Visual impairment, blindness and retinopathy in older Icelanders

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Thesis for the degree of Philosophiae Doctor
University of Iceland
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Elín Gunnlaugsdóttir

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Ágrip

Íslendingar njóta einna mesta langlífis á heimsvísu og hlutfall aldraðra einstaklinga fer stækkandi. Hækkandi aldri fylgir aukin hætta á sjóntapi og sjónhimnuskemmdum og þörfin á heilbrigðisþjónustu og endurhæfingu eykst í samræmi við það. Upplýsingar um sjónskerpu og sjónhimnuskemmdir miðaldra og eldri Íslendinga geta orðið að gagni þegar kannað er hvaða sjúkdóma má fyrirbyggja og meðhöndla og þegar skipuleggja á hversu umfangsmikla heilbrigðisþjónustu þessir einstaklingar koma til með að þurfa.

Tilgangur:

Að kanna orsakir, algengi og 5 ára nýgengi sjónskerðingar og blindu miðaldra og eldri Íslendinga ásamt því að afla upplýsinga um algengi og áhættuþætti sjónhimnuskemmda aldraðra einstaklinga með og án sykursýki.

Aðferðir:

Hluti I og II:

Þátt tóku 1045 einstaklingar í Reykjavíkuraugnrannsókninni. Allir voru 50 ára eða eldri og valdir með slembiúrtaki úr Þjóðskrá. Þátttakendur gengust undir nákvæma augnskoðun árið 1996 og 5 árum síðar var hún endurtekin meðal 846 eftirlifenda. Sjónskerðing var skilgreind samkvæmd flokkun Alþjóðaheilbrigðismálastofnunarinnar sem besta sjónskerpa (með sjónglerjum ef þörf var á) á bilinu 3/60 til < 6/18 eða sjónsvið sem nemur ≥ 5° en < 10° umhverfis miðjupunkt. Sjónskerpa sem nemur minna en 3/60 kallast blinda. Einnig var stuðst við bandaríska skilgreiningu sem flokkar sjónskerpu á bilinu > 6/60 til < 6/12 sem sjónskerðingu og sjónskerpa ≤ 6/60 er kölluð blinda. Könnuð var orsök sjóntapsins í öllum augum sem reyndust vera sjónskert eða blind.

Hluti III:

Þátttakendur í Öldrunarrannsókn Hjartaverndar, sem áttu augnbotnamyndir sem hægt var að vinna með og upplýsingar um aðra þætti sem skoða skyldi, voru 4994 talsins, allir 67 ára eða eldri. Einstaklingar voru taldir hafa sykursýki ef þeir höfðu áður fengið sykursýkigreiningu (að eigin sögn), höfðu HbA1c gildi ≥ 6,5% (≥ 48 mmól/mól) eða tóku blóðsykurslækkandi lyf. Sjónhimnuskemmdir voru greindar af augnbotnaljósmyndum og alvarleiki metinn samkvæmt Airlie House aðlögun á stöðlum Early Treatment Diabetic Retinopathy rannsóknarinnar. Könnuð voru tengsl sjónhimnuskemmda við ýmsa þekkta áhættuþætti með fjölþátta aðhvarfsgreiningu.

Niðurstöður:

Hluti I og II:

Þegar stuðst var við skilgreiningu Alþjóðaheilbrigðismálastofnunarinnar var algengi sjónskerðingar í Reykjavíkuraugnrannsókninni 1,0% (95% öryggismörk 0,4-1,6) og blindu 0,6% (95% öryggismörk 0,1-1,0). Fimm ára nýgengi sjónskerðingar var 1,1% (95% öryggismörk 0,4-1,8) og blindu 0,4% (95% öryggismörk 0,0-0,8). Algengi sjónskerðingar sem einskorðarist við eitt auga var 4,4% (95% öryggismörk 3,2-5,7) og 1,7% (95% öryggismörk 0,9-2,5) voru blindir á öðru auganu. Við 5 ára eftirfylgdarskoðun höfðu 3,5% (95% öryggismörk 2,3-4,8) hlotið sjónskerðingu á einu auga og 1,2%

(95% öryggismörk 0,5-2,0) höfðu hlotið blindu á einu auga. Bandaríska skilgreiningin er víðtækari og gaf örlítið hærri algengis- og nýgengistölur.

Aldursbundin hrörnun í augnbotnum var helsta orsök sjónskerðingar og blindu, bæði við upphafs- og eftirfylgdarskoðun þegar sjóntap var skilgreint samkvæmt skilgreiningum Alþjóðaheilbrigðismála-stofnunarinnar. Ef stuðst var við bandaríska skilgreiningu reyndist skýmyndun á augasteini vera aðal orsök vægari sjónskerðingar. Helstu orsakir sjóntaps, sem einskorðaðist við aðeins eitt auga, voru latt auga og skýmyndun á augasteini.

Hluti III:

Sykursjúkir einstaklingar í Öldrunarrannsókn Hjartaverndar reyndust vera 516 talsins (10,3%) og augnbotnamyndir voru til í 512 tilfellum. Algengi sjónhimnuskemmda meðal sykursjúkra var 27,0% (95% öryggismörk 23,2-31,0). Fimm einstaklingar (1,0%; 95% öryggismörk 0,3-2,3) höfðu alvarlegar sjónhimnuskemmdir með nýæðamyndun og aðrir fimm höfðu bjúg í makúlu (1,0%; 95% öryggismörk 0,3-2,3). Sjónhimnuskemmdir greindust í 476 einstaklingum sem höfðu engin merki um sykursýki (10,7%; 95% öryggismörk 9,8-11,6) og aðrir þrír höfðu bjúg í makúlu. Áhættuþættir sjónhimnuskemmda meðal sykursjúkra reyndust vera hækkað HbA1c, aukinn slagbils blóðþrýstingur og notkun insúlíns og annarra blóðsykurslækkandi lyfja. Í einstaklingum án sykursýki voru hækkandi aldur og albúmínmiga tengd aukinni hættu á sjónhimnuskemmdum.

Ályktanir:

Algengi og 5 ára nýgengi sjónskerðingar og blindu jókst með aldri í Reykjavíkuraugnrannsókninni. Aldursbundin hrörnun í augnbotni var helsta orsök alvarlegs sjóntaps en skýmyndun á augasteini var algeng orsök vægari sjónskerðingar.

Heildaralgengi sjónhimnuskemmda í Öldrunarrannsókn Hjartaverndar var 12,4%. Líkurnar á að sykursjúkur einstaklingur hefði sjónhimnuskemmdir voru 2,5x hærri en fyrir þá sem ekki voru sykursjúkir. Þrátt fyrir þetta var heildarfjöldi einstaklinga með sjónhimnuskemmdir þrefalt hærri í hópnum sem ekki hafði sykursýki.

Lykilorð:

Aldursbundin augnbotnahrörnun – blinda – sjónhimnuskemmdir - sjónskerðing – sykursýki

Abstract

Iceland enjoys one of the highest life expectancies in the world and the population of middle-aged and elderly Icelanders is growing. Frequency of visual loss and retinopathy rises with increasing age and increases the need for assistance and rehabilitation. Cause-specific data on visual impairment, blindness and retinopathy help identify preventable and treatable causes of visual loss and provide insight into which problems should be taken into consideration when planning future eye health care services.

Aims:

The aim of this thesis is to describe the prevalence and 5-year incidence of visual impairment and blindness among middle-aged and older Icelanders, to provide information on the major causes of visual loss, and to update data on the prevalence of retinopathy and risk factors associated with retinopathy in older persons with and without diabetes mellitus.

Methods:

Papers I and II:

A random sample of 1,045 persons aged 50 years or more participated in the population-based Reykjavik Eye Study. All participants underwent a detailed eye examination in 1996, and 846 of the survivors participated in a follow-up examination in 2001. Visual impairment was defined according to the World Health Organization's definitions as a best-corrected visual acuity of <6/18 but no worse than 3/60, or a visual field of ≥5° and <10° around a fixation point in the better eye. Best-corrected visual acuity of <3/60 in the better eye was defined as blindness. We also used United States criteria, which define visual impairment as best-corrected visual acuity of <6/12 and >6/60 in the better eye and blindness as best-corrected visual acuity ≤6/60. Causes of visual loss were determined for all eyes. Deterioration or improvement in vision were defined as a loss or gain of 2 or more Snellen lines.

Paper III:

A study population of 4,994 persons aged 67 years or more participated in the Age/Gene/Environment Susceptibility-Reykjavik Study. Diabetes Mellitus was defined as HbA1c ≥6.5% (≥48 mmol/mol), a self-reported history of diabetes, or use of diabetes medication. Retinopathy was assessed by grading fundus photographs using the modified Airlie House adaptation of the Early Treatment Diabetic Retinopathy Study protocol. Associations between retinopathy and risk factors were estimated for persons with and without diabetes by using odds ratios from logistic multivariate analyses.

Results:

Papers I and II:

Using World Health Organization criteria, the prevalence of bilateral visual impairment and blindness was 1.0% (95% CI 0.4-1.6) and 0.6% (95% CI 0.1-1.0), respectively. The 5-year incidence was 1.1% (95% CI 0.4-1.8) for visual impairment and 0.4% (95% CI 0.0-0.8) for blindness. The prevalence of unilateral visual impairment and blindness according to World Health Organization criteria was 4.4% (95% CI 3.2-5.7) and 1.7% (95% CI 0.9-2.5), respectively, and the 5-year incidence was 3.5% (95% CI 2.3-4.8) and 1.2% (95% CI 0.5-2.0). The United States criteria are more inclusive and gave slightly higher figures.

Using World Health Organization criteria, the major cause of bilateral visual impairment and blindness both at baseline and follow-up was age-related macular degeneration. According to United States criteria, we detected milder forms of visual loss and found that unoperated cataract was the major cause of less severe bilateral visual impairment at both baseline and 5-year follow-up. Regardless of the criteria used, the two most common causes of unilateral visual impairment at baseline were amblyopia and cataract, and at 5-year follow-up, cataract was the main cause of unilateral visual impairment.

Paper III:

Among the 516 persons (10.3%) with diabetes mellitus in the Age,Gene/Environment Susceptibility-Reykjavik Study, gradable fundus photos were available for 512. The prevalence of retinopathy among persons with diabetes was 27.0% (95% CI 23.2-31.0). Five persons (1.0%; 95% CI 0.3-2.3) had proliferative retinopathy and another five had clinically significant macular edema (1.0%; 95% CI 0.3-2.3). Retinopathy was present in 476 persons (10.7%; 95% CI 9.8-11.6) without diabetes mellitus and three had clinically significant macular edema. Independent risk factors for retinopathy in persons with diabetes mellitus in a multivariate model were increased HbA1c, insulin use, use of oral hypoglycemic agents and higher systolic blood pressure. In persons without diabetes mellitus, increasing age and microalbuminuria were independent risk factors for retinopathy.

Conclusions:

Prevalence and 5-year incidence of both uni- and bilateral visual impairment and blindness increased with age in the Reykjavik Eye Study. Age-related macular degeneration was the leading cause of severe visual loss in this population of middle-aged and older Icelanders, and unoperated cataract caused less severe visual loss.

The overall prevalence of retinopathy in our large, population-based Age/Gene/Environment Susceptibility-Reykjavik Study sample was 12.4%. Persons with diabetes mellitus were 2.5 times more likely to have retinopathy than persons without diabetes. However, the total number of people with retinopathy was threefold higher in the non-diabetic group, accounting for 75% of retinopathy cases.

Keywords

Age-related macular degeneration - blindness – diabetes mellitus - retinopathy - visual impairment

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This thesis is based on data obtained from two large population-based studies: the Reykjavik Eye Study (RES) and the Age, Gene/Environment Susceptibility - Reykjavik Study (AGES-R). I am sincerely grateful to the Reykjavik Eye Study group and staff of the Icelandic Heart Association, who collectively gathered the data I used, and to everyone who contributed to this study in any way. My deepest thanks go to the numerous participants who provided their time by cooperating in the studies.

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Conflicts of interest. None.

Contents

List of abbreviations

AGES-R	The Age, Gene/Environment Susceptibility Reykjavik Study
AMD	Age-related Macular Degeneration
BCVA	Best-Corrected Visual Acuity
BMI	Body-Mass Index
BP	Blood Pressure
BRVO	Branch Retinal Vein Occlusion
CI	Confidence Interval
CRVO	Central Retinal Vein Occlusion
CSME	Clinically Significant Macular Edema
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
DR	Diabetic Retinopathy
ETDRS	Early Treatment of Diabetic Retinopathy Study
g	Gram
GA	Geographic Atrophy
GFR	Glomerular Filtration Rate
HbA1c	Hemoglobin A1c
HDL	High Density Lipoprotein
ICD	International statistical Classification of Diseases
IHA	Icelandic Heart Association
IRMA	Intraretinal Microvascular Abnormalities
kg	Kilogram
L	Liter
LogMAR	logarithm of the Minimum Angle of Resolution
m^2	Square meter
ME	Macular Edema
MESA	Multi-Ethnic Study of Atherosclerosis
mg	Milligram
ml	Milliliter
mmHg	Millimeters of mercury
mmol	Milli moles
µm	Micrometer
n	Number
NHANES	National Health and Nutrition Examination Survey
NPL	No Perception of Light
OR	Odds Ratio

p	Probability value
PDR	Proliferative Diabetic Retinopathy
PL	Perception of Light
RES	Reykjavik Eye Study
SD	Standard Deviation
T1DM	Type-1 Diabetes Mellitus
T2DM	Type-2 Diabetes Mellitus
UKPDS	United Kingdom Prospective Diabetes Study
US	United States
VA	Visual Acuity
WHO	World Health Organization

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List of papers

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals (I-III):

I. Gunnlaugsdottir E., Arnarsson A. and Jonasson F. (2008). Prevalence and causes of visual impairment and blindness in Icelanders aged 50 years and older: the Reykjavik Eye Study. *Acta Ophthalmologica 86 (7):* 778-785.

II. Gunnlaugsdottir E., Arnarsson A. and Jonasson F. (2010). Five-year incidence of visual impairment and blindness in older Icelanders: the Reykjavik Eye Study. *Acta Ophthalmologica 88 (3):* 358-366.

III. Gunnlaugsdottir E., Halldorsdottir S., Klein R., Eiriksdottir G., Klein B. E., Benediktsson R., Harris T. B., Launer L. J., Aspelund T., Gudnason V., Cotch M. F., Jonasson F. (2012). Retinopathy in old persons with and without diabetes mellitus: the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-R). *Diabetologia 55(3)*: 671-680.

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Declaration of contribution

Elín Gunnlaugsdóttir drafted the manuscripts in papers I-III. She contributed to data collection, statistical analysis, interpretation of results, and manuscript revision in all papers.

Friðbert Jónasson contributed to the study design, manuscript drafting, analysis, result interpretation, and revision of manuscripts in all papers.

Ársæll Már Arnarsson contributed to the statistical analysis and revision of the manuscript in papers I and II, and approved the final versions of the manuscripts in both papers.

Thor Aspelund and Sigrún Halldórsdóttir contributed to statistical analysis in paper III, as well as to result interpretation, and reviewing of the manuscript.

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1 Introduction

1.1 Visual impairment and blindness – a global perspective

The World Health Organization (WHO) has estimated that in 2010, 246 million people in the world suffered from visual impairment and another 39 million were blind (Pascolini and Mariotti, 2012). The burden of visual impairment and blindness is unevenly distributed throughout the world, and the evidence suggests that more than 90% of all people with visual loss live in the developing world (Cunningham, 2001). Global visual loss data indicates the prevalence of blindness in people aged ≥50 years to range from 3 to 7% in the Southeast Asian and Eastern Mediterranean regions to 9% in African regions (Pascolini and Mariotti, 2012; Resnikoff *et al*., 2004).

However, in the Australian, European and North American regions, the prevalence of blindness among middle-aged and older people is generally reported to be as low as ≤1% (Attebo *et al*., 1996; Buch *et al*., 2001b; Hirvelä and Laatikainen, 1995; Klaver *et al*., 1998; Klein *et al*., 1991a; Laitinen *et al*., 2010; Muñoz *et al*., 2000; VanNewkirk *et al*., 2001). Depending on which criteria are used to define visual loss (see chapter 1.4 Visual Impairment and Blindness), the prevalence of visual impairment in developed countries has been reported by several studies to range between 1 and 5% (Attebo *et al*., 1996; Buch *et al*., 2001a; Buch *et al*., 2004; Klein *et al*., 1991a; Laitinen *et al*., 2010; Muñoz *et al*., 2000; VanNewkirk *et al*., 2001).

Previous Icelandic studies have focused mostly on blindness, and very little data are available on the cause-specific prevalence of visual impairment. The first known inquiry on blindness in Iceland was conducted in 1940 by collecting ophthalmological data of all those registered as blind by the Medical Director General. The prevalence of blindness among Icelanders aged 59 years or older at that time was estimated to be around 2.5% (Sveinsson, 1944). In the 1950's, Björnsson (1955) found that the Icelandic blindness rate among people aged 60 years or older was much higher than in Europe or North America. He estimated that almost every tenth Icelandic person aged 80-89 years old and every fourth person over 90 years of age was blind. Over the following decades, there was no organized registration of visual loss in Iceland until two epidemiological studies were published in the 1980s. Icelandic ophthalmologist Guðmundur Björnsson (1980) examined around 60% of the population aged 40 years or more between 1976 and 1978 in a western region of Iceland, and in 1979 reviewed blind registers and other sources of visual acuity for the whole country. He presented a blindness prevalence of less than 2% among middle-aged and older persons in the Western region and corrected a WHO statement made in 1976 that Iceland had the highest prevalence of blindness in Europe (Björnsson, 1981). From 1980 through 1984, another Icelandic ophthalmologist, Friðbert Jónasson, examined over 80% of the population aged 43 years or more in a rural area of eastern Iceland and reported a 2.1% blindness prevalence (Jonasson and Thordarson, 1987). To date, this was the last epidemiological study focusing on the prevalence of visual loss among adult Icelanders.

According to the Icelandic Low Vision and Rehabilitation Institute's annual report for 1996 (the year the Reykjavik Eye Study [RES] baseline examinations took place), the prevalence of legal blindness in people aged ≥50 years in Iceland was 0.6%. Visual impairment and blindness data has mainly focused on bilateral visual loss, and prior to the present study, no Icelandic data were available for unilateral visual loss.

According to the scarce epidemiological research studies that have addressed the problem of unilateral visual loss in Australia, Europe and North America, the prevalence of unilateral blindness seems to range between 2% and 4% (Attebo *et al*., 1996; Buch *et al*., 2001a; Klein *et al*., 1991a; Muñoz et *al*., 2000; Wang *et al*., 2000).

The European population of middle-aged and elderly people is growing. In 2003, the WHO estimated that the population of persons aged 65 years and older in the European Union would increase by 17 million by the year 2023 (an increase of 30%) and that the population of people over 80 years of age in that region would increase by 39% (Heikkinen, 2003). An even larger trend towards population ageing is seen in Iceland, since the total number of Icelanders aged 65 years or older is expected to increase by 72% from 2003 to 2023 and the population of people over 80 years in Iceland during that period is expected to increase by 60% (Statistics Iceland, 2012). Accordingly, Iceland enjoys one of the highest life expectancies in the world, an average of 81.5 years for Icelanders born in 2010 (Organization for Economic Co-operation and Development, 2012).

Disability in old age is frequent, and while several studies have shown that the frequency of visual loss rises with increasing age (Attebo *et al.*, 1996; Buch *et al.*, 2004; Klaver *et al.*, 1998; Klein *et al.*, 1991a; Muñoz et al., 2000; VanNewkirk *et al.*, 2001), WHO has estimated that 82% of all blind people in the world are 50 years or older (Pascolini and Mariotti, 2012). Visual loss affects the quality of life (Seland *et al.*, 2011) by interfering with the ability to maintain independence in a safe manner, increasing the need for assistance and rehabilitation (Wang *et al.*, 1999; West *et al.*, 2002).

In 1999, the global initiative program, “Vision 2020, the Right to Sight,” was launched in an attempt to reduce preventable blindness in the world by 80%. The aim was to increase both public awareness of eye disease and the availability of eye health care services (Bourne, 2012). In order to identify preventable causes of visual impairment and blindness it is important to carry out site-specific epidemiological studies. Prevalence measures the number of affected individuals in a sample at a given time (Last, 2001). In epidemiological research, incidence is often preferred over prevalence, since it represents the actual occurrence and distribution of disease over a certain time period. Cause-specific incidences of visual impairment and blindness help improve knowledge of the development and progression of disease, while identifying preventable causes of visual loss and providing insight into which problems should be taken into consideration when planning future eye health care services.

Data presenting the incidence of visual loss is scarce, but according to previously published studies, the 5-year incidence of bilateral visual impairment in developed countries seems to range between 1 and 2% (depending on the criteria applied) and the 5-year incidence of blindness is usually reported to be as low as <0.5% in Caucasian populations (Dimitrov *et al.*, 2003; Foran *et al.*, 2003; Klein *et al.*, 1996).

1.2 Visual acuity

Visual acuity is most often defined according by using the Snellen visual acuity chart, which was introduced around 1860 by the Dutch ophthalmologist Herman Snellen (Linksz, 1972). This method assesses a person’s ability to recognize progressively smaller letters (or forms, in case of illiteracy) on a chart from a set distance. The Snellen table consists of black characters or symbols against a white background (see figure 1) and the test letters are designed to measure visual acuity in angular terms.

Figure 1. Snellen visual acuity chart.
Line 1 equals a visual acuity of 6/60 (0.1), whereas line 10 equals visual acuity of 6/6 (1.0). Photograph by Johnny Ring.

The visual angle is defined in arc minutes (arcmin). The letters are of different sizes, and the Snellen notation is defined as the testing distance divided by the distance at which the letter would subtend 5 arcmin (see figure 2). Thus, visual acuity is defined with the testing distance in meters as the numerator and the distance at which a letter spans the visual angle of 5 arcmin as the denominator. On the 6/6 line the letters subtend an angle of 5 arcmin when viewed at 6 meters, but on the 6/12 line the letters subtend an angle of 5 arcmin when viewed at 12 meters (Atebara, 2011).

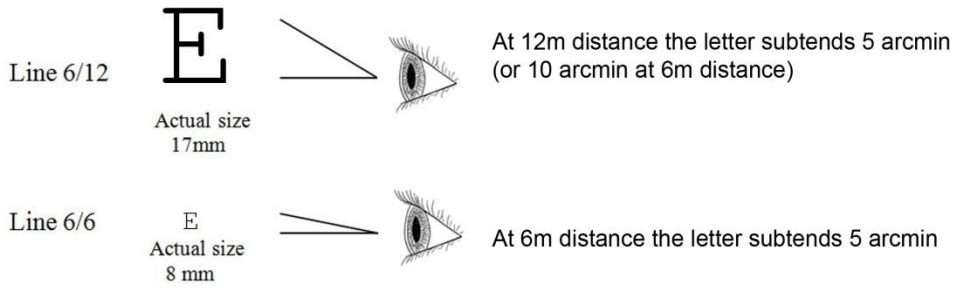

Figure 2. Visual angle in arcmin.
At 6 meters distance, a letter in line 6/12 subtends 10 arcmin and a letter in line 6/6 subtends 5 arcmin.

Normal vision is defined as a visual acuity of 6/6, but can also be expressed as a decimal. Thus, a person with a visual acuity of 6/6 (or 1.0) is able to read the 6/6 line on a Snellen chart at a distance of 6 meters. If the person is only able to read the 6/12 line at 6 meters, it indicates a visual acuity of 0.5.

The letters on the lower lines of the Snellen chart are more crowded together than those higher up. Therefore, alternative visual acuity charts like the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart have been developed, in which each line of the chart comprises five letters and the spacing between each letter is related to the width of the letter and the spacing between the rows is related to the height of the letters (see figure 3).

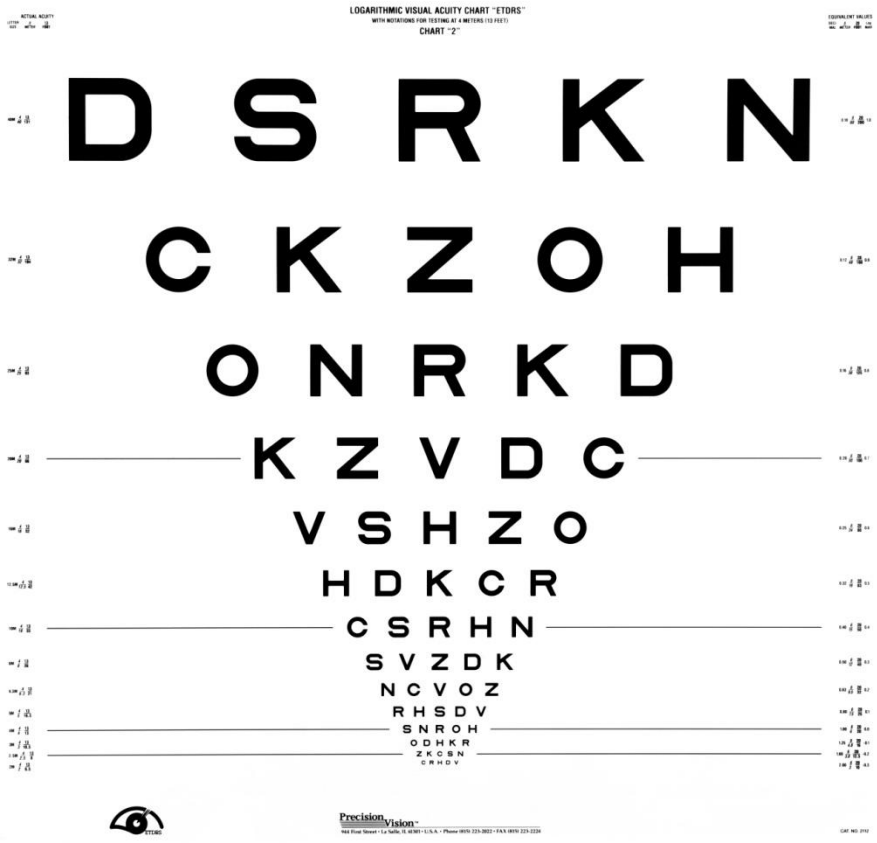

Figure 3. ETDRS visual acuity chart.
This chart is adjusted to test subjective visual acuity from a measuring distance of 4 meters. The top line equals visual acuity of 6/60 (0.1) and the fourth line from the bottom equals visual acuity of 6/6 (1.0). Photograph by Johnny Ring.

Using the ETDRS chart, the Snellen fraction may be expressed as the logarithm of the minimum angle of resolution (LogMAR). By this method, 6/6 equals a minimum angle of resolution of 1.0 arcmin, a LogMAR of 0.00 (table 1). If visual acuity is worse than 6/60, it is described as counting fingers or hand motion at a certain distance. If visual acuity is less than hand motion, it may be described as perception of light (PL), or in more severe cases, no perception of light (NPL) (Atebara, 2011).

Visual acuity	Snellen fraction meters	LogMAR
1.0	6/6	0.00
0.7	6/9	0.18
0.5	6/12	0.30
0.3	6/18	0.48
0.1	6/60	1.00
0.05	3/60	1.30

Table 1. Visual acuity described as the Snellen fraction in meters and logarithm of the minimum angle of resolution (LogMAR).

1.3 Visual field

A normal visual field extends about 60° nasally and superiorly around a fixation point, to 70° inferiorly, and to over 90° temporally. The visual field may be measured and quantified using automated perimetry testing, which is usually only done within 30° from the fixation point. Each eye is tested separately. The patient is instructed to look at a light (fixation point) and to press a button when he/she sees other flashes of light. A standardized algorithm then maps the degree of visual field and loss of visual field is presented as dark-grey or black areas on the visual field measurement. Figure 4 illustrates how most visual field defects are not perceived by the patient since they present as negative scotomas in the form of blurred areas (Heijl *et al.,*2012).

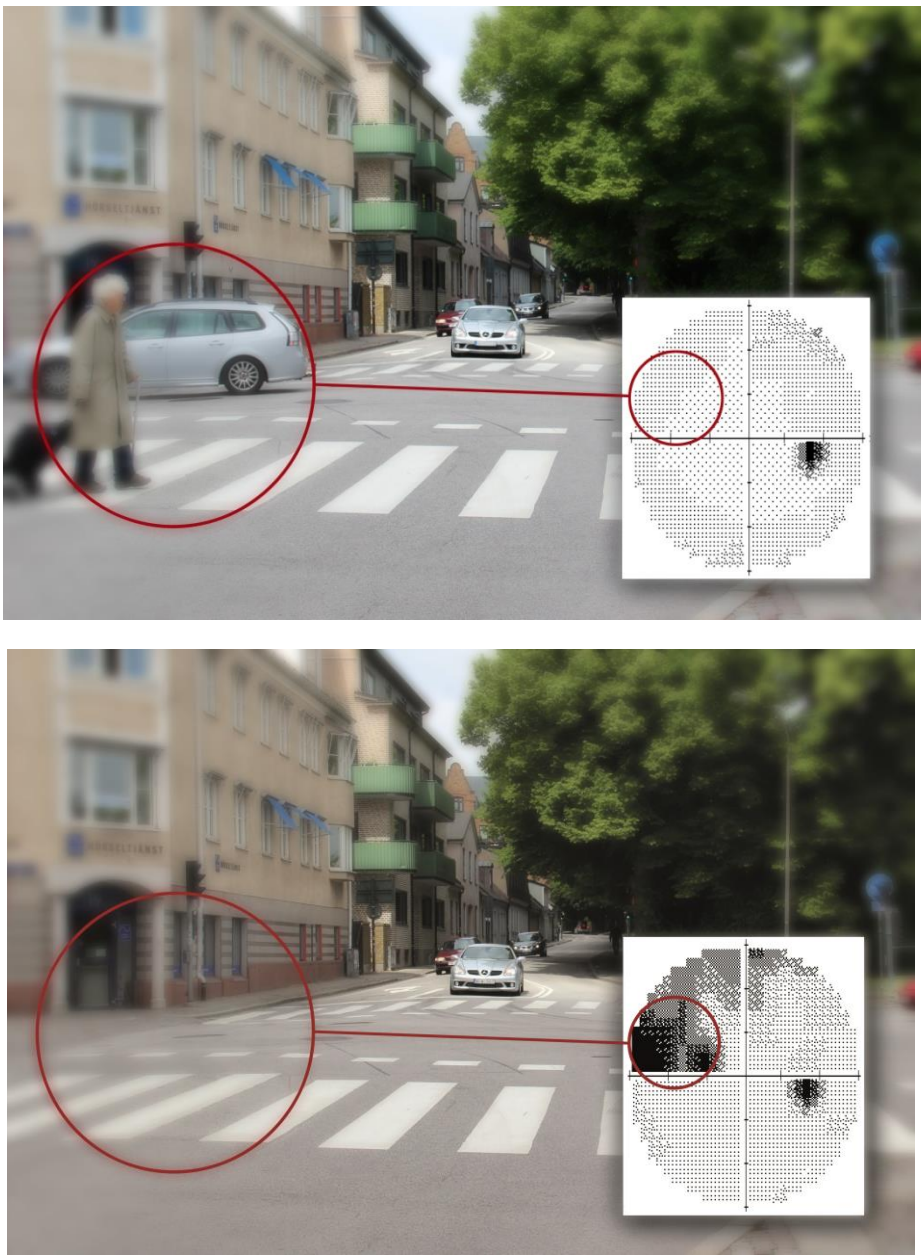

Figure 4a and b. Visual field defect in a patient with a negative scotoma.

This figure illustrates how a patient with normal central visual acuity but a nasal visual field defect in the form of negative scotoma may fail to see the pedestrian and car shown on the left in figure 4a. Figure 4b shows how the brain causes a so-called “filling-in,” creating an inaccurate but “believable” image in the part of the defective visual field.

Reprinted with permission from: Heijl A., Patella V.M. and Bengtsson B. (2012). *The field analyzer primer: effective perimetry (4th ed.)*. Dublin, California: Carl Zeiss Meditec, Inc.

1.4 Visual impairment and blindness

From 1910 to 1950, blindness in Iceland was registered annually by parish records and municipal authorities, using a questionnaire stating that "all persons who are totally blind or unable to find their way in places previously unknown to them by means of their sight" shall be registered as blind (Björnsson, 1955). In January 1951, Iceland began recording diseases according to the International Statistical Classification of Diseases and Related Health Problems (ICD), which defined blindness as best-corrected visual acuity (BCVA) of 6/60 or less or a visual field of 20° or less around a fixation point (Björnsson, 1955). Today, the most widely accepted criteria for defining visual impairment and blindness is found in the tenth ICD version, which defines visual impairment based on 1972 WHO recommendations. According to this forty-year-old WHO classification, visual impairment is defined as a BCVA of less than 6/18 or a visual field of ≥5° and <10° around a fixation point.

Blindness is defined as BCVA of less than 3/60 or a visual field of less than 5° around a fixation point in the better-seeing eye (World Health Organization, 2003). The same classification also divides visual impairment into five subcategories defining the severity of visual impairment (table 2)

Category	Classification	Visual acuity
0	Normal vision / mild visual impairment	6/6 - 6/18
1	Moderate visual impairment	< 6/18 - 6/60
2	Severe visual impairment	< 6/60 - 3/60
3	Blindness category 3	< 3/60 - 1/60
4	Blindness category 4	< 1/60 - PL
5	Blindness category 5 - total blindness	NPL

Table 2. Subcategories of visual acuity and blindness according to World Health Organization classification.
PL= perception of light; NPL= no perception of light.

In 2006, Dandona and Dandona (2006) proposed a revision of the WHO classification of visual impairment and blindness which suggested that the definitions be based on presenting visual acuity rather than BCVA. Thus, people with visual loss due to uncorrected refractive errors would be included, since the previous classification greatly underestimated the total burden of the global visual impairment problem. Therefore, in recent vision research, the trend is toward including data for both presenting and best-corrected visual acuity.

In the United States (US), a more inclusive criterion is used to define visual impairment and blindness. It defines visual impairment as a BCVA in the better-seeing eye of <6/12 and >6/60 and blindness as a visual acuity of 6/60 or less (National Eye Institute, 2012). Using this definition, the Icelandic Low-Vision Institute classifies persons with a visual acuity of 6/60 or less as legally blind.

1.5 Major causes of visual impairment and blindness

In 2010, the WHO Prevention of Blindness and Deafness Programme carried out a global estimation of the causes of visual impairment according to presenting vision. Their data indicated that up to 80% of visual impairment in all age groups is caused by preventable eye diseases, the main cause being uncorrected refractive errors (43%), followed by unoperated cataract (33%) (Attebo *et al.*, 1999; Pascolini and Mariotti, 2012).

Refractive errors among Icelanders aged 50 years and older were addressed in the RES, and the need for spectacles found to be generally met (Gudmundsdottir *et al.*, 2000; Gudmundsdottir *et al.*,

2005; Olsen *et al*., 2007; Qu *et al*., 2010)). For various reasons, such as differences in the quality and access of health care services, the main causes for visual impairment and blindness can vary greatly between developing and developed world regions. It is therefore important to carry out site-specific epidemiological research such as the RES in order to more precisely map the main causes of visual impairment and blindness relevant to each world region, and in particular to identify which causes are preventable. Since many eye diseases are age-related, multiple ocular conditions may occur in the same individual and therefore it is also important to evaluate for each case which disease is most likely to contribute to visual loss. The following discussion will provide a brief overview of the four diseases that most contribute to blindness in middle-aged and older Icelanders over recent decades (based on previously published Icelandic data). Anatomic and pathophysiological processes will not be described in detail.

1.5.1 Late age-related macular degeneration

Late age-related macular degeneration (AMD) is the advanced stage of age-related maculopathy associated with severe visual loss. It is a degenerative disease that is categorized into geographic atrophy (GA) and exudative AMD. GA is defined by discrete areas of retinal depigmentation with sharp borders and visible underlying choroidal vessels. The exudative form includes neovascularization with serous detachment of the retinal pigment epithelium or sensory retina, the presence of subretinal fibrous scaring, and subpigment epithelium hemorrhage (Bird *et al*., 1995, Jonasson *et al*., 2003a). Loss of central vision in advanced AMD is a result of atrophic, hemorrhagic, or fibrous damage to the macula.

The RES presented an age-related increase in late AMD (in either eye) from 5.8% in participants in their 70s to 30.8% among those 80 years and older (Jonasson *et al*., 2003a). The Age, Gene/Environment Susceptibility Reykjavik Study (AGES-R) examined an even larger sample of persons aged 67 years or more and found that persons in the oldest age group (≥85 years) had a ten-fold higher prevalence of late AMD in either eye than those 70-74 years old (Jonasson *et al*., 2011). Both studies found the proportion of GA in Icelanders to be somewhat higher than in other Caucasian populations. Icelanders are predominantly descendants of settlers who arrived from Scandinavia and the British Isles 1,100 years ago, and the RES found that all those with GA had a common ancestor six generations back, whereas more than ten generations were required for those with exudative AMD (Jonasson *et al*., 2005). In 2005, several studies (Edwards *et al*., 2005; Haines *et al*., 2005; Klein *et al*., 2005) identified a T402H single-nucleotide complement factor H polymorphism on chromosome 1 as a major risk factor for AMD, which was also confirmed in Iceland (Magnusson e*t al*., 2006). In the same year, another major genetic risk factor was detected on chromosome 10 (Jakobsdottir *et al*., 2005; Rivera *et al*., 2005). In addition to age and genetic factors, tobacco smoking has been identified as an important risk factor for AMD, but results regarding other risk factors such as obesity, and in particular hypertension and nuclear cataract are conflicting (Smith *et al*., 2001).

In 1950, the prevalence of bilateral blindness due to “senile macular degeneration” in persons aged 60 or more was only 8.0% in Iceland (Björnsson, 1955). The two Icelandic epidemiological studies published in the 1980’s indicated that this condition was by then the most common cause of visual loss, being responsible for more than half of all legal blindness in the Icelandic population (Björnsson, 1980; Jonasson and Thordarson, 1987).

1.5.2 Age-related cataract

Age related cataract is a progressive loss of the transparency of the lens and is associated with visual loss. Depending on which part of the lens is affected, cataract is usually classified into three main types: cortical, nuclear, and posterior subcapsular, and is graded by severity (Sasaki, 1991). As the lens ages, new layers of cortical fibers are produced concentrically, leading to thickening and

hardening of the lens. Lens proteins (crystallins) undergo chemical modification and their pigmentation increases, which in turn reduces transparency of the lens (Bobrow, 2011). The opacified lens leads to visual loss by obstructing the passage of light to the sensory retina

Arnarsson *et al* (1999) examined the prevalence of cataract in the RES, and found that only one out of every four eyes in persons aged 60-69 years who had not been operated for cataract had clear lenses and around 6% of those aged 70-79 years had clear lenses, whereas no subject 80 years or older had a clear lens. However, vision is generally not much affected in eyes with early lens opacification. In spite of high prevalence, cataract only accounts for up to 6% of bilateral blindness in Icelandic epidemiologic studies on older populations (Björnsson, 1981; Jonasson and Thordarson, 1987). Even though cataract has been an uncommon cause of blindness in Iceland, it was the commonest cause for bilateral partial sight in Iceland in the early 1980's (Jonasson and Thordarson, 1987), however, this was before the main impact of intraocular lens implantation. The RES, conducted in the mid 1990s, found the prevalence of implanted intraocular lenses to be 1% among persons 60-69 years old and over 30% in those 80 years and older (Sasaki *et al.*, 2000).

1.5.3 Primary open-angle glaucoma

Glaucoma is traditionally divided into primary and secondary, and classified as open-angle or closed-angle. This group of diseases is characterized and diagnosed by visual field loss and optic nerve damage associated with loss of ganglion cells and their axons (Foster *et al.*, 2002). Primary open-angle glaucoma (previously known as glaucoma simplex or glaucoma chronicum) can be a slowly progressive, chronic disease and is commonly associated with resistance to the aqueous outflow through the trabecular meshwork Schlemm's canal system in the absence of gross anatomic obstruction (Cioffi, 2011). However, in most population-based studies, including the RES, around one-third of patients have so-called "normal-tension" glaucoma (Jonasson *et al.*, 2003b).

While visual field loss may be significant, central visual acuity can be relatively unaffected until late in the disease. Glaucoma is an age-related disease, and the RES reported a 10.0% annual increase for open-angle glaucoma after 50 years of age, with the prevalence being as high as 12.8% of eyes in people aged 80 years or older (Jonasson *et al.*, 2003b). Around one-third of these eyes have high-tension primary open-angle glaucoma, one-third have normal tension primary open-angle glaucoma, and one-third has exfoliation glaucoma, the latter sometimes being classified as secondary glaucoma, which is common in Iceland. As for age-related macular degeneration, genetic factors have been recognized as important in this disease, and the first common genetic variants associated with exfoliation glaucoma (Thorleifsson *et al.*, 2007) and primary open-angle glaucoma (Thorleifsson *et al.*, 2010) were both discovered in Iceland.

Primary open-angle glaucoma is more common in blacks than in whites, and in prevalence studies, high intraocular pressure has also been confirmed as a reliable risk factor. In addition, decreased central corneal thickness, myopia, and vascular factors such as hypertension, diabetes, and ocular blood flow have been suggested as risk factors (Yanagi *et al.*, 2011), but more evidence is needed to confirm this association, in particular with respect to the latter three mentioned.

Primary open-angle glaucoma was found to be the most common cause of blindness in Iceland in 1950, accounting for over 50% of cases of bilateral blindness (Björnsson, 1955). Epidemiological surveys over the next decades showed a rapid fall in glaucoma blindness (Björnsson, 1967) and between the 1980s and 1990s, glaucoma blindness had fallen from approximately 18% to less than 10% (Björnsson, 1980; Jonasson and Thordarson, 1987; Sverrisson *et al.*, 1990; Viggósson *et al.*, 1986).

1.5.4 Retinopathy – see chapter 1.6

1.6 Retinopathy

Retinopathy is a general term referring to a vascular disease of the retina and is frequently an ocular manifestation of a systemic disease, the two most common of which are diabetic retinopathy (DR) and hypertensive retinopathy. Retinopathy in persons without diabetes, sometimes mistakenly diagnosed and referred to as DR in ophthalmic research, is estimated to occur in up to 15% of general Caucasian populations in developed countries. This prevalence has been attributed to older age and systemic hypertension, which affects precapillary arterioles and capillaries. Chronic nonperfusion at various retinal levels due to hypertension can lead to ischemic retinal lesions similar to those found in DR (Cugati *et al.*, 2006; Klein *et al.*, 1993; Klein *et al.*, 2006; Ojaimi *et al.*, 2011).

The following is an overview of the diagnosis and classification of diabetes and the processes leading to DR. Information on the prevalence of retinopathy is important when evaluating the quality of health checkups and eye care services in Iceland. In addition, knowledge of associated risk factors is of great importance in identifying the need for further preventive measures among specific subgroups.

1.6.1 Diabetes mellitus

Diabetes mellitus (DM) is a group of metabolic diseases characterized by high blood sugar levels (hyperglycemia) due to the inability to produce or respond to insulin. The disease is associated with complications in the vascular system (micro- and macrovascular), as well as neuropathic complications (Alberti and Zimmet, 1998). The terminology has been changing over the years and can be confusing. However, the vast majority of diabetes cases fall into two main categories, which are most often referred to as type-1 diabetes mellitus (T1DM, previously known as insulin-dependent or juvenile-onset diabetes) and type-2 diabetes mellitus (T2DM, previously known as non-insulin-dependent or adult-onset diabetes). WHO has suggested a classification consisting of stages that include various degrees of hyperglycemia, reflecting that T1DM, T2DM, and other forms of diabetes can progress through several clinical stages, regardless of etiology. The severity may range from a preclinical stage of normoglycemia to insulin-requiring disease, and diabetes is subdivided into the following categories: “Insulin-requiring for survival;” “Insulin-requiring for control;” and “not insulin-requiring” (Alberti and Zimmet, 1998).

T1DM usually accounts for less than 10% of diabetes cases and is caused by deficient insulin production due to autoimmune destruction of insulin-producing pancreatic β-cells at some point leading to absolute insulin deficiency and requiring insulin for survival. T2DM is a vastly more common disease, accounting for over 90% of individuals with diabetes. It is a result of a combination of insulin resistance, reduced insulin production, and inadequate compensation for reduced insulin secretion. The detailed etiology of T2DM is not fully understood, but does not seem to display autoimmune destruction of pancreatic insulin-producing cells. (American Diabetes Association, 2008; Alberti and Zimmet, 1998). T2DM is often associated with a genetic predisposition (Saxena *et al.*, 2012), but has also been strongly related to lifestyle factors. Obesity can cause a certain degree of insulin resistance, and the risk of developing this form also increases with age and lack of physical activity (American Diabetes Association, 2008; Risérus *et al.*, 2009).

A single measurement of fasting blood glucose is often used for screening purposes, and diabetes mellitus is defined as blood glucose of ≥7.0 mmol/l (126 mg/ml), in addition to a history of diabetes and/or use of diabetic medication. The blood glucose cutoff value of ≥7.0 mmol/l has been used both by WHO (Alberti and Zimmet, 1998) and the American Diabetes Association (2008), but recently, WHO has recommended using glycosylated hemoglobin (Hemoglobin A1c; HbA1c) in the diagnosis of diabetes mellitus to avoid the problem of day-to-day variation in fasting blood glucose values. HbA1c

reflects average plasma glucose levels over the previous 8 to 12 weeks, for which a cutoff value of ≥6.5% (48 mmol/l) is now recommended in diagnosing diabetes (World Health Organization, 2011).

The number of people in the world with diabetes had increased from 153 million in 1980 to 347 million in 2008, and WHO has estimated that the number of people with diabetes in the world will double between 2000 and 2030 (Wild *et al*., 2004). The Icelandic Heart Association's Reykjavik Study confirmed that the diabetes trend in Iceland parallels that observed globally, since the prevalence of T2DM doubled from 1967-2002 (Bergsveinsson *et al*., 2007; Thorsson *et al*., 2009; Vilbergsson *et al*., 1997). This coincides with the growth and ageing of the Icelandic population, as well as with the increasing body-mass index (BMI) in Icelanders. The obesity rate (BMI >30 kg/m^2) based on self-reported height and weight among Icelandic adults reached 21% in 2010 and was the highest among the Nordic countries (Organization for Economic Co-operation and Development, 2012).

1.6.2 Diabetic retinopathy

Although new evidence has indicated that retinal neurodegeneration is an early event in the pathogenesis of DR (Villaroel *et al*., 2010) it is still clinically considered mainly as a microvascular disease characterized by structural and physiologic damage to retinal capillaries caused by long-term hyperglycemia. The exact mechanism is unknown, but a number of biochemical and physiologic changes have been described. In general, the basement membrane may become thicker, leading to capillary occlusion. Abnormal permeability may also result in weakening or out-pouching of vessel walls and result in the formation of microaneurysms (figure 5), which can rupture and bleed into the retina (figure 6). The permeability of the damaged vessels increases and causes serum leakage, which clinically appears as retinal thickening with exudation (figure 6). If the leakage involves the macula, the serous edema that results can cause visual impairment. Reduction in blood flow to the retina due to vessel damage and occlusion and compensatory mechanisms leads to the formation of shunt capillaries, intraretinal microvascular abnormalities (IRMA) and dilatation of veins, as well to as venous beading. In advanced cases, vasoproliferative factors may form and trigger the formation of new vessels that are delicate and rupture easily, due to traction from the vitreous. New vessel formation is a sign of proliferative DR (PDR). The ruptured vessels then bleed into the vitreous cavity or the preretinal space (figure 7) and cause visual loss (Crawford *et al*., 2009; Frank, 1994; Roy *et al*., 2010).

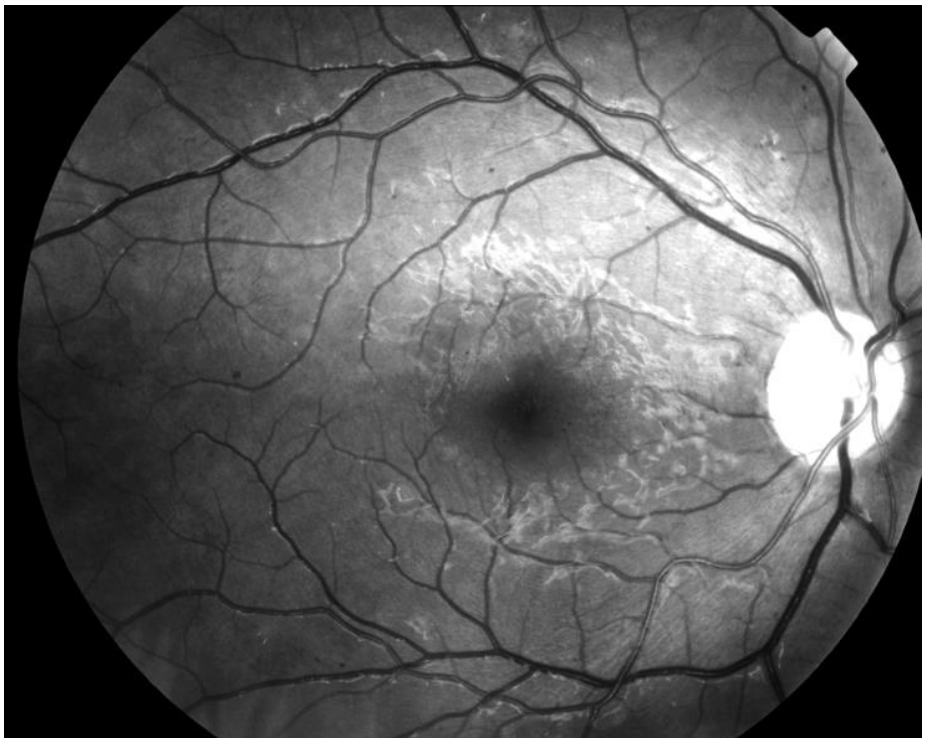

Figure 5. Mild retinopathy.
A fundus picture from a patient with microaneurysms (visible as dark dots).
Courtesy of professor Elisabet Agardh.

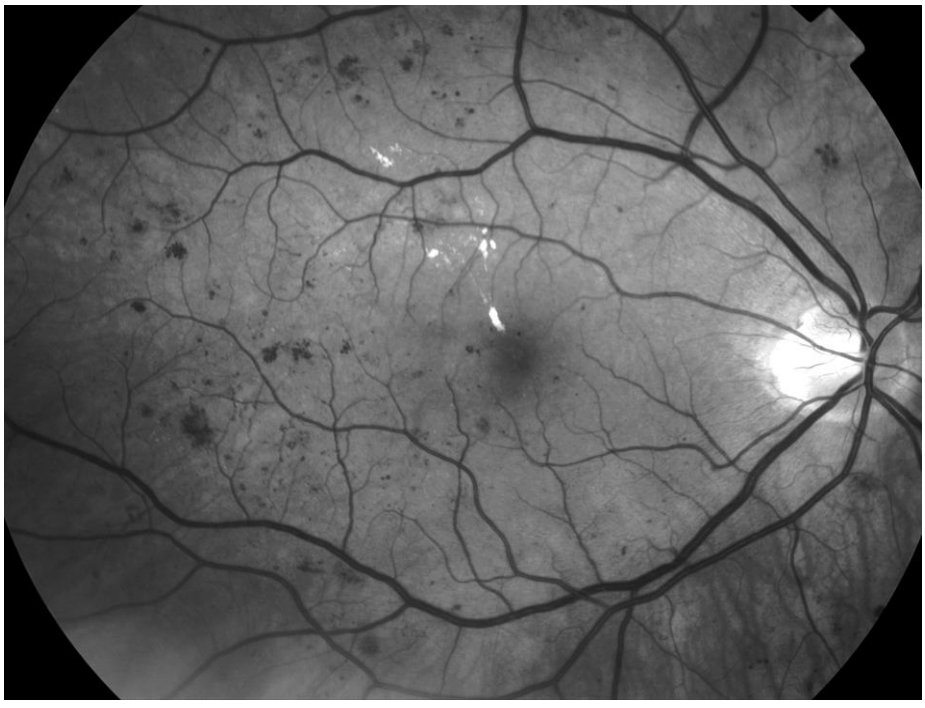

Figure 6. Moderate retinopathy with clinically significant macular edema
A fundus picture from a patient with retinal bleedings (visible as dark areas) and hard exudates (visible as bright white changes). The hard exudates are in this case combined with a thickening of the retina located within 500µm of the fovea and therefore classified as clinically significant.
Courtesy of professor Elisabet Agardh.

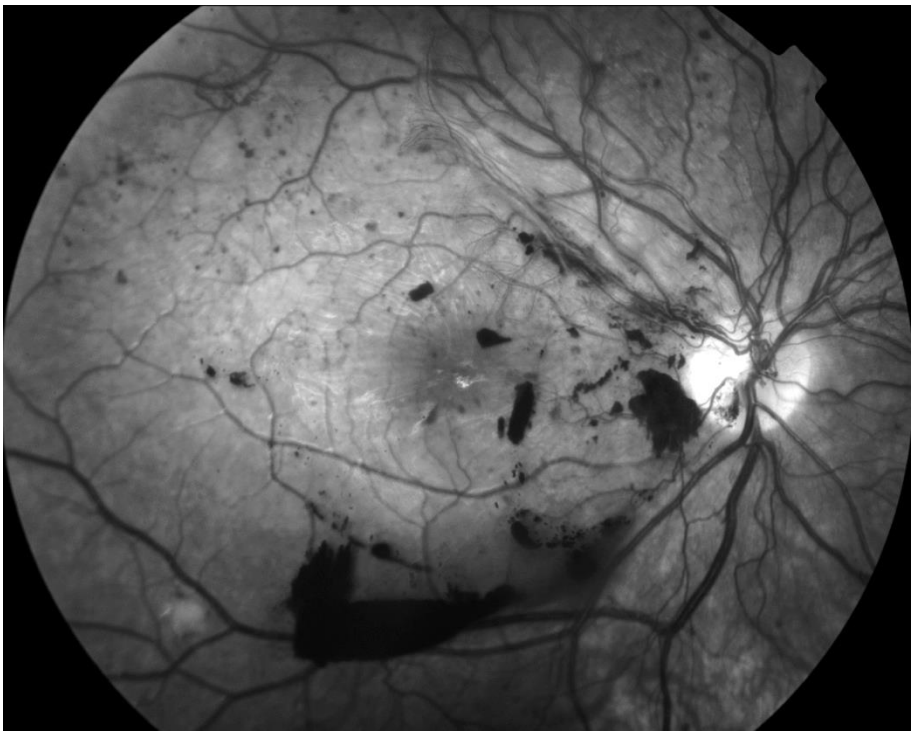

Figure 7. Proliferative retinopathy.
A fundus picture from a patient with multiple bleedings in the retina (small dark areas) and new-vessel formation located on the optic nerve and along the superior temporal arcade. The vessels have ruptured and bled into the preretinal space (visible as larger “ink-like” dark grey areas).
Courtesy of professor Elisabet Agardh.

The Early Treatment Diabetic Retinopathy Study (ETDRS) provided a widely used classification system for severity levels of DR and macular edema (ME) based on characteristic lesions (Diabetic Retinopathy Research Study Group, 1981). The classification (table 3) is a modification of the Airlie House Symposium’s classification of DR (Early Treatment Diabetic Retinopathy Study Research Group, 1991a).

Level	Description
10	No diabetic retinopathy (DR)
12	Retinopathy that is non-diabetic in nature, but which could be mistaken for DR
13	Questionable DR. Usually one questionable microaneurysm
14	Hard or soft exudates, IRMA or venous loops present without microaneurysms
15	Retinal hemorrhage present without any definite microaneurysms
20	Microaneurysms only with no other diabetic lesions present.
31	Microaneurysms and one or more of the following: hemorrhages fewer than in a standard comparison photo hard exudates venous loops questionable soft exudates (cotton wool spots) questionable IRMA questionable venous beading
41	Microaneurysms and one or more of the following: soft exudates IRMA less than in a standard comparison photo
51	Microaneurysms and one or more of the following: venous beading hemorrhages and microaneurysms more than in a standard comparison photo IRMA more than in a standard comparison photo
60	Fibrous proliferation only with no other proliferative lesions
61	No retinopathy but scatter treatment scars present
62	Level 20 (microaneurysms only) and scatter treatment scars present
63	Level 31 and scatter treatment scars present
64	Levels 41 or 51 and scatter treatment scars present
65 + 70	Proliferative DR
80	Total vitreous hemorrhage

Table 3. Retinopathy severity levels based on the Early Treatment Diabetic Retinopathy Study classification of Diabetic Retinopathy.
DR= Diabetic Retinopathy; IRMA = intra-retinal microvascular abnormalities.

The severity of retinopathy varies greatly among persons with diabetes mellitus, but at some point many become affected. A few years ago, Williams *et al.* (2004) published a systematic review report of the literature on the prevalence and incidence of DR and macular edema. They reviewed a total of 359 publications from over 50 countries and found conflicting reports on the prevalence and incidence of DR in diabetic populations. They found that many of the studies were quite outdated and heterogeneous in nature, and emphasized the importance of providing new epidemiologic data, since therapies for DR and associated complications are emerging. Recently, Yau *et al.* (2012) presented the overall prevalence of any DR to be 34.6% worldwide. Their estimation is based on data from 35 population-based studies on individuals aged 20-79 years with DM in the US, Australia, Europe, and Asia.

North-American and European studies on Caucasians with T2DM have reported a DR prevalence of around 25% to 35% (Danielsen *et al.*, 1983; Heintz *et al.,* 2010; Henricsson *et al.*, 1996; Hove *et al.*, 2004; Klein *et al.*, 1984a; Klein *et al.*, 1984b; Mitchell *et al.*, 1998; Stratton *et al.*, 2001; Williams *et al.*, 2004; Wong *et al.*, 2006; Zhang *et al.*, 2010).

1.6.3 Factors associated with retinopathy

Several studies conducted in mainly white populations have identified various factors associated with the risk of developing DR. The most consistent factor associated with DR is duration of diabetes. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, which took place in 1979-1980, reported that after more than 15 years of T1DM, almost 98% of the patients had some sign of DR (Klein *et al.,* 1984a). A study carried out almost 30 years later in the same geographical area on persons with T1DM concluded that with improved diabetes control and management, the severity level of retinopathy had decreased over the decades (LeCaire *et al.,* 2012). After more than 15 years diabetes duration, over 60% of patients with T2DM showed some sign of DR (Klein *et al.*, 1984b; Williams *et al.*, 2004). The same trend is seen in the Icelandic T1DM population, since no DR is described at diagnosis, whereas almost 90% have DR after 20 years of diabetes (Kristinsson *et al.*, 1997; Stefansson *et al.*, 2000).

Insulin use is commonly considered an indicator of more severe diabetes and longer disease duration, and has been recognized as an important factor associated with the development of retinopathy (Hove *et al.*, 2004; Mitchell *et al.*, 1998; Varma *et al.*, 2007; Wong *et al.*, 2006, Zhang *et al.*, 2010). In addition, hypertension and high systolic blood pressure have repeatedly been confirmed to increase the risk of DR, due to increased retinal blood flow in hypertensive states (Hove *et al.*, 2004; Kohner *et al.*, 1998; Patel *et al.*, 1992; Varma *et al.*, 2007; Zhang *et al.*, 2010). High fasting glucose and chronic hyperglycemia (presenting as an increased level of HbA1c) often reflect suboptimal diabetes control or a progression of the disease, and have consistently been identified as an independent risk factor for DR (Hove *et al.*, 2004; Klein *et al.*, 1988; Varma *et al.*, 2007; Wong *et al.*, 2006; Zhang *et al.*, 2010).

Associations with various inflammatory factors, hyperlipidemia, obesity (in the form of increased body-mass index; BMI) have been suggested, but been less consistent in epidemiological studies (Ferris III *et al.*, 1996; Klein *et al.*, 1997; Mitchell *et al.*, 1998; Stratton *et al.*, 2001; Varma *et al.*, 2007; Wong *et al.*, 2006; Zhang *et al.*, 2010).

1.6.4 Screening and prevention of diabetic blindness

The key systemic factors in preventing diabetic blindness are tight blood sugar and blood pressure control (UK Prospective Diabetes Study Group, 1998). However, regular eye screening and laser treatment have shown to be one of the most cost-effective health procedures available by reducing the risk of diabetic visual loss (Agardh *et al.*, 1996; The Diabetic Retinopathy Study Research Group, 1976; Early Treatment Diabetic Retinopathy Study Research Group, 1991b; Javitt and Aiello, 1996; Scott *et al.*, 2009; Stefánsson *et al.*, 2000). In accordance, a low incidence of diabetic blindness has been reported after institution of a screening program for DR (Agardh *et al.*, 1993, Olafsdottir *et al.*, 2007) and a significant relationship between screening compliance and visual outcome has been confirmed in the Icelandic screening program, which started in 1980 (Kristinsson *et al.*, 1997; Zoega *et al.*, 2005). The Icelandic system of annual visits for patients with retinopathy and biannual screening for patients without retinopathy (and in certain cases more frequent visits if the DR is severe) has proven to be adequate (Kristinsson *et al.*, 1995; Olafsdottir and Stefánsson, 2007; Zoega *et al.*, 2005). With new information technology and individualized DR risk assessment based on each person's risk profile, screening visits may be reduced even further (Aspelund *et al.*, 2011). In Sweden, a three-year interval screening program for T2DM patients without DR has been recommended (Agardh and Tababat-Khani, 2011).

Diabetic blindness is uncommon in Iceland. In an epidemiological study carried out in 1950 (Björnsson, 1950), described no cases of bilateral blindness due to DR, but by 1980, before laser treatment and regular eye screening were available in Iceland, the prevalence of bilateral diabetic blindness had risen to 2.4%, possibly due to improved registration of diabetic blindness (Björnsson,

1981; Danielsen *et al.*, 1982). In 1994, 14 years after the initiation of regular diabetic eye screening and laser treatment, the prevalence of bilateral legal blindness had fallen to 0.5% in patients with T1DM and 1.6% in T2DM patients (Kristinsson *et al.*, 1994a, Kristinsson *et al.*, 1994b).

2 Aims

The general aim of this thesis is to provide up-to-date epidemiologic data on visual loss and retinopathy in Iceland, in order to assess the magnitude of visual impairment and blindness and to identify the main causes of visual loss and factors associated with the risk of retinopathy. It can perhaps also be used as an aid in evaluating the quality and need for health- and eye-care services among specific population subgroups in Iceland and elsewhere, as well as in assessing the need for preventive measures in the effort to minimize the risk of visual impairment and blindness.

The specific objectives of each of the four published articles that substantially contribute to this thesis, papers I-III, were as follows:

Paper I: To describe the prevalence and causes of bilateral and unilateral visual impairment and blindness in a random population-based sample of Icelanders aged 50 years and older.

Paper II: To examine the 5-year incidence of bilateral and unilateral visual impairment and blindness in the same population-based sample as used for paper I. The aim was to describe changes in visual acuity (deterioration and improvement), as well as to identify causes of visual loss over a 5-year period.

Paper III: To describe the prevalence of retinopathy in a population-based cohort of Icelanders aged 67 years and older; and to identify risk factors associated with retinopathy in persons with and without diabetes mellitus.

3 Methods:

3.1 Participants and study details

3.1.1 Reykjavik Eye Study (papers I and II)

In papers I and II, we assessed the cause-specific prevalence and incidence of visual impairment and blindness using data from the 1996 and 2001 RES population-based prospective cohort survey databases. Participants were randomly sampled from among the Icelandic national population census. All were inhabitants of Reykjavik at least 50 years of age (born before 1947). The sample included 6.4% of both sexes of the Reykjavik population for each birth year we studied. Baseline interviews and eye examinations took place in September and October 1996, and follow-up examinations and interviews exactly five years later, in September and October 2001. All subjects were Caucasian. Previous RES publications described the general methodology and examination protocols in detail.

Of the 1,635 persons who were randomly sampled from among the Icelandic national population census, we were able to contact 1,379 non-institutionalized persons, 1,045 (461 male and 584 female) of whom agreed to participate in the RES. Of the 1,045 subjects who underwent the baseline examination, 846 (81.0%) also participated in the 2001 follow-up examination Eighty-six subjects (8.2%) had died during the previous 5 years, and the remaining 113 (10.8%) could not or did not want to participate in the 5-year follow-up examination. They were evenly distributed with respect to age, gender, and reason for non-participation.

Appropriate ethical approvals were obtained from the Landspitali University Hospital Ethics Committee and the Icelandic Data Protection Commission, according the guidelines of the Helsinki Declaration.

3.1.2 Age, Gene/Environment Susceptibility – Reykjavik Study (Paper III)

In paper III, the prevalence of retinopathy and factors associated with retinopathy in persons with and without diabetes was assessed using information from the AGES-R database. The AGES-R study is a population-based survey, and is aimed at investigating genetic and environmental factors that contribute to diseases (Harris et al., 2007). The AGES-R study is derived from the Icelandic Heart Association's (IHA) Reykjavik study which was conducted between 1967 and 1997. The AGES-R study cohort consisted of men and women 67 years and older (born before 1935) living in the Reykjavik area at the time the IHA-Reykjavik Study was conducted. At the time of recruitment, 11,549 (37.5%) of participants from the IHA-Reykjavik Study were still alive. The AGES-R examinations took place from February 2002 through February 2006, and included 5,764 survivors who were randomly sampled from the IHA-Reykjavik Study cohort. All participants underwent a three-visit protocol at the IHA Research Center over a period of 3 to 6 months. Participants were asked to bring all the medications they had used during the two weeks prior to the first visit. Transportation to the IHA research clinic was provided for participants who requested it. Venous blood specimens were drawn after overnight fasting and an eye examination was conducted (see below).

Previous AGES-R publications have described the methodology and examination protocol in detail (Eiriksdottir *et al.*, 2006; Harris *et al.*, 2007; Jonasson *et al.*, 2010; Olafsdóttir *et al.*, 2009; Qiu *et al.*, 2008; Qiu *et al.*, 2009; Saczynski *et al.*, 2008). The study was approved by the Icelandic National Bioethics Committee in Iceland, which acts as the Institutional Review Board for the Icelandic Heart

Association (VSN-00-063) and for the United States National Institute on Aging Intramural Institutional Review Board.

In both studies, informed consent was obtained from all participants, who completed a questionnaire regarding lifestyle, general health including cardiovascular history, diabetes, eye health, surgery, and medication.

3.2 Eye examinations

3.2.1 Reykjavik Eye Study (papers I and II)

Participants were subjected to a standard examination protocol, using the same procedures at baseline and at follow-up, 5 years later. Presenting visual acuity (VA) was measured in each eye, using a standard illuminated Snellen chart at 6 meters distance. If 6/6 vision could not be obtained, best-corrected visual acuity (BCVA) was measured using auto-refractokeratometry results (Nidek ARK 900; Nidek Co. Ltd, Gamagori, Japan) in a trial frame, aided by subjective refraction. If no letters could be read at 6 meters, the distance was reduced to 3 meters. If still no letters could be identified, the distance was reduced to 2 meters, and then to 1 meter. If visual acuity could not be measured with the Snellen chart at 1 meter, the following tests were conducted at 1 meter and 0.5 meter distances: counting fingers, hand movement, and light perception. Other parts of the examination protocol included air-puff tonometry (Nidek NT 2000; Nidek Co. Ltd) and Scheimpflug photography of the anterior eye segment (Nidek EAS 1000; Nidek Co. Ltd). Subjects' pupils were then dilated with tropicamide 1% and phenylephrine 10%, and slit-lamp biomicroscopy was carried out by an ophthalmologist. Scheimpflug- and retroilluminated images of the lens were also taken. Simultaneous stereo 30-degree fundus photographs were then taken by a trained ophthalmic photographer (Nidek 3Dx/NM; Nidek Co. Ltd), one centered on the optic disc (field 1) and the other on the macula (field 2). Visual field testing (Octopus G1X; Interzeag AG, Schilieren, Switzerland) and gonioscopy (Goldmann single mirror lens) were accomplished approximately 3 to 12 months after the initial examination for subjects with a history of glaucoma or who were suspected to have glaucoma based on optic disc appearance.

3.2.2 Age, Gene/Environment Susceptibility – Reykjavik Study (Paper III)

The VA of each eye was measured using an auto-refractokeratometer (Nidek ARK-760A) with a built-in Snellen chart. Pupils were then dilated with tropicamide 1% and photographs were taken of the retina. Two 45-degree digital retinal images centered on the optic disc (field 1) and the macula (field 2), respectively, were taken of each eye, using a Canon CR6 nonmydriatic camera with a Canon D60 camera back. Images were evaluated at the Ocular Epidemiology Reading Center at the University of Wisconsin, using the modified Airlie House Classification system (Early Treatment Diabetic Retinopathy Study Research Group, 1991a). EyeQ Lite image processing software was used, and graders were blinded to participants' health status.

3.3 Definition of visual impairment and blindness

To enable the comparison of our data on visual loss with those of other population-based studies, visual impairment and blindness were defined according to both WHO and US criteria. Bilateral visual impairment was defined as BCVA in the better-seeing eye of <6/18 and ≥3/60 or a visual field of ≥5° and <10° around a fixation point (WHO criteria), and as <6/12 and >6/60 (US criteria). Blindness was defined as BCVA in the better seeing eye of <3/60 or a visual field of <5° around a fixation point (WHO criteria) and BCVA of ≤6/60 in the better-seeing eye (US criteria). If a person was blind in one eye and

visually impaired in the other, she/he was considered to have bilateral visual impairment. Unilateral visual impairment and blindness were based on BCVA in the worse eye.

A change in VA between baseline and follow-up examinations amounting to two or more lines on the Snellen chart was defined as an improvement or deterioration. Participants with a VA of better than light perception were considered to be able to lose vision, and if visual acuity was less than 6/6, improvement in vision was considered possible.

3.4 Causes of visual impairment and blindness

In papers I and II, the causes of visual loss were determined for all visually impaired and blind participants. If the primary cause was unclear or the patient appeared to have more than one disease affecting vision, the senior author (FJ) reviewed the study data, including fundus photographs, and hospital records, or recalled the patients for another clinical examination, which was done by the senior author, in order to determine which disease had lead to the visual loss and indicating it to be the leading cause. If the causes for bilateral visual impairment or blindness were not the same for both eyes, the person was noted to have two causes. For example, a person with AMD in one eye and cataract in the other was classified as having AMD/cataract as the cause. Fundus photograps were framed and analyzed using a pocket stereoscope (Cartographic Engineering Ltd, Hampshire, England, United Kingdom).The RES had an agreement with the Moorfields Eye Hospital Reading Centre, in London, where chorioretinal disease was diagnosed and graded by the same two graders for both baseline and incidence data. GA was defined as an area of retinal depigmentation (>75µ in diameter) with a sharp edge and visible choroidal vessels. Exudative AMD was diagnosed if a serous or hemorrhagic detachment of the retinal pigment epithelium or the sensory retina was found, or if subretinal or subpigment epithelium hemorrhage or subretinal fibrous scars were present (Jonasson et al., 2003a; Jonasson et al., 2005; Klein et al., 1991b).

The diagnosis of cataract required slit-lamp microscopy and Scheimpflug slit- and retroillumination images of the lens. Grading was done using the Japanese cooperative cataract epidemiology study group system and the Kanazawa Medical University system (Arnarsson *et al.*, 1999; Katoh *et al.*, 2001; Sasaki *et al.*, 2000)

Glaucoma was assigned as the leading cause of impairment, based on a typical glaucomatous visual field defect and/or structural changes typical of glaucoma, the latter graded by a single grader using the stereofundus photographs centered on the optic disc. Glaucoma cases were divided into the following two categories: Category 1 demanded the presence of glaucomatous visual field defect and two of the following: 97.5th percentile for vertical cup:disc ratio; assymmetry between the eyes, and focal glaucomatous disc change. Category 2 included glaucoma subjects in whom visual fields could not be assessed or were unreliable, and required the presence of two of the following: 99.5th percentile vertical cup:disc ratio; asymmetry between the eyes, and focal glaucomatous disc change (Jonasson *et al.*, 2003). Amblyopia was assigned as the primary cause of unilateral visual loss if the affected eye had a best BCVA of less than 6/9 that was not attributable to any underlying structural abnormality of the eye or visual pathway (Attebo *et al.*, 1998).

3.5 Definition of diabetes mellitus, retinopathy, and macular edema

Diabetes mellitus was diagnosed if participants self-reported diabetes in the questionnaire, used glucose-lowering medications, or had an HbA1c of ≥6.5% (≥48 mmol/mol). To be able to compare our results with earlier publications, we also used fasting serum glucose of ≥7 mmol/l for undiagnosed diabetes mellitus in a separate analysis. The criteria for T1DM included age ≤25 years at diagnosis and insulin dependence. In accordance with previous AGES-R publications, participants older than 25 years at diagnosis were classified as having T2DM, regardless of treatment form.

If a grader was at least 90% certain that a retinopathy lesion was present, he marked the lesion as definite and assigned a retinopathy level according to the Modified Airlie House adaptation from the Early Treatment Diabetic Retinopathy Study protocol (see chapter 1.6.2 Diabetic retinopathy). The following grading criteria were used: no DR (levels 10-13), mild nonproliferative DR (levels 14-31), moderate to severe nonproliferative DR (levels 41-51), and PDR (levels 60-80). Macular edema was defined as rings of organized hard exudates, localized areas of color change, or deviation from the normal pathway of retinal blood vessels was observed. Clinically significant macular edema was considered present when edema involved the fovea or was within 500µm of the fovea, or when an area larger than 1 disc area in diameter was present, at least a portion of which was within the macula.

3.6 Assessment of risk factors associated with retinopathy (paper III)

The duration of diabetes was calculated as the difference between reported age of diabetes at diagnosis from the interview and the year of the AGES-R examination. Medications use was noted from medications brought to the clinic and from the self-report questionnaire. Blood pressure was assigned using the mean value of two blood pressure measurements with a large cuff mercury sphygmomanometer. Hypertension was defined by self-reported doctor's diagnosis of hypertension, use of hypertensive medication, or measured systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. BMI was calculated from measured height and weight (kg/m^2). Blood samples were drawn after overnight fasting. Total cholesterol, high-density lipoprotein (HDL) cholesterol, triacylglycerol, high-sensitivity C-reactive protein, serum glucose, and HbA1c were analyzed using a Hitachi 912 analyzer (Mito, Japan) using reagents from Roche Diagnostics (Mannheim, Germany) and following the manufacturer's instructions. Microalbuminuria was noted as present if the albumin-creatinine ratio in a random urine sample was 30-300 mg/g. Glomerular filtration rate (GFR) (ml min^{-1} 1.73 m^2) was estimated using the Modification of Diet in Renal Disease formula (Levey et al., 1999). The coefficient of variation (%) was 1.8 for serum glucose, 1.4 for total cholesterol, 2.3 for HDL, and 4.8 for urinary albumin.

3.7 Data handling and statistical analysis

All data were coded with ID numbers, and for statistical analysis we used SPSS (version 13.0 in paper I and version 12.1 in paper II, SPSS Inc. Chicago, Illinois, USA). For analysis in paper III, we used SAS Enterprise Guide software, version 9.1 (SAS Institute, Cary, NC, USA). In both studies, differences between groups were tested using the chi-square test for categorical variables and the t test for continuous variables. Confidence intervals for ratios were calculated using binomial distribution.

In papers I and II, the prevalence and incidence of visual impairment and blindness was calculated in 10-year age groups with 95% confidence intervals. Linear models were used to estimate visual loss and logistic models to calculate mortality and the risk of visual impairment.

In paper III, analysis of retinopathy was based on the participant's worse eye (with the most severe retinopathy lesions). If images from one eye were ungradeable or if fundus photographs were unavailable, scores from the contralateral eye were used. Logistic regression models adjusting for age and sex were run for each risk factor. In multivariate models, we included age, sex, systolic blood pressure, and hypertension as a categorical variable, HbA1c, and microalbuminuria; for participants with diabetes, we used duration of diabetes and use of glucose-lowering medication. HbA1c was imputed for 7% of the participants for whom these data were missing by applying the expectation-maximization algorithm in the PROC MI statistical program (SAT/STAT Institute, Cary, NC, USA). The imputation was made separately for participants with and without diabetes, according to medication use, and by using age, fasting serum glucose, and duration of diabetes as predictors for HbA1c

values. Persons with missing HbA1c values were not more likely to have diabetes or retinopathy than those with available HbA1c. HbA1c was imputed for five persons with undiagnosed T2DM. However, their fasting serum glucose levels were 8.9 mmol/l or higher.

4 Results

4.1 Reykjavik Eye Study (papers I and II)

The participation rate was 75.8% (n=1,045: 461 men and 584 women) in the 1996 baseline study. At the 5-year incidence examination in 2001, 86 persons (8.2%) had died, and of the 959 eligible participants, 88.2% (n=846; 377 men and 469 women) took part in the follow-up study.

Age- and sex-distributions were similar among participants and non-participants in the baseline study. The mean age of participants in the baseline study was 64.7 years. Of those aged 80 years or more at baseline, 33.3% had deceased before the 5-year follow-up examination, and an additional 24.4% did not participate in it for health-related reasons.

Persons with VA <6/12 at baseline were significantly older than those with better vision (mean age 78.2 years and 64.3 years, respectively; $p < 0.001$). In the follow-up study, 52.3% of those who had VA <6/12 at baseline had died, compared to 16.0% of participants with better vision ($p < 0.001$). The higher mortality risk among the visually impaired and blind remained significant even after controlling for the effects of age (odds ratio (OR) = 3.8; 95% CI 1.7-8.3; $p = 0.001$).

4.1.1 Bilateral visual impairment and blindness

Table 4 presents the prevalence of bilateral visual impairment and blindness by age and sex, according to WHO and US criteria.

		Bilateral visual impairment prevalence						Bilateral blindness prevalence					
		WHO criteria			US criteria			WHO criteria			US criteria		
Age	**All**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
All													
50-59	360	0	0	-	1	0.3	0.0-0.8	0	0	-	0	0	-
60-69	355	2	0.6	0.0-1.4	3	0.8	0.0-1.8	0	0	-	0	0	-
70-79	254	2	0.8	0.0-1.9	8	3.2	1.0-5.3	1	0.4	0.0-1.2	2	0.8	0.0-1.9
80+	76	6	7.9	1.7-14.1	9	11.8	4.4-19.3	5	6.6	0.9-12.3	6	7.9	1.7-14.1
All	1045	10	1.0	0.4-1.6	21	2.0	1.2-2.9	6	0.6	0.1-1.0	8	0.8	0.2-1.3
Men													
50-59	165	0	0	-	0	0	-	0	0	-	0	0	-
60-69	145	1	0.7	0.0-2.1	1	0.7	0.0-2.1	0	0	-	0	0	-
70-79	118	1	0.9	0.0-2.5	3	2.5	0.0-5.4	0	0	-	1	0.8	0.0-2.5
80+	33	2	6.1	0.0-14.7	3	9.1	0.0-19.4	1	3.0	0.0-9.2	2	6.1	0.0-14.7
All	461	4	0.9	0.0-1.7	7	1.5	0.4-2.6	1	0.2	0.0-0.6	3	0.7	0.0-1.4
Women													
50-59	195	0	0	-	1	0.5	0.0-1.5	0	0	-	0	0	-
60-69	210	1	0.5	0.0-1.4	2	1.0	0.0-2.3	0	0	-	0	0	-
70-79	136	1	0.7	0.0-2.2	5	3.7	0.5-6.9	1	0.7	0.0-2.2	1	0.7	0.0-2.2
80+	43	4	9.3	0.3-18.4	6	14.0	3.2-24.7	4	9.3	0.3-18.4	4	9.3	0.3-18.4
All	584	6	1.0	0.2-1.9	14	2.4	1.2-3.6	5	0.9	0.1-1.6	5	0.9	0.1-1.6

Table 4. Prevalence of bilateral visual impairment and blindness.
WHO = World Health Organization; US = United States; n = number; 95% CI = 95% confidence Interval

According to WHO criteria 1.0% of participants in the RES had bilateral visual impairment and 0.6% were blind at baseline. Using the US criteria, 2.0% of participants were visually impaired and 0.8% were blind. One participant had visual impairment due to visual field defects only. No gender difference was found. As seen in table 4 the prevalence of visual impairment and blindness, using either set of criteria, rises greatly in the oldest age group. In accordance, all those defined as blind according to WHO criteria and seven of the eight subjects (87.5%) defined as blind according to US criteria, were older than 75 years at baseline examination.

Table 5 presents the 5-year incidence of bilateral visual impairment and blindness using WHO and US criteria.

	Bilateral visual impairment 5-year incidence								**Bilateral blindness 5-year incidence**							
	WHO criteria				**US criteria**				**WHO criteria**				**US criteria**			
Age	**At risk**	**n**	**%**	**95% CI**	**At risk**	**n**	**%**	**95% CI**	**At risk**	**n**	**%**	**95% CI**	**At risk**	**n**	**%**	**95% CI**
All																
50-59	303	0	0	-	303	1	0.3	0.0-1.0	303	0	0	-	303	0	0	-
60-69	301	2	0.7	0.0-1.6	301	5	1.7	0.1-3.1	303	1	0.3	0.0-1.0	303	2	0.7	0.0-1.6
70-79	203	5	2.5	0.3-4.6	195	16	8.2	4.3-12.1	204	1	0.5	0.0-1.5	203	3	1.5	0.0-3.2
80+	35	2	5.7	0.0-13.8	32	7	21.9	6.7-37.0	36	1	2.8	0.0-8.4	35	3	8.6	0.0-18.3
All	842	9	1.1	0.4-1.8	831	29	3.5	2.2-4.7	846	3	0.4	0.0-0.8	844	8	1.0	0.3-1.6
Men																
50-59	142	0	0	-	142	0	0	-	142	0	0	-	142	0	0	-
60-69	123	1	0.8	0.0-2.4	123	3	2.4	0.0-5.2	124	1	0.8	0.0-2.4	124	2	1.6	0.0-3.9
70-79	95	3	3.2	0.0-6.7	92	8	8.7	2.8-14.6	96	1	1.0	0.0-3.1	95	2	2.1	0.0-5.1
80+	14	1	7.1	0.0-22.6	13	2	15.4	0.0-38.1	15	1	6.7	0.0-21.0	14	2	14.3	0.0-35.3
All	374	5	1.3	0.2-2.5	370	13	3.5	1.6-5.4	377	3	0.8	0.0-1.7	375	6	1.6	0.3-2.9
Women																
50-59	161	0	0	-	161	1	0.6	0.0-1.9	161	0	0	-	161	0	0	-
60-69	178	1	0.6	0.0-1.7	178	2	1.1	0.0-2.7	179	0	0	-	179	0	0	-
70-79	108	2	1.9	0.0-4.4	103	8	7.8	2.5-13.0	108	0	0	-	108	1	0.9	0.0-2.8
80+	21	1	4.8	0.0-14.7	19	5	26.3	4.5-48.1	21	0	0	-	21	1	4.8	0.0-14.7
All	468	4	0.9	0.0-1.7	461	16	3.5	1.8-5.2	469	0	0	-	469	2	0.4	0.0-1.0

Table 5. Five-year incidence of bilateral visual impairment and blindness.
WHO = World Health Organization; US = United States; n = number; 95% CI = 95% confidence Interval

The 5-year incidence of bilateral visual impairment and blindness was 1.1% and 0.4%, respectively, according to WHO criteria. Using the more inclusive US criteria, we found a 3.5% incidence of visual impairment and 1.0% incidence of blindness. No gender difference was found in the 5-year incidence using either set of criteria.

Those who developed bilateral visual impairment were significantly older at baseline than those who did not (75 years versus 65 years; $p<0.001$). As seen in table 5, using US criteria, the 5-year incidence of bilateral visual impairment increased from 0.3% in the youngest age group to 21.9% in the oldest age group.

According to WHO criteria, seven of the nine persons who developed bilateral visual impairment and two of the three blind had a BCVA ≥6/12 in the better eye at baseline.

4.1.2 Unilateral visual impairment and blindness

According to WHO criteria 4.4% of the subjects had unilateral visual impairment (19 right eyes and 27 left eyes) and 1.7% were unilaterally blind (five right eyes and 13 left eyes). Using the US criteria, 5.5% of the subjects were visually impaired (30 right eyes and 27 left eyes), and 3.1% were blind in only one eye (10 right eyes and 22 left eyes). Men were more likely than women to have unilateral blindness according to WHO criteria (OR = 2.7; 95% CI 1.0-7.3; p <0.05). Age was strongly associated with the risk of unilateral visual loss. Table 6 presents the prevalence of unilateral visual loss by age and sex.

		Unilateral visual impairment prevalence						Unilateral blindness prevalence					
		WHO criteria			US criteria			WHO criteria			US criteria		
Age	**All**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
All													
50-59	360	6	1.7	0.3-3.0	10	2.8	1.1-4.5	2	0.6	0.0-1.3	2	0.6	0.0-1.3
60-69	355	13	3.7	1.7-5.6	13	3.7	1.7-5.6	3	0.9	0.0-1.8	8	2.3	0.7-3.8
70-79	254	16	6.3	3.3-9.3	21	8.3	4.9-11.7	10	3.9	1.5-6.3	16	6.3	3.3-9.3
80+	76	11	14.5	6.4-22.6	13	17.1	8.4-25.8	3	3.9	0.0-8.4	6	7.9	1.7-14.1
All	1045	46	4.4	3.2-5.7	57	5.5	4.1-6.8	18	1.7	0.9-2.5	32	3.1	2.0-4.1
Men													
50-59	165	4	2.4	0.1-4.8	5	3.0	0.4-5.7	1	0.6	0.0-1.8	1	0.6	0.0-1.8
60-69	145	5	3.5	0.4-6.5	4	2.8	0.1-5.5	3	2.1	0.0-4.4	6	4.1	0.9-7.4
70-79	118	8	6.8	2.2-11.4	10	8.5	3.4-13.6	6	5.1	1.1-9.1	8	6.8	2.2-11.4
80+	33	2	6.1	0.0-14.7	4	12.1	0.4-23.9	2	6.1	0.0-14.7	2	6.1	0.0-14.7
All	461	19	4.1	2.3-5.9	23	5.0	3.0-7.0	12	2.6	1.1-4.1	17	3.7	2.0-5.4
Women													
50-59	195	2	1.0	0.0-2.5	5	2.6	0.3-4.8	1	0.5	0.0-1.5	1	0.5	0.0-1.5
60-69	210	8	3.8	1.2-6.4	9	4.3	1.5-7.1	0	0.0	-	2	1.0	0.0-2.3
70-79	136	8	5.9	1.9-9.9	11	8.1	3.5-12.7	4	2.9	0.1-5.8	8	5.9	1.9-9.9
80+	43	9	20.9	8.3-33.6	9	20.9	8.3-33.6	1	2.3	0.0-7.0	4	9.3	0.3-18.4
All	584	27	4.6	2.9-6.3	34	5.8	3.9-7.7	6	1.0	0.2-1.9	15	2.6	1.3-3.9

Table 6. Prevalence of unilateral visual impairment and blindness.
WHO = World Health Organization; US = United States; n = number; 95% CI = 95% confidence Interval

During the 5-year follow-up period, 3.5% of the subjects developed unilateral visual impairment (17 right eyes and 11 left eyes) according to WHO criteria, and 5.9% according to US criteria (22 right eyes and 26 left eyes). Using either set of criteria, we found 10 persons who developed unilateral blindness. No gender difference was found regarding incident unilateral visual loss (see table 7).

Participants who developed unilateral blindness were significantly older at baseline than the remainder of the cohort (77 years *vs* 64 years; p < 0.001).

	Unilateral visual impairment 5-year incidence								Unilateral blindness 5-year incidence							
	WHO criteria				US criteria				WHO criteria				US criteria			
Age	**At risk**	**n**	**%**	**95% CI**	**At risk**	**n**	**%**	**95% CI**	**At risk**	**n**	**%**	**95% CI**	**At risk**	**n**	**%**	**95% CI**
All																
50-59	296	4	1.4	0.0-2.7	297	6	2.0	0.4-3.6	302	0	0	-	302	0	0	-
60-69	289	5	1.7	0.2-3.2	296	13	4.4	2.0-6.7	300	2	0.7	0.0-1.6	297	3	1.0	0.0-2.2
70-79	178	15	8.4	4.3-12.6	185	26	14.1	9.0-19.1	193	5	2.6	0.3-4.9	185	3	1.6	0.0-3.5
80+	28	4	14.3	0.5-28.1	30	3	10.0	0.0-21.4	34	3	8.8	0.0-18.9	31	4	12.9	0.4-25.4
All	791	28	3.5	2.3-4.8	808	48	5.9	4.3-7.6	829	10	1.2	0.5-2.0	815	10	1.2	0.5-2.0
Men																
50-59	138	1	0.7	0.0-2.2	136	1	0.7	0.0-2.2	142	0	0	-	142	0	0	-
60-69	117	3	2.6	0.0-5.5	117	5	4.3	0.6-8.0	121	1	0.8	0.0-2.5	120	1	0.8	0.0-2.5
70-79	82	5	6.1	0.8-11.4	77	9	11.7	4.4-19.0	90	1	1.1	0.0-3.3	86	2	2.3	0.0-5.6
80+	11	1	9.1	0.0-29.4	9	1	11.1	0.0-36.7	13	0	0	-	11	1	9.1	0.0-29.4
All	348	10	2.9	1.1-4.6	339	16	4.7	2.5-7.0	366	2	0.6	0.0-1.3	359	4	1.1	0.0-2.2
Women																
50-59	158	3	1.9	0.0-4.1	161	5	3.1	0.4-5.8	160	0	0	-	160	0	0	-
60-69	172	2	1.2	0.0-2.8	179	8	4.5	1.4-7.5	179	1	0.6	0.0-1.7	177	2	1.1	0.0-2.7
70-79	96	10	10.4	4.2-16.6	108	17	15.7	8.8-22.7	103	4	3.9	0.1-7.7	99	1	1.0	0.0-3.0
80+	17	3	17.7	0.0-37.9	21	2	9.5	0.0-23.2	21	3	14.3	0.0-30.6	20	3	15.0	0.0-32.2
All	443	18	4.1	2.2-5.9	469	32	6.8	4.5-9.1	463	8	1.7	0.5-2.9	456	6	1.3	0.3-2.4

Table 7. Five-year incidence of unilateral visual impairment and blindness.
WHO = World Health Organization; US = United States; n = number; 95% CI = 95% confidence Interval

4.1.3 Causes of bilateral visual loss

When examining both prevalence and 5-year incidence of bilateral visual impairment according to WHO criteria, AMD was the primary cause, accounting for over one-half of all cases. Unoperated cataract was the cause for one-third of 5-year incident visual impairment according to WHO criteria.

When the criteria were expanded to the broader US definitions, the two main causes were unoperated cataract and AMD. Each accounted for 38.1% of the prevalence of bilateral visual impairment, but when looking at the 5-year incidence, cataract was the principal cause and AMD the second most common cause.

Other causes can be seen in table 8, which presents the prevalent and 5-year incident causes for bilateral visual impairment by age and sex.

Primary cause	Bilateral visual impairment prevalence				Bilateral visual impairment 5-year incidence			
	WHO criteria		US criteria		WHO criteria		US criteria	
	n	%	n	%	n	%	n	%
AMD	5	50	8	38.1	5	55.6	8	27.6
Cataract	0	-	8	38.1	3	33.3	13	44.8
Corneal opacity	1	10	1	4.8	0	-	1	3.4
Glaucoma	1	10	0	-	0	-	0	-
Ocular albinism	1	10	1	4.8	0	-	0	-
Leber's optic atrophy	1	10	0	-	0	-	0	-
AMD/Cataract	0	-	1	4.8	0	-	0	-
AMD/CRVO	1	10	1	4.8	0	-	0	-
AMD/Amblyopia	0	-	0	-	0	-	2	6.9
Cataract/Amblyopia	0	-	0	-	0	-	1	3.4
Cataract/CRVO	0	-	0	-	0	-	1	3.4
Cataract/Corneal opacity	0	-	0	-	0	-	1	3.4
Diabetic retinopathy	0	-	0	-	1	11.1	1	3.4
Bullous Keratopathy	0	-	0	-	0	-	1	3.4
Unknown	0	-	1	4.8	0	-	0	-
All	10	100	21	100	9	100	29	100

Table 8. Prevalent and five-year incident causes of bilateral visual impairment.
WHO = World Health Organization; US = United States; n = number; AMD = Age-related Macular Degeneration; CRVO = Central Retinal Vein Occlusion

Regardless of the criteria applied, AMD was the primary cause of both prevalent and 5-year incident bilateral blindness. It accounted for 83.4% of prevalent bilateral blindness according to the WHO definition and 75.0% of both prevalent and 5-year incident bilateral blindness according to US criteria.

Of the six persons identified with prevalent bilateral blindness (US criteria) due to AMD, three had GA in both eyes, one had exudative AMD in both eyes, and two had GA in one eye, but exudative AMD in the other eye.

Other causes for prevalent and 5-year incident bilateral blindness were uncommon and are presented in figures 8 and 9.

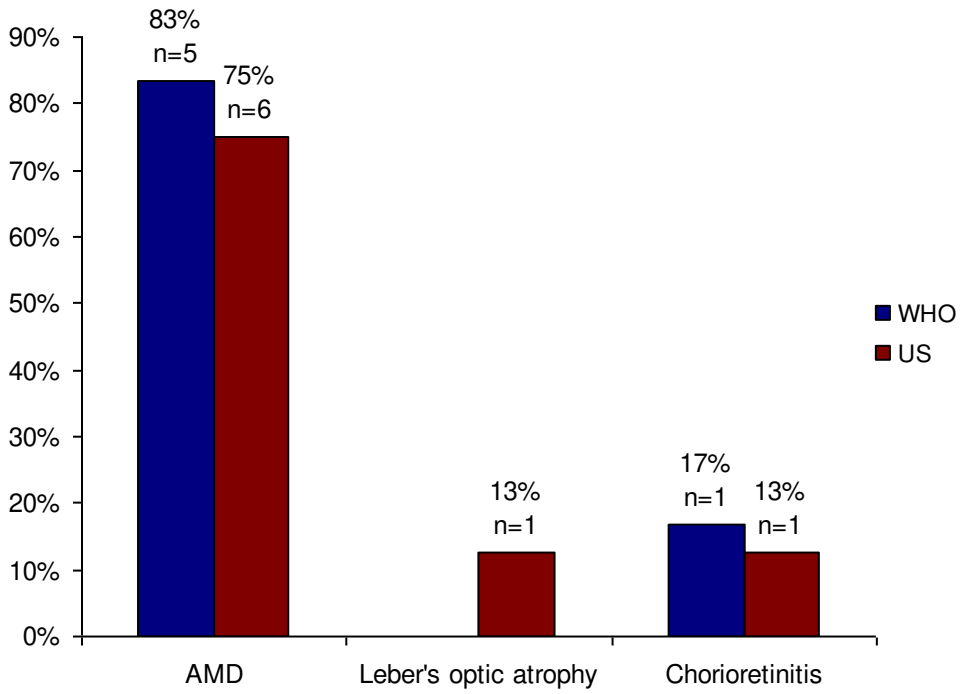

Figure 8. Causes of prevalent bilateral blindness.
WHO = World Health Organization criteria; US = United States criteria;
n = number; AMD = Age-related Macular Degeneration

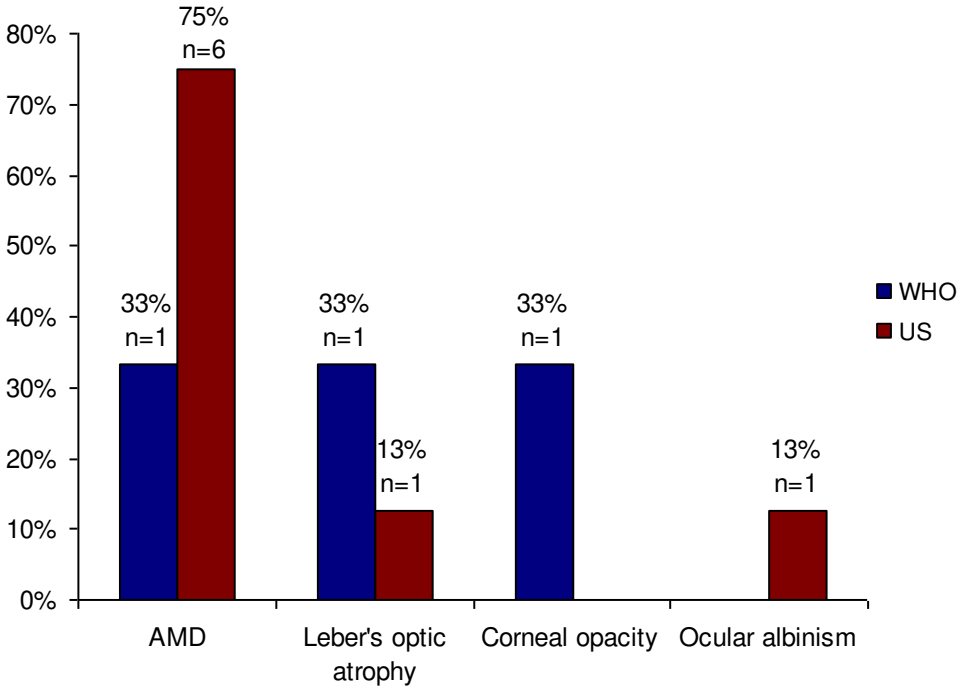

Figure 9. Causes of five-year incident bilateral blindness.
WHO = World Health Organization criteria; US = United States criteria;
n = number; AMD = Age-related Macular Degeneration

4.1.4 Causes of unilateral visual loss

According to WHO criteria, the three major causes of prevalent unilateral visual impairment were amblyopia (43.5%), unoperated cataract (30.4%), and AMD (10.9%). When using US criteria, the major causes remained the same. Table 9 presents the prevalent and 5-year incident causes of visual impairment.

Amblyopia was by far the most common cause of prevalent unilateral visual impairment in persons aged 50-74 years, while cataract was more common in the older age groups.

When studying the causes of incident unilateral visual impairment, cataract was by far the main cause, accounting for 50.0% using WHO criteria and 64.6% using US criteria. AMD was the second most common cause for developing unilateral visual impairment over the 5-year period.

Primary cause	Unilateral visual impairment prevalence				Unilateral visual impairment 5-year incidence			
	WHO criteria		US criteria		WHO criteria		US criteria	
	n	%	n	%	n	%	n	%
Amblyopia	20	43.5	20	35.1	0	-	2	4.2
Cataract	14	30.4	20	35.1	14	50.0	31	64.6
AMD	5	10.9	9	15.8	9	32.1	9	18.8
Corneal opacity	3	6.5	4	7.0	0	-	0	-
Retinal detachment	0	-	0	-	1	3.6	0	-
Diabetic retinopathy	1	2.2	2	3.5	0	-	1	2.1
Temporal arteritis	1	2.2	1	1.8	0	-	0	-
Macular hole	1	2.2	0	-	0	-	1	2.1
Bullous keratopathy	0	-	0	-	2	7.1	1	2.1
BRVO	0	-	0	-	1	3.6	1	2.1
Trauma	0	-	0	-	1	3.6	0	-
Unknown	1	2.2	1	1.8	0	-	2	4.2
All	46	100	57	100	28	100	48	100

Table 9. Prevalent and five-year incident causes of unilateral visual impairment.
WHO = World Health Organization; US = United States; n = number; AMD = Age-related Macular Degeneration; BRVO = Branch Retinal Vein Occlusion

Regardless of the criteria used, the three main causes of prevalent unilateral blindness were amblyopia, glaucoma, and AMD. Two persons had an artificial eye, one due to an infection during childhood and the other due to trauma. AMD was by far the largest cause of incident unilateral blindness. Other causes of unilateral visual impairment and blindness appear in table 10.

Primary cause	Unilateral blindness prevalence				Unilateral blindness 5-year incidence			
	WHO criteria		US criteria		WHO criteria		US criteria	
	n	%	n	%	n	%	n	%
Amblyopia	6	33.3	14	43.7	1	10.0	1	10.0
AMD	4	22.2	5	15.7	6	60.0	5	50.0
Glaucoma	5	27.8	4	12.5	0	-	0	-
Corneal opacity	1	5.6	3	9.4	1	10.0	0	-
Cataract	0	-	3	9.4	0	-	1	10.0
Trauma	1	5.6	1	3.1	0	-	1	10.0
Macular hole	0	-	1	3.1	1	10.0	0	-
Infection	1	5.6	1	3.1	0	-	0	-
Retinal detachment	0	-	0	-	0	-	1	10.0
Facial cancer	0	-	0	-	1	10.0	1	10.0
All	18	100	32	100	10	100	10	100

Table 10. Prevalent and five-year incident causes of unilateral blindness.
WHO = World Health Organization; US = United States; n = number; AMD = Age-related Macular Degeneration

4.1.5 Deterioration and improvement in vision

Figure 10 compares the VA in right eyes in 1996 and 2001. Decline in VA was significantly related to age at baseline (p=0.006). No gender difference was found. The same trend was seen when analysis was based on left eyes.

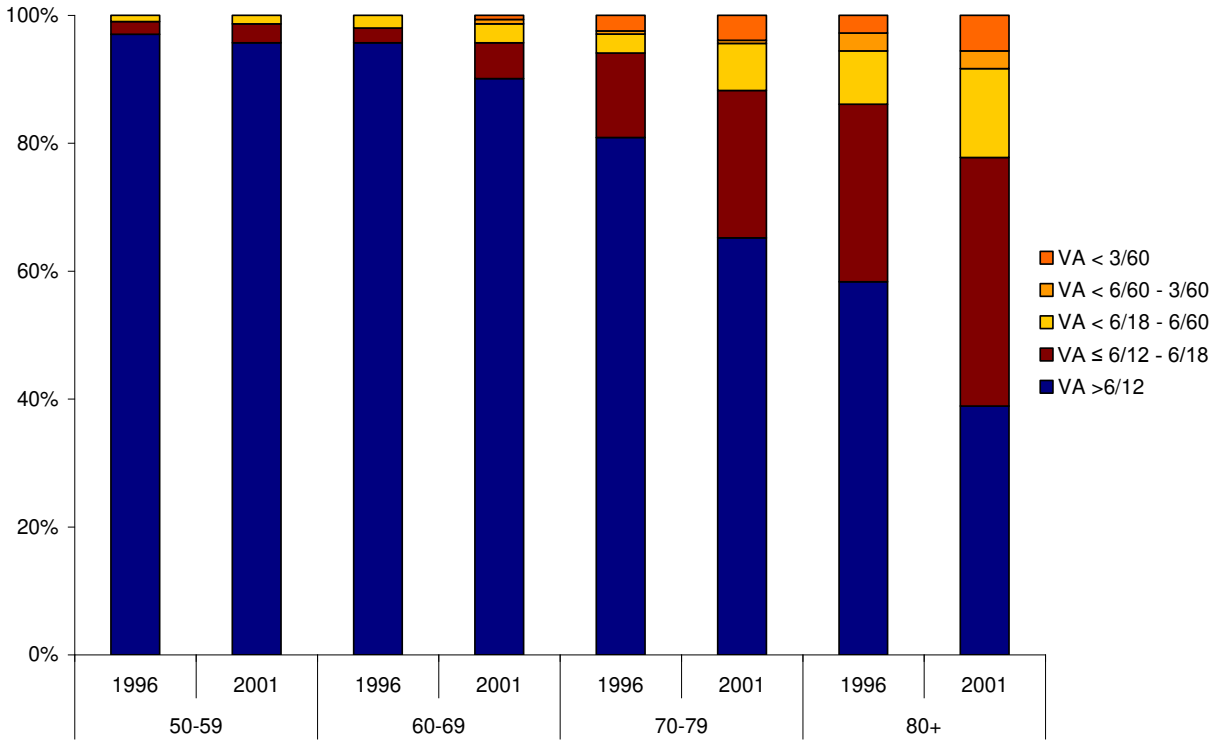

Figure 10. Distribution of visual acuity (VA) in the right eye in 1996 (n=1045) and 2001 (n=846).

Bilateral deterioration of ≥2 Snellen lines was observed in 16.5% of those with BCVA of better than light perception at baseline, and 21.6% had suffered from unilateral deterioration at the follow-up examination. Of those with VA of less than 6/6 at baseline, 12.9% gained two or more Snellen lines in both eyes during the 5-year follow-up, and another 26.0% improved by two or more Snellen lines in one eye only. In the oldest age group (persons aged ≥ 80 years at baseline), 44.4% of those who had BCVA of better than light perception at baseline developed a visual loss of ≥2 Snellen lines in both eyes and 30.6% in one eye during the 5-year follow-up period. In the younger age groups, improvement was more common than deterioration and among persons aged 50-59 years at baseline; 37.8% gained vision in one eye and 20.0% in both eyes. Improvement was associated with cataract surgery in about one-third of all eyes, but we were unable to determine the cause for all cases with a change in visual acuity.

4.2 Age, Gene/Environment Susceptibility – Reykjavik Study (Paper III)

Of the 5,764 AGES-R participants, 4,994 had available laboratory test results and fundus photographs of at least one eye. Of the 4.994, 516 (10.3%) fulfilled criteria for diagnosis of DM. Two persons (both women) were classified as having T1DM, on the basis of age <25 years at diagnosis and insulin use, and were included in the analysis. Table 11 presents the main characteristics of participants by diabetes status and treatment profiles.

	Total group (n=4994)			DM by diagnosis time (n=516)			DM by treatment (n=516)			
	No DM	DM	p value	Undiagnosed	Previously known	p value	Insulin ± oral[a]	Only oral[a]	Only diet	p value[b]
n (%)	4478 (89.7)	516 (10.3)	–	83 (16.1)	433 (83.9)	–	37 (6.2)	273 (52.9)	206 (40.0)	–
Male sex, n (%)	1880 (42.0)	272 (52.7)	<0.001	36 (43.4)	236 (54.5)	0.06	21 (56.8)	164 (60.1)	87 (42.2)	0.61
Age (years)	76.4 +/- 5.5	76.4 +/- 5.3	0.97	76.6 +/- 5.3	76.5 +/- 5.4	0.89	75.7 +/- 4.6	76.3 +/- 5.2	76.9 +/- 5.6	0.35
Age at DM diagnosis (years)	–	64.9 +/- 12.6	–	76.3 +/- 5.4	63.7 +/- 12.6	<0.001	53.1 +/- 13.5	64.7 +/- 10.2	67.7 +/- 13.7	<0.001
DM duration (years)	–	10.3 (11.2)	–	0	12.4 (11.2)	<0.001	24.9 (13.7)	11.1 (9.7)	6.8 (10.4)	<0.001
Hypertension, n (%)	3579 (79.9)	466 (90.3)	<0.001	72 (86.8)	394 (91.0)	0.23	33 (89.2)	250 (91.6)	184 (89.3)	0.81
Systolic BP (mmHg)	141.9+/-20.2	146.0+/-20.4	<0.001	141.6+/- 21.9	146.0 +/- 20.4	0.10	145.6 +/- 19.8	145.2+/-20.6	145.4 +/- 21.0	0.93
Body Mass Index (kg/m²)	26.8 +/- 4.3	28.9 +/- 4.7	<0.001	27.8 +/- 4.4	28.6 +/- 4.6	0.14	28.5 +/- 5.8	28.6 +/- 4.4	28.2 +/- 4.5	0.94
Measured HbA1c (%)	5.6 +/- 0.3	6.5 +/- 0.9	<0.001	7.0 +/- 0.9	6.5 +/- 0.9	<0.001	7.4 +/- 0.9	6.6 +/- 0.9	6.5 +/- 1.0	<0.001
Imputed HbA1c (%)	5.9+/- 0.3	6.5 +/- 0.9	<0.001	7.0 +/- 0.8	6.5 +/- 0.9	0.007	7.3 +/- 0.9	6.6 +/- 0.9	6.5 +/- 1.0	<0.001
Measured HbA1c (mmol/mol)	37.6+/- 3.5	48.8 +/- 10.4	<0.001	53.1 +/- 9.5	48.0 ± 10.3	<0.001	56.9 +/- 9.5	48.6 +/- 9.7	47.6 +/- 10.8	<0.001
Imputed HbA1c (mmol/mol)	37.6 +/- 3.4	48.7+/- 10.1	<0.001	53.0 +/- 9.3	47.8 +/- 10.1	0.007	56.5 +/- 9.4	48.6 +/- 9.4	47.3 +/- 10.6	<0.001
Fasting glucose (mmol/l)	5.5 +/- 0.6	7.8 +/- 2.1	<0.001	7.6 +/- 2.6	7.8 +/- 2.4	0.50	9.2 +/- 3.8	8.1 +/- 2.1	7.1 +/- 2.3	<0.001
Total cholesterol (mmol/l)	5.7 +/- 1.1	5.2 +/- 1.1	<0.001	5.4 +/- 1.2	5.1 +/- 1.1	0.007	4.6 +/- 1.1	5.0 +/- 1.1	5.4 +/- 1.1	0.008
GFR <60 ml min^{-1} 1.73^{-2}, n (%)	1336 (29.8)	206 (39.9)	<0.001	34 (41.0)	172 (39.7)	0.83	17 (45.9)	105 (38.5)	84 (40.8)	0.33
Current smoker, n (%)	546 (12.2)	60 (11.6)	0.71	10 (12.0)	50 (11.6)	0.90	5 (13.5)	34 (12.5)	21 (10.2)	0.71
Ever smoker, n (%)	2550 (56.9)	305 (59.1)	0.34	47 (56.6)	258 (59.7)	0.25	25 (67.6)	161 (59.0)	119 (57.8)	0.28
Previous CVD, n (%)	921 (20.6)	160 (31.0)	<0.001	21 (25.3)	139 (22.3)	0.20	14 (37.8)	95 (34.8)	51 (24.8)	0.30
Microalbuminuria, n (%)	434 (7.4)	101 (19.6)	<0.001	10 (12.0)	91 (21.3)	0.06	11 (29.7)	66 (24.2)	24 (11.7)	0.12

Table 11. Comparison of participants' characteristics in the Age, Gene/Environment Susceptibility – Reykjavik Study (AGES-R).
DM= diabetes mellitus; n = number; BP = Blood Pressure; GFR = Glomerular Filtration Rate; CVD = Cardiovascular Disease; [a] Oral hypoglycaemic agents; [b] For insulin users compared with the two other treatment groups combined

Males were significantly more likely than females to have diabetes. Persons with diabetes were more likely to have hypertension, higher BMI, as well as higher serum glucose and HbA1c levels than non-diabetics. They were also more likely to have suffered from a previous cardiovascular disease and to have microalbuminuria. The 83 participants with undiagnosed DM had a mean age of 76.3 years. Age at DM diagnosis was strongly associated with treatment modality, those on insulin being the youngest and those whose diabetes was managed by diet or who were left untreated being in the oldest age group. Participants with undiagnosed DM had higher HbA1c and total cholesterol levels than participants whose DM was previously known. However, no difference was seen in fasting glucose levels between the two groups. (see table 11)

4.2.1 Prevalence of retinopathy in persons with diabetes mellitus:

Gradable fundus photographs from at least one eye were available from 512 of the 516 with DM. We found a 27.0% prevalence of any DR in one or both eyes. Tables 12 and 13 show the prevalence of DR and macular edema by age, sex, diabetes duration and diabetes treatment.

Of the five persons with PDR in the worse eye, two had PDR in both eyes and three had milder forms of non-proliferative DR in the better eye. Among those with DM, there were no statistically significant age- or sex specific differences in the prevalence of any DR measure. Of the 82 persons with undiagnosed DM before the study and readable fundus photographs, nine (11.0%) had some DR (eight mild and one moderate non-proliferative DR). Insulin-treated diabetics had a longer duration of diabetes than persons receiving other forms of treatment, with a mean diabetes duration of 24.9 years (Standard Deviation; SD = 13.7), compared with 11.2 years (SD = 9.7) for those using any glucose-lowering medications and 6.8 years (SD = 10.4) for those without medical treatment. Insulin users also had a significantly higher prevalence of any DR and clinically significant ME (CSME) than persons who were receiving other forms of treatment.

Persons with any DR were younger at the time of DM diagnosis (mean age 61.1 years; SD = 14.4) than those without DR (mean age 66.3 years; SD = 11.6).

4.2.2 Prevalence of retinopathy in non-diabetic persons

Of the 4,478 non-diabetic persons in the sample, 4,453 had gradable fundus photographs. Of these, retinopathy was found in 476 (10.7%) as shown in Table 14. Macular edema was present in five persons (0.1%), all of whom had branch retinal vein occlusion. There was no sex-specific difference in the prevalence of retinopathy among non-diabetic persons. After adjusting for age and sex, persons with retinopathy were not more likely to have hypertension, higher fasting glucose, or higher BMI than those without retinopathy.

	Persons with DM (n=512)			Age group						Sex					
				67-74 (n=190)			≥ 75 (n=322)			Male (n=272)			Female (n=240)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Retinopathy															
Any	138	27.0	23.2-31.0	52	27.7	21.2-34.3	86	26.7	22.0-31.9	78	28.7	23.4-34.4	60	25.0	19.8-31.0
NPDR															
Mild	120	23.4	19.8-27.4	45	23.7	17.8-30.4	75	23.3	18.8-28.3	74	26.4	20.3-31.0	51	21.3	16.3-27.0
Moderate	13	2.5	1.4-4.3	4	2.1	0.6-5.3	9	2.8	1.3-5.2	8	2.9	1.3-5.7	5	2.1	0.7-4.8
PDR	5	1.0	0.3-2.3	3	1.6	0.3-4.5	2	0.6	0.1-2.2	1	0.4	0.0-2.0	4	1.7	0.5-4.2
Macular edema															
Any	9	1.8	0.8-3.3	3	1.6	0.3-4.5	6	1.9	0.7-4.0	4	1.5	0.4-3.7	5	2.1	0.7-4.8
CSME	5	1.0	0.3-2.3	2	1.1	0.1-3.7	3	0.9	0.2-2.7	1	0.4	0.0-2.0	4	1.7	0.5-4.2

Table 12. Prevalence and severity of retinopathy and macular edema by age and sex in persons with diabetes mellitus (DM).
n = number; 95% CI = 95% confidence interval; NPDR = Non-Proliferative Diabetic Retinopathy; PDR = Proliferative Diabetic Retinopathy; CSME = Clinically Significant Macular Edema.

	DM by diagnosis time						DM by treatment								
	Undiagnosed (n=82)			Previously known (n=430)			Insulin users +/- oral[a] (n=37)			Only oral[a] (n=270)			Only diet (n=205)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Retinopathy															
Any	9	11.0	5.1-19.8	129	30.0	25.7-34.6	24	64.9	47.5-79.8	82	30.4	24.9-36.2	32	15.6	10.9-21.3
NPDR															
Mild	8	9.8	4.3-18.3	112	26.1	22.0-30.5	14	37.8	22.5-55.2	76	28.1	22.9-33.9	30	14.6	10.1-20.2
Moderate	1	1.2	0.0-6.6	12	2.8	1.5-4.8	7	18.9	8.5-35.2	4	1.5	0.4-3.8	2	1.0	0.1-3.5
PDR	0	0	0.0-4.4	5	1.2	0.4-2.7	3	8.1	1.7-21.9	2	0.7	0.1-2.7	0	0	0.0-1.8
Macular edema															
Any	0	0	0.0-4.4	9	2.1	1.0-3.9	4	10.8	3.0-25.4	4	1.5	0.4-3.7	1	0.5	0.0-2.7
CSME	0	0	0.0-4.4	5	1.2	0.4-2.7	2	5.4	0.7-18.2	3	1.1	0.2-3.2	0	0	0.0-1.8

Table 13. Prevalence and severity of retinopathy and macular edema by duration of diabetes mellitus (DM) and treatment form
n = number; 95% CI = 95% confidence interval; NPDR = Non-Proliferative Diabetic Retinopathy; PDR = Proliferative Diabetic Retinopathy; CSME = Clinically Significant Macular Edema; [a] Oral hypoglycaemic agents

	Persons without DM (n=4453)			Age group						Sex					
				67-74 (n=1828)			75+		(n=2625)	Male (n=1817)			Female (n=2554)		
	n	%	95% CI	n	%	95% CI	N	%	95% CI	n	%	95% CI	n	%	95% CI
Retinopathy															
Any	476	10.7	9.8-11.6	169	9.2	8.0-10.7	307	11.7	10.5-13.0	201	10.7	9.4-12.2	275	10.7	9.5-11.9
NPDR															
Mild	472	10.6	9.7-11.5	167	9.4	7.9-10.6	305	11.6	10.4-12.9	199	10.6	9.3-12.1	273	10.6	9.4-11.8
Moderate	4	0.1	0.0-0.2	2	0.1	0.0-0.4	2	0.1	0.0-0.3	2	0.1	0.0-0.4	2	0.1	0.0-0.3
PDR	0	0	0.0-0.1	0	0	0.0-0.2	0	0	0.0-0.1	0	0	0.0-0.2	0	0	0.0-0.1
Macular edema															
Any	5	0.1	0.0-0.3	3	0.2	0.1-0.5	2	0.1	0.0-0.3	2	0.1	0.0-0.4	3	0.1	0.0-0.3
CSME	3	0.1	0.0-0.2	2	0.1	0.0-0.4	1	0	0.0-0.2	0	0	0.0-0.2	3	0.1	0.0-0.3

Table 14. Prevalence and severity of retinopathy and macular edema by age and sex in persons without diabetes mellitus (DM)

n = number; 95% CI = 95% confidence interval; NPDR = Non-Proliferative Diabetic Retinopathy; PDR = Proliferative Diabetic Retinopathy; CSME = Clinically Significant Macular Edema.

4.2.3 Factors associated with retinopathy:

Among persons with diabetes, factors associated with increased risk of having any DR in a multivariate analysis were elevated HbA1c, insulin use, use of oral glucose-lowering medications, and systolic blood pressure (see table 15).

	With diabetes mellitus[a]			Without diabetes mellitus[b]		
Multivariate	**n**	**OR (95% CI)**	**p value**	**n**	**OR (95% CI)**	**p value**
Age, per 10 years	-	0.9 (0.6-1.3)	0.47	-	1.3 (1.1-1.6)	0.004
Sex, male vs female	-	1.0 (0.6-1.5)	0.87	-	1.0 (0.8-1.2)	0.72
Systolic BP, per 10 mmHg	-	1.2 (1.0-1.3)	0.01	-	1.1 (1.0-1.1)	0.07
Duration per 10 years	-	1.2 (1.0-1.5)	0.06	-	-	-
Insulin use, yes vs no	-	3.5 (1.6, 7.8)	0.002	-	-	-
Oral hypoglycaemic, yes vs no	-	1.9 (1.2, 3.1)	0.01	-	-	-
HbA1c per percentage point	-	1.4 (1.1-1.7)	0.01	-	0.9 (0.7-1.3)	0.64
Hypertension	-	1.2 (0.5-2.9)	0.62	-	1.0 (0.8-1.3)	0.97
Microalbuminuria, yes vs no	-	1.5 (0.9-2.5)	0.14	-	1.8 (1.3- 2.4)	<0.001
Univariate						
Age, per 10 years	512	0.9 (0.6-1.3)	0.52	4453	1.4 (1.2-1.6)	<0.001
Sex, male vs female	512	1.2 (0.8-1.8)	0.35	4453	1.0 (0.8-1.2)	0.92
Systolic BP, per 10 mmHg	512	1.2 (1.1-1.3)	0.001	4452	1.1 (1.0-1.1)	0.01
Duration per 10 years	498	1.4 (1.2-1.7)	<0.001	-	-	-
Insulin use, yes vs no	512	5.8 (2.9-11.8)	<0.001	-	-	-
Oral hypoglycaemic, yes vs no	512	2.2 (1.4-3.3)	<0.001	-	-	-
HbA1c per percentage point	512	1.4 (1.2-1.7)	<0.001	4453	0.9 (0.7-1.3)	0.67
Hypertension	512	1.5 (0.7-3.1)	0.26	4453	1.1 (0.9-1.4)	0.39
Microalbuminuria, yes vs no	506	2.0 (1.2-3.2)	0.01	4403	1.8 (1.3-2.5)	<0.001

Table 15. Univariate and multivariate logistic regression results on risk factors for any retinopathy in persons with and without diabetes mellitus

n = number; OR = Odds Ratio; 95% CI = 95% Confidence Interval; BP = Blood Pressure ;

[a] n=496 for multivariate analysis, n=512 for univariate analysis; [b] n=4402 for multivariate analysis, n=4453 for univariate analysis

The use of insulin or oral glucose-lowering medications was associated with longer duration of diabetes. In other words, use of insulin or oral glucose-lowering medications were confounding factors for the duration of DM. Because of this, we included duration of DM it in the multivariate model even though the p value did not attain statistical significance. If we only included persons with more than 10 years' duration of DM in multivariate analysis, the association was statistically significant. The categorical variable for hypertension was not associated with increased risk of DR.

Factors associated with any DR in non-diabetics in a multivariate model were older age and microalbuminuria. Higher systolic blood pressure was significantly associated with DR in the age- and sex-adjusted model, but did not remain significant in the multivariate analysis.

5 Discussion

This thesis covers the cause-specific prevalence and 5-year incidence of visual impairment and blindness among Icelanders aged 50 years and older. Our results confirm that increasing age is associated with increased prevalence and incidence of uni- and bilateral visual loss. We have also confirmed that AMD and cataract are the two principal causes contributing to visual handicap in middle-aged and older Icelanders. In addition, we described the prevalence of retinopathy in Icelanders aged 67 years and older and identified risk factors associated with retinopathy in persons with and without diabetes mellitus. The major findings of the RES and the AGES-R are discussed separately below.

5.1 Reykjavik Eye Study (RES) (papers I and II)

The participation rate in these studies was 76.8% at baseline examination. A total of 88.2% of the survivors participated in the 5-year follow-up examination. A common problem in epidemiological studies is nonparticipation among the oldest subjects, who are more likely to have poor physical or mental health. Some studies (Buch *et al.*, 2004; Klein *et al.*, 1991a) try to avoid this problem by excluding participants 85 years or older. In the RES, we had no upper age-limit for participants, and the drop in participation was greatest in subjects who were older than 80 years at the time of the baseline examination, mostly due to decreased mobility. The Blue Mountain Eye Study (Attebo *et al.*, 1996) suggests that non-participation in the oldest age group may lead to overestimation of the prevalence of visual loss, since non-participants in that study were less likely to use glasses and had better self-reported vision compared to those who participated. However, in the Rotterdam Study (Klaver *et al.*, 1998), non-participants were more likely to have problems with their vision, as well as other health issues. Of those unable or unwilling to participate in RES follow-up examinations in 2001, 91 persons (27.2%) did not keep their appointments, 80 (24.0%) could not participate because of poor health, and 55 (16.5%) were “too busy to participate.” Non-participants were evenly distributed with respect to age, gender, and reason for non-participation. We hope this did not adversely affect our results.

To facilitate comparison of our data with other population-based studies, we applied two widely accepted criteria to define visual impairment and blindness. The WHO definition does not consider vision to be impaired until below VA levels of 6/18. Limitations may occur at VA levels that are less severe than 6/18, and in order to avoid underestimating the social impact of visual handicaps, it is of great value to also include the more inclusive US criteria.

In more recent clinical vision research, it is common practice to use a logMAR chart to measure VA according to a modified ETDRS protocol, which has been shown to be more sensitive in detecting changes in VA, particularly among those with severe visual loss (Falkenstein *et al.*, 2008) than the Snellen chart. Since the number of people with very severe visual loss or blindness in our study group is quite low, we believe the effect caused by limitations of the Snellen chart to be minimal.

5.1.1 Prevalence and 5-year incidence of visual impairment and blindness

Prevalence of bilateral visual impairment and blindness were respectively 1.0% and 0.6% according to WHO criteria, and respectively 2.0% and 0.8% using the US criteria, which is somewhat lower than in the Beaver Dam and the Blue Mountains Eye Studies. When the Beaver Dam (Klein *et al.*, 1991a; Klein *et al.*, 1996) and Blue Mountain Eye Studies (Attebo *et al.*, 1996; Foran *et al.*, 2003) were carried

out during the late 1980s and early 1990s, few current population-based estimates of visual loss were available. In recent research on Caucasian populations, the prevalence of bilateral visual impairment is generally reported to be around 1.5% in studies that used the WHO definition (Buch *et al.*, 2001b; Klaver *et al.*, 1998; VanNewkirk *et al.*, 2001) and 3% to 5% in those that used the US criteria (Attebo *et al.*, 1996; Klaver *et al.*, 1998; Klein *et al.*, 1991a; Muñoz *et al.*, 2000; Wang *et al.*, 2000). The prevalence of bilateral visual impairment in the Beaver Dam (4.0%) and Blue Mountains (4.7%) Eye Studies is somewhat higher than in the RES, a difference which may be explained by the fact that their definition of visual impairment includes a VA of 6/12 or less, whereas the US standards we adopted define visual impairment as a VA of worse than 6/12 (Klein *et al.*, 1991a; Attebo *et al.*, 1996). The Copenhagen City Eye Study (Buch *et al.*, 2001a; Buch *et al.*, 2001b) reports a 2.9% prevalence of bilateral visual impairment, which is also higher than in the RES, possibly due to the slightly higher mean age in the Copenhagen City Eye Study (69.9 years *vs* 64.7 years).

In 1996 (the year of the RES baseline examinations), the Icelandic Low Vision and Rehabilitation Institute reported a 0.4% (WHO criteria) and 0.6% (US criteria) prevalence of bilateral blindness. These numbers are slightly lower than in the RES, suggesting some degree of under-registration of visual loss at the Low Vision and Rehabilitation Institute.

As in the present RES study, prevalence and 5-year incidence of bilateral blindness presented in other studies is generally ≤1%, independently of the criteria used, although the US definition is more inclusive (Attebo *et al.*, 1996; Buch *et al.*, 2001a; Dimitrov *et al.*, 2003; Foran *et al.*, 2003; Klein *et al.*, 1991a; Klein *et al.*, 1996; Muñoz *et al.*, 2000; VanNewkirk *et al.*, 2001).

The 5-year incidence of bilateral visual impairment and blindness in our study were respectively 1.1% and 0.4%, using WHO criteria, and 3.5% and 0.9% according to the US criteria. Incidence data is scarce, but whereas the 5-year incidence in the RES is quite similar to those established by the Visual Impairment Project in Australia (Dimitrov *et al.*, 2003), it seems to be slightly higher than those reported in the Beaver Dam (Klein *et al.*, 1996) and Blue Mountains (Foran *et al.*, 2003) Eye Studies, a difference which may possibly reflect differences in the age distributions of survivors.

The RES is the first Icelandic study to present population-based data on unilateral visual loss. Our prevalence of unilateral visual impairment and blindness was respectively 4.4% and 1.7% using WHO criteria, and 5.5% and 3.1% according to US criteria. The 5-year incidence of unilateral visual impairment was 3.5% (WHO criteria) and 5.9% (US criteria). The 5-year incidence of unilateral blindness was 1.2%, irrespective of the criteria applied. Data on unilateral visual loss is scarce, but our prevalence of unilateral visual impairment is somewhat lower than that reported in the Beaver Dam (Klein *et al.*, 1991a) and Blue Mountains (Attebo *et al.*, 1996) Eye Studies, again probably due to differences in definitions. However, the prevalence and 5-year incidence of unilateral blindness is quite similar to that presented in studies of Caucasian populations (Attebo *et al.*, 1996; Buch *et al.*, 2001a; Foran *et al.*, 2003; Klein *et al.*, 1991a; Klein *et al.*, 1996; Muñoz *et al.*, 2000)

Both the prevalence and incidence of visual loss increased with older age, especially after 75 years. Improvement in visual acuity was more common than deterioration in the younger age groups, with the single most common cause of improvement being cataract surgery. Of those younger than 70 years at baseline, around 22% had improved vision (≥2 Snellen lines) in both eyes at follow-up examination, while one out of ten in the same age group suffered from deterioration of vision (loss of ≥2 Snellen lines). In the oldest age group in the RES, deterioration was much more common than improvement among persons aged 80 years or more at baseline. Only 5.0% of the population aged 80 years or more gained two or more lines of visual acuity in both eyes between examinations, whereas 44.4% lost two or more lines in both eyes over the five-year follow-up period.

5.1.2 Causes of visual impairment and blindness

In general, variations reported in the prevalence and incidence of the main causes of visual loss could be explained by differences between studies with respect to the methods used to define diseases or to the measuring techniques used, or could even indicate variations in treatment of ocular disease. Previous studies (Buch *et al.*, 2001b; Klaver *et al.*, 1998) on visual impairment also indicate that the distribution of causes may differ among age groups included and criteria applied. This complicates comparison of cause-specific estimates of visual loss.

In 2004, WHO estimated that around 145 million people in the world were visually impaired and another 8 million were blind due to undercorrected refractive errors (Resnikoff *et al.*, 2008). Since this cause is easily corrected by the use of glasses or contact lenses, it has been neglected in many previous epidemiological studies. In Iceland, people have good access to optometric and ophthalmological services, and three out of four participants in baseline examinations had seen an ophthalmologist during the previous two years. Presenting vision and best corrected vision were similar in most of the participants at the follow-up examination, suggesting that undercorrected refractive error is not a major cause of low vision in the middle-aged and older Icelandic population. In comparison, half the participants in the Australian Visual Impairment Project study had not been assessed by an optometrist or an ophthalmologist within the past two years, and undercorrected refractive error accounted for more than half of visual impairment cases (VanNewkirk *et al.*, 2001). In order to comprehend the actual burden of this problem, an increasing number of studies now include presenting visual acuity data in addition to BCVA to define and assess visual loss.

Late AMD was by far the most common cause of visual handicap, representing over half of all bilateral visual impairment (WHO criteria) at both baseline and 5-year follow-up examinations. In addition, it was the primary cause of bilateral legal blindness (VA ≤6/60 in the better eye) in three out of four cases at both examinations. The fact that late AMD was by far the most common cause of bilateral visual impairment but only the third main cause of unilateral visual impairment at baseline examinations and the second most common cause at 5-year follow up confirms that the disease is symmetrical and tends to affect both eyes. In agreement, previous reports on middle-aged and older Caucasian populations have shown that late AMD is a frequent and significant cause of low vision, since it is the primary cause of bilateral visual impairment in up to half of all cases, and ranges from less than a third to over 80% of blindness cases (Attebo *et al.*, 1996; Buch *et al.*, 2001a; Buch *et al.*, 2001b; Jonasson and Thordarson, 1987; Klaver *et al.*, 1998; Klein *et al.*, 1995; Muñoz *et al.*, 2000).

In RES baseline examinations, we found that GA outranked exudative AMD as a cause of blindness by approximately 2:1. In accordance, Icelandic studies on middle-aged and older populations have found the prevalence of GA to be somewhat higher than in other Caucasian populations (Jonasson *et al.*, 2003a; Jonasson *et al.*, 2011), whereas the Beaver Dam Eye Study (Klein *et al.*, 1995) did not find a higher frequency of legal blindness in eyes with GA than with exudative AMD. Genetic and epidemiological studies of AMD in Iceland have not been able to explain why GA is more common in Iceland than elsewhere (Arnarsson *et al.*, 2006; Magnusson *et al.*, 2006).

When defining bilateral visual impairment according to US criteria, cataract and late AMD were equally common as the primary cause at baseline examination. In the RES, each represented 38.1% of the cases but five years later, cataract accounted for 44.8% of incident bilateral visual impairment, whereas late AMD was the leading cause in less than 30%. In support of results reported in other studies (Buch *et al.*, 2001b; Klaver *et al.*, 1998; Muñoz *et al.*, 2000) indicating cataract to be an uncommon cause of severe visual loss in developed countries, using the WHO definition, we found no subjects in whom cataract caused bilateral visual loss. Successful treatment for cataract is readily available, and the low numbers of bilateral visual loss due to this cause indicate that cataract surgical services function well in Iceland, and suggest that when VA has deteriorated to 6/18 due to cataract, surgery is likely to occur shortly thereafter. Among persons aged >75 years, the major cause of

unilateral visual impairment at baseline was cataract. Cataract surgeons often prefer to operate on the right eye first, which may explain the (non-significant) preponderance of unilateral visual impairment in left rather than right eyes. Many of these subjects had undergone cataract extraction in one eye (often the right one) and felt they did not need to undergo surgery in the other, now worse, eye, which might reflect the fact that the minimum visual acuity requirement for a driver's license in Iceland is binocular VA of at least 6/12.

When considering all types and grades of cataract at baseline and their clinical consequences over the 5-year period, around 12% of all eyes with any grade of cortical or nuclear lens opacification were operated during the follow-up period. Furthermore, around one-third of those with posterior subcapsular or mixed-type cataract underwent surgery during this period (Sasaki *et al.*, 2000). Prevalence studies (Buch *et al.*, 2001a; Buch *et al.*, 2004; Klaver *et al.*, 1998; Klein *et al.*, 1995; Muñoz *et al.*, 2000; VanNewkirk *et al.*, 2001) have shown cataract to be an infrequent cause of blindness in the developed world, a claim that has been confirmed by incidence studies (Foran *et al.*, 2002; Klein *et al.*, 1996).

Glaucoma was not associated with bilateral blindness in any subject in the RES, but accounted for unilateral blindness in five persons (US criteria), a finding that concurs with records held by the 1996 Icelandic Blind Registry, indicating that glaucoma accounts for only 5% of all cases of blindness in Iceland. Matching results from other studies (Attebo *et al.*, 1996; Buch *et al.*, 2001b; Klein *et al.*, 1995; Muñoz *et al.*, 2000) in Caucasian populations, in our study glaucoma was not identified as a cause of any clinically meaningful visual loss. There appears to have been a great reduction in glaucoma blindnesss in Iceland over the last 50 years. In 1950, Björnsson attributed half of all cases of blindness in Iceland to open-angle glaucoma (Björnsson, 1955). In the 1980s, legal blindness due to glaucoma had dropped to around 18%, and by the 1990s, glaucoma blindness prevalence had fallen to below 10% (Björnsson, 1980; Jonasson and Thordarson, 1987; Sverrisson *et al.*, 1990; Viggósson *et al.*, 1986). In the early stages of the disease, glaucoma tends to affect the peripheral visual field, sparing the central vision. The great reduction in glaucoma-related blindness in Iceland may reflect a shift from advanced glaucoma to milder forms, due to increased access to ophthalmologists, new medications, and laser treatment, as well as to improved surgical techniques, which may all halt progression.

Amblyopia was the most frequent cause of unilateral blindness in all age groups and of visual impairment in people aged 50-74 years in our baseline examinations, which is similar to the findings of other studies (Attebo *et al.*, 1998; Buch *et al.*, 2001b; Wang *et al.*, 2000) and probably reflects lack of treatment in this age group. This emphasizes the importance of early screening programs and treatment in childhood to prevent conditions leading to amblyopia (Robaei *et al.*, 2006; Wallace *et al.*, 2006). This cause of unilateral visual impairment is likely to decrease significantly, since formal screening programs for amblyopia for 3.5 to 4-year old children in Iceland began in the early 1970s, too late to benefit the participants in the present study, all of whom were born before 1947.

In the present study, DR was not identified as a cause of bilateral blindness in any subject and accounted for bilateral visual impairment in only one person at 5-year follow-up. It was also the primary cause of unilateral visual impairment (US criteria) in two persons at baseline and in one person at the 5-year follow-up examination. Blindness from DR has been uncommon in Iceland, accounting for only 2.4% of all legal blindness during the early 1980s (Björnsson, 1981; Danielsen *et al.*, 1982). An Icelandic study on the prevalence of retinopathy and proteinuria in type-1 diabetics, carried out in 1981, the year the first ophthalmic laser went into operation in Iceland, found the prevalence of proliferative DR to be rather lower than rates reported by similar studies from other countries, and reported a 1.8% prevalence of legal blindness due to DR among type-1 diabetics in Iceland (Danielsen *et al.*, 1982). In agreement, other population-based studies on aged Caucasians (Attebo *et al.*, 1996; Klaver *et al.*, 1998; Muñoz *et al.*, 2000) have failed to identify DR as a major cause of visual loss.

A systematic eye screening program for persons with diabetes started in Iceland around 1980, and by 1994, the prevalence of legal blindness among diabetics had fallen below 0.5% (Kristinsson *et al*., 1994b; Stefansson *et al*., 2000). Since then, Olafsdóttir *et al* (2007) found diabetes to be an uncommon cause for vision loss among a population in which screening methods for diabetic retinopathy are good. In addition to patient education and effective screening methods leading to timely treatment of vision threatening conditions, better metabolic control and selective mortality may also influence the small effect of diabetes on visual loss.

5.2 Age, Gene/Environment Susceptibility – Reykjavik Study (paper III)

A strength of the AGES-R study of retinopathy in diabetic and non-diabetic subjects is that the participant sample was drawn from a large, randomly selected cohort of aged Icelanders with a high mean age of 76.4 years.

To define DM, we used a recently recommended approach, with an HbA1c cut-off point of ≥6.5% (≥48 mmol/mol). This classification is presumed to better capture chronic hyperglycemia than the fasting glucose level, and may be better at predicting the development of retinopathy (Tapp *et al*., 2008), while also avoiding the problem of day-to-day variation in blood glucose values (WHO, 2011). In earlier publications on retinopathy, the diagnosis of DM is commonly based on WHO recommendations, using fasting glucose values of ≥7mmol/l. This recommendation was based on the fact that DR has been believed to demonstrate a strong glucose threshold effect. Wong *et al.* (2008) suggested that the criteria for diagnosing diabetes could need reassessment, since the prevalence of retinopathy is high even at lower fasting glucose levels, with analyses of various population-based samples suggesting a more continuous relationship.

Unfortunately, HbA1c data were missing for 7% of the participants in this study, but imputation was performed separately for participants with and without DM, according to medication use, and using age, fasting serum glucose level, and duration of diabetes as predictors for HbA1c level. No associations were found between missing HbA1c values and the presence of retinopathy.

In order to facilitate comparison of our data with previous work, we did additional risk factor analysis, using the fasting glucose definition of ≥7 mmol/l for the diabetic group. Interestingly, using fasting glucose as an indicator of DM, we found 164 persons with undiagnosed DM, but when the analysis was based on HbA1c, only half of those (82 persons) had chronic hyperglycemia with an HbA1c of ≥6.5%, leading to a diagnosis of diabetes. In general, results were otherwise similar between the two classifications. The Reykjavik-IHA Study was conducted by the Icelandic Heart Association in several phases over a 30-year period between 1967 and 1997. All participants in the AGES-R are survivors of the Reykjavik-IHA Study, which tested for diabetes at each examination, using a fasting glucose cut-off of ≥7 mmol/l. Therefore, it is unlikely that any of the undiagnosed DM persons had the disease at the time of previous visits to the research clinic. Another strength of the AGES-R study is the use of photographic documentation of each fundus through dilated pupils and masked grading of retinopathy using standardized methods.

5.2.1 Retinopathy in persons with diabetes mellitus

The prevalence of any DR was 27.0% according to HbA1c criteria and 25.3% when applying a fasting glucose criteria cut-off point. This is lower than the 41% reported in a 1994 Icelandic study (Kristinsson et al., 1994b), in which the sample group derived from referrals to a diabetic eye-screening program, therefore not randomly selected, which could explain the difference in prevalence.

Due to the extremely low number of T1DM cases (n=2) in our study, no statistical analysis was done separately for this group. Both were women, younger than 25 years at diabetes diagnosis, and insulin-dependent. One was 67 years at the time of examination and had PDR in both eyes. The other

was 74 years at examination and had no signs of DR. If we had defined T1DM by onset of younger than 35 years, three more persons would also have been classified as having T1DM.

Direct comparison of prevalence between studies is somewhat limited, due to variations among studies in inclusion criteria and examination methods. The Beaver Dam (Klein *et al.*, 1992) and Blue Mountains (Mitchell *et al.*, 1998) Eye Studies used different definitions for T2DM, including higher fasting glucose values than the AGES-R, leading to higher DR prevalence. The DR prevalence was 36.8% in the Beaver Dam Eye Study and 32.4% in the Blue Mountains Eye Study. In addition, comparison is also complicated by differences in photographic techniques, since the older studies documented more fields in the fundus and might have documented more peripheral retinopathy lesions.

The prevalence of DR has been shown to vary among ethnic groups. The prevalence of any DR in the AGES-R study is quite similar to that found among white participants in the Multi-Ethnic Study of Atherosclerosis (MESA) and the National Health and Nutrition Examination Survey (NHANES). The MESA (Wong et *al.,* 2006) used a fasting glucose cut-off value of ≥7 mmol/l to define diabetes and presented a 24.8% of any DR. The NHANES (Zhang *et al.,* 2010) defined diabetes using the HbA1c ≥6.5% definition and reported a 26.4% of any retinopathy. Both studies included participants who were younger than those in the AGES-R, with a lower age limit of 45 years in the MESA and 40 years in the NHANES. The NHANES also differs from the AGES-R and MESA studies in that fundus photographs were taken through non-pharmacologically dilated pupils, possibly leading to an underestimation of peripheral retinopathy lesions.

Recently, Yau *et al.* (2012) provided a global estimate of the prevalence of DR, using data from 35 population-based studies on individuals aged 20-79 years with DM in the US, Australia, Europe, and Asia. They reported an overall prevalence of 34.6% for any DR and confirmed diabetes duration, HbA1c, and blood pressure as DR risk factors.

In the present study, duration of diabetes was highly confounded by type of treatment, since use of diabetes medication was an indicator of longer DM duration. Due to colinearity, fasting glucose and HbA1c could not be kept in the multivariate model at the same time, but if the fasting glucose level was selected in the model before HbA1c, it was also found to be significantly associated with any DR.

HbA1c ≥6.5% (48 mmol/mol), insulin use, and use of oral hypoglycemic agents were associated with increased risk of retinopathy in persons with diabetes in a multivariate model. Several studies have confirmed these associations with any DR (Danielsen *et al.*, 1983; Henricsson *et al.*, 1996; Klein *et al.*, 1984b, Klein *et al.*, 1992; Klein *et al.*, 1994; Mitchell *et al.*, 1998; Varma *et al.*, 2007; Wong *et al.*, 2006; Zhang *et al.*, 2010). The United Kingdom Prospective Diabetes Study (UKPDS) showed that strict glucose control, resulting in a 1% lowering of HbA1c, equated to a 31% reduction in retinopathy (Kohner, 2008). However, lowering of glucose values may be difficult and must be done carefully in persons with diabetes, due to the risk of hypoglycemia (Kohner, 2008; The Diabetes Control and Complications Trial Research Group, 1993).

In agreement with similar studies (Mitchell *et al.*, 1998; Varma *et al.*, 2007; Wong *et al.*, 2006; Zhang *et al.*, 2010), we did not find hypertension, diastolic blood pressure, or BMI to be associated with any DR. However, as in the NHANES (Zhang *et al.*, 2010), a significant correlation was found between any DR and higher systolic blood pressure in a multivariate model. Supporting the importance of tight blood-pressure control, the UKPDS found that a 10 mmHg lowering of systolic blood pressure equated to an 11% reduction in photocoagulation treatment or vitreous hemorrhage (Kohner, 2008).

Regrettably, we were unable to carry out risk factor analysis on persons with PDR or CSME, due to the extremely low prevalence of these conditions. The lack of the power of a study to detect factors significantly associated with these sight-threatening stages of DR is a common problem in epidemiological research (Yau *et al.*, 2012).

Only 1.0% of DR cases were classified as proliferative in the AGES-R, and 1.0% had clinically significant macular edema, *i.e.*, a minority of cases had treatment-requiring retinopathy. This indicates that eye-screening programs and primary health care providing good metabolic control function well in Iceland. In accordance, none of the DR among patients who were diagnosed with DM in the AGES-R examination was of treatment-requiring severity.

5.2.2 Retinopathy in non-diabetic persons

The prevalence of retinopathy in non-diabetic participants was 10.7%. The MESA study reported a similar prevalence of 11.9% among Caucasian persons without diabetes mellitus (Ojaimi *et al.*, 2011). Interestingly, although the prevalence of retinopathy is higher among persons with DM, the actual number of individuals with retinopathy is threefold higher among non-diabetic persons in our study. Almost all (99.2%) of the retinopathy cases among non-diabetic persons were mild and therefore did not require any treatment. Although previous studies have found retinopathy lesions among non-diabetics to be associated with older age and hypertension (Cugati *et al.*, 2006; Klein *et al.*, 2006; Wong *et al.*, 2001), participants in the AGES study with this form of retinopathy were not more likely to have hypertension, higher fasting glucose, or higher BMI than those without retinopathy. However, higher systolic pressure was significantly associated with retinopathy in age- and sex-adjusted risk factor analysis, but did not remain significant in the multivariate model. The presence of microalbuminuria was strongly associated with retinopathy in our sample of non-diabetic persons. Previous studies (Cheung *et al.*, 2008; Qiu *et al.*, 2008) have suggested that since microvascular damage also manifests in organ systems other than the eye, retinopathy and nephropathy may share a common pathogenesis and be signs of systemic microvascular dysfunction. Supporting this statement, Wong *et al.* (2004) found that after controlling for age, gender, race, diabetes, blood pressure, and other risk factors, individuals with retinopathy were more likely to develop renal dysfunction than individuals without retinopathy.

The Blue Mountains Eye Study describes most retinopathy lesions among non-diabetics as being transient, with only 3.5% of persons with this form of retinopathy developing DM over a five-year period (Ojaimi *et al.*, 2011). Practicing clinicians may wonder about the clinical relevance of this finding, and whether they should refer non-diabetic patients with retinopathy for a diabetic or cardiovascular workup. In order to make evidence-based recommendations, longitudinal data is needed in order to further understand the pathophysiology underlying this form of retinopathy.

6 Conclusions

The RES and AGES-R are population-based studies of middle-aged and older Icelanders that employ standardized methods to diagnose eye disease and grade visual loss and retinopathy.

Increasing age is associated with increased prevalence and incidence of uni-and bilateral visual loss. Using WHO criteria, the prevalence of bilateral visual impairment and blindness in the RES was respectively 1.0% and 0.6%. The 5-year incidence of bilateral visual impairment and blindness was respectively 1.1% and 0.4%. Unilateral visual impairment was found in 4.4% and blindness in 1.7%. The 5-year incidence was 3.5% for unilateral visual impairment and 1.2% for blindness. The more inclusive US criteria gave slightly higher figures.

According to data published by the Icelandic Statistical Bureau (Statistics Iceland, 2012), there is a trend towards ageing of the Icelandic population, and from 1996 (the year of the baseline RES examinations) to 2012, the population of those aged 50 years or older increased almost 50% from 64 thousand to 97 thousand. With increasing life expectancy and the growth in the aging Icelandic population, the number of people with age-related eye diseases and subsequent visual loss is expected to also rise. Our data presents population-based prevalent and incident figures, thus providing accurate information on the actual occurrence of diseases over time. This may be helpful when planning and managing future eye healthcare services, and hopefully aid in improving quality of life in old age.

Using WHO criteria, the major cause of bilateral visual impairment and blindness both at baseline and follow-up was age-related macular degeneration. Using the US criteria, we detected milder forms of visual loss and found that cataract was the largest cause of less severe bilateral visual impairment at both examinations. Using either set of criteria, the two most common causes of unilateral visual impairment at baseline were amblyopia and cataract. Visual loss due to amblyopia in this population is likely to decrease significantly, due to formal screening programs for children that lead to early diagnosis and timely treatment of amblyopia by forcing the use of the amblyopic eye with occlusion treatment for example. In our study, unoperated cataract was the main cause of unilateral visual impairment at 5-year follow-up. With modern surgery, the effect of visual impairment due to cataract is treatable, and with improved treatment possibilities and preventive measures, glaucoma and diabetes do not cause any meaningful visual handicap.

The overall prevalence of retinopathy in our large, population-based AGES-R sample is 12.4%. Persons with diabetes are 2.5 times more likely to have retinopathy than persons without diabetes. However, the total number of people with retinopathy was threefold higher in the non-diabetic group, accounting for 75% of retinopathy cases. With optimal glucose and blood pressure control, vision may be preserved and quality of life in old age maintained longer. Retinopathy in persons with diabetes was associated with insulin use, use of oral glucose-lowering medications, higher systolic blood pressure, and higher HbA1c. This underlines the importance of using a multidisciplinary approach in managing patients with diabetes.

In our non-diabetic sample, older age and microalbuminuria were associated with increasing risk of retinopathy. Longitudinal data and further studies on the relationship between retinopathy and microalbumiuria are needed to provide insight into the progression of retinopathy and underlying systemic disease processes.

This thesis has described visual impairment, blindness and retinopathy in Iceland and is an important addition to the global information available.

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Original publications