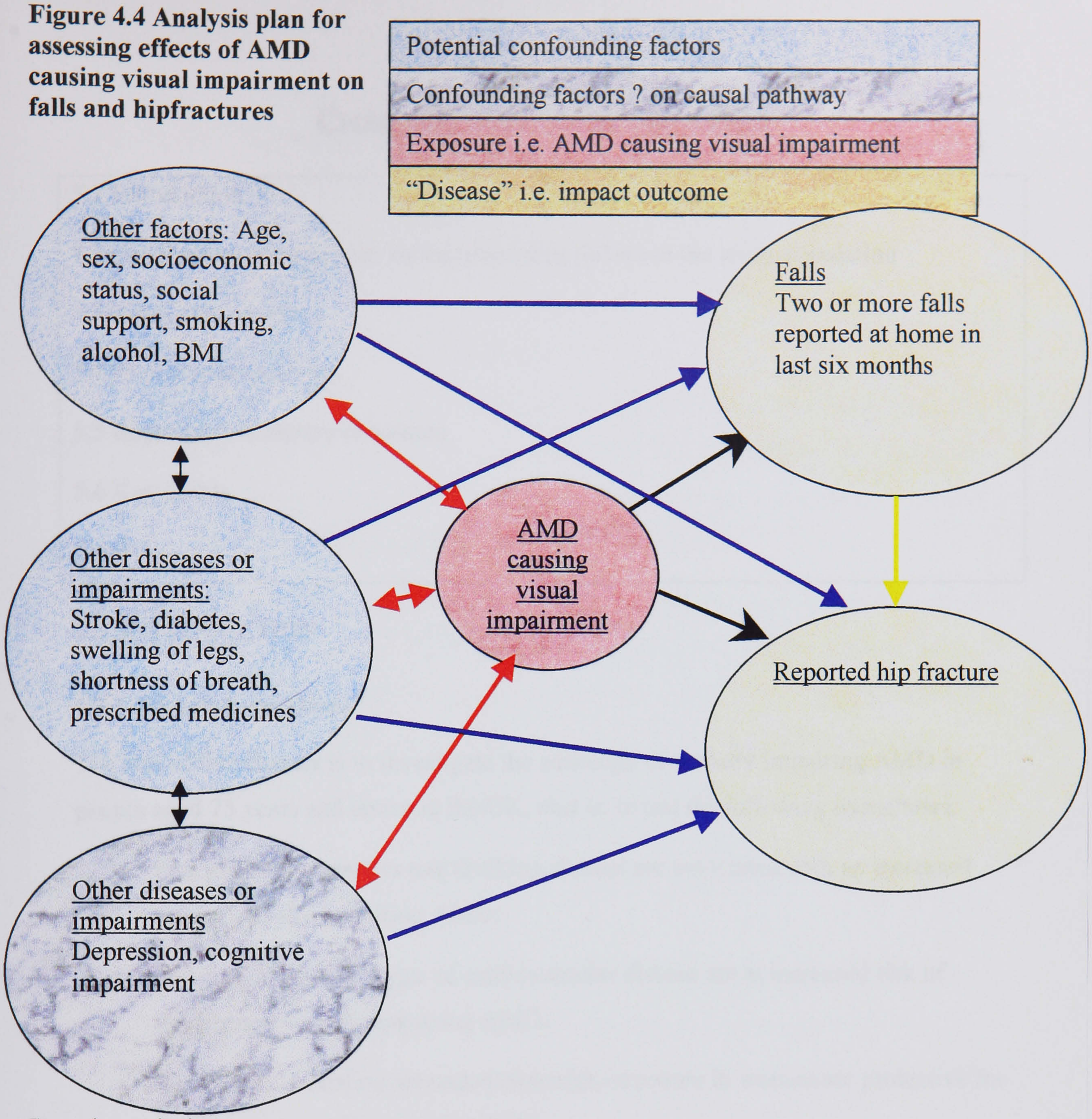
Steps in analysis

(1) Association between potential confounding factor and AMD causing visual impairment: if design-based χ^2 <0.05 included as a confounding factor in (2)

(2) Effect of confounding factor on outcome: logistic model, outcome as dependent variable, terms for age, sex and confounder, if Wald test <0.05 included as a confounding factor in (3).

(3) Effect of AMD causing visual impairment on outcome, controlling confounders identified above: logistic model, outcome as dependent variable, terms for age, sex, confounders and AMD causing visual impairment

Figure 4.4 Analysis plan for assessing effects of AMD causing visual impairment on falls and hipfractures



Steps in analysis

(1) Association between potential confounding factor and AMD causing visual impairment: if design-based χ^2 <0.05 included as a confounding factor in (2)

(2) Effect of confounding factor on outcome: logistic model, outcome as dependent variable, terms for age, sex and confounder, if Wald test <0.05 included as a confounding factor in (3).

(3) Effect of AMD causing visual impairment on outcome, controlling confounders identified above: logistic model, outcome as dependent variable, terms for age, sex, confounders and AMD causing visual impairment

CHAPTER FIVE RISK FACTORS

5.1 INTRODUCTION

5.1.1 Research questions

The aim of this chapter is to investigate the aetiology of visually impairing AMD in people aged 75 years and above in the UK, *that is,* to test the following hypotheses:

- that smoking cigarettes and drinking alcohol are associated with an increased risk of visually impairing AMD;
- that people with evidence of cardiovascular disease are at increased risk of developing visually impairing AMD;
- that factors indicating increased oestrogen exposure in women are protective for developing visually impairing AMD.

5.1.2 Terminology

The terminology used in this chapter is as follows. The outcome under study was case/control status with cases being people with AMD causing visual impairment and controls being people with good vision (binocular acuity of 6/6 or better). The risk factors studied were termed exposures (e.g. smoking). All exposures were also considered as possible confounding factors for other exposures i.e. as variables associated with both exposure and outcome that might influence the observed association. Other confounding factors were identified by review of the literature.

Confidence intervals and statistical significance

As for chapter four, 95% confidence intervals are reported in brackets (lower to upper) after the effect estimates (odds ratio). If the effect estimate is already in brackets the 95% confidence intervals are quoted after a comma. Statistical significance ($p<0.05$) is assumed whenever the confidence intervals do not cross unity.

5.1.3 A note about choice of control group

In the case-control study described in this chapter, I have a population-based group of people with severe AMD and I want to compare them to a population-based group of people without AMD. The aim behind selecting the control group for the case-control study is to minimise the proportion of controls who had AMD.

If this had been a cross-sectional eye survey where *everybody* was examined for signs of AMD, then the control group would clearly be everyone in the survey who did not have AMD. However, I was unable to examine the controls. I therefore decided to select a control group of people with good vision who would be less likely to have ARM or AMD. I felt that it was important in the analyses of aetiological risk factors because I wanted to assess potential causes of AMD. This decision was taken *before* I did any analyses. In case-control studies it is common to define cases and controls at each end of a spectrum.

It must be noted that this study design is different to the previous chapters. In chapter three, I considered the prevalence of AMD causing visual impairment. When calculating a prevalence figure p, the comparison group is, by definition 1-p. In chapter four, I was investigating the *functional* impact of AMD, therefore the existence of asymptomatic signs of AMD in people not visually impaired was not of concern.

5.2 Distribution of exposures and confounding factors in the study population

Table 5.3 shows the distribution of all risk factors in the study population.

9.7% of the population were current smokers. Smoking decreased with increasing age ($p<0.001$) and was higher in men (12.2%) than women (7.7%) ($p<0.001$). 79.2% of the population reported that they had taken an alcoholic drink in the last year. This

proportion decreased with increasing age (P<0.001) and was lower in women (74.4%) than in men (85.4%) (p<0.001).

A majority of the population had systolic blood pressure over 140mmHg (62.8%), however, reported high blood pressure was lower at 33.5%. Reported high blood pressure decreased with increasing age (p=0.001) and was higher in women (p<0.001) whereas systolic blood pressure did not change with age (p=0.292).

5.7% of the population reported that they had been told that they had diabetes. This proportion was slightly higher in men (6.7%) than women (5.0%) and there was no clear pattern with age.

5.4% of the population had a body mass index (BMI) of less than 20 and 16.2% had a BMI greater than 30. The proportion underweight increased with increasing age (p<0.001) and was higher in women (p<0.001).

69.9% of the population owned their own homes, 23.7% lived in rented accommodation and 6.4% lived in sheltered accommodation. The proportion in sheltered accommodation increased with increasing age from 4.3% at ages 75-79 to 23.2% at ages 90+.

30.4% of the population reported being very physically active and 3.0% reported being not at all physically active. Physical activity declined with increasing age (p<0.001). Women were more likely to report lower levels of physical activity (p=0.001).

5.3 UNIVARIATE ANALYSES

Table 5.4 shows the associations between AMD causing visual impairment and the risk factors studied, after controlling for age and sex.

Smoking was associated with AMD causing visual impairment. Current smokers were twice as likely to be a case compared to non-smokers (odds ratio 2.28, 1.61 to 3.24). Ex-smokers were at intermediate risk (odds ratio 1.11, 0.87 to 1.43).

Alcohol consumption in the past year was not significantly associated with AMD causing visual impairment (odds ratio 0.86, 0.57 to 1.29). People drinking more than 20 units per week had a non-significant increased odds of AMD causing visual impairment (odds ratio 1.72, 0.77 to 3.85).

Of the cardiovascular disease variables, reported stroke was associated with being a case (odds ratio 1.82, 1.28 to 2.57). There was no statistically significant association between high blood pressure, systolic blood pressure >140mmHg and angina and AMD causing visual impairment and a marginally significant association with reported heart attack (odds ratio 1.35, 0.98 to 1.84 p=0.063).

Reported diabetes was associated with AMD causing visual impairment (odds ratio 1.56, 1.05 to 2.32).

People who were relatively thin with a BMI of less than 20 were also at increased risk of having AMD causing visual impairment. The three groups 20-<25, 25-<30 and 30+ had similar risks. These three groups were combined for future analysis and used as the referent group. Comparing people with BMI of <20 to those with a BMI of 20 or more gave an odds ratio of 1.60 (1.07 to 2.40).

People in sheltered housing had a greater risk of being a case compared to those in their own homes (odds ratio 1.62, 1.04 to 2.54).

Reported physical activity was strongly associated with being a case. People who reported that they were "not at all" physically active had a greatly increased risk of having AMD causing visual impairment with an odds ratio of 6.90 (3.73 to 12.77) compared to people who were very physically active.

5.4 MULTIVARIATE ANALYSES

5.4.1 Final model

A logistic regression model was constructed including all the variables significant on the univariate screen. It had the following terms: age (75-79,80-84,85-89,90+), sex (male, female), smoking (never smoked, ex-smoker, current smoker), reported stroke (no, yes), reported diabetes (no, yes), body mass index (20 or more, less than 20), housing tenure (owner occupier, rented housing, sheltered housing) and reported physical activity (very, fairly, not very, not at all). AMD causing visual impairment was the dependant variable (0=control 1=case). Table 5.5 shows the results of that model.

The most important risk factor for development of AMD causing visual impairment was age. People who were 90 or more had 50 times the risk of having the condition compared to people aged 75-79 (odds ratio 54.49, 29.88 to 99.36). Women were also at

increased risk with an odds ratio of 1.76 (1.39 to 2.22). The other factor most strongly associated with being a case was physical activity. People reporting that they were "not at all" physically active were nearly five times more likely to have AMD causing visual impairment compared to those who reported that they were "very" physically active (odds ratio 4.96, 2.50 to 9.85).

The only other exposure that appeared to be important was smoking. Current smokers were at an 80% increased odds of developing AMD causing visual impairment (odds ratio 1.79, 1.16 to 2.75).

As reported stroke, reported diabetes, body mass index and housing tenure did not improve the fit of the model (adjusted Wald test p=0.1029) they were dropped from the model. Table 5.6 shows the final model.

5.4.2 Smoking

Only smoking was left in the final model and therefore it was investigated in more detail as set out in the analysis strategy (*see section 5.1.4*).

Firstly, interaction terms for age and smoking were entered into the model. Looking at the odds ratios suggested that the effect of smoking was different in people aged 75 to 79 compared to those aged 80 years and above. The interaction terms for age (two groups 75-79, 80+)*smoking contributed significantly to the fit of the model (p=0.027). A further two models were fitted, one for people aged 75-79 and including terms for age (75,76,77,78,79), sex and physical activity (four groups), and one for people aged 80 years and above and including terms for age (80-84, 85-89,90+), sex and physical activity (four groups). Table 5.7 shows the results of those models for smoking.

Smoking was a significant risk factor for developing AMD causing visual impairment in people aged 75 to 79, however, its effect in people aged 80 years and above was less strong. In the older age-groups, current smokers were at a two-fold risk however ex-smokers had the same risk as never smokers (odds ratio 0.96, 0.70 to 2.92).

The duration and dose of exposure to cigarette smoking was evaluated by pack years. This variable is a combination of daily cigarettes smoked (one pack = 20 cigarettes) and number of years smoked. Thus it combines dose and duration of smoking. Table 5.8 shows the association between pack-years and risk of AMD causing visual impairment. In people aged 75-79, there was an increasing risk of AMD causing visual impairment

with increased number of pack years of exposure. In people aged 80 and above, there was no obvious relationship between pack-years and risk of AMD causing visual impairment.

Table 5.9 shows the relationship between years since stopping smoking and AMD causing visual impairment. In people aged 75-79, there was an increased risk of AMD causing visual impairment with decreased time since stopping smoking. People who had stopped smoking 40 or more years ago, although the odds ratio was raised, it was not statistically significant (odds ratio 1.37, 0.39 to 4.81). In people aged 80 years and above, there was some evidence of a trend with increased risk of AMD causing visual impairment with decreased time since stopping smoking.

5.5 REPRODUCTIVE FACTORS IN WOMEN

Table 5.10 shows the distribution of the various reproductive factors in women in the MRC Trial. The mean age of starting menstruation was 13.6 years. Older women had a marginally later age of menstruation. The mean number of years of menstruation was 34.7 years. This decreased slightly with increasing age. The percentage of women with early menopause, i.e. menopause less than 40 years of age was 5.7%. This was highest in the 75-79 age-group (6.3%). The proportion of women with menopause at less than 45 years of age due to surgery was 6.1%. This was highest in the 75-79 age-group (6.6%) and lowest in the 90 and above age-group (4.0%).

Table 5.11 shows the association between various measures of reproductive status and AMD causing visual impairment, controlled for age, physical activity and smoking. There was little evidence that reproductive indicators of relatively low lifetime levels of oestrogen were associated with an increased risk of being visually impaired due to AMD.

Including number of years of menstruation as a continuous variable in a logistic regression gave an odds ratio of 0.99 (0.96 to 1.03). Women having their menopause at 40 years or younger had a non-significant, increased risk of being a case (odds ratio 1.87, 0.95 to 2.71). This study did not confirm the findings of Vingerling et al in Rotterdam that menopause before 45 years of age due to surgery was a strong risk factor for AMD (odds ratio 1.06, 0.61 to 1.85).

5.6 KEY POINTS

Smoking and alcohol consumption

There was a strong association between smoking status and risk of being visually impaired due to AMD. This effect was particularly strong in people aged 75-79 years of age. In these people there was a dose-response relationship between pack years of smoking and risk of AMD causing visual impairment. People giving up smoking less than 40 years ago were at increased risk.

There was no statistically significant association between alcohol consumption and AMD causing visual impairment.

Cardiovascular disease profile

Cases were more likely to report that they had had a stroke, heart attack or diabetes.

Cases were also more likely to be relatively thin (BMI <20).

After controlling for confounding factors, none of the risk factors indicating cardiovascular disease or a cardiovascular disease risk profile were associated with an AMD causing visual impairment.

People who reported that they were "not at all" physically active were more likely to have AMD causing visual impairment

Reproductive factors in women

There was little indication that women with relatively low lifetime oestrogen levels were at increased risk of developing visually impairing AMD. The study was underpowered to investigate some of these exposures, such as early menopause.

Table 5.1 Cases and controls by age and sex

	Controls			Cases		
	Male	Female	Total	Male	Female	Total
75-79	1344	1504	2848	26	48	74
80-84	511	633	1144	47	112	159
85-89	123	187	310	45	131	176
90+	21	41	62	20	87	107
Total	1999	2365	4364	138	378	516

"Cases" are people with AMD causing visual impairment. "Controls" are people with 6/6 vision or better (binocular acuity). Data from the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 5.2 Power (%) of study of 500 cases and 4,500 controls to detect various odds ratios

Risk factor		Prevalence in control group*	Odds ratios				
			1.2	1.5	2	3	5
Smoking	Current smoker	9%	15.1	59.3	97.1	>99	>99
	Ex-smoker	53%	32.2	92.6	>99	>99	>99
Alcohol consumption	Drink in last year	80%	19.2	69.8	99	>99	>99
	Drank 10 or more units last week	10%	16.1	63.0	98.0	>99	>99
Cardiovascular disease	Systolic blood pressure >140mmHg	63%	29.2	89.3	>99	>99	>99
	Reported stroke	6%	11.5	44.8	90.4	>99	>99
	Reported heart attack	10%	16.1	63.0	98.0	>99	>99
	Reported hypertension	34%	31.5	92.1	>99	>99	>99
	Definite angina	7%	12.7	50.6	93.7	>99	>99
	Reported diabetes	6%	11.5	44.8	90.4	>99	>99
Reproductive factors	Menopause <45 years due to surgery	3%	7.5	27.1	68.8	98.1	>99

Power calculated assuming a design effect of 1.5 and therefore an effective sample size of 500/1.5 = 333 cases

*Control group - people with binocular acuity 6/6 or better in MRC Trial.

Table 5.3 Distribution of risk factors in the study population

Risk factor	% with risk factor All ages N=4880	% with risk factor in each age-group				% with risk factor in men and women	
		75-79 N=2922	80-84 N=1303	85-89 N=486	90+ N=169	Men N=2137	Women N=2743
Never smoked	38.2	35.2	39.5	46.5	57.2	20.0	52.2
Ex-Smoker	52.1	54.2	51.9	45.5	36.7	67.8	40.2
Current smoker	9.7	10.6	8.5	8.0	6.2	12.2	7.7
% taken alcoholic drink in last year	79.2	81.7	78.9	68.7	67.9	85.4	74.4
Reported high blood pressure	33.5	34.9	34.0	27.3	22.4	28.2	37.6
Reported stroke	6.7	6.1	7.3	10.1	8.4	7.6	6.4
Reported heart attack	10.0	9.6	10.2	11.5	10.8	13.1	7.5
Systolic blood pressure >140mmHg	62.8	62.4	64.8	60.6	61.0	59.8	65.2
Angina	6.6	7.3	6.5	3.4	3.6	6.9	6.4
Reported diabetes	5.7	5.4	6.0	7.0	5.4	6.7	5.0
Body mass index <20	5.4	4.4	5.6	9.0	12.8	3.5	6.9
20-<25	35.4	33.4	37.7	41.5	38.4	33.5	36.9
25-<30	43.1	44.6	41.6	39.9	34.6	48.6	38.7
30+	16.2	17.7	15.1	9.7	14.3	14.4	17.6
Housing tenure Owner occupier	69.9	72.8	68.5	61.3	54.9	74.0	66.8
Rented housing	23.7	22.8	24.5	26.9	22.0	22.2	24.8
Sheltered housing	6.4	4.3	7.0	11.9	23.2	3.9	8.4
Reported physical activity Very	30.4	33.9	28.2	19.6	15.9	31.7	29.3
Fairly	52.8	53.3	53.1	52.7	42.7	54.2	51.7
Not very	13.9	10.9	15.6	21.5	31.1	11.9	15.4
Not at all	3.0	1.9	3.2	6.2	10.4	2.3	3.5

Data from 4364 controls and 516 cases in the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 5.4 Univariate analyses

Risk factor	N	Odds ratio	95% confidence interval	Wald test
Never smoked	1815	1		
Ex-Smoker	2480	1.11	0.87 to 1.43	0.389
Current smoker	458	2.28	1.61 to 3.24	<0.001
% taken alcoholic drink in last year	3830	0.86	0.57 to 1.29	0.446
Number of units drunk in last week None	2543	1		
1/9	1889	0.83	0.62 to 1.10	0.182
10/19	305	0.62	0.29 to 1.30	0.202
20 or more	143	1.72	0.77 to 3.85	0.180
Reported high blood pressure	1629	0.99	0.78 to 1.26	0.947
Reported stroke	335	1.82	1.28 to 2.57	0.001
Reported heart attack	483	1.35	0.98 to 1.84	0.063
Systolic blood pressure >140mmHg	3046	1.09	0.93 to 1.29	0.268
Angina	318	1.04	0.63 to 1.74	0.866
Reported diabetes	281	1.56	1.05 to 2.32	0.030
Body mass index				
<20	249	1		
20-<25	1640	0.63	0.41 to 0.91	0.037
25-<30	1995	0.60	0.40 to 0.91	0.017
30+	748	0.67	0.39 to 1.14	0.135
Body mass index <20	249	1.60	1.07 to 2.40	0.022
Socio-economic status	3389	1		
Owner				
Rented housing	1147	1.34	0.99 to 1.81	0.058
Sheltered housing	311	1.62	1.04 to 2.54	0.034
Reported physical activity	1472	1		
Very				
Fairly	2564	2.20	1.57 to 3.08	<0.001
Not very	670	4.94	3.56 to 6.84	<0.001
Not at all	145	6.90	3.73 to 12.77	<0.001

Odds ratios are derived from logistic regression models including terms for age (75-79,80-84,85-89 and 90+), sex and each risk factor separately. Confidence intervals adjusted for clustered design of the study. Data from 4364 controls and 516 cases in the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 5.5 Multivariate analyses

Risk factor	Odds ratio	95% confidence interval	Wald test
Age 75-79	1		
80-84	5.08	3.93 to 6.55	<0.001
85-89	17.38	11.92 to 25.33	<0.001
90+	54.49	29.88 to 99.36	<0.001
Men	1		
Women	1.76	1.39 to 2.22	<0.001
Never smoker	1		
Ex-Smoker	1.07	0.82 to 1.40	0.604
Current smoker	1.79	1.16 to 2.75	0.009
No reported stroke	1		
Reported stroke	1.37	0.92 to 2.05	0.118
No reported diabetes	1		
Reported diabetes	1.31	0.84 to 2.03	0.228
Body mass index 20 or more	1		
Body mass index <20	1.39	0.91 to 2.13	0.125
Housing tenure	1		
Owner occupier			
Rented housing	1.24	0.90 to 1.71	0.183
Sheltered housing	1.25	0.81 to 1.93	0.315
Very physically active	1		
Fairly physically active	1.99	1.46 to 2.71	<0.001
Not very physically active	4.06	2.89 to 5.70	<0.001
Not at all physically active	4.96	2.50 to 9.85	<0.001

Odds ratios derived from a logistic regression model including terms for all risk factors together. Confidence intervals adjusted for clustered design of the study. Data from 4364 controls and 516 cases in the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 5.6 Final model

Risk factor	Odds ratio	95% confidence interval	Wald test
Age 75-79	1		
80-84	5.01	4.02 to 6.24	<0.001
85-89	17.86	12.72 to 25.1	<0.001
90+	54.62	33.0 to 90.28	<0.001
Men	1		
Women	1.84	1.44 to 2.35	<0.001
Never smoker	1		
Ex-Smoker	1.10	0.84 to 1.45	0.489
Current smoker	2.97	1.32 to 2.95	0.001
Very physically active	1		
Fairly physically active	2.12	1.52 to 2.96	<0.001
Not very physically active	4.48	3.24 to 6.20	<0.001
Not at all physically active	6.28	3.43 to 11.51	<0.001

Derived from a logistic regression model including terms for all risk factors included on the table. Confidence intervals adjusted for clustered design of the study. Data from 4364 controls and 516 cases in the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 5.7 Smoking and AMD causing visual impairment, stratified by age

Risk factor	Odds ratio	95% confidence interval	Wald test
People aged 75-79			
Never smoker	1		
Ex-Smoker	2.34	1.30 to 4.22	0.006
Current smoker	3.41	1.36 to 8.54	0.010
People aged 80 and above			
Never smoker	1		
Ex-Smoker	0.96	0.70 to 2.92	0.771
Current smoker	1.85	1.17 to 3.20	0.010

People aged 75-79: Odds ratios derived from a logistic regression model including terms for age (75,76,77,78,79), sex and physical activity (very, fairly, not very, not at all physically active). People aged 80 years and above: Odds ratios derived from a logistic regression model including terms for age (80-84,85-89,90+), sex and physical activity (very, fairly, not very, not at all physically active). Confidence intervals adjusted for clustered design of the study. Data from 4364 controls and 516 cases in the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 5.8 Smoking (pack years) and AMD causing visual impairment, stratified by age

Risk factor	Odds ratio	95% confidence interval	Wald test
People aged 75-79			
Never smoked	1		
Less than 20 pack years	2.23	1.09 to 4.58	0.030
20 to less than 40 pack years	3.06	1.48 to 6.36	0.003
40 to less than 60 pack years	2.15	0.64 to 7.22	0.209
60 or more pack years	3.73	1.62 to 8.61	0.003
People aged 80 and above			
Never smoked	1		
Less than 20 pack years	1.01	0.69 to 1.49	0.956
20 to less than 40 pack years	0.99	0.65 to 1.49	0.956
40 to less than 60 pack years	1.10	0.65 to 1.85	0.715
60 or more pack years	0.74	0.33 to 1.64	0.447

People aged 75-79: Odds ratios derived from a logistic regression model including terms for age (75,76,77,78,79), sex and physical activity (very, fairly, not very, not at all physically active). People aged 80 years and above: Odds ratios derived from a logistic regression model including terms for age (80-84,85-89,90+), sex and physical activity (very, fairly, not very, not at all physically active). Confidence intervals adjusted for clustered design of the study. Data from 4364 controls and 516 cases in the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 5.9 Years since stopping smoking and AMD causing visual impairment, stratified by age

Risk factor	Odds ratio	95% confidence interval	Wald test
People aged 75-79			
Never smoked	1		
Stopped 40 or more years ago	1.37	0.39 to 4.81	0.613
Stopped 20 to 39 years ago	2.49	1.14 to 5.41	0.023
Stopped less than 20 years ago	2.71	1.36 to 5.40	0.006
Current smoker	3.42	1.37 to 8.51	0.009
People aged 80 and above			
Never smoked	1		
Stopped 40 or more years ago	0.88	0.59 to 1.30	0.500
Stopped 20 to 39 years ago	0.75	0.50 to 1.13	0.160
Stopped less than 20 years ago	1.49	0.99 to 2.24	0.055
Current smoker	1.85	1.17 to 2.92	0.010

People aged 75-79: Odds ratios derived from a logistic regression model including terms for age (75,76,77,78,79), sex and physical activity (very, fairly, not very, not at all physically active). People aged 80 years and above: Odds ratios derived from a logistic regression model including terms for age (80-84,85-89,90+), sex and physical activity (very, fairly, not very, not at all physically active). Confidence intervals adjusted for clustered design of the study. Data from 4364 controls and 516 cases in the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 5.10 Distribution of reproductive factors in women

Risk factor	% with risk factor All ages N=2449	% with risk factor in each age-group			
		75-79 N=1429	80-84 N=656	85-89 N=274	90+ N=90
Mean age (SD) menstruation started	13.6 (1.5)	13.5 (1.5)	13.7 (1.5)	13.6 (1.4)	14.2 (1.4)
Mean (SD) years of menstruation	34.7 (5.4)	34.8 (5.5)	34.7 (5.2)	34.6 (5.3)	33.7 (5.4)
% with early menopause i.e. menopause at less than 40 years of age	5.7	6.3	4.8	5.3	5.4
% with menopause less than 45 years due to surgery	6.1	6.6	5.8	5.0	4.0

Data from 2365 controls and 378 cases in the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

Table 5.11 Reproductive factors in women and AMD causing visual impairment

Risk factor	Odds ratio	95% confidence interval	Wald test
Number of years of menstruation	0.99	0.96 to 1.03	0.705
Years of menstruation			
Lowest quartile	1		
2nd quartile	0.69	0.43 to 1.10	0.120
3rd quartile	0.93	0.58 to 1.49	0.759
Highest quartile	1.03	0.66 to 1.60	0.895
Menopause before 40 years of age	1.87	0.95 to 2.71	0.074
Menopause before 45 years of age due to surgery	1.06	0.61 to 1.85	0.835

Odds ratios derived from logistic regression models all of which included terms for age (75-79, 80-84,85-89 and 90+), physical activity (very, fairly, not very, not at all physically active) and smoking (never, ex, current smoker). Confidence intervals adjusted for clustered design of the study. Data from 2365 controls and 378 cases in the 49 practices taking part in the cause of visual impairment study out of 53 practices in the universal arm of the MRC Trial.

CHAPTER SIX DISCUSSION

The overall aim of this thesis was to investigate the prevalence and impact of AMD causing visual impairment in people aged 75 years and above in the UK. A secondary, albeit more limited, objective was to investigate a small number of potential risk factors for AMD. The study was an add-on study to the large MRC Trial of the Assessment and Management of Older People in the Community.

In this chapter I will consider the strengths and weaknesses of the study, discuss the main findings and compare these to other studies. This will be followed by discussion of the implications for future research and policy.

6.1 STRENGTHS AND WEAKNESSES

6.1.1 Strengths

- The MRC Trial was a nationwide, representative population-based study providing a large sample of people aged 75 years and above

Combining all previous published population-based studies together shows that, worldwide, prior to the MRC Trial, less than 7,000 people aged 75 years and above have been assessed for visual impairment (*see chapter one table 1.5*). In the current study, visual acuity tests were done on nearly 15,000 people aged 75 years and above.

Obtaining large numbers of population-based cases of visual impairment makes this a unique study in eye epidemiology in the UK, increasing its precision. The national representativeness of the sample increases the generalisability of the results. Many previous studies have been conducted in a single cluster, a problem that is avoided in this study. Population-based studies, particularly in older people, are very expensive requiring much nurse time and home visits. Nationwide studies are even more so. It was a costly exercise collecting data at the MRC Trial detailed assessment, including visual acuity screening. The resources required for the add-on study ascertaining the causes of visual impairment were a fraction of the total costs of the MRC Trial.

- It was straightforward to identify suitable comparison groups

This study offered a large population-based case-group (n=516) of people visually impaired due to AMD. This meant that it was relatively straightforward to identify a group of population-based controls. For the case-control study of risk factors, these were people with good vision (6/6 or better) who took part in the MRC Trial. For the cross-sectional analyses of impact, these were people visually impaired due to other causes, and people not visually impaired. This is the first time that investigation of the association between AMD and functioning and quality of life has included a population-based group of controls.

- Independent collection of linked data

In order to avoid bias, identification of cases or outcome should be independent of exposure. Non-random misclassification of AMD was unlikely as all medical records were reviewed by practice nurses who were unaware of the study hypotheses and did not have access to data on exposure. Some of the nurses had undertaken the detailed

assessments six or months before, however, this was a very long complicated examination and questionnaire. It is unlikely that the nurses would have been able to remember all responses for each of the several hundred patients assessed. Data on quality of life was collected by independent fieldworkers.

6.1.2 Weaknesses

- Visual acuity was measured using a simple, portable chart

The MRC Trial aimed to test multi-dimensional assessment in the general practice setting. Simple, portable interventions that could be used by nurses were chosen. The visual acuity test, therefore, was a simple one that nurses could use easily and take with them on home visits. The Glasgow acuity chart follows the principles of the Bailey-Lovie chart which has now become the gold standard method for measuring visual acuity in research studies(Bailey and Lovie 1976). The Glasgow chart has approximately equally legible letters on each row and the separation of the letters within rows is uniform so that contour interaction is controlled. Each row is presented separately. The visual task at each level of the chart is therefore the same irrespective of acuity or test distance. The chart employs a logarithmic progression of sizes. The logMAR visual acuity notation (*see Appendix B)*, which corresponds to the logarithm of the reciprocal of the Snellen notation, is now recognized as the most logical measure of visual acuity. 95% of vision measurements made with the Glasgow Acuity Chart differ by less than 0.07 log unit compared to the Bailey-Lovie chart(McGraw *et al.* 2000).

The method of testing acuity followed recommended guidelines(Ferris, III and Bailey 1996) with the exception of the lack of standardisation of illumination. It has been recommended that high contrast charts and illumination of between 807 to 1345 lux is used(Ferris and Sperduto 1982). The Glasgow acuity chart is easy to use and, being portable, could be taken into people's home. Nurses were trained in the use of the chart, including supervised practice with the method. During the training session, they were given details on how to make sure that ensure good lighting conditions during the visual screening test. The charts are high contrast and in general, most surgeries will have had fluorescent lighting, this illumination will have been achieved. However, vision was measured in 53 general practice surgeries, spread throughout the country, and on home visits. Standardisation of the lighting conditions was therefore not possible. This may have introduced increased between-practice variation(Silver *et al.* 1978).

For logistic reasons each nurse only had one chart. If they were suspicious that a participant may have memorised the letters they were to ask the participant to read the letters from right to left (Appendix B Measuring visual acuity). However, as this test was only done on one occasion, it is likely that the impact of learning effects will be small.

- A pinhole occluder was used to correct for refractive error

The results are for presenting vision, *that is*, visual acuity as used in every day life by the people taking part in the MRC Trial. This measure of visual impairment is the most relevant for public health purposes. It is often usual in eye surveys to present visual impairment *after* correction for refractive error. There were limited data on refractive error in the population through the use of the pinhole test.

The pinhole test is not as good an assessment as subjective refraction but has been assessed to be adequate in validation studies(Ederer *et al.* 1986). It was not easily used in this population with nearly 40% of visually impaired people not having a pinhole test. This fact must be borne in mind when comparing the results of this study to other population-based studies (*see table 6.1*). Studies using refraction to correct for refractive error consistently estimate a lower prevalence of visual impairment.

- Visual impairment was assessed using distance visual acuity only

Other studies have shown that visual field loss can contribute considerably to the overall burden of visual impairment and blindness with nearly three times as many people visually impaired because of visual field loss than visual acuity loss(Taylor *et al.* 1997). In the current study, people were included who had good central visual acuity but who were registered blind or partially sighted because of visual field loss. It is likely, however, that we have underestimated the level of visual impairment because we did not measure visual fields. AMD affects primarily the central vision so the number of people visually impaired due to AMD who were not detected in the study will be not as great as for eye diseases that affect primarily the visual field, for example, glaucoma.

- Data on cause of visual impairment was obtained from medical record review and contact with hospital ophthalmologists

The size and geographical spread of practices, combined with the age of the participants, meant that it was not possible to arrange for a standardised ophthalmic

examination of everyone identified as visually impaired during the trial. Causes of visual loss were identified using a combination of medical record review in the general practice and hospital ophthalmologist questionnaire. There was good agreement at the hospital and general practice level. It is likely that, for the simple categories of cause presented, this method of assessment has worked well.

There is a particular difficulty with assessing cause of visual loss from the medical notes. The coding is dependent on the thoroughness with which the health care staff recorded the eye conditions. Essentially we have no idea of the extent to which data are missing. However, comparing the information from the hospital and general practice suggested that in fact the hospital ophthalmologist who knew the patient involved was less likely to record so many conditions. Omission is not so likely to have been a problem and it is more likely that conditions not severe enough to cause visual loss have been recorded.

Although this method of case ascertainment for AMD must be considered less robust than cross-sectional survey using standardised methods, it is important to remember that this study deals with a particularly functionally impaired group of people. There will undoubtedly be some misclassification (as there is in all epidemiological studies). However, I would argue that, on the whole, this study has "captured" a representative group of people with late stage AMD severe enough to cause visual impairment. There is always a tradeoff between very precise classification of disease (which requires time and resources, particularly for AMD) and statistical precision (which requires large numbers of participants). The size and representativeness of this study means that it provides important information about the prevalence and impact of AMD causing visual impairment in the UK. The fact that the risk factor analyses confirm the findings from previous studies adds to the credibility of the findings presented here.

In the USA several important studies have used a similar method of case ascertainment to the current study. In the Nurses' Health Study and Physicians' Health Study, a diagnosis of AMD was self-reported by the participants and followed by questionnaire to their ophthalmologist(Seddon *et al.* 1996; Cho *et al.* 2000; Christen *et al.* 1996; Ajani *et al.* 1999). These studies were very large and ophthalmic examination of all participants, as in the MRC Trial, would have been prohibitively expensive and unnecessary. As it was, these two studies have demonstrated convincing dose-related relationships between smoking and AMD.

Random misclassification of AMD will mean that the effect estimates are in fact underestimates of the true effects. Non-random misclassification is unlikely as the ascertainment was independent of exposure measurement.

- People with macular degeneration and vision ≥6/18 were not counted in this study

As the MRC Trial was a pragmatic assessment of simple assessment methods in general practice, the cutoff for referral was less than 6/18. As eye examinations were not undertaken on all the participants, information on eye disease was restricted to people who failed the visual acuity test. This selects out a particularly functionally visually impaired group, however, information was not available on people with AMD whose visual function was not so affected. For the prevalence estimates, these results will be an underestimate of the impact of AMD as many people will be visually impaired to lesser levels. A visual acuity of less than 6/12 but greater than 6/18 will have many disadvantages, for example, being unable to drive.

- Some people in the control or comparison groups will have AMD.

When identifying cases for a case-control study, high specificity is important, i.e. the case definition should make it unlikely that people without AMD were included in the case group(Copeland *et al.* 1977). All cases had a written diagnosis of AMD and hospital and general practice sources of data agreed well. A high sensitivity in case detection is less important. As the control group was large with over 4,000 people, some cases may be included in the control group with little impact on study results.

There is little published information on visual acuity and AMD. Owen et al performed a systematic review pooling data on the prevalence of visual impairment (acuity 6/18 or worse) due to AMD and prevalence of geographic atrophy and neovascular disease separately(Owen *et al.* 2002). The data were drawn from six population-based studies in North America, Australia and Europe. The difference between prevalence of visual impairment due to AMD and prevalence of geographic atrophy or neovascular AMD gives a rough indicator of the prevalence of AMD <u>not</u> causing visual impairment. Applying the estimates to the control group population structure suggests that, at the most, 3% of people not visually impaired could have late stage AMD. In the case-control study, even smaller numbers will have AMD because the control group only contained people with good vision (6/6 or better). Klein et al showed in the Beaver Dam Eye Study that visual acuity and late stage AMD are strongly correlated such that on

average, a diagnosis of late stage AMD is associated with a loss of vision of 30 letters acuity (sufficient to drop from 6/5 to 6/18)(Klein *et al.* 1991b). Therefore, the proportion of the control group in the case-control study with late stage AMD is likely to be very small.

The prevalence of early ARM in the control group will be higher. This proportion will be minimised by including only people with good vision as early ARM is also associated with a small decrease in vision. The presence of early ARM in the control group will have the effect of biasing the estimates of effect towards null.

- The case definition included macular degeneration and vision loss

The fact that the group of people with AMD have, by definition, visual impairment as well, means that these two parameters are very much linked. This means that the results apply to the most important group of people with AMD, i.e. those who have the disease to such an extent that they have suffered significant visual loss. However, when considering, in particular, the analyses of the impact of AMD, there is a conundrum. It is of interest to know how much of the impact of the disease is due to the visual impairment and how much due to AMD itself. Within the visually impaired group I was able to control for visual acuity in order to investigate whether the poor prognosis of AMD had any effects over and above those of visual impairment. For most of the results, with the notable exception of tasks requiring reading, AMD did not appear to have any extra impact over and above its effect on vision. It is perhaps unsurprising that most, if not all, of the impact of AMD comes through its effect on vision.

- Not all potential confounders were measured

In an ideal world, it would have been good to have information on genetics, dietary and blood levels of antioxidant micronutrient intake and an assessment of lifetime light exposure. In particular, it would be interesting to see whether the impact of, for example, smoking differs in different genetic groups. It is likely that AMD is a group of diseases with a common phenotype, however, the study of the genetics of AMD is not well established(Gorin *et al.* 1999; Yates and Moore 2000). Previous studies on smoking have not indicated any major confounding effects of antioxidants or light exposure, although these could be argued theoretically(Eye Disease Case-Control Study Group 1992).

- Prevalent rather than incident cases of AMD

The analyses presented in the thesis related to the baseline analyses of the MRC Trial, i.e. the data were cross-sectional. This means that prevalent rather than incident cases of AMD were identified. This is the most usual aetiological study design in AMD research and can be justified on the basis that AMD is a chronic, non-fatal disease(Rothman 1986).

- Exposure and outcome were assessed concurrently

One of the weaknesses of cross-sectional studies is the concurrent assessment of exposure and outcome. Ensuring that these are collected independently has been addressed above. In this case, historical data, for example, number of years smoked, is more powerful than purely cross-sectional data, for example, current blood pressure. It is important to be aware of the possibility of reverse causation, i.e. an exposure occurring after the incidence of the disease. More emphasis has been placed on historical exposures, such as smoking, than concurrent measures such as obesity.

- People in nursing homes were excluded from the study

People in residential or sheltered accommodation were included in the MRC Trial, however, people in nursing homes, i.e. accommodation where residents receive nursing care, were not.

9.5% of the population aged 75 years and above in the UK are in nursing homes(Office for National Statistics 2002). Other studies have shown a high prevalence of visual impairment in nursing homes(Tielsch *et al.* 1995; Mitchell *et al.* 1997; VanNewkirk *et al.* 2000b). For example, in people aged 85 years and above taking part in the NDNS study, 30% of those living in the community were visually impaired (<6/18) compared to 47% of those living in residential nursing homes, i.e. a prevalence ratio of 1.6(van der Pols *et al.* 2000). If we assume a similar increased prevalence of visual impairment in the nursing home population (multiplying 10% by 1.6 to get 16%), and that 10% of the population was excluded on the basis of being in nursing homes, the overall estimate of prevalence increases from 10% to 10.6%. It is likely that excluding the nursing home population will not have affected the prevalence estimates substantially.

- There were missing data for some people

71% of eligible people in the 53 practices in the universal arm of the study were given a detailed assessment (*see chapter three figure 3.2*). Table 1.2 (chapter one) shows the

response rate in other comparable studies. These range from 46% to 95%, with a median of value of 75%.

People taking part in the study were of a similar age (on average one year younger) than those who did not, however, women were less likely to take part. People who did not have a vision test were older, more likely to be women and more likely to be cognitively impaired. As older people and women have higher rates of visual impairment and visual impairment due to AMD, the effect of this is to make the estimates of prevalence presented in this thesis *conservative,* i.e. minimum estimates.

There was a group of visually impaired people for whom I could not find out the cause of visual impairment. These people had a similar age and sex distribution compared to people for whom cause was available. They had better visual acuity, i.e. less severe visual loss. As AMD was associated with more severe visual loss, I chose not to make any assumptions about people for whom cause of visual loss was missing. I calculated the prevalence rates for AMD causing visual impairment, assuming that *none* of these people had AMD. This, again, is a conservative assumption and leads to minimum estimates of the prevalence of AMD causing visual impairment.

There is no reason to suppose that the missing data will have affected the associations examined, either in terms of examining the impact of AMD causing visual impairment, or the potential risk factors. It is likely that the associations observed apply in the non-participants as well. Bias could occur if, for example, smokers with AMD causing visual impairment were more likely to participate or non-smokers without AMD causing visual impairment were less likely to participate. This does not seem very likely. Similarly in the analyses of impact of AMD causing visual impairment, people with functional difficulties and AMD would have to be more likely to participate or people with no functional difficulties and no AMD less likely to participate. Again this seems unlikely.

- Lack of information on ethnic group

Causes of visual impairment are likely to differ in different ethnic groups in Britain. The prevalence of AMD may well vary. The age-structure of immigrant communities is younger than the native British population. The MRC Trial aimed to select a population representative of the UK population, however, the proportion of people in ethnic minorities in the over 75s population is small and did not permit independent analysis.

6.2 PREVALENCE OF VISUAL IMPAIRMENT

6.2.1 Principal Findings

Visual impairment (binocular acuity less than 6/18) is common in this age-group. 12% of people in the study were visually impaired. The risk of visual impairment increased steeply in these older age-groups. 37% of people aged 90 years and above were visually impaired. There was a higher risk of visual impairment in women.

Using mid-2001 population estimates for the UK* there are approximately 609,000 people aged 75 years and above living in the community with visual impairment (95% confidence interval 475,000 to 745,000) of who 157,000 are aged 90 years or above. As women experienced higher levels of visual impairment and also make up a larger proportion of the elderly, the majority of the burden of visual impairment in this age-group is borne by women. Out of the estimated 609,000 people visually impaired 453,000 (74%) are women.

6.2.2 Comparison with other studies

The most recent study of visual acuity in the British population was a sample of 1,362 participants aged 65 years and above taking part in the National Diet and Nutrition Survey (NDNS) which estimated the prevalence of visual impairment (<6/18) to be 12% (van der Pols *et al.* 2000). This is comparable to the estimate of 12.4% from this study. The NDNS sample, however, included people resident in nursing homes who had a higher prevalence of visual impairment. Reidy et al in a study of 1,547 people aged 65 years and above in north London found that 30% of their sample had bilateral visual acuity worse than 6/12 (Reidy *et al.* 1998). This is similar to the current study where 29.2% (28.5% to 29.9%) of people 75 years and above had a binocular acuity worse than 6/12.

Studies of vision in the British population tend to report higher levels of visual impairment than studies in equivalent populations in other part of Europe, North America and Australia. Part of this can be attributed to different methods, particularly the emphasis on best corrected acuity and use of subjective refraction in studies in other countries. However in the Salisbury Eye Evaluation project approximately 9% of white

---

* http://www.gad.gov.uk/population/1998/pop5yearuk98-08.html, accessed 14th August 2001

participants aged 75 to 84 years had presenting acuity worse than 6/12 in the better eye (Rubin *et al.* 1997). This compares with 15% of people aged 75 to 84 in the MRC Trial having a binocular acuity worse than 6/12. These differences may reflect differences in study methods and or in use of services, especially cataract services.

There was a significant increased risk of visual impairment in women which agrees with the results of a recent meta-analysis showing an odds ratio for women of 1.63 for industrialised countries (Abou-Gareeb *et al.* 2001). It is not clear whether this excess in women represent differences in the incidence of conditions causing vision impairment or differences in access and use of services.

6.2.3 Comments

This study is the largest nationwide study undertaken to date and, for that reason, provides more precise estimates of the size of the problem. The prevalence of visual impairment presented here is clearly a minimum or conservative measure. The numbers of people with less severe, but still significant, visual impairment are considerably higher.

6.3 CAUSES OF VISUAL IMPAIRMENT

6.3.1 Principal findings

One in four people were visually impaired due to refractive error. There was a strong relationship with visual acuity – cataract causing more moderate visual impairment whereas AMD resulted in poorer vision. This effect was independent of age.

AMD was the most important cause of visual loss in people aged 75 years and above, being either the major or an important contributory cause in 48% of the sample. There was a strong age effect, whereby people aged 90 years or above were proportionately more affected.

6.3.2 Comparison with other studies

Previous studies into the causes of visual impairment in this age-group either have not been representative of the general population(Evans 1995). or have had a small numbers of people identified with visual impairment. Table 6.2 compares these results with other published studies from similar populations in North America, Australia and Europe. The number of people with low vision (n=727) and blindness (n=249) with cause of

visual loss identified in the MRC Trial was substantially larger than for other comparable studies (range 10 to 42 blind people and 21 to 134 people with low vision). The results of the MRC Trial compare well with other studies and show that the pattern of cause of visual loss differs according to the level of visual loss. AMD is proportionately a more important cause of blindness than of low vision; conversely cataract is generally, although not always, found to be a more important cause of low vision than AMD.

Other studies have shown a strong age effect as well, whereby people aged 90 years and above were proportionately more affected by AMD(Klaver *et al.* 1998).

6.3.3 Comments

The MRC Trial provided the opportunity to identify a large group of visually impaired older people and ascertain the cause of visual loss. This study highlights the importance of refractive error, AMD and cataract as the main causes of visual loss in older people. AMD is particularly important in the very elderly, and cataract appears to be a more important cause of visual loss in women. It is likely that this study underestimates the impact of refractive error as not everyone could use the pinhole occluder.

6.4 PREVALENCE OF AMD CAUSING VISUAL IMPAIRMENT

6.4.1 Principal findings

The prevalence of AMD causing visual impairment was estimated at 3.7% (3.2% to 4.2%) in people aged 75 years and above. This prevalence increased with age. The prevalence was 14.4% (11.6% to 17.2%) at 90 years and above. There was a higher risk of AMD causing visual impairment in women.

There were estimated to be approximately 192,000 people aged 75 years and above in the UK living in the community with visual impairment due to AMD (95% confidence interval 144,000 to 239,000) of whom 60,000 are aged 90 years or above. As for visual impairment, the majority of the burden of visual impairment in this age-group is borne by women. Out of the estimated 192,000 people visually impaired due to AMD, 146,000 (76%) are women.

The prevalence of AMD causing visual impairment did not vary by socio-economic group or region.

6.4.2 Comparison with other studies

In a recent review pooling data from several international studies of AMD the prevalence of visual impairment due to AMD was estimated as: 75-79 1.55%, 80-84 3.58%, 85-89 8.07% and 90+ 15.3% (Owen *et al.* 2002). These results compare well with the estimates of prevalence from the MRC Trial: 1.2%, 3.6%, 6.6% and 14.1%.

Previous estimates of the prevalence of visual impairment due to AMD have been much higher, for example, the RNIB website estimates that there are 750,460 people visually impaired people aged 75 years and above of whom half, i.e. approximately 375,000 will have AMD.* These figures were based on the RNIB Survey(Bruce *et al.* 1991). As has been pointed out elsewhere (Owen *et al.* 2002), this report extrapolated from a highly selected interviewed group and did not provide confidence intervals around the estimates.

The current study found a statistically significant increased risk of AMD causing visual impairment in women. Pooled analysis of previous population-based studies have not indicated such a strong risk (Smith *et al.* 1997). However, examination of figure 1.4 (chapter one) shows that there is the possibility of an age-effect such that there is a greater increased risk for women at older ages. As the MRC Trial was a substantially older population than most previous population-based studies this could be the explanation.

6.4.3 Comments

The prevalence estimates presented here are minimum estimates. However, they agree well with the estimates expected on the basis of applying a pooled analysis of the major population-based prevalence studies of AMD to the UK population and are substantially lower than the estimates that are currently commonly used.

---

* http://www.rnib.org.uk/wesupply/fctsheet/authuk.htm [Accessed December 2002]

6.5 FUNCTIONAL ABILITY

6.5.1 Principal findings

People visually impaired due to AMD were more likely to report that they had a lot of difficulty reading newsprint, difficulty managing finances, were more likely to be in the worst quintile on the ADL scale compared to people not visually impaired. They appeared to be at an extra disadvantage compared to people visually impaired due to other causes, even after adjusting for visual acuity.

6.5.2 Comparison with other studies

Previous population-based studies have considered the association between visual impairment and functional ability(Marx *et al.* 1992; Carabellese *et al.* 1993; Salive *et al.* 1994; West *et al.* 1997; Valbuena *et al.* 1999). Studies of AMD have been confined to single case groups of people with AMD attending for health care or to take part in a trial(Williams *et al.* 1998; Mangione *et al.* 1999). These studies have had no control group and so have been limited to comparisons with other patient groups.

Several studies have demonstrated that visual impairment is associated with decreased functional ability, generally as measured by the ADL scale(Marx *et al.* 1992; Carabellese *et al.* 1993; Salive *et al.* 1994; West *et al.* 1997). This finding is confirmed in the current study. Studies of AMD specifically, have found that patients with AMD were more likely to have problems with activities of daily living compared to other national samples(Williams *et al.* 1998). Mangione et al found that more severe AMD was associated with more difficulties with Activities of Daily Vision, however, this could be attributed to increased vision loss(Mangione *et al.* 1999). In the current study people with AMD were more likely to be in the worst quintile for ADL score than people visually impaired due to other causes, even after controlling for binocular acuity score.

6.5.3 Comments

This is the first population-based study of its kind whereby people with AMD causing visual impairment have been compared to people not visually impaired and people visually impaired due to other causes.

People aged 75 years and above have many other problems that affect their daily life. The number of disabling health problems increases with age. People with AMD have two additional problems: firstly, and most importantly, is the loss of vision; secondly, the effect of having AMD, either the impact of the diagnosis or the specific visual handicap that the disease brings.

6.6 SELF-REPORTED HEALTH AND PHYSICAL ACTIVITY

6.6.1 Principal findings

People with AMD were more likely to report "fair/poor" health compared to people not visually impaired. They appeared to rate their health worse than people visually impaired due to other causes, even after controlling for visual acuity. People with AMD had a non-significant increased odds of reporting being "not at all" physically active compared to people not visually impaired.

6.6.2 Comparison with other studies

One other study has examined the relationship of a single item measure of self-rated health with visual impairment(Wang *et al.* 2000). In the Blue Mountains Eye Study, decreased vision was found to have an independent impact on global health ranking by person younger than 80 years of age but not by older persons. Williams found that 16% of a sample of 86 people with AMD reported "fair or poor" health in contrast to 23% of people with AMD causing visual impairment in the current study(Williams *et al.* 1998). This may well be attributable to the fact that this group of people with AMD were older (average age 86 years) compared to the people in the American study (average age 79 years).

6.6.3 Comments

This study of older people repeats Wang et al observations in the Blue Mountains Eye Study that visual impairment did not have a statistically significant impact on self-reported health. However, the confidence intervals in the current study ranged from near 1 (0.98) to 1.47 and therefore are consistent with a moderate impact of visual impairment on self-reported health. The measures of effect in this study differed in statistical significance (but not much in size) depending on whether depression, cognitive impairment, falls and hip fractures were included as confounding factors.

Self-reported or perceived health is a complicated measure. Some authors have pointed out the difficulties in its interpretation(Bowling 1997). Poor mental health can distort perceptions of health but poor physical health can also lead to poor mental health. Why do people with AMD apparently report worse health than other people of similar age and with similar levels of visual acuity? This may reflect their perception that they have an incurable cause of visual loss that may get worse over time.

6.7 Sickness Impact Profile and Philadelphia Geriatric Morale Scale

6.7.1 Principal findings

Four dimensions of the Sickness Impact Profile (SIP) were studied in the current study: home management, mobility, body care and movement and social interaction. Home management, mobility and body care and movement were significantly associated with visual impairment. There was little evidence of any extra impact of AMD. It was interesting to note that for home management and body care and movement, men appeared to be worse affected by visual impairment and AMD than women.

There was a non-significant increased risk of being in the worst quintile for social interaction and PGMS in visually impaired people compared to non-visually impaired people. There was little difference between AMD and other causes.

People with visual impairment due to AMD were less likely to suffer problems on the body care and movement dimension of the SIP.

6.7.2 Comparison with other studies

The Sickness Impact Profile has been used in hospital-based studies (for example (Desai *et al.* 1996)) but few population-based studies. The SEE project reported that they examined the social interaction scales from the SIP. They found that visual impairment was one of the most important predictors of reporting no social activities or no religious activities. However, the results were a little confusing because they categorised social activities as <1 per month, 1-3 per month and $\geq$ 1 times per week. However, the SIP responses are of the yes/no variety. In contrast to the SEE project, the current study did not find a statistically significant association with the social interaction dimension of the SIP however the confidence intervals range from 0.89 to

1.97 and are therefore consistent with nearly a two-fold odds of experiencing difficulties with social interaction.

In a small study comparing 30 cases of AMD with 30 age and sex-matched controls people with AMD had lower life satisfaction, as measured by the Life Satisfaction Index Wellbeing (Davis *et al.* 1995). However the difference was small (3 points on the scale) and although statistically significant may not have represented an important difference.

6.7.3 Comments

The analyses of SIP and PGMS were more problematic because these measures were only collected in a subset of 11 practices. This meant that it was difficult to include all potential confounding factors in the model at the same time. The analysis strategy used was to identify the most important confounders by selecting those that affected the odds ratio by 10% or more (in contrast to the other analyses which included confounders that were significantly associated with exposure and outcome). Although there were few confounders that affected the odds ratio substantially, for the analyses examining the relationship between visual impairment, AMD and SIP, the possibility of residual confounding is more of a problem.

People with AMD had less problems with the body care and movement dimension of SIP (*see Appendix E*). A number of these questions relate to more intrinsic features of bodily functioning, for example, *"I move my hands or fingers with some difficulty or limitation"*. It may be that some of the people visually impaired due to other causes were suffering from systemic illness, such as stroke, that would affect their body care and movement. It is perhaps unsurprising that this visual impairment due to AMD had less effect on this dimension of quality of life.

6.8 Depression and cognitive impairment

6.8.1 Principal findings

After controlling for appropriate confounding factors and compared to people not visually impaired, visually impaired people had an approximately 50% increased chance of depression and 70% increased chance of cognitive impairment. There was little evidence of any differences between people visually impaired due to AMD and those visually impaired due to other causes.

6.8.2 Comparison with other studies

Carabellese found that visual impairment was associated with an increased risk for depression (Carabellese *et al.* 1993). A couple of studies have examined relatively small cohorts of people with AMD and reported the rates of depression (Rovner *et al.* 2002; Brody *et al.* 2001). Both studies found that approximately 33% were depressed. In the absence of a control group, this figure is a little difficult to interpret, however, Brody et al compared it to other studies of community-dwelling elderly people and found it to be double the rate expected (Brody *et al.* 2001). This contrasts to the current study where 15% of people with AMD causing visual impairment were depressed. However, this was approximately double the rate found in people not visually impaired (7%). The difference in rates of depression is probably due to the measures used. The definition of depression in the study by Brody et al was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Depressed subjects had a mean GDS score of 5.86. This suggests that some of the participants in the MRC Trial who had GDS scores of less than six may have been classified as depressed by the alternative measure.

6.8.3 Comments

An association between visual impairment and depression does not necessarily mean that there is a causal link. It may be that there is a confounding factor that we have not considered. Another possibility is that depressed people are not so good at doing visual acuity tests. There is little evidence that this is the case, although some studies have suggested that people with clinical depression are more likely to perceive ambient light as being dimmer than usual (Friberg and Borrero 2000), and experience increased rates of disturbed colour vision (Heim and Morgner 1997). The mechanisms by which visual impairment may lead to depression may relate to social isolation, adjustment to loss of vision, difficulties with daily activities, lack of exercise. It has also been noted that people with severe loss of vision may experience sleep problems (Tabandeh *et al.* 1998).

The diagnosis of AMD is one of a chronic, progressive disease leading to "blindness". There is little in the way of treatment that can slow down progression and none that can restore vision. The hypothesis that such a diagnosis may lead to increased levels of depression, compared to other diagnoses such as cataract, has not been borne out in this study. Some studies have found that the longer the duration of vision loss occurs the

less it is associated with emotional distress(Williams *et al.* 1998; Ip *et al.* 2000). It may be that in this older population a certain amount of adjustment to the diagnosis has occurred.

Severely cognitively impaired people are likely to have difficulties doing the visual acuity test. In our sample, 23.3% of cognitively impaired people did not do a vision test compared to 2.4% of not impaired people. People with a clinical diagnosis of dementia have been found to have higher rates of visual impairment (Uhlmann *et al.* 1991). and people visually impaired more likely to develop delirium (Inouye *et al.* 1993).

The MMSE is divided up into two sections – a verbal section with a maximum score of 21, and a performance section (involving, for example, copying a drawing) with a maximum score of 9. The following cut-points have generally been accepted: 24-30 no cognitive impairment, 18-23 mild cognitive impairment, 0-17 severe cognitive impairment. The MMSE shows high levels of sensitivity for detecting severe cognitive impairment (Tombaugh and McIntyre 1992).

The corresponding cut-point for severe cognitive impairment, when using only the verbal section is less than 12. Analyses using data from the verbal section only were used in order to minimise the effect of vision on the performance of the test, independent of cognition. However, it is very likely that visual impairment makes it more difficult to do the MMSE, which is partly based on memory. Previous studies have demonstrated that people with visual impairment can achieve low scores on the MMSE despite having no clinical signs of dementia (Jagger *et al.* 1992). Memory and learning improve significantly when vision is restored after cataract surgery (Fagerstrom 1992).

6.9 FALLS AND HIP FRACTURES

6.9.1 Principal findings

Visually impaired people had a modest non-significant increased risk of reporting two or more falls at home in the last six months compared with people not visually impaired and a similar non-significant increased risk of reporting hip fracture compared with people not visually impaired. No difference between AMD and other causes of visual loss was observed. There was some evidence that the effect of visual impairment on hip fractures was different at different ages. In people aged 90 years and above, visual

impairment due to AMD was associated with nearly a four-fold increased chance of reporting hip fracture.

6.9.2 Comparison with other studies

There are a number of studies suggesting that people with impaired vision are more likely to fall(Klein *et al.* 1998a; Ivers *et al.* 1998; Jack *et al.* 1995). In the Beaver Dam Eye Study, 10.5% of people with a current binocular acuity of less than 20/25 reported a history of falls in the last year compared to 5.2% of people with vision of 20/20 or better (Klein *et al.* 1998a). This is very similar to the results of the current study where 13% of visually impaired people reported two or more falls in the last six months compared to 8% of people not visually impaired. Little further information was given in the Beaver Dam Study report, for example, no adjustment was made for confounding by age, sex or other factors.

In the Blue Mountains Eye Study, there was an increased risk of two or more falls in the past year associated with visual impairment, after adjustment for a variety of confounding factors (Ivers *et al.* 1998). The increased risk was of a similar order of magnitude to the current study. The Blue Mountains Eye Study examined the role of eye disease and falls. They found that AMD was not significantly associated with falling – a finding repeated in this study.

In contrast to the current study, a number of other studies have found a significant relationship between hip fractures and visual impairment. In the prospective osteoporotic fractures study, risk of hip fractures was associated with poor depth perception and poor contrast sensitivity (Cummings *et al.* 1995). In the retrospective Auckland Hip Fracture Study, binocular acuity less than 20/60 was significantly associated with increased risk of hip fractures after adjustment for various risk factors. The authors attributed 40% of fractures to poor visual acuity or stereopsis. In the Framingham Study, people with poor vision were more than twice as likely to have a hip fracture compared to those without (Felson *et al.* 1989). A similar risk was found in the EPIDOS prospective study (Dargent-Molina *et al.* 1996). Similarly, in the cross-sectional Beaver Dam Eye Study, 5.2% of people with vision 20/25 or worse reported hip fracture compared to 1.4% of people with vision 20/20 or better (Klein *et al.* 1998a).

6.9.3 Comments

There are many other illnesses and health problems that will co-exist due to the fact that people with AMD are, in general, older. However, the impact of AMD causing visual impairment on morbidity, i.e. a presumed causal link, is unlikely in most except for depression (considered above) and hip fracture.

In this study visual impairment was associated with a statistically non-significant 20% increased chance of falls and hip fractures. Only the 90 years and above age-group was visual impairment a significant risk factor for reported hip fracture. This estimate is substantially lower than that seen in other studies. It may in part be explained by the fact that more confounders were considered in this study. However, the odds ratio controlling only age and sex was 1.49 (1.28 to 1.74) for falls and 1.46 (1.14 to 1.88) for hip fractures.

6.10 MORTALITY

6.10.1 Principal findings

After controlling for all the potential confounders, visually impaired people had an increased risk of death compared to people not visually impaired. People visually impaired due to AMD had a lower risk compared to people visually impaired due to other causes. There did not appear to be any effect modification by age or sex.

6.10.2 Comparison with other studies

Previous studies have found that visual impairment is strongly associated with mortality (Klein *et al.* 1995a; Laforge *et al.* 1992; Lee *et al.* 2002; McCarty *et al.* 2001b; McCarty *et al.* 2001b; Reidy *et al.* 2002; Taylor *et al.* 2000; Thompson *et al.* 1989; Wang *et al.* 2001). In two of these studies, women and not men have been at increased risk(Lee *et al.* 2002; Reidy *et al.* 2002).

Few studies have examined AMD directly but, in contrast to cataract, it does not appear to be linked to an increased risk of mortality (Klein *et al.* 1995a). This was confirmed by the current study whereby visual impairment was strongly associated with mortality but the majority of this risk was related to vision impairment due to other causes and not AMD.

6.10.3. Comments

Other studies have found differences between men and women a finding that was not repeated in this study. It was not possible to assess the extent to which the association between mortality and visual impairment is due to accidents in visually impaired older people. However, controlling for falls had little effect on the relationship. Accidents account for only a small proportion of deaths in the elderly and it is likely that this is not the major explanation for the increased risk of mortality.

I did not distinguish the different causes of visual loss in the "other causes" group, however, cataract as a cause of visual loss is likely to predominate in that group and may well be the explanation for the excess mortality in that group.

6.11 SMOKING

6.11.1 Principal findings

Current smokers had a two-fold increased risk of being visually impaired due to AMD compared to non-smokers. This effect was particularly strong in people aged 75-79 years of age. In these people there was a three-fold increased risk and a dose-response relationship between pack years of smoking and risk of AMD causing visual impairment. People who stopped smoking more than 40 years ago had a similar risk to non-smokers. Based on these findings, approximately 28% of cases of AMD in this study population were attributable to smoking, either currently or in the past (attributable risk % = ((OR-1)/OR)*proportion exposed amongst cases)(Rothman 1986).

6.11.2 Comparison with other studies

Levels of smoking in the MRC Trial cohort were similar to those reported in the Health Survey for England 1997*. Approximately 12% of men and 8% of women reported being a current smoker in the MRC Trial cohort, compared to 12% of men and 11% of women aged 75 years and above in the Health Survey for England.

The results of this study are similar to other studies on smoking and AMD. The results of other studies on smoking are in table 1.11 in chapter one. The current study is the

---

* http://www.doh.gov.uk/stats/hstable.htm. Accessed June 17th 2003.

largest number of population-based cases of late-stage AMD identified to date. The size of effect is compatible with the other studies; most estimated a two-fold or three-fold risk.

A dose-response relationship has been seen in the prospective studies(Seddon *et al.* 1996; Christen *et al.* 1996), and the cross-sectional Rotterdam study(Vingerling *et al.* 1996). In the Physicians' Health Study, people who had stopped smoking 20 or more years before the start of the study had a borderline increased risk of AMD with vision loss. Similar results were seen in the Rotterdam Study. However, in these studies the number of cases was lower. Time since stopping smoking was grouped into broader categories than the current study.

In the Nurses Health Study 29% of cases of AMD were attributable to smoking(Seddon *et al.* 1996). This value is very similar to the results of the current study (28%).

6.11.3 Comments

This nested case-control study forms one of the largest case-control studies of AMD in the British population and one of the largest reported to date. It examined the role of smoking, alcohol consumption, cardiovascular disease and reproductive factors in women. The role of genetic factors, antioxidant micronutrients and light exposure were not studied. The results fit in remarkably well with results seen in other studies with different designs, ages studied and methods of ascertainment of AMD. Of the risk factors examined, the only one to emerge as being important is smoking, which is estimated to account for approximately one in three cases in this population of people aged 75 years and above living in Britain.

Possible explanations for the modification of the effect of smoking by age include that the measurement of disease or exposure may be more unreliable in the older age-groups. An alternative explanation is that, as smoking is an important cause of mortality, smokers surviving beyond the age of 80 years have more vigorous defense mechanisms to deal with the harmful effects of smoking. These mechanisms may also apply to AMD. Vingerling et al in the Rotterdam Study reported a similar effect modification by age(Vingerling *et al.* 1996), however this was later revised (Klaver *et al.* 1997).

The current study was limited by not having information on antioxidant intake. One alternative explanation is that smokers eat less fruit and vegetables and thereby increase their risk of AMD. However, in the Eye Disease Case-Control Study Group, plasma

levels of antioxidant micronutrients were adjusted for and a similar effect size reported (Eye Disease Case-Control Study Group 1992).

6.12 OTHER RISK FACTORS

6.12.1 Principal findings

Alcohol consumption

There was little indication that alcohol consumption was protective. People who reported that they had taken an alcoholic drink in the last year had a small (less than 20%) non-significant increased risk of visual impairment due to AMD. The majority of the "drinkers" had consumed less than 10 units in the previous week. There was a non-significant increased risk of visual impairment due to AMD in people who had drunk 20 or more units in the last week (equivalent to 160g ethanol) and reduced risks in people with moderate consumption compared to non-drinkers.

Cardiovascular disease

People with AMD were more likely to report that they had had a stroke, heart attack or diabetes. In the case of heart attack and diabetes this association was of marginal significance only. After controlling for other confounding factors, the association with reported stroke was attenuated and no longer statistically significant.

Reproductive factors in women

There was little indication that women with reproductive factors indicating relatively low lifetime oestrogen levels were at increased risk of developing visually impairing AMD.

6.12.2 Comparison with other studies

Alcohol consumption

Alcohol consumption in the MRC Trial was similar to that reported in the Health Survey for England 1997*. In the MRC Trial 84% of men and 70% of women reported having had a drink in the past year. This compares to 85% of men aged 75 years and

---

* http://www.doh.gov.uk/stats/hstable.htm. Accessed June 17th 2003.

above and 75% of women in the Health Survey for England who reported drinking in the previous week.

In the Blue Mountains Study, total alcohol intake was not associated with ARM(Smith and Mitchell 1996). In NHANES-I moderate wine consumption was associated with a decreased risk of AMD(Obisesan *et al.* 1998). However, this association was of marginal statistical significance (odds ratio 0.86, 0.74 to 0.996). In the Beaver Dam Study, men drinking 78g/week of alcohol or more from beer had a higher five-year age-adjusted incidence of early ARM(Moss *et al.* 1998). In the prospective Physicians Health Study, there was a small non-significant reduced risk for low to moderate levels of alcohol intake(Ajani *et al.* 1999). In the combined analysis of the Nurses' Health Study and the Health Professionals Follow-up Study, there was a suggestion of a moderate increased risk of the disease in women who drank 30g/day or more (relative risk 1.5,1.0 to 2.4)(Cho *et al.* 2000).

Cardiovascular disease

In the Health Survey for England 1998*, 73% of men and 78% of women aged 75 years and above had systolic blood pressure of 140mmHg or more or had a diastolic pressure of 90mmHg or over or were taking antihypertensive medication. This compares to 60% of men and 68% of women in the MRC Trial cohort who had high systolic or diastolic blood pressure (but not including those who were taking antihypertensive medication).

There has been inconsistent evidence for the relationship between cardiovascular disease and AMD with several studies finding an association(Chaine *et al.* 1998; Hyman *et al.* 2001; Goldberg *et al.* 1988a) and others not(Klein *et al.* 1993a; Smith *et al.* 1998b; Delcourt *et al.* 2001).

Oestrogens

The Eye Disease Case-Control Study Group was the first study to report on oestrogens(Eye Disease Case-Control Study Group 1992). Women taking oestrogen replacement were at a reduced risk of neovascular AMD compared to women who had never taken replacement therapy. However, it is known that women who take hormone

---

* http://www.archive.official-documents.co.uk/document/doh/survey98/hse-03.htm#3.2. Accessed June 17th 2003

replacement therapy are very different to those who do not and these differences may not have been adequately controlled for in the analysis. In the Rotterdam Study, women with early menopause after removal of one or both ovaries had an increased risk of macular degeneration compared to women who had their menopause at 45 years or later(Vingerling *et al.* 1995c). These results were not confirmed by the Beaver Dam Study(Klein *et al.* 1994a), or the Blue Mountains study(Smith *et al.* 1997) nor in the current study. Menopause before 45 years of age due to surgery was not a risk factor for AMD.

6.12.3 Comments

This study of over 500 cases of severe AMD had a reasonable power (over 80%) to investigate odds ratios of two or more (*see chapter five table 5.2*). An effect of smoking was observed. However, it may well be that the effect of alcohol on AMD is more modest. Previous studies have found non-significant increased risk or odds in the region of 30%. If the real effect is of that order, it will be quite difficult to detect reliably in observational studies. Firstly, the studies will need to accrue large numbers of cases of AMD, preferably prospectively. Secondly, even if a statistically significant risk of that order is observed, given that the increased risk is modest it will be difficult to be confident that it could not have been due to the effect of an unidentified confounder.

The measures of oestrogen used in this study were fairly crude. They consisted of measuring the years of menstruation or time since the menopause. It may be that these are not good measures of relative oestrogen exposure. In this particular cohort, it is unlikely that use of hormone replacement therapy will have been common. In the Health Survey for England 1997*, less than 3% of women aged 75 years and above reported ever using HRT. The difficulties with assessing the effects of exogenous oestrogen have been discussed. One of the ways forward in this area is to add an assessment of AMD in trials of hormone replacement therapy. This was to be one of the secondary outcomes of the MRC sponsored WISDOM trial. However, the trial has recently been abandoned.

---

* http://www.doh.gov.uk/stats/hstable.htm. Accessed June 17th 2003.

6.13 UNANSWERED QUESTIONS AND FUTURE RESEARCH

- Periodic assessment of the prevalence of visual impairment and AMD

The prevalence of visual impairment may change with changing circumstances. It would be useful to have regular (say five- or ten-yearly) assessment of the prevalence of visual impairment in the UK. This could take the form of adding on collection of data on visual acuity to other nationwide studies (as is done with NHANES in the USA). This study indicates a substantial burden of AMD causing visual impairment in this age-group which rises exponentially with increasing age. As for visual impairment, it would be useful to have regular assessment of the prevalence of AMD causing visual impairment in the UK. This could take the form of adding on collection of data on AMD to other nationwide studies.

Regular national assessment of the prevalence of this condition would make it possible to conduct ecological studies. For example, as the prevalence of smoking in the population changes over time, it would be interesting to examine whether corresponding changes in the prevalence of AMD could be observed.

A criticism of the current study is that AMD was assessed from medical record review rather than fundus photographs. Future prevalence studies, if adequately funded, could incorporate such data collection, even if only on a sample.

- Assessment of the prevalence of visual impairment and AMD in ethnic minorities

As the age-structures of these populations change, visual impairment and eye disease is likely to become more of a problem. Surveys in specific geographical locations will be required.

- Why do women have a higher risk of visual impairment than men?

Women aged 75 years and above have a higher risk of visual impairment than men. The reasons for this should be investigated in more detail. Is this due to lack of access to services or differences in incidence of eye disease causing visual impairment?

- Barriers to eye health care in older people

The majority of people with cataract or refractive error could have their sight restored with appropriate treatment. Further research as to why people do not get glasses or a cataract operation is needed. What are the barriers to access to optometric and cataract surgery services in this age-group?

- Further research on impact of AMD

This is the first time that the association between AMD and functional ability has been investigated in a population-based study with an appropriate control group. The observation that people with AMD are particularly disabled with respect to tasks requiring reading, in comparison to people with other causes of visual loss, has not been seen before, to my knowledge. Similarly, for the relationship between AMD and self-reported health and physical activity. This is the first time AMD has been studied in this context and this finding could usefully be studied again. If the finding is repeated, i.e. that people with AMD report worse health than people with visual loss due to other causes, in depth qualitative studies as to the determinants of this difference should be done.

For SIP, as for self-rated health, this is the first time AMD has been studied in this context and compared to an appropriate control group. Future studies could include vision related measures of quality of life such as the NEI-VFQ(Mangione *et al.* 2001). and other dimensions of SIP.

- What is the basis of the link between cognitive impairment and AMD causing visual impairment?

Are people with cognitive impairment not so good at doing visual acuity tests? Or does visual loss predispose towards either cognitive impairment, or difficulty doing the MMSE, independent of cognitive impairment. It is difficult to distinguish these hypotheses in a cross-sectional study. One option would be to assess the performance on the MMSE in people prior to cataract surgery. This could then be compared to their performance when vision is restored. The assumption would be that cognition would not have improved in a relatively short period and, any improvement in the MMSE test could be attributed to the change in vision.

- Counselling support for depression.

The link between visual impairment and depression, from this study and others, appears to be fairly well established. Future studies need to address what should be done about this problem. Counselling support for people with AMD needs to be developed. One small study has shown that it is possible to develop a self-management program with positive benefits on quality of life(Brody *et al.* 2002). Research at the primary care level as to how best to provide such support is needed.

- Why does visual impairment lead to an increased risk of death?

Is visual impairment harmful, *per se*, for example, leading to reduced nutrition or self-care, or is visual impairment a marker for failing health?

- Do changing rates of smoking in the population result in changing incidence rates of AMD?

Smoking is an example of an exposure where it is not possible to do a randomised controlled trial. An ecological study design to assess the impact of removing smoking as an exposure would be to examine whether changing rates of smoking over time are related to changing prevalence rates of AMD.

6.14 POLICY IMPLICATIONS

- Projected burden of AMD causing visual impairment in the UK for planning low vision services and hospital eye services

This study has shown that the burden of visual impairment due to AMD is considerable in people aged 75 years and above. Nearly 200,000 people aged 75 years and above are visually impaired due to AMD in the UK. This figure will rise as the population ages over the next few decades. Given the current prevalence of AMD, in the year 2051 the numbers of people affected in the 75 years and above age-group will be over twice as high.* Policy makers need to be aware of the prevalence of this condition when planning the need for low vision services and hospital eye services for AMD. Although the burden is substantial it is lower than some previous estimates.

A recent study of low vision services for vision rehabilitation in the UK showed that the distribution of low vision services was geographically uneven(Culham *et al.* 2002). Compared to the probable number of people with a visual impairment in the UK there were inadequacies in service provision. The authors concluded that a review of current services is needed.

Research into the effectiveness of low vision aids is limited but systematic reviews are underway(Virgili and Rubin 2002). More research is needed into which vision aids are

---

* Calculated by applying prevalence rates to projected population in 2051 obtained from http://www.gad.gov.uk [Accessed December 2002]

effective in this age-group and the best way in which they should be delivered. The differing needs of the very elderly should be considered separately.

New treatments for AMD are being developed and researched(Evans 2002). The implications of these for costs in the NHS need to be established against projected numbers with the disease in the UK.

- Should we be screening for AMD?

Currently there is little effective treatment for most people with AMD(Fine *et al.* 2000). A proportion of people with neovascular disease at its early stages may benefit from laser photocoagulation or photodynamic therapy. In the MRC Trial, visual acuity screening and referral for visual impairment was included in order to assess whether there was any benefit from such screening. The results of a nested trial of visual acuity screening suggests that there was not any benefit(Smeeth *et al.* 2002a). Possible reasons include a low referral rate by the general practitioners. Given that pragmatic screening in the community for visual impairment, much of which is caused by cataract which has a safe and effective cure, screening for AMD, which does not have such treatment is unlikely to be beneficial. However, education campaigns for AMD promoting awareness of visual symptoms such as distortion may increase the number of people coming forward with earlier stages of the disease for treatment.

- Visual impairment is extremely common in the very old, AMD is the most important cause of visual impairment

It is common to summarise the health experience of people over 65 or over 75 years of age. These summary figures hide a dramatically increased risk of visual impairment and blindness in people aged over 90 years.

The needs of very old people are likely to be quite different to the (nowadays) relatively active 75 year old person. The role of low vision aids and access to hospital eye services in this age-group may need to be addressed differently to the younger ages. More research into the effectiveness of low vision aids in the very elderly is needed.

- Much visual impairment in people aged 75 years and above could be alleviated by a pair of spectacles

Policy makers need to consider the role of the high street optician and mechanisms for providing cheap and reliable spectacles to groups of the population that may not be able to afford high street spectacles.

- Cataract causes much avoidable visual impairment in this age-group.

More investment in cataract surgery to reduce waiting list times along with research into the barriers to cataract surgery in this age-group is needed.

- The level of smoking in the population should be reduced and young people discouraged from taking up smoking

AMD is another reason why governments should act to reduce the level of smoking and should be included in public health campaigns aimed at reducing smoking. One in every three cases of AMD could be prevented if nobody smoked. This would have huge social and financial implications.

- Visual impairment predominately affects women. This has implications for delivery of services.

- More research into the causes and cure of AMD.

This study, along with others, has demonstrated the detrimental impact of visual impairment on quality of life, mental health, falls and mortality. Given the impact of visual impairment, research into the causes and cure of AMD must be maintained and developed. Clearly the role of genetics in the aetiology of AMD holds much promise; similarly, the possible role of a diet rich in antioxidant micronutrients has not been fully explored. A variety of treatments for AMD are currently being explored and trials of these need to be expedited.

Table 6.1 Comparison with other population-based studies on prevalence of visual impairment and blindness

			Prevalence of visual acuity less than 6/18					
			65 plus		75 plus		85 plus	
Country	Study	Correction of refractive error	N	%	N	%	N	%
UK	MRC Trial (current study)	Presenting binocular acuity <6/18			14600	12.4	3100	23.5
UK	Wormald et al	Pinhole <6/18	207	7.7	106	14.2		
**UK	Reidy et al	Presenting binocular acuity <6/12	1547	30.2				
UK	Van der Pols et al	Pinhole <6/18	1362	12.0				
**USA	SEE project	Presenting binocular acuity <6/12	2520	6.9	905	11.7		
Nether-lands	Rotterdam Study	Refraction	4214	2.2	1806	4.7	408	11.8
*USA	Baltimore Eye Study	Refraction	1751	2.6	836	4.8	206	13.1
USA	Beaver Dam Eye Study	Refraction	2073	2.7	795	6		
Australia	Blue Mountain Eye Study	Refraction	1990	2.1	783	5.0	132	13.6
*Australia	Melbourne Visual Impairment Project	Refraction	1467	2.8	605	6.2	161	18.8

Table 6.2 Comparison with other population-based studies on the causes of visual loss

Study	Year	Age	Definition of visual impairment	Number visually impaired	% with AMD	Cataract	Glaucoma	Diabetes	Other
Blindness									
MRC Trial	1995-98	75+	<3/60	249	66	7	12	3	11
Baltimore Eye Study	1988-89	65+	<=6/60	42	38	17	14	2	29
Beaver Dam Eye Study	1988-90	40+	<=6/60	21	57	5	0	10	28
SEE		>65	<6/60	15	40	13	33	0	13
Melbourne VIP		40+	<=6/60	24	88	4	0	0	8
Blue Mountains Eye Study		65-84	<=6/60	10	70	0	10	0	20
*Rotterdam Study	1990-93	75+	<3/60	50	70	8	6	0	16
Low vision									
MRC Trial	1995-98	75+	<6/18 - 3/60	728	41	39	8	3	9
Baltimore Eye Study	1988-89	65+	<6/12 - >6/60	134	25	44	3	0	28
SEE		40+	<6/18 - >=6/60	31	23	10	16	10	42
Melbourne VIP		>65	<6/18 - >6/60	21	38	33	10	5	14
Blue Mountains Eye Study		65-84	<6/12 - >6/60	50	32	42	2	8	16
*Rotterdam Study	1990-93	75+	<6/18 - 3/60	170	28	57	2	0	14

REFERENCES

Abou-Gareeb, I., Lewallen, S., Bassett, K., and Courtright, P. (2001) Gender and blindness: a meta-analysis of population-based prevalence surveys. *Ophthalmic Epidemiol* **8,** 39-56.

Ajani, U. A., Christen, W. G., Manson, J. E., Glynn, R. J., Schaumberg, D., Buring, J. E., and Hennekens, C. H. (1999) A prospective study of alcohol consumption and the risk of age-related macular degeneration. *Ann Epidemiol* **9,** 172-177.

Appollonio, I., Carabellese, C., Frattola, L., and Trabucchi, M. (1996) Effects of sensory aids on the quality of life and mortality of elderly people: a multivariate analysis. *Ophthalmol Physiol Opt* **25,** 89-96.

Appollonio, I., Carabellese, C., Magni, E., Frattola, L., and Trabucchi, M. (1995) Sensory impairments and mortality in an elderly community population: a six-year follow-up study. *Ophthalmol Physiol Opt* **24,** 30-36.

AREDS (2000) Risk factors associated with age-related macular degeneration ; A case-control study in the age-related eye disease study: age-related eye disease study report number 3. *Ophthalmology* **107,** 2224-2232.

Bailey, I. L. and Lovie, J. E. (1976) New design priniciples for visual acuity letter charts. *Am J Optom & Physiol Optics* **53,** 740-744.

Barrett-Connor, E. and Stuenkel, C. (1999) Hormones and heart disease in women: Heart and Estrogen/Progestin Replacement Study in Perspective. *Journal of Clinical Endocrinology & Metabolism* **84,** 1848-1853.

Beatty, S., Boulton, M., Henson, D., Koh, H., and Murray, I. J. (1999) Macular pigment and age related macular degeneration. *Br J Ophthalmol* **83,** 867-877.

Beatty, S., Koh, H. H., Phil, M., Henson, D., and Boulton, M. (2000) The Role of Oxidative Stress in the Pathogenesis of Age-Related Macular Degeneration. *Surv Ophthalmol* **45,** 115-134.

Bergner, M., Bobbitt, R. A., Carter, W. B., and Gilson, B. S. (1981) The Sickness Impact Profile: development and final revision of a health status measure. *Medical Care* **XIX,** 787-805.

Bird, A. C., Bressler, N. M., Bressler, S. B., Chisholm, I. H., Coscas, G., Davis, M. D., de Jong, P. T., Klaver, C. C., Klein, B. E., Klein, R., and et (1995) An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. *Surv Ophthalmol* **39,** 367-374.

Bjornsson, G. (1981) Blindness in Iceland. A review of legally blind persons in Iceland 1. Dec. 1979. *Acta Ophthalmol* **59,** 921-927.

Blumenkranz, M. S., Russell, S. R., Robey, M. G., Kott, B., and Penneys. N. (1986) Risk factors in age-related maculopathy complicated by choroidal neovascularization. *Ophthalmology* **93,** 552-558.

Bowling, A. (1997) *Measuring health: a review of quality of life measurement scales.* Open University Press: Buckingham.

Breeze, E. Health inequalities among older people in Great Britain. 2002. University of London.
Ref Type: Thesis/Dissertation

Breeze, E., Wilkinson, P., Grundy, C., and Fletcher, A. Inequalities in quality of life among people aged 75 and over. 2001. End of award report for ESRC Grant L408254018.
Ref Type: Report

Bressler, N. M., Bressler, S. B., West, S. K., Fine, S. L., and Taylor, H. R. (1989) The grading and prevalence of macular degeneration in Chesapeake Bay watermen. *Arch Ophthalmol* **107,** 847-852.

Bressler, N. M., Munoz, B., Maguire, M. G., Vitale, S. E., Schein, O. D., Taylor, H. R., and West, S. K. (1995) Five-year incidence and disappearance of drusen and retinal pigment epithelial abnormalities. Waterman study. *Arch Ophthalmol* **113,** 301-308.

Brody, B. L., Gamst, A. C., Williams, R. A., Smith, A. R., Lau, P. W., Dolnak, D., Rapaport, M. H., Kaplan, R. M., and Brown, S. I. (2001) Depression, visual acuity, comorbidity, and disability associated with age-related macular degeneration. *Ophthalmology* **108,** 1893-1900.

Brody, B. L., Roch-Levecq, A.-C., Gamst, A. C., Maclean, K., Kaplan, R. M., and Brown, S. I. (2002) Self-management of age-related macular degeneration and quality of life: a randomized controlled trial. *Arch Ophthalmol* **120,** 1477-1483.

Bruce, I., McKennell, A., and Walker, E. (1991) *Blind and partially sighted adults in Britain: the RNIB survey. Volume 1.* HMSO: London.

Bulpitt, C. J., Shipley, M. J., Demirovic, J., Ebi-Kryston, K. L., Markowe, H. L., and Rose, G. (1990) Predicting death from coronary heart disease using a questionnaire. *Int J Epidemiol* **19,** 899-904.

Carabellese, C., Appollonio, I., Rozzini, R., Bianchetti, A., Frisoni, G. B., Frattola, L., and Trabucchi, M. I. (1993) Sensory impairment and quality of life in a community elderly population. *J Am Geriatr Soc* **41,** 401-407.

Cederbaum, A. I. (1989) Role of lipid peroxidation and oxidative stress in alcohol toxicity. *Free Radic Biol Med* **7,** 537-539.

Chaine, G., Hullo, A., Sahel, J., Soubrane, G., Espinasse, B., Schutz, D., Bourguignon, C., Harpey, C., Brault, Y., Coste, M., Moccatti, D., and Bourgeois, H. (1998) Case-

control study of the risk factors for age related macular degeneration. France-DMLA Study Group. *Br J Ophthalmol* **82,** 996-1002.

Chan, C. W. and Billson, F. A. (1991) Visual disability and major causes of blindness in NSW: a study of people aged 50 and over attending the Royal Blind Society 1984 to 1989. *Aust N Z J Ophthalmol* **19,** 321-325.

Cho, E., Hankinson, S. E., Willett, W. C., Stampfer, M. J., Spiegelman, D., Speizer, F. E., Rimm, E. B., and Seddon, J. M. (2000) Prospective study of alcohol consumption and the risk of age-related macular degeneration. *Arch Ophthalmol* **118,** 681-688.

Christen, W. G., Glynn, R. J., Manson, J. E., Ajani, U. A., and Buring, J. E. (1996) A prospective study of cigarette smoking and risk of age-related macular degeneration in men. *JAMA* **276,** 1147-1151.

Copeland, K. T., Checkoway, H., McMichael, A. J., and Holbrook, R. H. (1977) Bias due to misclassification in the estimation of the relative risk. *Am J Epidemiol* **105,** 488-495.

Cox, D. R. (1972) Regression models and life-tables. *J R Statist Soc A*.

Cruickshanks, K. J., Hamman, R. F., Klein, R., Nondahl, D. M., and Shetterly, S. M. (1997) The prevalence of age-related maculopathy by geographic region and ethnicity. The Colorado-Wisconsin Study of Age-Related Maculopathy. *Arch Ophthalmol* **115,** 242-250.

Cruickshanks, K. J., Klein, R., and Klein, B. E. (1993) Sunlight and age-related macular degeneration. The Beaver Dam Eye Study. *Arch Ophthalmol* **111,** 514-518.

Cruickshanks, K. J., Klein, R., Klein, B. E., and Nondahl, D. M. (2001) Sunlight and the 5-year incidence of early age-related maculopathy: the Beaver Dam Eye Study. *Arch Ophthalmol* **119,** 246-250.

Culham, L. E., Ryan, B., Jackson, A. J., Hill, A. R., Jones, B., Miles, C., Young, J. A., Bunce, C., and Bird, A. C. (2002) Low vision services for vision rehabilitation in the United Kingdom. *Br J Ophthalmol* **86,** 743-747.

Cummings, S. R., Nevitt, M. C., Browner, W. S., Stone, K., Fox, K. M., Ensrud, K. E., Cauley, J., Black, D., and Vogt, T. M. (1995) Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* **332,** 767-773.

Dahlin-Ivanoff, S., Sonn, U., and Svensson, E. (2001) Development of an ADL instrument targeting elderly persons with age-related macular degeneration. *Disability & Rehabilitation* **23,** 69-79.

Dargent-Molina, P., Favier, F., Grandjean, H., Baudoin, C., Schott, A. M., Hausherr, E., Meunier, P. J., and Breart, G. (1996) Fall-related factors and risk of hip fracture: the EPIDOS prospective study. *Lancet* **348,** 145-149.

Darzins, P., Mitchell, P., and Heller, R. F. (1997) Sun exposure and age-related macular degeneration. An Australian case-control study. *Ophthalmology* **104,** 770-776.

Das, B. N., Thompson, J. R., Patel, R., and Rosenthal, A. R. (1994) The prevalence of eye disease in Leicester: a comparison of adults of Asian and European descent. *J Roy Soc Med* **87,** 219-222.

Davis, C., Lovie, K., and Thompson, B. (1995) Psychosocial adjustment to age-related macular degeneration. *J Vis Impairm Blindn* **89,** 16-27.

de Jong, P. T., Klaver, C. C., Wolfs, R. C., Assink, J. J., and Hofman, A. (1997) Familial aggregation of age-related maculopathy. *Am J Ophthalmol* **124,** 862-863.

de Mheen, P. J. M., Shipley, M. J., Witteman, J. C. M., Marmot, M. G., and Gunning-Schepers, L. J. (2001) Decline of the relative risk of death associated with low employment grade at older age: the impact of age related differences in smoking, blood pressure and plasma cholesterol. *J Epidemiol Community Health* **55,** 24-28.

Delaney, W. V. and Oates, R. P. (1982) Senile macular degeneration: a preliminary study. *Ann Ophthalmol* **14,** 21-Apr.

Delcourt, C., Diaz, J. L., Ponton, S., and Papoz, L. (1998) Smoking and age-related macular degeneration. The POLA Study. Pathologies Oculaires Liees a l'Age. *Arch Ophthalmol* **116,** 1031-1035.

Delcourt, C., Michel, F., Colvez, A., Lacroux, A., Delage, M., Vernet, M. H., and The POLA Study Group (2001) Associations of cardiovascular disease and its risk factors with age-related macular degeneration: the POLA study. *Ophthalmic Epidemiol* **8,** 237-249.

Desai, P., Reidy, A., Minassian, D. C., Vafidis, G., and Bolger, J. (1996) Gains from cataract surgery: visual function and quality of life. *Br J Ophthalmol* **80,** 868-873.

Dickinson, A. J., Sparrow, J. M., Duke, A. M., Thompson, J. R., Gibson, J. M., and Rosenthal, A. R. (1997) Prevalence of age-related maculopathy at two points in time in an elderly British population. *Eye* **11,** 301-314.

Dosso, A. A. and Bovet, J. (1992) Monozygotic twin brothers with age-related macular degeneration. *Ophthalmologica* **205,** 24-Aug.

Dunlop, D. D., Hughes, S. L., and Manheim, L. M. (1997) Disability in activities of daily living: patterns of change and a hierarchy of disability. *Am J Publ Hlth* **87,** 378-383.

Ederer, F., Krueger, D. E., Mowery, R. L., Connett, J., and Wentworth, D. (1986) Lessons from the Visual Acuity Impairment Survey Pilot Study. *Am J Publ Hlth* **76,** 160-165.

Eltinge, J. L. and Sribney, W. M. (1996) Some basic concepts for design-based analysis of complex survey data. *Stata Technical Bulletin* **31,** 3-6.

Evans, J. and Wormald, R. (1996) Is the incidence of registrable age-related macular degeneration increasing? *Br J Ophthalmol* **80,** 9-14.

Evans, J. R. (1995) *Causes of blindness and partial sight in England and Wales 1990-1991. Studies on Medical and Population Subjects 57*. HMSO: London.

Evans, J. R. (2001a) Antioxidant vitamin and mineral supplements for age-related macular degeneration (Cochrane review). Ed The Cochrane Library. Update Software: Oxford.

Evans, J. R. (2002) Age-related macular degeneration (in press). In: *Evidence-based Ophthalmology*, Eds R. P. L. Wormald, L. Smeeth, K. Henshaw. BMJ.

Evans, J. R. (2001b) Risk Factors for Age-related Macular Degeneration. *Prog Ret Eye Res* **20,** 227-253.

Eye Disease Case-Control Study Group (1992) Risk factors for neovascular age-related macular degeneration. *Arch Ophthalmol* **110,** 1701-1708.

Eye Disease Case-Control Study Group (1993) Antioxidant status and neovascular age-related macular degeneration. *Arch Ophthalmol* **111,** 104-109.

Fagerstrom, R. (1992) Correlations of memory and learning with vision in aged patients before and after a cataract operation. *Psychol Rep* **71,** 675-686.

Felson, D. T., Anderson, J. J., Hannan, M. T., Milton, R. C., Wilson, P. W., and Kiel, D. P. (1989) Impaired vision and hip fracture. The Framingham Study. *J Am Geriatr Soc* **37,** 495-500.

Ferris, F. L., III and Bailey, I. L. (1996) Standardizing the measurement of visual acuity for clinical research studies: guidelines from the Eye Care Technology Forum. *Ophthalmology* **103,** 181-182.

Ferris, F. L. and Sperduto, R. D. (1982) Standardized illumination for visual acuity testing in clinical research. *Am J Ophthalmol* **94,** 97-98.

Fine, S. L., Berger JW, Maguire, M., and Ho AC (2000) Drug therapy: age-related macular degeneration (review). *N Engl J Med* **342,** 483-492.

Finkel, T. and Holbrook, N. J. (2000) Oxidants, oxidative stress and the biology of ageing. *Nature* **408,** 239-247.

Fletcher, A. E., Jones, D. A., Bulpitt, C. J., and Tulloch, A. J. (2002) The MRC Trial of assessment and management of older people in the community: objectives, design and interventions [ISRCTN23494848]. *BMC Health Services Research* **2,** 21.

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12,** 189-198.

Friberg, T. R. and Borrero, G. (2000) Diminished perception of ambient light: a symptom of clinical depression? *Journal of Affective Disorders* **61,** 113-118.

Friedman, E. (1997) A hemodynamic model of the pathogenesis of age-related macular degeneration. *Am J Ophthalmol* **124,** 677-682.

Gaziano, J. M., Buring, J. E., Breslow, J. L., and et al (1993) Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. *N Engl J Med* **329,** 1829-1834.

Gibson, J. M., Rosenthal, A. R., and Lavery, J. (1985) A study of the prevalence of eye disease in the elderly in an English community. *Trans Ophthalmol Soc U K* **104,** 196-203.

Goldberg, J., Flowerdew, G., Smith, E., Brody, J. A., and Tso, M. O. (1988a) Factors associated with age-related macular degeneration. An analysis of data from the first National Health and Nutrition Examination Survey. *Am J Epidemiol* **128,** 700-710.

Goldberg, J., Flowerdew, G., Tso, M. O. M., and Brody, J. A. (1988b) Age-related macular degeneration and cataract: are dietary antioxidants protective? *Am J Epidemiol* **128,** 904-905.

Gorin, M. B., Breitner, J. C., de Jong, P. T., Hageman, G. S., Klaver, C. C., Kuehn, M. H., and Seddon, J. M. (1999) The genetics of age-related macular degeneration. *Mol Vis* **5,** 29.

Gottfredsdottir, M. S., Sverrisson, T., Musch, D. C., and Stefansson, E. (1999) Age related macular degeneration in monozygotic twins and their spouses in Iceland. *Acta Ophthalmol Scand* **77,** 422-425.

Graf, M., Halbach, E., and Kaufmann, H. (1999) Causes of blindness in Hessia. *Klin Monatsbl Augenheilkd* **215,** 50-55.

Grizzard, W. S. and Beck, R. W. (1994) Twin study of age related macular degeneration. *Invest Ophthalmol Vis Sci* **35,** 1504.

Hansen, E. (1981) Blindness in Norway, causes and prophylactic attempts. *Tidsskr nor Laegeforen* **101,** 187-193.

Heiba, I. M., Elston, R. C., Klein, B. E., and Klein, R. (1994) Sibling correlations and segregation analysis of age-related maculopathy: the Beaver Dam Eye Study. *Genet Epidemiol* **11,** 51-67.

Heim, M. and Morgner, J. (1997) [Color vision defects in endogenous depression]. [German]. *Psychiatrische Praxis* **24,** 73.

Hennekens, C. H. and Buring, J. E. (1987) *Epidemiology in medicine*. Little, Brown and Company.: Boston, Mass.

Heuberger, R. A., Mares-Perlman, J. A., Klein, R., Klein, B. E., Millen, A. E., and Palta, M. (2001) Relationship of dietary fat to age-related maculopathy in the Third National Health and Nutrition Examination Survey. *Arch Ophthalmol* **119,** 1833-1838.

Hirvela, H., Luukinen, H., Laara, E., Sc, L., and Laatikainen, L. (1996) Risk factors of age-related maculopathy in a population 70 years of age or older. *Ophthalmology* **103,** 871-877.

Hunt, S. M. (1984) Nottingham Health Profile. In: *Assessment of quality of life in clinical trials of cardiovascular therapies*, Eds N. K. Wenger, C. D. Mattson, C. D. Furberg. Le Jacq: New York.

Hyman, L., Schachat, A. P., Qimet, H., and Leske, M. C. (2001) Hypertension, cardiovascular disease, and age-related macular degeneration. *Arch Ophthalmol* **117,** 351-358.

Hyman, L. G., Lilienfeld, A. M., Ferris, F. L., and Fine, S. L. (1983) Senile macular degeneration: a case-control study. *Am J Epidemiol* **118,** 213-227.

Inouye, S. K., Viscoli, C. M., Horwitz, R. I., Hurst, L. D., and Tinetti, M. E. (1993) A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. *Ann Intern Med* **119,** 474-481.

Ip, S. P., Leung, Y. F., and Mak, W. P. (2000) Depression in institutionalised older people with impaired vision. *Int J Ger Psych* **15,** 1120-1124.

Ivers, R. Q., Cumming, R. G., Mitchell, P., and Attebo, K. (1998) Visual impairment and falls in older adults: The Blue Mountains Eye Study. *J Am Geriatr Soc* **46,** 58-64.

Ivers, R. Q., Mitchell, P., and Cumming, R. G. (2000) Visual function tests, eye disease and symptoms of visual disability: a population-based assessment. *Clin Exp Ophthalmol* **28,** 41-47.

Jack, C. I., Smith, T., Neoh, C., Lye, M., and McGalliard, J. N. (1995) Prevalence of low vision in elderly patients admitted to an acute geriatric unit in Liverpool: elderly people who fall are more likely to have low vision. *Gerontology* **41,** 280-285.

Jagger, C., Arthur, A. J., Spiers, N. A., and Clarke, M. (2001) Patterns of onset of disability in activities of daily living with age. *J Am Geriatr Soc* **49,** 404-409.

Jagger, C., Clarke, M., Anderson, J., and Battcock, T. (1992) Misclassification of dementia by the Mini-Mental State Examination - are education and social class the only factors? *Age & Ageing* **21,** 404-411.

Jampol, L. M. and Tielsch, J. (1992) Race, macular degeneration and the macular photocoagulation study. *Arch Ophthalmol* **110,** 1699-1700.

Jarman, B. (1983) Identification of underprivileged areas. *Br Med J (Clin Res Ed)* **286,** 1705-1709.

Jonasson, F. and Thordarson, K. (1987) Prevalence of ocular disease and blindness in a rural area in the eastern region of Iceland during 1980 through 1984. *Acta Ophthalmol Suppl* **182,** 40-43.

Juni, P., Altman, D., and Egger, M. (2001) Assessing the quality of randomised controlled trials. In: *Systematic reviews in health care: meta-analysis in context*, pp. 87-108. Eds M. Egger, G. Davey Smith, D. G. Altman. BMJ Publishing Group: London.

Kahn, H. A., Leibowitz, H. M., Ganley, J. P., Kini, M. M., Colton, T., Nickerson, R. S., and Dawber, T. R. (1977a) The Framingham Eye Study. I. Outline and major prevalence findings. *Am J Epidemiol* **106,** 17-32.

Kahn, H. A., Leibowitz, H. M., Ganley, J. P., Kini, M. M., Colton, T., Nickerson, R. S., and Dawber, T. R. (1977b) The Framingham Eye Study. II. Association of ophthalmic pathology with single variables previously measured in the Framingham Heart Study. *Am J Epidemiol* **106,** 33-41.

Katz, S., Ford, A. B., Moskowitz, R. W., and et al (1963) Studies of illness in the aged: the index of ADL - a standardized measure of biological and psychosocial function. *JAMA* **185,** 914-919.

Keeffe, J. E., Lam, D., Cheung, A., Dinh, T., and McCarty, C. A. (1998) Impact of vision impairment on functioning. *Aust N Z J Ophthalmol* **26,** S16-S18.

Kini, M. M., Leibowitz, H. M., Colton, T., Nickerson, R. J., Ganley, J., and Dawber, T. R. (1978) Prevalence of senile cataract, diabetic retinopathy, senile macular degeneration, and open-angle glaucoma in the Framingham eye study. *Am J Ophthalmol* **85,** 28-34.

Klaver, C. C., Assink, J. J., van Leeuwen, R., Wolfs, R. C., Vingerling, J. R., Stijnen, T., Hofman, A., and de Jong, P. T. (2001) Incidence and progression rates of age-related maculopathy: the Rotterdam Study. *Invest Ophthalmol Vis Sci* **42,** 2237-2241.

Klaver, C. C., Assink, J. J., Vingerling, J. R., Hofman, A., and de Jong, P. T. (1997) Smoking is also associated with age-related macular degeneration in persons aged 85 years and older: The Rotterdam Study. *Arch Ophthalmol* **115,** 945.

Klaver, C. C., Wolfs, R. C., Vingerling, J. R., Hofman, A., and de Jong, P. T. (1998) Age-specific prevalence and causes of blindness and visual impairment in an older population: the Rotterdam Study. *Arch Ophthalmol* **116,** 653-658.

Klein, B. E. and Klein, R. (1982) Cataracts and macular degeneration in older Americans. *Arch Ophthalmol* **100,** 571-573.

Klein, B. E., Klein, R., Jensen, S. C., and Ritter, L. L. (1994a) Are sex hormones associated with age-related maculopathy in women? The Beaver Dam Eye Study. *Trans Am Ophthalmol Soc* **92,** 289-295.

Klein, B. E., Klein, R., and Lee, K. E. (2000) Reproductive exposures, incident age-related cataracts, and age-related maculopathy in women: the beaver dam eye study. *Am J Ophthalmol* **130,** 322-326.

Klein, B. E., Klein, R., Lee, K. E., and Cruickshanks, K. J. (1998a) Performance-based and self-assessed measures of visual function as related to history of falls, hip fractures, and measured gait time. The Beaver Dam Eye Study. *Ophthalmology* **105,** 160-164.

Klein, B. E., Klein, R., Lee, K. E., and Jensen, S. C. (2001a) Measures of obesity and age-related eye diseases. *Ophthalmic Epidemiol* **8,** 251-262.

Klein, B. E., Klein, R., Lee, K. E., Moore, E. L., and Danforth, L. (2001b) Risk of incident age-related eye diseases in people with an affected sibling : The Beaver Dam Eye Study. *Am J Epidemiol* **154,** 207-211.

Klein, M. L., Mauldin, W. M., and Stoumbos, V. D. (1994b) Heredity and age-related macular degeneration. Observations in monozygotic twins. *Arch Ophthalmol* **112,** 932-937.

Klein, R., Clegg, L., Cooper, L. S., Hubbard, L. D., Klein, B. E. K., King, W. N., and Folsom, A. R. (1999a) Prevalence of age-related maculopathy in the atherosclerosis risk in communities study. *Arch Ophthalmol* **117,** 1203-1210.

Klein, R., Davis, M. D., Magli, Y. L., Segal, P., Klein, B. E. K., and Hubbard, L. (1991a) The Wisconsin age-related maculopathy grading system. *Ophthalmology* **98,** 1128-1134.

Klein, R., Klein, B. E., and Cruickshanks, K. J. (1999b) The prevalence of age-related maculopathy by geographic region and ethnicity. *Prog Ret Eye Res* **18,** 371-389.

Klein, R., Klein, B. E., and Franke, T. (1993a) The relationship of cardiovascular disease and its risk factors to age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology* **100,** 406-414.

Klein, R., Klein, B. E., and Jensen, S. C. (1997a) The relation of cardiovascular disease and its risk factors to the 5-year incidence of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology* **104,** 1804-1812.

Klein, R., Klein, B. E., Jensen, S. C., Mares, P., Cruickshanks, K. J., and Palta, M. (1999c) Age-related maculopathy in a multiracial United States population: the National Health and Nutrition Examination Survey III. *Ophthalmology* **106,** 1056-1065.

Klein, R., Klein, B. E., Jensen, S. C., and Meuer, S. M. (1997b) The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology* **104,** 7-21.

Klein, R., Klein, B. E., Jensen, S. C., and Moss, S. E. (2001c) The relation of socioeconomic factors to the incidence of early age-related maculopathy: the Beaver Dam Eye Study. *Am J Ophthalmol* **132,** 128-131.

Klein, R., Klein, B. E., Jensen, S. C., Moss, S. E., and Cruickshanks, K. J. (1994c) The relation of socioeconomic factors to age-related cataract, maculopathy, and impaired vision. The Beaver Dam Eye Study. *Ophthalmology* **101,** 1969-1979.

Klein, R., Klein, B. E., and Linton, K. L. (1992a) Prevalence of age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology* **99,** 933-943.

Klein, R., Klein, B. E., Linton, K. L., and De Mets, D. L. (1991b) The Beaver Dam Eye Study: visual acuity. *Ophthalmology* **98,** 1310-1315.

Klein, R., Klein, B. E., and Moss, S. E. (1992b) Diabetes, hyperglycemia, and age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology* **99,** 1527-1534.

Klein, R., Klein, B. E., and Moss, S. E. (1995a) Age-related eye disease and survival. The Beaver Dam Eye Study. *Arch Ophthalmol* **113,** 333-339.

Klein, R., Klein, B. E., and Moss, S. E. (1998b) Relation of smoking to the incidence of age-related maculopathy. The Beaver Dam Eye Study. *Am J Epidemiol* **147,** 103-110.

Klein, R., Klein, B. E. K., Linton, K. L. P., and DeMets, D. L. (1993b) The Beaver Dam Eye Study: The relation of age-related maculopathy to smoking. *Am J Epidemiol* **137,** 190-200.

Klein, R., Rowland, M. L., and Harris, M. I. (1995b) Racial/ethnic differences in age-related maculopathy. Third National Health and Nutrition Examination Survey. *Ophthalmology* **102,** 371-381.

Krumpaszky, H. G. and Klauss, V. (1992) Cause of blindness in Bavaria. Evaluation of a representative sample from blindness compensation records of Upper Bavaria. *Klin Monatsbl Augenheilkd* **200,** 142-146.

Laatikainen, L. and Hirvela, H. (1995) Prevalence and visual consequences of macular changes in a population aged 70 years and older. *Acta Ophthalmol Scand* **73,** 105-110.

Laforge, R. G., Spector, W. D., and Sternberg, J. (1992) The relationship of vision and hearing impairment to one-year mortality and functional decline. *Journal of Aging & Health Vol* **4,** 126-148.

Lawton, M. P. (1975) The Philadelphia Geratric Center Morale Scale: A Revision. *J Gerontol* **30,** 85-89.

Lee, D. J., Gomez-Marin, O., Lam, B. L., and Zheng, D. (2002) Visual acuity impairment and mortality in US adults. *Arch Ophthalmol* **120,** 1544-1550.

Maclure, M. and Willett, W. C. (1987) Misinterpretation and misuse of the kappa statistic. *Am J Epidemiol* **126,** 161-169.

Maltzman, B. A., Mulvihill, M. N., and Greenbaum, A. (1979) Senile macular degeneration and risk factors: a case-control study. *Ann Ophthalmol* **11,** 1197-1201.

Mangione, C. M., Gutierrez, P. R., Lowe, G., Orav, E. J., and Seddon, J. M. (1999) Influence of age-related maculopathy on visual functioning and health- related quality of life. *Am J Ophthalmol* **128,** 45-53.

Mangione, C. M., Lee, P. P., Gutierrez, P. R., Spritzer, K., Berry, S., Hays, R. D., and National Eye Institute (2001) Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol* **119,** 1050-1058.

Mangione, C. M., Phillips, R. S., Seddon, J. M., Lawrence, M. G., Cook, E. F., Dailey, R., and Goldman, L. (1992) Development of the 'Activities of Daily Vision Scale'. A measure of visual functional status. *Medical Care* **30,** 1111-1126.

Mares-Perlman, J. A., Brady, W. E., Klein, R., Klein, B. E., Bowen, P., Stacewicz-Sapuntzakis, M., and Palta, M. (1995a) Serum antioxidants and age-related macular

degeneration in a population-based case-control study. *Arch Ophthalmol* **113,** 1518-1523.

Mares-Perlman, J. A., Brady, W. E., Klein, R., VandenLangenberg, G. M., Klein, B. E., and Palta, M. (1995b) Dietary fat and age-related maculopathy. *Arch Ophthalmol* **113,** 743-748.

Mares-Perlman, J. A., Klein, R., Klein, B. E., Greger, J. L., Brady, W. E., Palta, M., and Ritter, L. L. (1996) Association of zinc and antioxidant nutrients with age-related maculopathy. *Arch Ophthalmol* **114,** 991-997.

Martinez, G. S., Campbell, A. J., Reinken, J., and Allan, B. C. (1982) Prevalence of ocular disease in a population study of subjects 65 years old and older. *Am J Ophthalmol* **94,** 181-189.

Maruo, T., Ikebukuro, N., Kawanabe, K., and Kubota, N. (1991) Changes in causes of visual handicaps in Tokyo. *Jpn J Ophthalmol* **35,** 268-272.

Marx, M. S., Werner, P., Cohen, M., and Feldman, R. (1992) The relationship between low vision and performance of activities of daily living in nursing home residents. *J Am Geriatr Soc* **40,** 1018-1020.

McCarty, C. A., Mukesh, B. N., Fu, C. L., Mitchell, P., Wang, J. J., and Taylor, H. R. (2001a) Risk factors for age-related maculopathy: the Visual Impairment Project. *Arch Ophthalmol* **119,** 1455-1462.

McCarty, C. A., Nanjan, M. B., and Taylor, H. R. (2001b) Vision impairment predicts 5 year mortality. *Br J Ophthalmol* **85,** 322-326.

McCarty, C. A. and Taylor, H. R. (2002) A review of the epidemiologic evidence linking ultraviolet radiation and cataracts. *Dev Ophthalmol* **35,** 21-31.

McGraw, P. V. and Winn, B. (1993) Glasgow Acuity Cards: a new test for the measurement of letter acuity in children. *Ophthalmol Physiol Opt* **13,** 400-404.

McGraw, P. V., Winn, B., Gray.L.S., and Elliott, D. B. (2000) Improving the reliability of visual acuity measures in young children. *Ophthalmol Physiol Opt* **20,** 173-184.

Meade, T. W., Chakrabarti, R., Haines, A. P., and et al (1979) Characteristics affecting fibrinolytic activity and plasma fibrinogen concentration. *BMJ* **1,** 153-156.

Melrose, M. A., Magargal, L. E., and Lucier, A. C. (1985) Identical twins with subretinal neovascularization complicating senile macular degeneration. *Ophthalmic Surg* **16,** 648-651.

Mitchell, P., Hayes, P., and Wang, J. J. (1997) Visual impairment in nursing home residents: the Blue Mountains Eye Study. *Med J Aust* **166,** 73-76.

Mitchell, P., Smith, W., Attebo, K., and Wang, J. J. (1995) Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. *Ophthalmology* **102,** 1450-1460.

Mitchell, P., Smith, W., and Wang, J. J. (1998) Iris color, skin sun sensitivity, and age-related maculopathy. The Blue Mountains Eye Study. *Ophthalmology* **105,** 1359-1363.

Mitchell, P., Wang, J. J., Foran, S., and Smith, W. (2002) Five-year incidence of age-related maculopathy lesions: The Blue Mountains Eye Study. *Ophthalmology* **109,** 1092-1097.

Moss, S. E., Klein, R., Klein, B. E., Jensen, S. C., and Meuer, S. M. (1998) Alcohol consumption and the 5-year incidence of age-related maculopathy: the Beaver Dam eye study. *Ophthalmology* **105,** 789-794.

Obisesan, T. O., Hirsch, R., Kosoko, O., Carlson, L., and Parrott, M. (1998) Moderate wine consumption is associated with decreased odds of developing age-related macular degeneration in NHANES-1. *J Am Geriatr Soc* **46,** 1-7.

Office for National Statistics (2002) *Census 2001: First results on population for England and Wales*. HMSO: London.

Osborn, D. P., Fletcher, A. E., Smeeth, L., Stirling, S., Nunes, M., Breeze, E., and Siu-Woon Ng, E. (2002) Geriatric Depression Scale Scores in a representative sample of 14 545 people aged 75 and over in the United Kingdom: results from the MRC Trial of Assessment and Management of Older People in the Community. *Int J Ger Psych* **17,** 375-382.

Owen, C. G., Fletcher, A. E., Donoghue, M., and Rudnicka, A. R. (2003) How big is the burden of visual loss caused by age-related macular degeneration in the UK? *Br J Ophthalmol*. **87**, 312-317.

Pagliarini, S., Moramarco, A., Wormald, R. P., Piguet, B., Carresi, C., Balacco, G., Sehmi, K. S., and Bird, A. C. (1997) Age-related macular disease in rural southern Italy. *Arch Ophthalmol* **115,** 616-622.

Piguet, B., Wells, J. A., Palmvang, I. B., Wormald, R., Chisholm, I. H., and Bird, A. C. (1993) Age-related Bruch's membrane change: a clinical study of the relative role of heredity and environment. *Br J Ophthalmol* **77,** 400-403.

Rao, J. N. K. and Thomas, D. R. (1989) Chi-squared tests for contingency tables. In: *Analysis of Complex Surveys*, pp. 89-114. Eds C. J. Skinner, D. Holt, T. M. F. Smith. John Wiley & Sons: New York.

Reidy, A., Minassian, D. C., Desai, P., Vafidis, G., Joseph, J., Farrow, S., and Connolly, A. (2002) Increased mortality in women with cataract: a population based follow up of the North London Eye Study. *Br J Ophthalmol* **86,** 424-428.

Reidy, A., Minassian, D. C., Vafidis, G., Joseph, J., Farrow, S., Wu, J., Desai, P., and Connolly, A. (1998) Prevalence of serious eye disease and visual impairment in a north London population: population based, cross sectional study. *BMJ* **316,** 1643-1646.

Renaud, S. C., Beswick, A. D., Fehily, A. M., and et al (1992) Alcohol and platelet aggregation: the Caerphilly Prospective Heart Disease Study. *Am J Clin Nutr* **55,** 1012-1017.

Ritter, L. L., Klein, R., Klein, B. E., Mares, P., and Jensen, S. C. (1995) Alcohol use and age-related maculopathy in the Beaver Dam Eye Study. *Am J Ophthalmol* **120,** 190-196.

Rose, G., McCartney, P., and Reid, D. D. (1977) Self-administration of a questionnaire on chest pain and intermittent claudication. *Br J Prev Soc Med* **31,** 42-48.

Rothman, K. J. (1986) *Modern Epidemiology*. Little, Brown and Company: Boston/Toronto.

Rovner, B. W., Casten, R. J., and Tasman, W. S. (2002) Effect of depression on vision function in age-related macular degeneration. *Arch Ophthalmol* **120,** 1041-1044.

Rubin, G. S., Bandeen-Roche, K., Huang, G. H., Munoz, B., Schein, O. D., Fried, L. P., and West, S. K. (2001) The association of multiple visual impairments with self-reported visual disability: SEE project. *Invest Ophthalmol Vis Sci* **42,** 64-72.

Rubin, G. S., West, S. K., Munoz, B., Bandeen-Roche, K., Zeger, S., Schein, O., and Fried, L. P. (1997) A comprehensive assessment of visual impairment in a population of older Americans. The SEE Study. Salisbury Eye Evaluation Project. *Invest Ophthalmol Vis Sci* **38,** 557-568.

Salive, M. E., Guralnik, J., Glynn, R. J., Christen, W., Wallace, R. B., and Ostfeld, A. M. (1994) Association of visual impairment with mobility and physical function. *J Am Geriatr Soc* **42,** 287-292.

Sanders, T. A., Haines, A. P., Wormald, R., Wright, L. A., and Obeid, O. (1993) Essential fatty acids, plasma cholesterol, and fat-soluble vitamins in subjects with age-related maculopathy and matched control subjects. *Am J Clin Nutr* **57,** 428-433.

Schachat, A. P., Hyman, L., Leske, M. C., Connell, A. M., and Wu, S. Y. (1995) Features of age-related macular degeneration in a black population. The Barbados Eye Study Group. *Arch Ophthalmol* **113,** 728-735.

Schaumberg, D. A., Christen, W. G., Hankinson, S. E., and Glynn, R. J. (2001) Body mass index and the incidence of visually significant age-related maculopathy in men. *Arch Ophthalmol* **119,** 1259-1265.

Scott, I. U., Schein, O. D., West, S., Bandeen-Roche, K., Enger, C., and Folstein, M. F. (1994) Functional status and quality of life measurement among ophthalmic patients. *Arch Ophthalmol* **112,** 329-335.

Seddon, J. M., Ajani, U. A., and Mitchell, B. D. (1997) Familial aggregation of age-related maculopathy. *Am J Ophthalmol* **123,** 199-206.

Seddon, J. M., Ajani, U. A., Sperduto, R. D., Hiller, R., Blair, N., Burton, T. C., Farber, M. D., Gragoudas, E. S., Haller, J., Miller, D. T., and et (1994) Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group. *JAMA* **272,** 1413-1420.

Seddon, J. M., Rosner, B., Sperduto, R. D., Yannuzzi, L., Haller, J. A., Blair, N. P., and Willett, W. (2001) Dietary fat and risk for advanced age-related macular degeneration. *Arch Ophthalmol* **119,** 1191-1199.

Seddon, J. M., Willett, W. C., Speizer, F. E., and Hankinson, S. E. (1996) A prospective study of cigarette smoking and age-related macular degeneration in women. *JAMA* **276,** 1141-1146.

Sheik, J. I. and Yesavage, J. A. (1986) Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. *Clin Geront* **37,** 819-820.

Silver, J. H., Gould, E. S., Irvine, D., and et al (1978) Visual acuity at home and in eye clinics. *Trans Ophthalmol Soc U K* **98,** 262-266.

Silvestri, G., Johnston, P. B., and Hughes, A. E. (1994) Is genetic predisposition an important risk factor in age-related macular degeneration? *Eye* **8,** 564-568.

Simes, R. J. (1986) Publication bias: the case for an international registry of clinical trials. *J Clin Oncol* **4,** 1529-1541.

Simons, K. (1993) Artificial light and early-life exposure in age-related macular degeneration and in cataractogenic phototoxicity. *Arch Ophthalmol* **111,** 297-298.

Skinner, C. J., Holt, D., and Smith, T. M. F. (1989) *Analysis of complex surveys*. John Wiley & Sons: New York.

Smeeth, L., Fletcher, A. E., Hanciles, S., Evans, J. R., and Wormald, R. P. L. Screening older people for impaired vision in primary care: a cluster randomised trial within the MRC trial of the assessment and management of older people in the community. 2002a.
Ref Type: Unpublished Work

Smeeth, L., Fletcher, A. E., Ng, E. S., Stirling, S., Breeze, E., Bulpitt, C. J., Jones, D., and Tulloch, A. (2002b) Reduced hearing, ownership, and use of hearing aids in elderly people in the UK - the MRC Trial of the Assessment and Management of Older People in the Community: a cross-sectional survey. *Lancet* **359,** 1466-1470.

Smith, W., Assink, J., Klein, R., Mitchell, P., Klaver, C. C., Klein, B. E., Hofman, A., Jensen, S., Wang, J. J., and de Jong, P. T. (2001) Risk factors for age-related macular degeneration: Pooled findings from three continents. *Ophthalmology* **108,** 697-704.

Smith, W. and Mitchell, P. (1996) Alcohol intake and age-related maculopathy. *Am J Ophthalmol* **122,** 743-745.

Smith, W. and Mitchell, P. (1998) Family history and age-related maculopathy: the Blue Mountains Eye Study. *Aust N Z J Ophthalmol* **1998 Aug;26,** 203-206.

Smith, W., Mitchell, P., and Leeder, S. R. (1996) Smoking and age-related maculopathy. The Blue Mountains Eye Study. *Arch Ophthalmol* **114,** 1518-1523.

Smith, W., Mitchell, P., Leeder, S. R., and Wang, J. J. (1998a) Plasma fibrinogen levels, other cardiovascular risk factors, and age-related maculopathy: the Blue Mountains Eye Study. *Arch Ophthalmol* **116,** 583-587.

Smith, W., Mitchell, P., Leeder, S. R., and Wang, J. J. (1998b) Plasma fibrinogen levels, other cardiovascular risk factors, and age-related maculopathy: the Blue Mountains Eye Study. *Arch Ophthalmol* **116,** 583-587.

Smith, W., Mitchell, P., and Wang, J. J. (1997) Gender, oestrogen, hormone replacement and age-related macular degeneration: results from the Blue Mountains Eye Study. *Aust N Z J Ophthalmol* **25,** S13-S15.

Snow, K. K. and Seddon, J. M. (1999) Do age-related macular degeneration and cardiovascular disease share common antecedents? *Ophthalmic Epidemiol* **6,** 125-143.

Sperduto, R. D. and Hiller, R. (1986) Systemic hypertension and age-related maculopathy in the Framingham Study. *Arch Ophthalmol* **104,** 216-219.

StataCorp . Stata Statistical Software. [Release 7.0]. 2001. Stata Corporation, College Station, TX.
Ref Type: Computer Program

Steinberg, E. P., Tielsch, J. M., Schein, O. D., Javitt, J. C., Sharkey, P., Cassard, S. D., Legro, M. W., Diener-West, M., Bass, E. B., and Damiano, A. M. (1994) The VF-14. An index of functional impairment in patients with cataract. *Arch Ophthalmol* **112,** 630-638.

Swan, I. R. and Browning, G. G. (1985) The whispered voice as a screening test for hearing impairment. *J Roy Coll Pract* **35,** 197.

Tabandeh, H., Lockley, S. W., Buttery, R., Skene, D. J., Defrance, R., Arendt, J., and Bird, A. C. (1998) Disturbance of sleep in blindness. *Am J Ophthalmol* **126,** 707-712.

Tamakoshi, A., Yuzawa, M., Matsui, M., Uyama, M., Fujiwara, N. K., and Ohno, Y. (1997) Smoking and neovascular form of age related macular degeneration in late middle aged males: findings from a case-control study in Japan. Research Committee on Chorioretinal Degenerations. *Br J Ophthalmol* **81,** 901-904.

Taylor, H. R. (1989) Ultraviolet radiation and the eye: an epidemiologic study. *Trans Am Ophthalmol Soc* **87,** 802-853.

Taylor, H. R., Livingston, P. M., Stanislavsky, Y. L., and McCarty, C. A. (1997) Visual impairment in Australia: distance visual acuity, near vision, and visual field findings of the Melbourne Visual Impairment Project. *Am J Ophthalmol* **123,** 328-337.

Taylor, H. R., McCarty, C. A., and Nanjan, M. B. (2000) Vision impairment predicts five-year mortality. *Trans Am Ophthalmol Soc* **98,** 91-96.

Taylor, H. R., Munoz, B., West, S., Bressler, N. M., Bressler, S. B., and Rosenthal, F. S. (1990) Visible light and risk of age-related macular degeneration. *Trans Am Ophthalmol Soc* **88,** 163-173.

Thompson, J. R., Gibson, J. M., and Jagger, C. (1989) The association between visual impairment and mortality in elderly people. *Ophthalmol Physiol Opt* **18,** 83-88.

Tielsch, J. M., Javitt, J. C., Coleman, A., Katz, J., and Sommer, A. (1995) The prevalence of blindness and visual impairment among nursing home residents in Baltimore. *N Engl J Med* **332,** 1205-1209.

Tombaugh, T. N. and McIntyre, N. J. (1992) The Mini-Mental State Examination: a comprehensive review. *J Am Geriatr Soc* **40,** 922-935.

Uhlmann, R. F., Larson, E. B., Koepsell, T. D., Rees, T. S., and Duckert, L. G. (1991) Visual impairment and cognitive dysfunction in Alzheimer's disease. *J Gen Int Med* **6,** 126-132.

Valbuena, M., Bandeen-Roche, K., Rubin, G. S., Munoz, B., and West, S. K. (1999) Self-reported assessment of visual function in a population-based study: the SEE project. Salisbury Eye Evaluation. *Invest Ophthalmol Vis Sci* **40,** 280-288.

van der Pols, J. C., Bates, C. J., McGraw, P. V., Thompson, J. R., Reacher, M., Prentice, A., and Finch, S. (2000) Visual acuity measurements in a national sample of British elderly people. *Br J Ophthalmol* **84,** 165-170.

VandenLangenberg, G. M., Mares-Perlman, J. A., Klein, R., Klein, B. E., Brady, W. E., and Palta, M. (1998) Associations between antioxidant and zinc intake and the 5-year incidence of early age-related maculopathy in the Beaver Dam Eye Study. *Am J Epidemiol* **148,** 204-214.

VanNewkirk, M. R., Nanjan, M. B., Wang, J. J., Mitchell, P., Taylor, H. R., and McCarty, C. A. (2000a) The prevalence of age-related maculopathy: the visual impairment project. *Ophthalmology* **107,** 1593-1600.

VanNewkirk, M. R., Weih, L., McCarty, C. A., Stanislavsky, Y. L., Keeffe, J. E., and Taylor, H. R. (2000b) Visual impairment and eye diseases in elderly institutionalized Australians. *Ophthalmology* **107,** 2203-2208.

Vinding, T. (1989) Age-related macular degeneration. Macular changes, prevalence and sex ratio. An epidemiological study of 1000 aged individuals. *Acta Ophthalmol Copenh* **67,** 609-616.

Vinding, T. (1990) Visual impairment of age-related macular degeneration. An epidemiological study of 1000 aged individuals. *Acta Ophthalmol* **68,** 162-167.

Vinding, T. (1995) Age-related macular degeneration. An epidemiological study of 1000 elderly individuals. With reference to prevalence, funduscopic findings, visual impairment and risk factors. *Acta Ophthalmol Scand Suppl* **73,** 1-32.

Vinding, T., Appleyard, M., Nyboe, J., and Jensen, G. (1992) Risk factor analysis for atrophic and exudative age-related macular degeneration. An epidemiological study of 1000 aged individuals. *Acta Ophthalmol* **70,** 66-72.

Vingerling, J. R., Dielemans, I., Bots, M. L., Hofman, A., Grobbee, D. E., and de Jong, P. T. (1995a) Age-related macular degeneration is associated with atherosclerosis. The Rotterdam Study. *Am J Epidemiol* **142,** 404-409.

Vingerling, J. R., Dielemans, I., Hofman, A., Grobbee, D. E., Hijmering, M., Kramer, C. F., and de Jong, P. T. (1995b) The prevalence of age-related maculopathy in the Rotterdam Study. *Ophthalmology* **102,** 205-210.

Vingerling, J. R., Dielemans, I., Witteman, J. C. M., Hofman, A., Grobbee, D. E., and de Jong, P. T. V. M. (1995c) Macular degeneration and early menopause: a case-control study. *BMJ* **310,** 1570-1571.

Vingerling, J. R., Hofman, A., Grobbee, D. E., and de Jong, P. T. (1996) Age-related macular degeneration and smoking. The Rotterdam Study. *Arch Ophthalmol* **114,** 1193-1196.

Virgili, G. and Rubin, G. (2002) Orientation and mobility training for adults with low vision (Protocol for a Cochrane Review). Update Software: Oxford.

Wang, J. J., Mitchell, P., Simpson, J. M., Cumming, R. G., and Smith, W. (2001) Visual impairment, age-related cataract, and mortality. *Arch Ophthalmol* **119,** 1186-1190.

Wang, J. J., Mitchell, P., and Smith, W. (2000) Vision and low self-rated health: the Blue Mountains Eye Study. *Invest Ophthalmol Vis Sci* **41,** 49-54.

Weiter, J. J., Delori, F. C., Wing, G. L., and Fitch, K. A. (1985) Relationship of senile macular degeneration to ocular pigmentation. *Am J Ophthalmol* **99,** 185-187.

West, S., Vitale, S., Hallfrisch, J., Munoz, B., Muller, D., Bressler, S., and Bressler, N. M. (1994b) Are antioxidants or supplements protective for age-related macular degeneration? *Arch Ophthalmol* **112,** 222-227.

West, S., Vitale, S., Hallfrisch, J., Munoz, B., Muller, D., Bressler, S., and Bressler, N. M. (1994a) Are antioxidants or supplements protective for age-related macular degeneration? *Arch Ophthalmol* **112,** 222-227.

West, S. K., Munoz, B., Rubin, G. S., Schein, O. D., Bandeen-Roche, K., Zeger, S., German, P. S., and Fried, L. P. (1997) Function and visual impairment in a population-based study of older adults. *Invest Ophthalmol Vis Sci* **38,** 72-82.

West, S. K., Rosenthal, F. S., Bressler, N. M., Bressler, S. B., Munoz, B., Fine, S. L., and Taylor, H. R. (1989) Exposure to sunlight and other risk factors for age-related macular degeneration. *Arch Ophthalmol* **107,** 875-879.

WHO (1977) *International Classification of Diseases 9th Revision.* WHO: Geneva.

Williams, R. A., Brody, B. L., Thomas, R. G., Kaplan, R. M., and Brown, S. I. (1998) The psychosocial impact of macular degeneration. *Arch Ophthalmol* **116,** 514-520.

World Health Organization (1992) *International Statistical Classification of Diseases and Related Health Problems Tenth Revision.* WHO: Geneva.

Wu, L. H. (1987) Study of aging macular degeneration in China. *Jpn J Ophthalmol* **31,** 349-367.

Yates, J. R. W. and Moore, A. T. (2000) Genetic susceptibility to age related macular degeneration. *J Med Genet* **37,** 83-87.

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., and Leirer, V. O. (1982) Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* **17,** 37-49.

Young, R. W. (1988) Solar radiation and age-related macular degeneration. *Surv Ophthalmol* **32,** 252-269.

Zack, D. J., Dean, M., Molday, R. S., Nathans, J., Redmond, T. M., Stone, E. M., Swaroop, A., Valle, D., and Weber, B. H. (1999) What can we learn about age-related macular degeneration from other retinal diseases? *Mol Vis* **5,** 30.

APPENDICES

APPENDIX A MRC TRIAL STUDY TEAM

The MRC Trial is a large community-based randomised trial taking place in England, Wales and Scotland (Britain). Participating practices belong to the MRC General Practice Research Framework (GPRF) which is a network of practices interested in research co-ordinated by the MRC Epidemiology Unit at Northwick Park Hospital.

Investigators: Professor Astrid Fletcher, London School of Hygiene and Tropical Medicine, Dr Dee Jones, University of Wales College of Medicine, Professor Chris Bulpitt, Imperial College School of Medicine, Dr Alistair Tulloch, University of Oxford

Principal Investigator: Professor Astrid Fletcher

Centres: Practices from the Medical Research Council General Practice Research Framework (MRC GPRF), Director Dr Madge Vickers

Collaborators on economic analyses: Professor Mike Drummond (University of York), Linda Davies (University of Manchester)

Sponsor: Medical Research Council, Department of Health, Scottish Office

Trial Steering Committee: Professor Sir John Grimley Evans (Chair from Jan 2001), Dr Carol Brayne, Professor Andy Haines (Chair 1994-2000), Professor Karen Luker, Dr Madge Vickers

London School of Hygiene and Tropical Medicine : Elizabeth Breeze, Edmond Ng, Gill Price, Liam Smeeth, Susannah Scott, Susan Stirling, Rakhi Kabiwala, Jabibi Mazar

Imperial College of Medicine: Maria Nunes, Ruth Peters,

University of Wales College of Medicine: Amina Latif, Elaine Stringer

APPENDIX B: MEASURING VISUAL ACUITY

Instructions on measuring visual acuity from the manual of operations for the MRC Trial of the assessment and management of older people in the community

Do the test under well-lit conditions but avoid strong overhead lights which may dazzle the patient. Light should shine on the chart but not into the patient's eyes. Keep the lighting conditions constant.

Measure visions at 3 metres. Use the string provided to measure distance. It is very important that the test is done at 3 metres - considerable effort should be made to find suitably lit 3 metre space in the practice. If this really is not possible, you may do the test at 1 metre but this will have to be agreed with your trainer before you do so because doing the visual acuity test at 1 metre is not a very accurate test for people who have good vision. For home visits more flexibility may be required.

Tick the box on the form to indicate at which distance the test was done.

Start by testing both eyes, then each eye separately. When testing one eye the patient must be asked to cover the other eye with the palm of their hand, or with the "occluder" part of the pinhole, depending on what is easiest for them. Alternatively a patch may be used.

The patient should wear the glasses they normally use for driving or watching television. If they normally do not wear spectacles but use them for specific activities requiring distance vision they should put these spectacles on for the entire visual acuity test. We want to measure visual deficit arising because patients do not have spectacles rather than because they choose not wear the spectacles which they have been prescribed. Hold the booklet vertically. If it is held at an angle reflections will make the letters difficulty to see.

Ask the participant to read the letter on screening cards (cards 1 - 3). The patient should be encouraged to respond until they get a letter wrong. The last successful response is used to determine the starting point for the measurement of line acuity. The appropriate card is selected and the patient should attempt to identify each of the 4 letters presented. If the patient is able to identify correctly 3 or more letters on a line then the next card in the series should be presented. If they identify 3 or more letters, go on to the next card. If they can read at least one letter

on this card, the number of letters they identify correctly should be used to score the vision. If they cannot read any of this line, go back to the previous line and ask them to re-read it. Score this line even if they can still read 3 or 4 letters - you know they cannot read the next line.

The patient should be encouraged to read every letter on the line. Do not let them stop if they say they cannot see it. A phrase such as "It doesn't matter if you get it wrong but have a try" may be used to persuade them to finish the line.

If you think the participant may be memorizing the letters, you may ask them to read a line from right to left.

The vision is scored according to the number of letters read on the last line on which at least 1 letter can be read. The score should be read off from the score card on the back of the card. For example, if they read 3 letters on line 1 (HVYU) then their score is 0.825. A larger score indicates a worse vision.

If a participant is unable to read Line 1 (the biggest letters) at 3 metres, reduce the test distance to 1 metres (again using the string provided). Take the vision as before, score for "1 metre". If they are still unable to read Line 1 this means that they have a visual acuity defined as "blind" by WHO (<3/60); the appropriate box in the questionnaire should be ticked, and patient referred to the ophthalmic team if not investigated in the last year.

If the score is 0.5 or greater then retest using the pinhole. Pinhole vision will only be taken for each eye separately. Take the vision at 3 metres to start with, even if the patient was down to 1 metre distance for initial testing. If the patient has problems holding the pinhole they may balance it on their nose - using the "occluder" part to cover the other eye; this is why it is the shape it is.

If the score improves with pinhole to less than 0.5 then the participant should be referred to the optician, because when the vision improves with pinhole it indicates that the vision may be improved with spectacles.

Anyone whose vision score is 0.5 or more using the pinhole should be referred to the ophthalmic team if not investigated in the last year.

Do not be alarmed if vision gets worse with pinhole - this sometimes happens. Use the non-pinhole vision score for your referral criteria in that situation.

Appendix B: MRC Elderly Study regional trainers checklist for visual acuity

1. Is the Glasgow Acuity Chart in good condition?
2. Is the test being conducted in appropriate conditions?
3. Is the room well lit?
4. Are strong overhead lights avoided?
5. Is the distance measured correctly (3 metres/1 metre)?
6. Is the patient wearing appropriate glasses (glasses used for seeing better in the distance)?
7. Does the nurse conduct the test satisfactorily?
8. Is the chart held vertically?
9. Are the screening cards used properly?
10. Does the nurse stop at the correct line?
11. Does the nurse use the appropriate encouragement?
12. Is the score recorded correctly?
13. Is the pinhole used at the right cut-off?
14. Does the nurse understand the referral criteria?

Appendix B: Snellen acuity and logMAR score

LogMAR means logarithm of the minimal angle of resolution. Snellen notation refers to the angle detected such that the reciprocal of the Snellen fraction represents the number of minutes. Thus logMAR and Snellen are related by the following equation.

LogMAR = log (1/Snellen fraction)

The following table shows equivalent values for the two scales

Snellen	LogMAR
6/6	0
6/12	0.301
6/18	0.477
6/60	1
3/60	1.30

APPENDIX C DATA COLLECTION FORMS

MRC ELDERLY STUDY:
IDENTIFYING CAUSE OF VISUAL IMPAIRMENT

ID NUMBER ☐☐☐☐☐☐

Date of detailed examination: _____ / _____ / _____

Please go through the notes and identify ALL the letters which refer to eye problems or deal with referrals to or from any eye specialist - optician, ophthalmologist or eye hospital. Please look through all the notes, not just since the start of the MRC Elderly Study. We are interested in all eye problems, not just those identified during the study.

Total number of letters (correspondence) identified in the medical notes: ☐☐

Please allocate a number to the letters in chronological order. Letter number 1 being the first letter identified in the notes. If there are more than 7 letters please use extra sheets being sure to fill in the id number for each. For each letter please complete the following information:

LETTER NUMBER __1__ **Date of letter** _____ / _____ / _____

PURPOSE OF LETTER: *eg, report from ophthalmologist, referral to optician*

DIAGNOSIS: *Please write down any terms which you think refer to the diagnosis even if you are not sure what they mean.* ***Please record any vision measurements.***

TREATMENT: *Please write down any terms which you think refer to treatment even if you are not sure what they mean*

If you have any problems completing this form please contact
Jennifer Evans on 0171 566 2819

Hospital form

<PATIENT DETAILS ON FRONT SHEET WHICH WAS DETACHED BEFORE RETURNING THE FOLLOWING FORM>

Patient Id Number <generated automatically>

This patient was given a visual acuity examination as part of the MRC Elderly Trial on <date generated automatically>. At that time they were visually impaired i.e. they had a central acuity of less than 6/18 in the better eye *or* reported that they were on the Blind or Partial Sight Register. We would be grateful if you could let us know what was the **main cause of visual loss** for this person on the <date generated automatically>, whether or not they have since died. If there is more than one cause of visual loss please indicate which cause, in your opinion, contributes most to the visual loss by writing 1,2 or 3 as appropriate in the "cause rating" circle.

Please tick the relevant box (es).

Cause	**Both**	**Right**	**Left**	**Cause rating**
Age-related macular degeneration				
Exudative disease ("wet") (new vessels) (PED)..	☐	☐	☐	○
Geographic atrophy ("dry") (no new vessels)	☐	☐	☐	○
Other, specify _____	☐	☐	☐	○
Cataract				
Age-related	☐	☐	☐	○
Congenital	☐	☐	☐	○
Other, specify _____	☐	☐	☐	○
Glaucoma				
Primary open-angle	☐	☐	☐	○
Primary closed-angle	☐	☐	☐	○
Other, specify. _____	☐	☐	☐	○
Diabetic eye disease				
Diabetic retinopathy	☐	☐	☐	○
Other, specify _____	☐	☐	☐	○
Myopic degeneration	☐	☐	☐	○
Other, specify _____	☐	☐	☐	○

If there is a different cause in each eye please indicate here by circling R or L which eye lost vision last.....R / L
Best corrected vision at hospital examination nearest to date of MRC Elderly Trial Examination on <date generated automatically> R_____ L_____

Name of person completing form: _____
Position in hospital: _____
Signature: Date / /

APPENDIX D CODING OF CAUSE OF VISUAL LOSS

coding of cause lookup table

Code	Description
10	AMD unspecified
11	AMD exudative disease
12	AMD geographic atrophy
16	Possible exudative
17	Possible geographic atrophy
18	Possible AMD
19	Other AMD
20	Cataract unspecified
21	Age-related cataract
22	Congenital cataract
29	Cataract other
30	Glaucoma unspecified
31	Primary open-angle
32	Primary closed-angle
39	Other glaucoma
40	Diabetes unspecified
41	Diabetic retinopathy
49	Diabetes other
51	CRAO
52	CRVO
53	BRAO

coding of cause lookup table

Code	Description
54	BRVO
59	Other / unspecified
60	Myopic degeneration
80	Other

APPENDIX E SICKNESS IMPACT PROFILE AND PHILADELPHIA GERIATRIC MORALE SCALE

The following questions comprise the four dimensions of the Sickness Impact Profile used and the Philadelphia Geriatric Morale Scale

Home management

I only do housework or work around the house for short periods of time or I rest often

I do less of the daily household chores than I used to do

I do not do any of the daily household chores that I used to do

I do not do any of the maintenance or repair work that I used to do in my home or garden

I do not do any of the shopping that I used to do

I do not do any of the cleaning that I used to do

I have difficulty using my hands, for example, turning tapes, using kitchen gadgets, sewing or doing repairs

I do not do any of the clothes washing that I used to do

I do not do heavy work around the house

I have given up taking care of personal or household business affairs, for example, paying bills, banking or doing household accounts

Mobility

I only get about in one building

I stay in one room

I stay in bed more

I stay in bed most of the time

I do not use public transport now

I stay at home most of the time

I only go out if there is a lavatory nearby

I do not go into town

I only stay away from home for short periods

I do not get about in the dark or in places that are not lit unless I have someone to help

Body care and movement

I make difficult movements with help, for example, getting in or out of the bath or a care

I do not get in and out of bed or chairs without the help of a person or mechanical aid

I only stand for short periods of time

I do not keep my balance

I move my hands or fingers with some difficulty or limitation

I only stand up with someone's help

I kneel, stoop or bend down only by holding onto something

I am in a restricted position all the time

I am very clumsy

I get in and out of bed or chairs by grasping something for support or by using a stick or walking frame

I stay lying down most of the time

I change position frequently

I hold onto something to move myself around in bed

I do not bath myself completely, for example, I need help with bathing

I do not bath myself at all, but am bathed by someone else

I use a bedpan with help

I have trouble putting on my shoes, socks or stockings

I do no have control of my bladder

I do not fasten my clothing, for example, I require assistance with buttons, zips or shoelaces

I spend most of the time partly dressed or in nightclothes

I do not have control of my bowels

I dress myself, but do so very slowly

I only get dressed with someone's help

Social interaction

I go out to visit people less often

I do not go out to visit people at all

I show less interest in other people's problems, for example, I don't listen when they tell me about their problems. I don't offer to help

I am often irritable with those around me, for example, I snap at people or criticise easily

I show less affection

I take part in fewer social activities that I used to

I am cutting down the length of visits with friends

I avoid having visitors

My sexual activity is decreased

I often express concern over what might be happening to my health

I talk less with other people

I make many demands on other people, for example, I insist that they do things for me or tell me how to do things

I stay alone much of the time

I am disagreeable with my family, for example, I act spitefully or stubbornly

I have frequent outburst of anger at my family, for example, I hit them, scream or throw things at them

I isolate myself as much as I can from the rest of my family

I pay less attention to the children

I refuse contact with my family, for example, I turn away from them

I do not look after my children or family as well as I used to do

I do not joke with members of my family as much as I used to do

Philadelphia Geriatric Morale Scale

Do things keep getting worse as you get older?

Do you have as much energy as you did last year?

Do you fell lonely much?

Do you see enough of your friends or relatives?

Do little things bother you more this year?

As you get older do you feel less useful?

Do you sometimes worry so much you can't sleep?

As you get older are things better than expected?

Do you sometimes feel that life isn't worth living?

Are you as happy now as you were when you were younger?

Do you have a lot to be sad about?

Are afraid of a lot of things?

Do you get angry more than you used to?

Is life hard for your most of the time?

Are you satisfied with your life today?

Do you take things to heart?

Do you get upset easily?

APPENDIX F SUPPLEMENTARY ANALYSES FOR CHAPTER FOUR

Table F.1 Association between variables indicating functional limitations and potential confounding factors, controlling age and sex

	A lot of difficulty reading newsprint	Difficulty managing finances	ADL score – worst quintile
Housing tenure	<0.001	0.014	<0.001
Smoking	0.173	0.465	0.006
Alcohol consumption	0.003	0.048	<0.001
Body mass index	0.015	0.054	0.003
Hearing impairment	0.012	0.003	0.005
Reported stroke	<0.001	<0.001	<0.001
Diabetes	0.004	0.183	<0.001
Urinary incontinence	<0.001	<0.001	<0.001
Lower legs swollen in morning	<0.001	0.003	<0.001
Severe shortness of breath	<0.001	<0.001	<0.001
Three or more prescribed medicines	<0.001	0.001	<0.001
Depression	<0.001	<0.001	<0.001
Cognitive impairment	<0.011	<0.001	<0.001
Two or more falls	<0.001	0.001	<0.001
Reported hip fracture	0.709	0.498	<0.001

Separate logistic regression models were constructed for each impact variable and each potential confounder and included terms for age (75-79, 80-84,85-89 and 90+) and sex. The values in this table are p-values derived from the adjusted Wald test.

Table F.2 Association between variables indicating perceived health and potential confounding factors, controlling age and sex

	Self-reported "fair/poor" health	Self-reported "not at all" physically active
Housing tenure	<0.001	<0.001
Smoking	<0.001	<0.001
Alcohol consumption	<0.001	0.009
Body mass index	<0.001	0.074
Hearing impairment	<0.001	0.139
Reported stroke	<0.001	<0.001
Diabetes	<0.001	<0.001
Urinary incontinence	<0.001	<0.001
Lower legs swollen in morning	<0.001	<0.001
Severe shortness of breath	<0.001	<0.001
Three or more prescribed medicines	<0.001	<0.001
Depression	<0.001	<0.001
Cognitive impairment	0.004	<0.001
Two or more falls	<0.001	<0.001
Reported hip fracture	<0.001	<0.001

Separate logistic regression models were constructed for each impact variable and each potential confounder and included terms for age (75-79, 80-84,85-89 and 90+) and sex. The values in this table are p-values derived from the adjusted Wald test.

Table F.3 Association between being in the worst quintile for Sickness Impact Profile variables and Philadelphia Geriatric Morale Scale and potential confounding factors, controlling age and sex

	Home management	*Mobility*	*Body care and movement*	*Social interaction*	*PGMS*
Housing tenure	<0.001	<0.001	<0.001	0.062	0.017
Smoking	0.005	0.025	0.004	0.015	0.003
Alcohol consumption	0.004	0.005	0.003	0.010	0.932
Body mass index	0.029	0.080	0.210	0.023	0.952
Hearing impairment	0.367	0.077	0.334	0.002	0.008
Reported stroke	<0.001	<0.001	<0.001	0.001	0.017
Diabetes	0.001	0.023	0.020	0.114	0.182
Urinary incontinence	<0.001	<0.001	<0.001	0.001	<0.001
Lower legs swollen in morning	<0.001	<0.001	<0.001	<0.001	0.005
Severe shortness of breath	<0.001	<0.001	<0.001	0.001	<0.001
3 or more prescribed medicines	<0.001	<0.001	<0.001	<0.001	<0.001
Depression	<0.001	<0.001	<0.001	<0.001	N/A
Cognitive impairment	0.034	0.001	0.102	0.016	0.580
Falls	0.006	<0.001	<0.001	<0.001	0.001
Hip fractures	0.036	0.003	0.005	0.483	0.925

Separate logistic regression models were constructed for each impact variable and each potential confounder and included terms for age (75-79, 80-84,85+) and sex. The values in this table are p-values derived from the adjusted Wald test.

Table F.4 Association between cognitive impairment and depression and potential confounding factors, controlling age and sex

	Cognitive impairment (MMSE less than 12)	Depression (GDS six or more)
Housing tenure	<0.001	<0.001
Smoking	0.001	<0.001
Alcohol consumption	<0.001	0.052
Body mass index	<0.001	0.005
Hearing impairment	<0.001	<0.001
Reported stroke	<0.001	<0.001
Diabetes	0.681	0.003
Urinary incontinence	<0.001	<0.001
Lower legs swollen in morning	0.560	<0.001
Severe shortness of breath	0.184	<0.001
Three or more prescribed medicines	0.927	<0.001
Two or more falls	0.044	<0.001
Reported hip fracture	0.498	0.043

Separate logistic regression models were constructed for each impact variable and each potential confounder and included terms for age (75-79, 80-84,85-89 and 90+) and sex. The values in this table are p-values derived from the adjusted Wald test.

Table F.5 Association between falls and hip fractures and potential confounding factors, controlling age and sex

	Two or more falls at home in last six months	Reported hip fracture
Housing tenure	<0.001	0.124
Smoking	0.577	0.029
Alcohol consumption	<0.001	0.822
Body mass index	0.037	0.003
Hearing impairment	<0.001	0.037
Reported stroke	<0.001	0.203
Diabetes	<0.001	0.586
Urinary incontinence	<0.001	0.193
Lower legs swollen in morning	<0.001	0.005
Severe shortness of breath	<0.001	0.124
3 or more prescribed medicines	<0.001	0.002
Depression	<0.001	0.039
Cognitive impairment	0.045	0.477

Separate logistic regression models were constructed for each impact variable and each potential confounder and included terms for age (75-79, 80-84,85-89 and 90+) and sex. The values in this table are p-values derived from the adjusted Wald test.

Table F.6 Association between mortality and potential confounding factors, controlling age and sex

	Mortality rate
Housing tenure	<0.001
Smoking	<0.001
Alcohol consumption	<0.001
Body mass index	<0.001
Hearing impairment	<0.001
Reported stroke	<0.001
Diabetes	<0.001
Urinary incontinence	<0.001
Lower legs swollen in morning	<0.001
Severe shortness of breath	<0.001
3 or more prescribed medicines	<0.001
Depression	<0.001
Cognitive impairment	<0.001
Falls	<0.001
Hip fractures	<0.001

These figures are derived from a series of Cox regression models. Each model included terms for age (75-79,80-84,85-89,90+) and sex and each potential confounder. The values in this table are p-values derived from the model.

APPENDIX G RELEVANT PUBLISHED WORK

Evans JR. In: Johnson GJ, Minassian DM, Weale RA, eds. *The epidemiology of eye disease*. London: Chapman and Hall, 1996.

Evans JR. Risk Factors for Age-related Macular Degeneration. *Progress in Retinal and Eye Research* 2001;**20**:227-53.

Evans JR, Fletcher AE, Wormald RPL, Siu-Woon Ng E, Stirling S, Smeeth L et al. Prevalence of visual impairment in people aged 75 years and older in Britain: results from the MRC trial of assessment and management of older people in the community. *Br J Ophthalmol* 2002;86: 795-800.

Evans JR, Fletcher AE, Wormald RPL. Causes of visual impairment in people aged 75 years and older in Britain: results from the MRC trial of assessment and management of older people in the community. *Br J Ophthalmol* 2003 in press.

Evans JR, Fletcher AE, Wormald RPL. Prevalence of AMD causing visual impairment in older people in the UK: results from the Medical Research Council trial of assessment and management of older people in the community. *Ophthalmology* 2003 in press