Changing Views on Open-Angle Glaucoma

The Rotterdam Study

R.C.W. Wolfs

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CHANGING VIEWS ON OPEN-ANGLE GLAUCOMA. THE ROTTERDAM STUDY.

VERANDERENDE INZICHTEN IN OPEN-KAMERHOEK GLAUCOOM. HET ERGO ONDERZOEK.

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CHAPTER 1

INTRODUCTION

The eye disease "glaucoma" was first described in Hippocrates' *Aphorisms* about 400 BC (glaukosis) as an ailment of old men.[1] However, it was not further explained and nobody was certain about the meaning of the word. Probably cataract was part of the diseases summarized by Hippocrates as glaukosis, next to the disease nowadays known as glaucoma. Several hypotheses were formed many years later. One of these explanations referred to the Greek word *glaucos,* meaning glaze [2], later more specified as a greenish glaze of the lens.[1] On examination with in that time available light 'equipment', a greenish light reflex could be seen, and this green light reflex became a prominent sign in the medical literature of that time.[3] Another suggestion for the derivation of the word glaucoma was from the Greek word *glaux,* meaning owl, those days the symbol of the goddess Athena; the dilated and oval pupil in acute glaucoma resembled the shape of the pupil of an owl-eye.[4]

The name glaucoma was applied to a condition or disease with an abnormality in the pupillary area (a change in color and/or shape), inescapably leading to total blindness.[3] The Greek new that some of these conditions could be cured and others not by surgical removing the lens.[5] Inflammation as cause of glaucoma was stressed in 1722 by Charles Saint-Yves in his textbook.[6] He related glaucoma to an acute inflammation of all coats of the eye but the conjunctiva, mostly accompanied by severe pain. [5, 6] In 1708 Hermann Boerhave described impairment of the aqueous drainage of the eye as the cause of glaucoma.

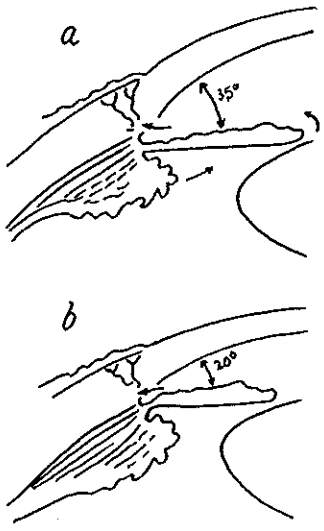
Inflammation remained a major sign in glaucoma over the next years until 1862 when Donders published his classical paper in which he made a division in two different types of glaucoma: glaucoma simplex, and glaucoma cum ophthalmia.[5] Glaucoma simplex was a disorder with increasing tension of the eye, excavation of the disc, shift of the vessels in the disc, loss of visual field and loss of vision without any symptoms of elevated intraocular pressure and clear ocular media often for years after complete blindness. Probably it was the same disorder as the "blindness with optic disc excavation" of Von Graefe.[5] Previously this condition was not regarded as a member of the glaucoma family.

Anterior chamber fluid hydrodynamics were first described in 1702 by Jacobus Hovius in his dissertation. However, elevated intraocular pressure was already known by the Arabs in the 10th century (Al Tabari), and in 1626 by Banister[3], but only after the publication of the work of Antoine-Pierre Demours (1818) the concept of elevated intra-ocular pressure in glaucoma became fully established.[6] In England Mackenzie mentioned this in 1830.[6] For nearly 150 years thus emphasis was put on the intraocular pressure in the diagnosis of glaucoma, only later to be followed by the appearance of the optic disc and the shape and amount of visual field loss. Digital tonometry became a special skill of ophthalmologists of that time. In the late 1800s mechanical tonometers were developed, but they were all difficult and awkward to use. In 1905, Schiøtz introduced his more practical indentation tonometer, which remained the instrument of choice for about 50 years. Next, in 1955, Goldmann introduced his applanation tonometer. This instrument avoided the artifacts of the Schiøtz tonometer and still is the standard device for measuring intraocular pressure.[7]

From 1853 on, the year of the introduction of the ophthalmoscope, a more extensive investigation of the eye was possible, and changes in the appearance of the optic disc in glaucoma patients were recognized. The observation of a depression in the center of the optic disc, firstly mistaken as a swelling by Jaeger and von Graefe, was interpreted as an effect of elevated intraocular pressure. From that time on, more studies were performed to investigate the etiology of glaucoma.[3, 6] Nowadays, ophthalmoscopy gradually has been replaced by (stereo) fundus photography when evaluating the optic disc for glaucoma research. Only in the last decade, new techniques have been developed to study the optic disc, using laser scanning devices or computerized digital analysis techniques based on conventional stereoscopic topographical data of the optic disc. All are focused on standardized quantification of glaucomatous damage of the optic disc. However, there can be considerable differences in the results of the various techniques.[8-13]

Methods for more or less accurate visual field testing were available since the mid-1800s. In 1856, von Graefe was the first to use a primitive campimeter to plot paracentral defects in the visual field. In 1889 Bjerrum introduced a

more quantitative method of perimetry, which became the standard for the next 40 years. In 1950, again Goldmann introduced his bowl perimeter. In the 1980s computerized perimetry was introduced, resulting in better standardization and sometimes a higher sensitivity in detecting small visual field defects, such as with blue stimuli on a yellow background. However, these testing programs require a cooperative patient and can be fatiguing, particularly in the elderly, which can result in artifactual field defects. Definite decisions about the presence of glaucomatous visual field test results must still be based on the judgement of skilled clinicians, with inherent variability.[7]



Configuration of the anterior chamber angles. a: normal angle; b: narrow angle.

Today glaucoma is defined as a disease (in which the intraocular pressure may be relatively too high for proper oxygenation of the eye and its ganglion cells) causing an optic neuropathy characterized by cupping of the optic disc with an associated visual field defect.[14] There are several types of glaucoma. They are classified according to age of onset: congenital vs. adult onset; etiology: primary vs. secondary; and pathophysiologic mechanism: open vs. closed angle. Congenital glaucoma most often is an autosomal recessive hereditary disorder.[15] Primary glaucoma is due to largely unknown mechanisms, and hereditary factors probably play a role in its etiology. Secondary glaucoma can arise from a large variety of injuries, medication, systemic disorders, or ocular diseases that affect the outflow channels. The terms *open angle* and *closed angle* refer to the configuration of the anterior chamber angle in the eye. In open angle glaucoma the anterior chamber angle has a normal configuration, but the flow through the trabecular meshwork is hampered. In closed angle glaucoma the root of the iris lies against the normal trabecular meshwork and prevents aqueous outflow.[14]

Primary open angle glaucoma is the most prevalent type of glaucoma in Western countries.[16] Its prevalence rises with ageing, which was already demonstrated in a clinic-based population by Donders in 1861 (see table).[5]

Prevalence of simple glaucoma according to age and gender.[5]

Age in years	Male	Female	Total
20 - 30	1	1	2
30 - 40	4	5	9
40 - 50	7	9	16
50 - 60	17	28	45
60 - 70	10	12	22
70 - 80	0	1	1
	39	56	95

The early detection of glaucoma is an important public health concern because there is evidence that, unlike many other forms of blindness, glaucomatous blindness may be prevented in cases with elevated intraocular pressure if the disease is treated adequately and if treatment is begun in time. However, once vision has been lost, it cannot be restored at present time by any form of treatment. Unfortunately, most patients with early glaucoma are asymptomatic, and much peripheral vision can be lost before the patient notices visual impairment. This means that only with routine screening of asymptomatic people early glaucoma cases can be detected. In the past this screening mainly was based on intraocular pressure measurement [17], and a cutoff point of 21 mmHg was used, based purely on statistical grounds.[18-20] Leydhecker found in 0.5% of all eyes of 10.000 healthy subjects an intraocular pressure higher than 22.4 mmHg (Schiøtz 3.5/5.5) and labeled them as "Glaukomverdacht". Today, with more advanced techniques, more emphasis is

given to optic disc appearance, visual field examination, and nerve fiber layer abnormalities.

Von Graefe described hereditary glaucoma that had been already more often mentioned by earlier authors. He attributed it to inflammatory glaucoma and mentioned that the disorder often started earlier in the next generation, something we now would call anticipation. In Berlin he knew several families with glaucoma for three to four generations. He also mentioned that one still does not know much about the etiology of glaucoma, a situation still valid 130 years later![21]

This thesis focuses on (primary) open-angle glaucoma. All studies were performed based on data from examinations of subjects from the Rotterdam Study, a population-based cohort study of subjects aged 55 years and over. In chapter 2 the definitions and prevalences of open-angle glaucoma in this population are described. Also the prevalence of visual field defects and its causes are described (chapter 3). First-degree relatives of glaucoma cases were examined, together with first-degree relatives of an age and gender matched control group. The prevalence figures of primary open-angle glaucoma in both groups of relatives was compared to study the effect of genetic factors (chapter 4). A technique, creating the possibility for accurate detection of damage to the optic nerve over time, was compared with standard ophthalmoscopy and is described in chapter 5. The influence of corneal thickness on the intraocular pressure measurement is discussed in chapter 6. Chapter 7 deals with the risk of inducing acute angle-closure glaucoma in a screening protocol for glaucoma. Finally, chapter 8 places the results of the previous studies in a larger perspective, discusses methodological considerations in relation to the previous studies and gives some suggestions for future research, followed by a summary in chapter 9.

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CHAPTER 2

CHANGING VIEWS ON OPEN-ANGLE GLAUCOMA

DEFINITIONS AND PREVALENCES

ABSTRACT

Purpose: To quantify in a masked way the prevalence of determinants of open-angle glaucoma (OAG) and their influence on the overall OAG prevalence.

Methods: A total of 6781 subjects aged 55 years or over participated in this population-based study (6293 independently living subjects and 488 living in nursing homes). The criteria for the diagnosis of OAG were based on semi-automated measurements of the optic disc (vertical cup-to-disc ratio (VCDR), minimal width of neural rim, or asymmetry in VCDR between both eyes) and visual field testing with kinetic Goldmann perimetry. All separate criteria for the diagnosis of OAG were assessed independently of each other.

Results: Mean VCDR was 0.49, and the 97.5th percentile was 0.70. The prevalence of visual field defects compatible with OAG and without other causes was 1.5%. Overall prevalence of OAG in the independently living subjects was 0.9% (95% CI 0.6, 1.1; 56 cases). Prevalence of OAG was almost three times higher in men than in women (Odds ratio 2.3, 95%CI 1.2, 4.5). The risk of OAG increased with 8% per year of age (95% CI 4.0%, 13.0%). Different commonly used criteria for diagnosis of OAG resulted in prevalence figures ranging from 0.1% to 1.2%.

Conclusion: The overall prevalence of OAG in the present study was 0.9%. The prevalence was higher in men than in women and increased with age. Prevalence figures differed by a factor 12 when using different criteria to define OAG. Diagnostic standardization is necessary for comparison of epidemiologic glaucoma studies.

Primary open-angle glaucoma (POAG) ranks third in causes of visual impairment in the Western world.[1-3] Despite this and prevalence figures in white subjects ranging from 0.8% to 3.0%[1, 4-12], little is known about its etiology. This may be partly due to the lack of a world-wide epidemiological definition of, or standard for diagnosis of POAG. As a result many (epidemiologic) studies are difficult to compare, due to the different criteria and methods used for diagnosis, hampering meta-analyses.

It is nowadays generally accepted that POAG is an optic neuropathy characterized by cupping of the optic nerve head, with nerve fiber loss and corresponding visual field defects. An elevated intraocular pressure (IOP) is considered to be a risk factor for POAG, as well as the presence of a first-degree relative with glaucoma.[13]

There have been relatively few population-based prevalence studies on POAG (Ferndale[4], Framingham[5], Dalby[6], Baltimore[7], Beaver Dam[8], Barbados[9], Blue Mountains[11], and Ponza[12]). The ophthalmological division of the Rotterdam Study focuses on POAG, and results of a prevalence study in a subset of the examined population using different criteria for POAG have been published before.[10] For the diagnosis POAG congenital forms of glaucoma have to be excluded, as well as secondary causes of glaucoma as pseudoexfoliation. Because we did not specifically exclude pseudoexfoliation at baseline, we will further write about open-angle glaucoma (OAG) instead of POAG.

The aim of the present study was to quantify independently the prevalence of determinants of OAG in a general Caucasian population, and to study the influence of various criteria for OAG on this prevalence.

MATERIALS AND METHODS

Population

The present study was performed as a part of The Rotterdam Study, a prospective cohort study of all residents, aged 55 years and over, living in a suburb of Rotterdam, The Netherlands. The objective of the Rotterdam Study is to investigate determinants of chronic disabling cardiovascular, neurogeriatric, locomotor and ophthalmologic diseases.[14] The study has been approved by the

Table 1. ***Response figures of the Rotterdam Study, 1990-1993***

Age-category (years)	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90+	TOTAL
Independent living subjects:									
Total eligibles	1480	1761	1737	1606	1286	799	404	88	9161
Total examined	1172 (79.2)	1421 (80.7)	1327 (76.4)	1157 (72.0)	834 (64.9)	417 (52.2)	141 (34.9)	25 (28.4)	6494 (70.9)
Ophthalmologically examined	1164 (78.6)	1401 (79.6)	1281 (73.7)	1108 (69.0)	798 (62.1)	394 (49.3)	124 (30.7)	23 (26.1)	6293 (68.7)
men	483 (75.1)	616 (79.1)	595 (76.6)	452 (69.5)	315 (63.0)	128 (50.6)	32 (32.7)	6 (23.1)	2627 (70.5)
women	681 (81.4)	785 (79.9)	686 (71.5)	656 (68.6)	483 (61.5)	266 (48.7)	92 (30.1)	17 (27.4)	3666 (67.5)
Nursing homes:									
Total eligibles	1	4	14	29	125	282	375	284	1114
Total examined	1 (100)	3 (75.0)	12 (85.7)	20 (69.0)	72 (57.6)	181 (64.2)	215 (57.3)	131 (46.1)	635 (57.0)
Ophthalmologically examined	0 (0.0)	1 (25.0)	8 (57.1)	12 (41.4)	61 (48.8)	144 (51.1)	156 (41.6)	106 (37.3)	488 (43.8)
men	0 (0.0)	0 (0.0)	4 (50.0)	4 (50.0)	18 (48.6)	43 (62.3)	37 (52.9)	16 (51.6)	122 (54.5)
women	0 (0.0)	1 (33.3)	4 (66.7)	8 (38.1)	43 (48.9)	101 (47.4)	119 (39.0)	90 (35.6)	366 (41.1)

Numbers between brackets are percentages of the number eligible subjects in each age-category.

Medical Ethics Committee of the Erasmus University and a written informed consent was obtained from all participants.

All residents were asked to participate in an extensive home interview, after which an appointment was made for a medical examination, including a complete ophthalmological examination. Interview data were collected for 78% (n=7983) of the eligible persons (N=10,275). The overall response rate for the center visit was 69% (n=7129). In Table 1 the absolute numbers of subjects are shown in the different age-categories as are the numbers of examined subjects living in nursing homes. In the nursing homes only a limited ophthalmological examination was possible; especially visual field screening was unreliable or impossible in the institutionalized subjects, mainly due to physical and mental disabilities.

Table 2. ***Ophthalmological examination - Rotterdam Study, 1990-1993***

Phase I:		
Autorefraction	-	Topcon RMA 2000*
Visual acuity	-	Lighthouse Visual Acuity Chart (2nd edition)
Slitlamp examination	-	Topcon SL-3E slitlamp*
Keratometry	-	Topcon OM-4 Ophthalmometer*
IOP measurement	-	Goldmann applanation tonometer†
Visual field screening	-	modified 76-point suprathreshold screening test central 25 degrees (Humphrey Visual Field Analyzer)‡
Photographs macular area	-	35° field; TRC-50VT camera*
Stereo photographs optic disc	-	20° field; TRC-SS2 camera*
Ophthalmoscopy	-	Direct and indirect (AusJena ophthalmoscope, bonoscope)
Phase II:		
Visual field screening	-	modified 76-point suprathreshold screening test central 25 degrees (Humphrey Visual Field Analyzer)‡
Phase III:		
Visual field screening	-	kinetic Goldmann perimetry†
IOP measurement	-	Goldmann applanation tonometer†
Gonioscopy	-	Goldmann 3-mirror contactlens†

* Tokyo Optical Co, Tokyo, Japan
† Haag Streit, Bern, Switzerland
‡ Zeiss, Oberkochen, Germany

Measurements

The ophthalmological screening (Table 2) was performed in three phases by three ophthalmologic residents and two technicians.

The *first phase* was focused on visual acuity, anterior chamber angle depth[15], and IOP.[16] The visual fields of both eyes were screened using a slightly modified 76-point suprathreshold test (Humphrey Visual Field Analyzer, Zeiss, Germany): only the central 52 points of the visual field were tested, reducing examination-time and also the chance on rim-artifacts. Three or more contiguously missed points on the screening test (blind spot excluded) were taken as evidence for a visual field defect. After perimetry, mydriatics were administered in both eyes (tropicamide 0.5 percent and phenylephrine 5 percent), irrespective of the anterior chamber angle depth or history of glaucoma.[17] Simultaneous stereoscopic fundus color transparencies of the optic disc were made (Kodak Rochester, New York, USA), and direct ophthalmoscopy was performed to assess the vertical cup-to-disc ratio (VCDR). Finally, one drop of thymoxamine-hydrochloride 0.5% was administered in both eyes to counteract the mydriatic eyedrops.

In the *second phase* of the glaucoma screening, about two weeks later, visual fields were retested with the same screening test in subjects who had either a visual field defect or an unreliable visual field test in the first phase.

In the *third phase*, some more weeks later, subjects with a visual field defect or unreliable field test in the second phase of the study, underwent kinetic Goldmann perimetry on both eyes, performed by a skilled perimetrist. Also, in cases with a glaucomatous visual field defect gonioscopy was performed (PTVMdJ) using a Goldmann three mirror lens to classify the anterior chamber angle according to Shaffer's grading system.

Due to logistics, subjects underwent a glucose tolerance test (by the cardiovascular research group) about twenty minutes prior to IOP measurement in the first testing phase. This glucose tolerance test was carried out by giving an oral glucose load of 75g in 200 ml of water, and was performed on all non-diabetic subjects. In a separate study it was found that the median IOP was lowered by 1.5 mmHg by this glucose load.[10]

Optic disc measurements and grading

Stereo transparencies from both eyes of all individuals were digitized and analyzed by two technicians with the Topcon image analyzer Imagenet, using the module for the retinal nerve fiber layer height. The system's hardware, its software modules and reproducibility of measurements have been described previously.[18, 19]

In subjects with complete semi-automated measurements, we considered a VCDR ≥ 0.7, or an asymmetric VCDR ≥ 0.3 between both eyes, or a minimal neural rim width < 0.10, as disc abnormalities suspect for OAG. In subjects without semi-automated measurements, we also considered a VCDR ≥ 0.7 or asymmetry ≥ 0.2 between both eyes estimated by ophthalmoscopy, as disc abnormalities suspect for OAG. Neural rim width was not ophthalmoscopically assessed. The cut-off points were based on the 97.5th percentiles of the distributions of the parameters.

Visual field grading and classification

All Goldmann visual field charts were independently graded by six different graders (three senior ophthalmologists, two residents, one perimetrist). Graders were masked for all clinical data and optic disc appearances. For fields with inconsistent classifications a consensus was reached by four graders. Classification of the defects was solely based on the shape and localization of the defect (e.g. nasal step, paracentral defects, arcuate scotomas, central rests, remaining peripheral islands, temporal nerve fiber bundle defects). All nerve fiber bundle defects were considered to be glaucomatous visual field defects when not explainable by other (neuro)ophthalmologic abnormalities. For exclusion of non-glaucomatous causes of field defects all other data available in The Rotterdam Study was used, including questionnaire data, fundus and optic disc photographs, neurological examination, and (history) data from general practitioners.

Criteria for OAG in the Rotterdam Study

Definite OAG was defined as presence of a glaucomatous visual field defect, in combination with an optic disc suspect for glaucoma (see Optic Disc Measurements and Grading section). Probable glaucoma was defined as the presence of visual field abnormalities on the Goldmann fields, not explainable by other causes, but with optic disc characteristics falling in the normal range, or as an optic disc suspect for OAG without visual field abnormalities. The IOP was not used as a criterion for OAG, nor was the use of IOP lowering medication or the performance of an IOP lowering operation in the absence of a visual field defect. At baseline pseudoexfoliation was not explicitly ruled out and a few cases with this syndrome might be included in the OAG group.

Ocular hypertension was defined as an IOP > 21 mmHg or IOP lowering treatment in the absence of a visual field defect or optic disc abnormalities suspect for OAG.

Finally, definitions of definite OAG used in other population based studies (Table 3) were, when available in the literature, applied to our data.

Data analysis

The distributions of IOP, VCDR, as well as the distribution of asymmetry in VCDR and minimal rim ratio of the semi-automated optic disc measurements were calculated. We calculated the influence of the glucose tolerance test on IOP with linear regression analysis. The prevalence of IOP lowering treatment was studied in different age-categories.

Prevalence figures of definite and probable OAG were calculated by 5 year age-categories and by gender. To estimate the risk of age and gender on OAG, logistic regression analysis was used with the odds ratio serving as an approximation of the relative risk. Sensitivity and specificity values of different cut-off points of VCDR, with or without elevated IOP, for the presence of a glaucomatous visual field defect were calculated.

All analyses were adjusted for age and gender when appropriate, and performed separately in the independently living subjects and in those living in nursing homes.

Table 3. ***Different criteria for (definite) Open-Angle Glaucoma.***

FRAMINGHAM STUDY [22]

- Visual field defect not explainable by other cases,
  combined with
- VCDR ≥ 0.6, or asymmetry in VCDR between both eyes ≥ 0.2.

BALTIMORE EYE SURVEY [9]

- Visual field defect not explainable by other causes,
  or
- VCDR ≥ 0.8, or asymmetry in VCDR between both eyes ≥ 0.3,
  or a neuroretinal rim width < 0.15.

BEAVER DAM EYE STUDY [8]

At least two of the following criteria:

- Visual field defect not explainable by other causes,
- VCDR ≥ 0.8 or an asymmetry in VCDR ≥ 0.2,
- IOP ≥ 22 mmHg or treatment

BLUE MOUNTAINS EYE STUDY [11]

- Visual field defect not explainable by other causes,
  combined with
- VCDR ≥ 0.7, or asymmetry in VCDR between both eyes ≥ 0.3.

ROTTERDAM STUDY (1999 CRITERIA)

- Visual field defect not explainable by other causes,
  combined with
- VCDR ≥ 0.7, or asymmetry in VCDR between both eyes ≥ 0.3, or
  minimal rim width < 0.10 with semi-automated measurements,
  or VCDR ≥ 0.7 or asymmetry in VCDR ≥ 0.2 on ophthalmoscopy.

RESULTS

Table 1 shows the response figures of the prevalence phase of the Rotterdam study, focused on the ophthalmological examinations. Tables 2 and 3 summarize the ophthalmological examinations in this study and the different definitions for OAG used in other population-based studies. Table 4 shows the

available ophthalmological data on independently living and nursing home subjects; the latter data were less complete. Especially the availability of gradable optic disc photographs was low in this subgroup.

Table 4. ***Available ophthalmological baseline data with regard to OAG in the Rotterdam Study, 1990-1993***

		Independently living subjects		Nursing home subjects	
		N	(%)	N	(%)
SUBJECTS EXAMINED		6293		488	
Applanation tonometry					
Reliable data on	both eyes	6214	(98.7)	451	(92.4)
	only one eye	23	(0.4)	10	(2.0)
No applanation tonometry		56	(0.9)	27	(5.5)
Optic disc					
Ophthalmoscopic estimates of VCDR					
Available on	both eyes	6154	(97.8)	443	(90.8)
	only one eye	45	(0.7)	27	(5.5)
No ophthalmoscopic VCDR available		94	(1.5)	18	(3.7)
Stereo optic disc photographs					
Gradable photographs of					
	both eyes	5025	(79.9)	215	(44.1)
	only one eye	656	(10.4)	92	(18.9)
No gradable photographs available		612	(9.7)	181	(37.1)
Visual field screening:					
Complete screening both eyes		5983	(95.1)	-	-
Only partial or no screening		310	(4.9)	-	-

The cumulative distribution of IOP is shown in Figure 1. There were no significant differences between independently living subjects and subjects in nursing homes, nor between men and women, and there was no clinically significant change in IOP with increasing age. Mean IOP was 14.5 mmHg (95% CI 14.4, 14.6; after exclusion of subjects with IOP lowering treatment) and the upper limit of normality (97.5th percentile) was 21 mmHg (i.e. an IOP > 21

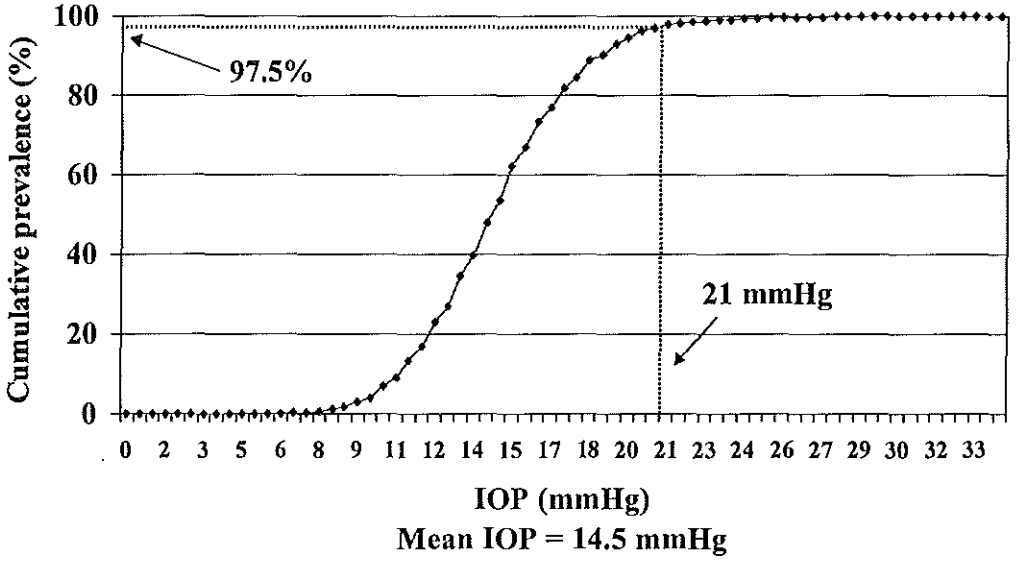

Figure 1. *Cumulative distribution and 97.5th percentile of the intraocular pressure in 6293 independently living subjects.*

mmHg was statistically abnormal). The prevalence figures of elevated IOP (> 21 mmHg) are shown in Table 5 for the independently living subjects. Men had a higher risk of having an IOP > 21 mmHg compared to women (Odds ratio 1.40, 95% CI 1.04, 1.96), and also a higher risk of having IOP lowering treatment (Odds ratio 1.3, 95% CI 1.0, 1.7). Ocular hypertension was present in 4.5% of the independently living subjects, and was more prevalent in men than in women (Odds ratio 1.36, 95% CI 1.06, 1.73). Subjects in nursing homes did not differ significantly from independently living subjects concerning prevalence figures of elevated IOP and IOP lowering treatment (data not shown). The effect of the glucose tolerance test on IOP was studied by comparing the IOP between subjects who had undergone a glucose tolerance test with subjects who had not. Subjects who had undergone a glucose tolerance test had a significantly lower mean IOP (-1.15 mmHg, 95% CI -1.45, -0.85). After correction for the IOP lowering effect of the glucose solution, the mean IOP was 15.6 mmHg (95% CI 15.5, 15.7), with an upper limit of normality of 22 mmHg.

Table 5. *Prevalence figures of elevated IOP and IOP lowering treatment.*

Age (years)	Men IOP > 21 mmHg (%)*	Men IOP lowering treatment (%)	Men Ocular hyper-tension (%)†	Women IOP > 21 mmHg (%)*	Women IOP lowering treatment (%)	Women Ocular hyper-tension (%)†	Total IOP > 21 mmHg (%)*	Total IOP lowering treatment (%)	Total Ocular hyper-tension (%)†
55-59	10/472 (2.1)	7/483 (1.4)	13/478 (2.7)	17/664 (2.6)	11/681 (1.6)	26/674 (3.9)	27/1136 (2.4)	18/1164 (1.5)	39/1152 (3.4)
60-64	23/593 (3.9)	19/616 (3.1)	33/604 (5.5)	14/764 (1.8)	13/785 (1.7)	20/774 (2.6)	37/1357 (2.7)	32/1401 (2.3)	53/1378 (3.8)
65-69	21/560 (3.7)	28/595 (4.7)	38/581 (6.5)	10/660 (1.5)	24/686 (3.5)	22/675 (3.3)	31/1220 (2.5)	52/1281 (4.1)	60/1256 (4.8)
70-74	10/422 (2.4)	27/452 (6.0)	22/439 (5.0)	15/623 (2.4)	26/656 (4.0)	26/638 (4.1)	25/1045 (2.4)	53/1108 (4.8)	48/1077 (4.5)
75-79	8/297 (2.7)	18/315 (5.7)	15/309 (4.9)	13/445 (2.9)	33/483 (6.8)	31/468 (6.6)	21/742 (2.8)	51/798 (6.4)	46/777 (5.9)
80+	10/151 (6.6)	14/166 (8.4)	13/159 (8.2)	14/345 (4.1)	24/375 (6.4)	18/359 (5.0)	24/496 (4.8)	38/541 (7.0)	31/518 (6.0)
Total	**82/2495 (3.3)**	**113/2627 (4.3)**	**134/2570 (5.2)**	**83/3501 (2.4)**	**131/3666 (3.6)**	**143/3588 (4.0)**	**165/5996 (2.8)**	**244/6293 (3.9)**	**277/6158 (4.5)**

IOP had to be higher than 21 mmHg in at least one eye.

* Subjects with IOP lowering treatment were excluded.

† Ocular hypertension was defined as an IOP higher than 21 mmHg or IOP lowering treatment in at least one eye, in combination with normal visual field tests and without optic disc abnormalities suspect for OAG.

Table 6. ***Prevalence figures of semi-automated and ophthalmoscopic optic disc characteristics in independently living subjects***

		Semi-automated measurements (SE)	Ophthalmoscopic estimates (SE)
Mean VCDR		0.49 (0.0018)	0.30 (0.0024)
Median asymmetry in VCDR		0.06	0.00
Mean minimal neural rim width		0.17 (0.001)	not assessed
Disc characteristics		Percentage of subjects	
VCDR ≥	0.4	77.2	39.1
	0.5	52.8	16.9
	0.6	23.2	7.3
	0.7	3.4	3.2
	0.8	0.2	1.0
Asymmetry in VCDR ≥	0.2	6.9	4.4
	0.3	1.2	1.3
	0.4	0.1	0.6
Minimal neural rim width <	0.25	84.5	not assessed
	0.20	63.1	not assessed
	0.15	28.9	not assessed
	0.10	4.8	not assessed
	0.05	0.1	not assessed

The distributions of semi-automated VCDR measurements and ophthalmoscopy are shown in Table 6. Mean VCDR, its asymmetry between both eyes, and mean minimal rim width were not significantly different in independently living subjects and those in nursing homes (data not shown). A VCDR ≥ 0.7 was for both semi-automated and ophthalmoscopic VCDR assessments statistically abnormal (above 97.5th percentile). Asymmetry in VCDR between both eyes of 0.26 or more was statistically abnormal for semi-automated measurements; for ophthalmoscopic VCDR estimates this cut-off point (97.5th percentile) was 0.20 or higher. A minimal rim width of 0.07 or less using semi-automated measurements was statistically abnormal.

Table 7. ***Prevalence of glaucomatous visual field defects****

Age (years)	Men (%)	Women (%)	Total (%)
55-59	2/474 (0.4)	0/668 (0.0)	2/1142 (0.2)
60-64	5/602 (0.8)	4/763 (0.5)	9/1365 (0.7)
65-69	11/579 (1.9)	7/658 (1.1)	18/1237 (1.5)
70-74	13/424 (3.1)	11/628 (1.8)	24/1052 (2.3)
75-79	8/282 (2.8)	7/444 (1.6)	15/726 (2.1)
80+	10/149 (6.7)	9/312 (2.9)	19/461 (4.1)
Total	**49/2510 (2.0)**	**38/3473 (1.1)**	**87/5983 (1.5)**

*For criteria see measurements section.

The prevalence of glaucomatous visual field defects is shown in Table 7. The overall prevalence of glaucomatous visual field defects was 1.5%. Men had a two times higher risk of visual field defects compared to women (Odds ratio 2.0, 95% CI 1.3, 3.1). The risk of field defects increased with age by 10% per year (Odds ratio 1.10, 95% CI 1.07, 1.12).

Although we did not include IOP in our OAG criteria, we give in Table 8 the different prevalence figures of OAG, using various cut-off points for VCDR, with or without elevated IOP for comparison with other studies. Also, sensitivity and specificity values are shown for optic disc parameters and IOP for the presence of a glaucomatous visual field defect. Figure 2 shows the prevalence figures of OAG by age in our study, when using OAG definitions from other large population-based studies. This resulted in prevalence figures varying between 0.0 and 1.4% in the youngest age-categories to prevalence figures between 0.9 and 5.9% in the oldest age-group.

Table 8. ***Prevalence of Open-Angle Glaucoma according to different cut-off points for VCDR and IOP.***

Criteria for OAG	Prevalence of OAG (%)	Sensitivity* (%)	Specificity* (%)
Glaucomatous visual field defect in combination with:			
VCDR ≥ 0.4	1.1	87.7	24.3
VCDR ≥ 0.5	1.0	76.9	46.4
VCDR ≥ 0.6	0.7	53.8	75.3
VCDR ≥ 0.7	0.5	36.9	95.5
VCDR ≥ 0.8	0.2	13.8	99.8
Glaucomatous visual field defect in combination with:			
VCDR ≥ 0.4 **or** IOP > 21 mmHg†	1.2	90.7	23.5
VCDR ≥ 0.5 **or** IOP > 21 mmHg†	1.0	81.3	44.4
VCDR ≥ 0.6 **or** IOP > 21 mmHg†	0.8	62.7	71.9
VCDR ≥ 0.7 **or** IOP > 21 mmHg†	0.6	52.0	90.9
VCDR ≥ 0.8 **or** IOP > 21 mmHg†	0.5	42.7	94.7
Glaucomatous visual field defect in combination with:			
VCDR ≥ 0.4 **and** IOP > 21 mmHg†	0.4	24.7	96.9
VCDR ≥ 0.5 **and** IOP > 21 mmHg†	0.4	24.7	97.7
VCDR ≥ 0.6 **and** IOP > 21 mmHg†	0.4	23.4	98.7
VCDR ≥ 0.7 **and** IOP > 21 mmHg†	0.3	19.5	99.6
VCDR ≥ 0.8 **and** IOP > 21 mmHg†	0.1	9.1	99.9
Glaucomatous visual field defect in combination with: VCDR ≥ 0.7, or asymmetry in VCDR ≥ 0.3, or minimal rim width < 0.10	0.6	70.3	76.9

* Sensitivity and specificity values of optic disc and/or IOP criteria described in the left column with regard to the presence of a glaucomatous visual field defect.
† or IOP lowering treatment.

Using our OAG criteria, 37 of the independently living subjects, had definite OAG (0.6%, 95% CI 0.4, 0.8%; Table 9). The risk of OAG increased with 8% per year of age (Odds ratio 1.08, 95% CI 1.04, 1.13). Men had a higher risk compared to women (Odds ratio 2.3, 95% CI 1.2, 4.5). In those subjects where semi-automated measurements of the optic disc were not available, ophthalmoscopic data were used to diagnose OAG. Using the ophthalmoscopic

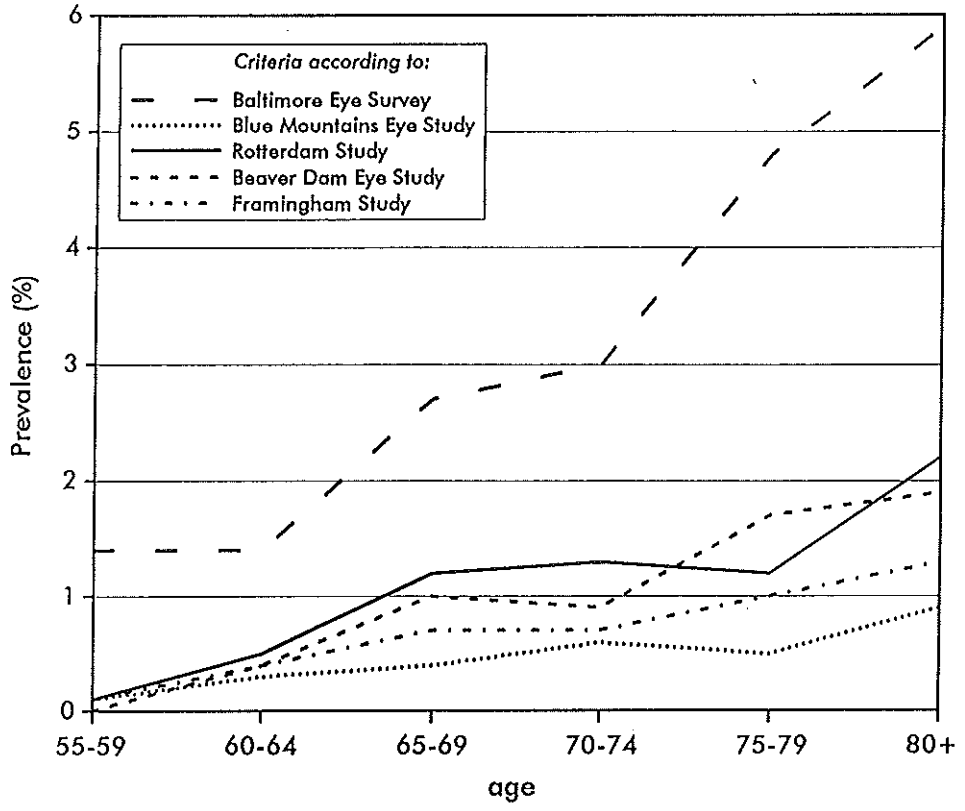

Figure 2. *Variation in prevalence figures of OAG in the Rotterdam Study depending on various definitions of OAG as used by other population-based studies.*

optic disc data, 19 (0.3%, 95% CI 0.2, 0.4%) additional cases were diagnosed. This yields a total prevalence of OAG of 0.9% (n=56; 95% CI 0.6, 1.1%). Due to our century-long affinity with IOP we also indicated at the bottom of Table 9 the IOP status of these cases. Combining the semi-automated and the ophthalmoscopic OAG cases did not significantly change the risk estimates for age and gender. Probable OAG, defined as the presence of a glaucomatous visual field defect without optic disc abnormalities, was present in 31 subjects (0.5%, 95% CI 0.3, 0.7%). Probable OAG, defined as an optic disc suspect for OAG without visual field abnormalities was present in 743 subjects (11.8%, 95% CI 11.0, 12.6%). Combined, this yields a prevalence of 12.3% (95% CI 11.5, 13.1%) for probable OAG.

Of the 56 diagnosed OAG cases, 23 subjects (41.1%, 95% CI 25.1, 48.1%) received IOP lowering treatment. On the other hand, only 23 of 244 subjects (9.4 %, 95% CI 6.8, 14.6%) with IOP lowering treatment, had OAG according to our criteria. The sensitivity of elevated IOP (> 21 mmHg) for OAG was 97.3%; the specificity was 15.2%. The predictive value of an IOP > 21 mmHg was 99.5%; the predictive value of an IOP ≤ 21 mmHg was only 3.0%.

Glaucomatous visual field defects were present in 8.6% of all subjects with a VCDR ≥ 0.7. This prevalence increased to 38% in subjects with a VCDR ≥ 0.8, and to 60% in subjects with a VCDR ≥ 0.9.

In nursing homes no visual field testing was performed. Only probable glaucoma could be diagnosed based on optic disc appearance. The prevalence of probable OAG was comparable with prevalence figures of probable OAG in the independently living subjects in the same age-categories.

DISCUSSION

In this study all parameters leading to an OAG diagnosis have been evaluated separately in a masked way, and criteria for OAG were strictly based on statistically accepted rules. Hitherto, studies used information on IOP or VCDR to grade visual field defects and OAG. Even though those studies used explicit diagnostic criteria, this may have introduced assessment bias.

In this population we found an overall prevalence of OAG of 0.9% in the independently living subjects. The prevalence increased with age and was more than two times higher in men than in women. Of all the OAG cases 59% had not been identified before. By estimating prevalence of OAG using criteria of other studies, we demonstrated that the influence of diagnostic criteria on the prevalence is large, and can vary ten-fold.

Our overall prevalence of OAG of 0.9%, is comparable with prevalence figures of the Framingham Study[20] (1.2%), The Baltimore Eye Survey[7] (1.1%), and with the prevalence found among the white subjects of the Barbados Eye Study[9] (0.8%). The Beaver Dam Eye Study and the Blue Mountains Eye Study on the other hand found a higher overall prevalence of 2.1%[8] and 3.0%[11] respectively.

Table 9. *Prevalence of Open-Angle Glaucoma (OAG) - The Rotterdam Study, 1990-1993*

category (years)	Men (%)	Definite OAG* (%)	Ophthal-moscopic† cases (%)	Probable OAG VFD‡ (%)	Probable OAG Optic disc§ (%)	Women (N)	Definite OAG* (%)	Ophthal-moscopic† cases (%)	Probable OAG VFD‡ (%)	Probable OAG Optic disc§ (%)
Independently living subjects.										
55-59	483	1 (0.2)	0 (0.0)	1 (0.2)	60 (12.4)	681	0 (0.0)	0 (0.0)	0 (0.0)	66 (9.7)
60-64	616	4 (0.6)	0 (0.0)	1 (0.2)	68 (11.0)	785	1 (0.1)	0 (0.0)	3 (0.4)	93 (11.8)
65-69	595	3 (0.5)	2 (0.3)	6 (1.0)	81 (13.6)	686	3 (0.4)	3 (0.4)	1 (0.1)	90 (13.1)
70-74	452	4 (0.9)	5 (1.1)	4 (0.9)	35 (7.7)	656	4 (0.6)	4 (0.6)	3 (0.5)	81 (12.3)
75-79	315	6 (1.9)	0 (0.0)	2 (0.6)	35 (11.1)	483	3 (0.6)	1 (0.2)	3 (0.6)	56 (11.6)
80+	166	4 (2.4)	3 (1.8)	3 (1.8)	36 (21.7)	375	4 (1.1)	1 (0.3)	4 (1.1)	42 (11.2)
Subtotal	**2627**	**22 (0.8)**	**10 (0.4)**	**17 (0.6)**	**315 (12.0)**	**3666**	**15 (0.4)**	**9 (0.2)**	**14 (0.4)**	**428 (11.7)**
Nursing home subjects.										
55-59	0				0 (0.0)	0				0 (0.0)
60-64	0				0 (0.0)	1				0 (0.0)
65-69	4				0 (0.0)	4				0 (0.0)
70-74	4				1 (25.0)	8				0 (0.0)
75-79	18				2 (11.1)	43				6 (14.0)
80+	96				19 (19.8)	310				47 (15.2)
Subtotal	**122**				**22 (18.0)**	**366**				**53 (14.5)**

Total number of definite and probable OAG cases in independently living subjects and nursing home subjects.

category (years)	Men (N)	Definite OAG* (%)	Ophthal-moscopic† cases (%)	Probable OAG VFD‡ (%)	Probable OAG Optic disc§ (%)	Women (N)	Definite OAG* (%)	Ophthal-moscopic† cases (%)	Probable OAG VFD‡ (%)	Probable OAG Optic disc§ (%)
TOTAL	2749	22 (0.8)	10 (0.4)	17 (0.6)	337 (12.3)	4032	15 (0.4)	9 (0.2)	14 (0.3)	481 (11.9)

IOP status in definite and probable OAG cases.

IOP status	Men	Definite OAG* (%)	Ophthal-moscopic† cases (%)	Probable OAG VFD‡ (%)	Probable OAG Optic disc§ (%)	Women	Definite OAG* (%)	Ophthal-moscopic† cases (%)	Probable OAG VFD‡ (%)	Probable OAG Optic disc§ (%)
Normal¶		10 (45.5)	5 (50.0)	11 (5.9)	296 (87.8)		8 (53.3)	5 (55.6)	13 (92.8)	440 (91.5)
Elevated#		3 (13.6)	0 (0.0)	3 (17.6)	6 (1.8)		1 (6.7)	1 (11.1)	1 (7.1)	19 (4.0)
Treated**		9 (40.9)	5 (50.0)	3 (17.6)	35 (10.4)		6 (40.0)	3 (33.3)	0 (0.0)	22 (4.6)

* Definite OAG was defined as presence of a glaucomatous visual field defect in combination with a VCDR ≥ 0.7, or asymmetry ≥ 0.3 in VCDR, or a minimal rim ≤ 0.10 with semi-automated measurements.

† Ophthalmoscopic cases were defined as subjects with a visual field defect, missing semi-automated measurements, but an ophthalmoscopic VCDR ≥ 0.7 or asymmetry ≥ 0.2 in VCDR.

‡ Probable OAG, defined as the presence of a glaucomatous visual field defect (VFD) without optic disc abnormalities suspect for OAG.

§ Probable OAG, defined as an optic disc suspect for OAG, but without glaucomatous visual field defect (VFD).

¶ Normal IOP was defined as an IOP ≤ 21 mmHg without treatment.

Elevated IOP was defined as an IOP > 21 mmHg without treatment.

** Treated = IOP lowering treatment.

Prevalence differences may reflect either real geographic differences in prevalence, or differences in measurement methods, subjective interpretation of these measurements, diagnostic criteria, or a combination of these. Since other sources of differences cannot be ruled out, conclusions on geographic differences are not justifiable. An interesting finding is that most studies report similar prevalences despite significant differences in methods and criteria. Differences in measurement methods mainly involve the use of suprathreshold or full-threshold perimetric techniques and the assessment of optic disc characteristics. Studies have shown that suprathreshold perimetry identifies about 2/3 of all cases identified by full-threshold perimetry.[21] Taking this into account, our prevalence would be about 1.4% if we had used full-threshold perimetry. Comparison with the Blue Mountains Eye Study, in which full-threshold perimetry actually was used, would in that case still result in a two-fold prevalence difference. This could indicate that geographic differences or differences in assessment of optic disc characteristics may be a major determinant of prevalence differences.

Our study differs from other large population-based studies, because optic nerve damage was mainly assessed by semi-automated optic disc measurements (enlargement of VCDR, narrow neuroretinal rim, asymmetry in cupping between both eyes). These measurements were unbiased by knowledge of visual field status or IOP of the subjects. Furthermore, the semi-automated system used strict criteria for defining the cup margins, based only on topographic data, therefore reducing variation due to different observers; that makes it also particularly interesting for follow-up studies.[18] We found a higher mean VCDR on semi-automated measurements (0.49) compared to other studies using other methods for examining the optic disc (mean VCDR 0.28[5], 0.3[10] using ophthalmoscopy by several examiners, 0.36[8] and 0.43[11] by grading of photographs). As a result, also the prevalence of an enlarged VCDR was higher in our study compared to other studies (VCDR $\geq$ 0.4: 77.2% in our study, compared to 27.1%[5], 37.0%[8]). However, our prevalence of a VCDR $\geq$ 0.7 was only slightly different from the findings of the Blue Mountain Eye Study (5.0%)[11]. Also, asymmetry in VCDR between both eyes was more prevalent in

our study, compared to findings of other studies (4.6% asymmetry ≥ 0.2[22], 0.7% asymmetry ≥ 0.3[11]). Differences in technique and criteria for defining the cup margins play an important role in the findings of the studies. Even interpretation of photographs is subject to interobserver variation.[23]

The visual field screening and grading procedure in our study resulted in a prevalence of 1.5% of visual field defects compatible with glaucoma. This is comparable with the findings of the Framingham Study (1.4%, enlargement of blind spot excluded)[22], but lower than that found in Australia (3.1%).[11] The Blue Mountains Eye Study used, after screening, Humphrey full threshold perimetry (C30-2), which is more sensitive compared to kinetic Goldmann perimetry[24], but also creates more false-positive results, especially in the elderly. This could explain the higher prevalence of visual field defects. Also screening algorithms differ between studies. The Blue Mountain Eye Study screened once with the same Humphrey suprathreshold test as ours followed by full-threshold perimetry, and some studies only performed perimetry in a selected subset of participants, while other studies performed perimetry in all subjects. Full threshold perimetry is nowadays considered to be the gold standard for visual field examination, but especially in older subjects may create more false positive errors compared to Goldmann perimetry.

The IOP is one of the three entities of the 'classical' OAG diagnosis. In the past, IOP measurement was the most important feature of the screening for glaucoma[25], and several recent studies have used elevated IOP as a criterion for glaucoma.[8, 12] However, nowadays most studies see elevated IOP more as a risk factor for glaucoma, and not as compulsory for the diagnosis.[7, 9, 11] The mean IOP of 14.5 mmHg found in our study was slightly lower than the mean IOP found in other studies.[4, 5, 8, 11, 26] Presumably, this can be explained by an IOP lowering effect of the glucose solution which was given to the participants. We found a significantly lower IOP in subjects who had undergone the glucose tolerance test compared to subjects who had not undergone this (mostly subjects with diabetes mellitus and subjects which had undergone a gastrectomy). Consequently, the prevalence of elevated IOP (2.8%) was lower than that in other studies (6.9%[22], 8.6%[4]) When we adjusted for the IOP lowering effect of

the glucose solution the prevalence of elevated IOP increased to 8.3%. Several studies found a positive relation between age and IOP[4, 5], which they found most apparent in the lower age-categories. We could not find a significant relation between age and IOP, nor did we find a significant difference in IOP between men and women, as was suggested by some studies.[4, 26] Other large population-based studies also failed to find a difference in IOP between men and women.[5, 8]

The relation between OAG and gender is still controversial. In Framingham[5] and Barbados[9] a higher prevalence of OAG was found in men, as we did in the present study. However, in the Blue Mountain Eye Study a (borderline significant) higher risk of glaucoma was found for women (Odds ratio 1.55)[11], and in Baltimore[7] and Beaver Dam[8] no difference was found. It might be that differences in age- and gender distributions in the different studies are the cause of the contrasting findings.

In nursing homes inhabitants we were not able to perform reliable visual field testing, due to many physical and mental disabilities. Data on IOP and VCDR were not significantly different from independently living subjects (adjusted for age and gender), suggesting that there were not many differences in prevalence of OAG in comparable age-categories. However, the response in the nursing homes was low, especially in the older subjects, increasing the risk of selection bias. The age distribution of subjects in nursing homes is very different from the age distribution of the independently living subjects. This could be a cause for a higher overall prevalence of OAG in nursing homes compared to independently living subjects, as was reported earlier.[27]

In this study, OAG was defined as a glaucomatous visual field defect with kinetic Goldmann perimetry, in combination with optic disc abnormalities suspect for glaucoma. These optic disc abnormalities were defined as a VCDR $\geq$ 0.7, or asymmetry $\geq$ 0.3 between both eyes, or a minimal rim width $<$ 0.10 using semi-automated measurements, or when semi-automated measurements were not available, an ophthalmoscopic estimated VCDR $\geq$ 0.7 or asymmetry $\geq$ 0.2 between both eyes. Cut-off points were all strictly based on statistical grounds (97.5th percentiles). We would like to propose this definition as a commencement for an international definition for OAG in epidemiologic

research. Further discussion on screening algorithms and methods is needed.

In conclusion, the overall prevalence of OAG in the Rotterdam Study was 0.9%, which is comparable to findings of other population-based studies on Caucasians. Men had a higher risk of having OAG compared to women. There was a significant increase in prevalence of OAG with increasing age. The overall prevalence of OAG varies strongly with different criteria and screening algorithms. Standardizing diagnostic procedures and definitions is needed to improve future (epidemiologic) glaucoma research.

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CHAPTER 3

VISUAL FIELD LOSS IN A GENERAL POPULATION

PREVALENCES, CAUSES AND ASSOCIATIONS WITH DAILY LIFE FUNCTIONING

ABSTRACT

Objective: To determine the prevalence and causes of central visual field loss (VFL) in the elderly. To determine the association between VFL and indicators of impairment in daily life.

Design: Prevalences and causes were measured cross-sectionally in a population-based cohort study. Indicators of impairment were measured both cross-sectionally and prospectively after a 2 year follow-up.

Participants: All community-dwelling inhabitants, aged 55 years or over, were invited to participate, 6250 (68%) of 9161 eligible residents took part in ophthalmological examinations.

Methods: Visual fields of both eyes were examined using a suprathreshold test designed for the central part of the visual field. The eye was re-tested when a defect was present in at least three adjacent points and Goldmann perimetry was performed if the defect persisted. Causes of defects were determined using eye and neurological examination data and history data from ophthalmologists and general practitioners. Interview data and data from medical records on disability in daily life, reading, use of walking aids, incident falling and incident fractures were used to assess impairment.

Results: The overall prevalence of defects was 5.6%, ranging from 3.0% in 55-64 year olds to 17.0% in 85+ year olds. Glaucoma was the leading cause at all ages. Before age 75 years, other optic disc diseases and stroke were the second and third most common cause. After this age, age-related macular degeneration and retinal vascular occlusive disease ranked second and third. Independent from having low vision, VFL was associated with disability, with diminished enjoyment of reading and watching TV, and with a higher risk of falling in the 2 years after the eye exam. Risk of hip fracture or any other fracture was, however, not significantly increased. Of all subjects with VFL, 28% was unaware of the defect and had never visited an ophthalmologist except for glasses.

Conclusions: VFL is as common as visual impairment and associated with serious impaired functioning in daily life in community dwelling elderly. Glaucoma is the leading cause at all ages. Other causes, some of which are partly preventable, vary by age.

The decline of visual function with age is well known and a source of major concern in the elderly. Besides visual acuity, visual function also largely depends on the quality of the visual field.[1] The prevalence of visual acuity loss in elderly has been well studied,[2] but data on the prevalence of visual field loss (VFL) are sparse. An Australian study found VFL to be present in 17% of all eyes in adults aged 40 and over.[3] Among elderly driving licence applicants, 13% had VFL.[4] However, these studies did not have the opportunity to investigate the causes of VFL. To plan research and to develop strategies for diagnosis, prevention and therapy of disabling eye disease, accurate data on causes of VFL are needed.

The presence of VFL may threaten the ability of community-dwelling elderly to maintain their independence. Impairment in daily life is well known to be associated with decreased visual acuity,[5] but recent studies indicated that VFL may also be causing impairment to a considerable extent. Field loss was shown to be associated with frequent falling and decreased quality of life.[6,7] Persons with VFL perceived more difficulty in daily activities even in the presence of good visual acuity.[8] However, these studies were cross-sectional and were clinic-based[7,8] or did not have the opportunity to exclude the influence of low visual acuity.[6] We set out to determine the prevalence and causes of visual field defects and their effects on daily life functioning among community-dwelling Caucasians, aged 55 years and over, in a large population-based study in Rotterdam, The Netherlands.

Material and Methods

This study was conducted as part of The Rotterdam Study, a prospective population-based study of determinants and prognosis of chronic diseases in subjects aged 55 years and over living in a city district of Rotterdam.[9] The study has been approved by the Medical Ethics Committee of Erasmus University Medical School and was conducted in accordance with the Declaration of Helsinki. From 1990 to 1993, baseline investigations were conducted. These consisted of a home interview and an eye and neurological examination at the research center. From 1993 to 1995, participants were re-interviewed at home after a mean interval of three years since their last visit. The present study is confined to community-dwelling subjects.

Eye examination.

The extensive eye examination has been described before.[2] It included indirect ophthalmoscopy of both the central and peripheral retina, photography of the macular area (35° field), stereo photography of the optic disc (20° field), and visual field testing.

The visual field of each eye was screened with a 52-point suprathreshold test, that covered the central part of the field with a 24 degree radius. The test was modified from a standard 76-points screening test (Humphrey Field Analyzer, Zeiss, Oberkochen, Germany). This test was repeated if defects were present. A defect was defined as not having responded to the light stimulus in at least three contiguous test points or four contiguous points if the scotoma included the blind spot. If fixation-losses, false-negative or false-positive results exceeded 20%, testing was halted and the participant was reinstructed before undertaking a new test. If the percentage of false-positive or false-negative results or fixation losses exceeded 33%, the test was considered to be unreliable. If defects were present on the second suprathreshold test in at least one eye, Goldmann kinetic perimetry was performed by an experienced perimetrist on both eyes according to a standard protocol.[10]

All Goldmann fields were independently graded by six researchers who had no information other than refractive error data. Each field was graded on the presence or absence of VFL and on the type of defect if present. Three graders were senior ophthalmologists , two were ophthalmologic residents and one grader was an experienced perimetrist. If there was disagreement in the grading of a Goldmann visual field, consensus was reached. Visual field loss was not considered to be present in case of a symmetrically enlarged blind spot.

Determination of causes of VFL.

For all eyes with VFL on Goldmann perimetry, a senior ophthalmologist (PTVMdJ) determined whether and where field loss was to be expected based on the presence and localization of retinal abnormalities using macular and optic disc centered transparencies. This was done without knowledge of the outcome of Goldmann perimetry. Control transparencies of subjects without defects on

Goldmann perimetry were mixed with the other transparencies, to prevent bias. If VFL did not correspond with a funduscopic lesion, the cause of VFL was determined using data from the ophthalmological examination, home interview, neurological assessment, and additionally obtained information from medical records of general practitioners and ophthalmologists. Sometimes multiple, related causes were present, e.g. diabetes-related proliferative retinopathy requiring laser coagulation. In these instances, the initiating process was recorded as the primary cause (in casu diabetes). Definite open-angle glaucoma, defined as VFL with corresponding optic nerve head damage, and possible open-angle glaucoma, defined as glaucomatous VFL in the absence of any other neurologic or ophthalmologic cause, were lumped. Age-related macular degeneration was defined as geographic atrophy or neovascular macular degeneration according to international standards.[11] Optic nerve head related disease was defined as all abnormalities or diseases primarily affecting the prechiasmal optic nerve excluding open-angle glaucoma. This included tilted disc, myelinated nerve fibers, secondary glaucoma, ischemic optic neuropathy and Leber's optic nerve atrophy. Peripapillary atrophy was also included in this disease group. Retinal vascular occlusive disease comprised central or branch arterial and venous occlusions. Because medical records often did not specify whether occlusion was arterial or venous in nature, they were lumped. Visual field loss due to stroke was diagnosed if the VFL was consistent with the neurological examination (see below) or if subjects reported that a physician had diagnosed stroke in the past. In keeping with World Health Organization criteria, low vision was defined as a best corrected visual acuity of less than 0.3 (20/60) in the better eye.[12]

Other measurements.

Subjects were neurologically assessed by a single team of physicians. In order to detect signs of stroke, the assessment comprised neurological history taking, testing of the glabellar, brachial tendon and gastrocnemius tendon reflexes, motor tone of the limbs, Romberg's cerebellar test and testing for hemiparesis.

At the home interview, responses were recorded for the questions " Have you ever visited an ophthalmologist because of trauma, diabetes, glaucoma or

otherwise?", "Did you ever experience a sudden loss in visual ability, which lasted less than 24 hours?", and "If you ever had eye surgery, did it involve the retina, the cornea or laser treatment?".

Disability in daily activities was measured in eight components (ie., dressing, rising, reaching, hygiene, eating, walking, grip, and activity) as described previously.[13] Moderate disability was present when subjects perceived difficulties in at least four of the eight components. In addition, subjects were asked "Are you homebound because of health problems?", "Do you use a walking aid?", "Do you fall more than once a month?" and "Have you had a broken bone in the past five years?". At the second interview, on average three years after the baseline examination, subjects were asked "Do you enjoy reading a book or watching television?", "Did you fall more than four times in the last two years?" and "If you have fallen, were any bones fractured?". If subjects had moved into a nursing home, they were also interviewed. Non-vertebral fractures occurring after the baseline examinations, up to March 1st, 1996, were reported by general practioners in the study district and verified by staff physicians using medical records and hospital discharge records. Mean follow-up period was 3.8 years and complete follow-up was available for 83% (5186/6250 subjects).

Statistical analysis.

All ophthalmologically examined subjects were included in the analyses unless they met one or more of the following exclusion criteria: (1) no visual field testing in either eye because of physical or mental disabilities or refusal; (2) missing ophthalmoscopic data. Characteristics of included subjects, excluded subjects and subjects refusing the eye exam were compared using multiple logistic regression analysis for categorical variables with adjustment for age and gender. For continuous variables, means and differences across the three groups were calculated using analysis of covariance with adjustment for age and gender. Prevalences are reported as percentages with their 95% confidence interval (CI). Associations of VFL with indicators of impairment in daily life measured at the second visit, were analyzed using logistic regression and adjusted for age and gender. Associations of VFL with the occurrence of fractures after the baseline

examinations were analyzed using Cox's proportional hazards model with adjustment for age, gender and presence of moderate disability. P-values lower or equal to 0.05 were considered to be statistically significant.

RESULTS

Of all 9161 eligible, community-dwelling subjects, 7086 (77%) participated and they were extensively interviewed at their homes. Participation among younger subjects was over 80%, declined with age, but was not sex-dependent (Figure 1). Of the 7086 participating subjects, 6322 underwent an ophthalmological examination at the research center. Ultimately, 6250 subjects, 68% of the eligible population, remained included after applying the exclusion criteria. General characteristics of the included and excluded subjects and participants who refused the eye exam, are presented in Table 1. Compared to included subjects, refusing subjects were significantly older, were more often homebound due to health problems and had visited the ophthalmologist more often because of diabetes, but not because of glaucoma.

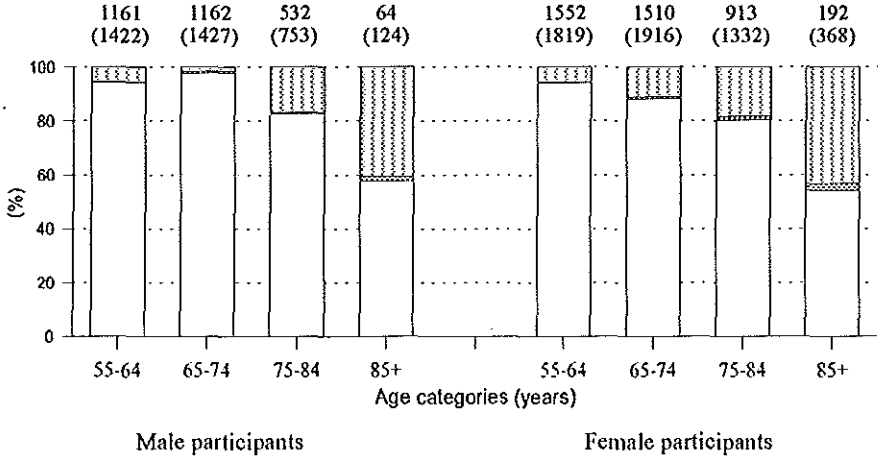

Figure 1. *Age and gender distribution of participating subjects who all consented to at least extensive interviewing (number on top of bars). Participants comprise subjects who refused the eye exam (white bars), subjects with an eye exam that were excluded afterwards (black bars) and included subjects (shaded bars). Numbers between brackets are the numbers of eligibles.*

Table 1. ***General and Clinical Characteristics of Subjects.***

	Included Subjects (n=6250)	Excluded Subjects (n=72)	Subjects refusing eye exam, but consenting to interview (n=764)
Mean age, yrs (unadjusted)	68	75†	74†
Women, % (unadjusted)	58	63	65†
Homebound for health reasons, %	29	9.7†	29.3†
Moderately disabled, %	259	82.9†	38.6†
Visual acuity best eye <0.5, %	23	35	not measured
Visited ophthalmologist for other reason than prescription of glasses, %	408	321	382
Visited ophthalmologist because of glaucoma, %	42	0†	32
Visited ophthalmologist because of diabetes, %	21	21	4.5†
Stroke diagnosed by physician, %	33	29	38

* Values are means, adjusted for age and gender, unless otherwise indicated.
† P<0.005 for the difference with included subjects

Table 2. ***Prevalence of Central Visual Field Loss by Age and Gender.***

		Visual Field Loss in at least One Eye	
	Age (years)	Subjects (N)	Prevalence n (%)
Men			
	55-64	1095	39 (3.6)
	65-74	1037	73 (7.0)
	75-84	440	52 (11.8)
	85+	39	9 (23.1)
	All men	2611	173 (6.6)
Women			
	55-64	1460	38 (2.6)
	65-74	1334	60 (4.5)
	75-84	738	57 (7.7)
	85+	107	19 (17.8)
	All women	3639	174 (4.8)
Total		6250	347 (5.6)

We identified 347 subjects, 5.6% (95% CI 5.0,6.1) of the included subjects, who had VFL in at least one eye. Table 2 gives the prevalence of VFL by age and gender. The prevalence of VFL rose sharply from 3% (77/2555) in those aged 55-64 years to 19% (28/146) in those aged 85 years and over. Women had less often VFL after adjustment for age (OR 0.63, 95% CI 0.38-0.79). Bilateral VFL was present in 1.7% (109/6250). Concentric constriction of the visual field to the central 10 degrees was present in four subjects.

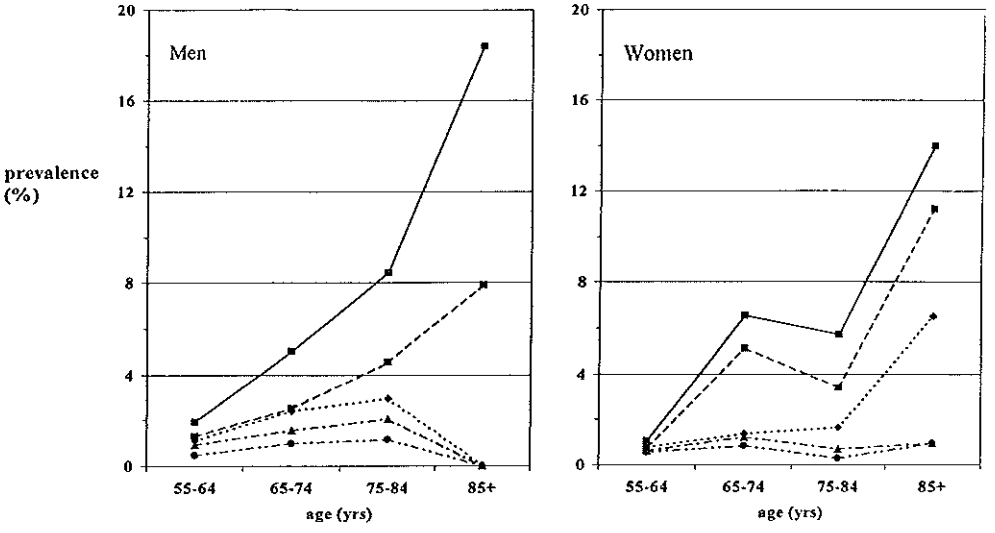

Figure 2. *Prevalences (%) of central visual field loss by cause and age-group in men (left) and women (right). Lines denote primary glaucoma (——), age-related macular degeneration (----), retinal vascular occlusive disease (•••), stroke (-•-•-•-) and optic nerve disease other than glaucoma (••-••-••). Ranking order of diseases may differ from that in Table 3, because prevalences pertain to individuals and not to eyes.*

In most cases, the cause of VFL was only present in one eye or was the same for both eyes. However, in 16% (56/347) of cases, fellow eyes differed in cause. Therefore, prevalences of various causes are most clearly represented as percentages of eyes rather than percentages of subjects. Table 3 gives the causes of VFL by age category. At all ages, open-angle glaucoma was the leading cause of VFL. In subjects aged 55 to 74 years, other optic nerve head diseases and stroke

ranked second and third as most frequent cause. In subjects aged over 75 years, AMD and retinal vascular occlusive disease ranked second and third. The cause of VFL in 23 eyes could not be determined, because records could not be traced or because causes were ambiguously recorded. Using macular and optic disc transparencies and ophthalmoscopic data, definite open-angle glaucoma, AMD, myopic macular changes, diabetic retinopathy and retinal detachment could be excluded as cause.

Table 3. ***Causes of Visual Field Loss in 435 Eyes of 347 Subjects by Age.***

	55-64 yrs	65-74 yrs	75-84 yrs	85+ yrs	All ages
Cause	Number of eyes *(%)*				
Open-Angle Glaucoma	12 *(14)*	61 *(36)*	35 *(24)*	11 *(31)*	119*(27)*
Age-related Macular Degeneration	4 *(5)*	9 *(5)*	32 *(15)*	15 *(43)*	60*(14)*
Retinal Vascular Occlusive Disease	6 *(7)*	19 *(11)*	9 *(6)*	6 *(17)*	40 *(9)*
Optic Nerve Head Disease other than open-angle glaucoma	16 *(18)*	20 *(12)*	6*(4)*	0 *(0)*	42*(10)*
Stroke	9 *(9)*	12 *(7)*	10*(6)*	1 *(3)*	30 *(7)*
Retinal Detachment	6 *(7)*	10 *(6)*	11*(6)*	0 *(0)*	24 (6)
Myopia	10 *(11)*	5 *(3)*	7 *(5)*	0 *(0)*	22 *(5)*
Diabetic retinopathy	4 *(5)*	3 *(2)*	10*(5)*	0 *(0)*	14 *(3)*
Ocular Trauma	4 *(5)*	3 *(2)*	4*(2)*	0 *(0)*	10 *(2)*
Rare causes (chorioretinitis, eye prosthesis, congenital abnormalities)*	11 *(12)*	16 *(10)*	11*(8)*	1 *(3)*	39 *(9)*
Combined mechanisms†	1 *(1)*	1 *(1)*	9 *(6)*	1 *(3)*	12 *(3)*
Unknown	5 *(6)*	9 *(5)*	9 *(6)*	0 *(0)*	23 *(5)*
All causes	88 *(100)*	168	144 *(100)*	35 *(100)*	435 *(100)*

* Rare causes included congenital cataracts (2 eyes), melanoma and other tumors (2 eyes), radiation optic neuropathy (1 eye), choroidal infarct (1 eye), retinitis pigmentosa (3 eyes) and meningitis (2 eyes).

† Combined mechanisms included secondary glaucoma and venous occlusion (1 eye), open-angle glaucoma and venous occlusion (2 eyes), open angle glaucoma and diabetic retinopathy (1 eye), secondary angle-closure glaucoma with Sjögrens syndrome (1 eye), AMD and peripheral retinal degeneration (1 eye), retinal detachment and chorioretinitis (1 eye), chorioretinis and optic atrophy (1 eye), AMD and POAG (2 eyes), and AMD and venous occlusion (1 eye).

Figure 2 shows the absolute prevalences of the five major causes by gender. For AMD, retinal vascular occlusive disease, stroke, optic nerve head disease,

statistically significant gender differences in prevalence were absent. Glaucoma, however, was less frequent in women (odds ratio 0.52, 95% CI 0.38-0.81). Bilateral VFL due to a single cause, was in 28% (30/109) of cases caused by primary glaucoma and in 21% (23/109) by AMD. Interestingly, stroke was diagnosed in 276 subjects, while only 4.7% of these had VFL.

Of those subjects with VFL, 28% indicated that they had never visited an ophthalmologist. Compared to those subjects who were aware of their VFL, unaware subjects were not different regarding age, gender, education and income. However, unaware subjects less often had low visual acuity (OR 0.22, 95% CI 0.07-0.65).

Associations of the presence of unilateral and bilateral VFL and indicators of impairment in daily life are shown in Table 4. To remove the contribution of low vision to impairment in daily life, we excluded subjects with low vision in additional analyses, if applicable. Associations with indicators of impairment tended to be larger for bilateral VFL as compared to unilateral or absent VFL. Satisfaction experienced from reading books or watching TV was lower in persons with bilateral VFL, even if vision was not low. Their chance of frequent falling was almost eight times higher compared to subjects without VFL. Nevertheless, incidences of wrist or hip fractures, both most commonly associated with falling, were not higher among subjects with bilateral VFL. Yet, subjects with unilateral VFL more often suffered from fall accidents in the two years after the eye examination and from wrist fractures during the follow-up period.

DISCUSSION

We have presented cause-specific prevalences of VFL in a general population of community-dwelling elderly. This study demonstrated that the prevalence of VFL rose sharply from 3% in 55-64 year olds to 19% in 85+ year olds. Unilateral VFL was present in 3.8%, bilateral VLF in 1.8%. Glaucoma was leading cause at all ages. Before age 75 years, other optic disc diseases and stroke were the second and third most common cause. After this age, age-related macular degeneration and retinal vascular occlusive disease ranked second and third.

Before these findings can be accepted, some methodological issues have to be

addressed. Firstly, a potential limitation of this study is the restriction to non-institutionalized subjects. Too often, physical or mental disabilities of institutionalized subjects prevented reliable field testing and the acquisition of a representative sample. Presumably, eye diseases associated with cardiovascular disease[14] or bilateral blindness[15] will be more frequent in these subjects. Associations of VFL with measures of functional impairment will therefore be even higher. However, the restriction to non-institutionalized elderly is necessary if one wants to estimate the impact of VFL on the ability to maintain independence in community-dwelling elderly.

Secondly, the generalizability of our results is a reflection of the examination techniques and the process of determining the cause. Small or shallow field defects will have remained undetected, because we required a minimum size for defects and used suprathreshold field testing. Nevertheless, it ensured the detection of clinically relevant scotomas in terms of size and depth. As for the determination of the cause, our cause-specific prevalences do not necessarily match the actual prevalence of VFL-causing lesions that can be seen on ophthalmoscopy. This is because we screened subjects initially on the central 48 degrees of the visual field. Yet, in determining disability in daily life, central VFL is clearly more relevant than peripheral VFL. Misdiagnosis could have occurred in those cases of asymptomatic retinal vascular occlusive disease that had glaucomatous VFL but no visible evidence on photographs or ophthalmoscopy. From a pragmatic viewpoint, we labeled these cases possible open-angle glaucoma, since these cases would be monitored for the progression of VFL.

Thirdly, an advantage of our study is its large size. This enabled preciser estimates of the relative contribution of different causes, in particular rare causes, to the prevalence. In view of the extensive neurological and ophthalmological examinations, the percentage of included persons, 68% of all eligibles, compares favorably with the 68%[8] and 82%[3] of other studies. Yet, as in every survey among elderly, non-participation remains a major concern. Though the number of 80+ years olds, 535 subjects, was considerable as compared to other studies,[3,8] non-participation was highest in this age group. Therefore, the prevalence of VFL in the highest age-groups may be underestimated. It cannot be excluded that non-

participation rates for glaucoma and AMD patients are different, because of frequency differences in disability due to visual acuity loss. However, interview data on 25% of the non-examined eligible subjects, indicated that use of eye care was not more frequent nor was the self-reported presence of glaucoma. This suggests that cause-related bias was not substantial.

Table 4. ***Visual Field Loss and Associations with Indicators of Impairment in Daily Life in 6250 Elderly Subjects.****

	Visual Field Loss		
	Absent n=5903 subjects	Unilateral n=238 subjects	Bilateral n=109 subjects
Low vision, visual acuity in better eye <0.3	0.5%	1.7%†	22.4%†
Homebound for health reasons but no low vision	2.7%	3.6%	6.2%†
Moderately disabled	4.1%	3.9%	10.6%†
Moderately disabled but no low vision	4.0%	3.8%	10.0%†
No enjoyment of reading books and watching TV	1.9%	4%	7.6%†
No enjoyment of reading books and watching TV, but no low vision	1.8%	4.4%	10.2%†
Use of walking aid	6%	9.1%	17%†
Use of walking aid but no low vision	5.9%	5.8%	8.8%
Hip fracture in history	5.5%	5.1%	3.3%
Falling more than 4 times in 2-year period after eye examination	0.55%	3.4%†	3.4%†
Falling more than 4 times in 2-year period after eye examination, but no low vision	0.55%	3.46%†	4.33%†
Any fracture after eye examination, Reported by general practitioner	4.9%	4.1%	6.7%
Wrist fracture after eye examination, Reported by general practitioner	1.2%	3.6%†	0%
Hip fracture after eye examination, Reported by general practitioner	5%	0%	0%

* Values are means or percentages, adjusted for age, gender and moderate disability if applicable.

† P<0.05 for the difference with subjects without field loss.

To our knowledge, three surveys have addressed the frequency of VFL in elderly persons.[3,4,8] A population-based study among subjects aged 40 years and over identified VFL in 17% of all right eyes and 17% of all left eyes, yielding a prevalence of at least 17%.[3] This threefold higher prevalence as compared to our study, can be explained by less strict criteria for size of defects, use of threshold testing, and the absence of confirmatory repeat testing. An 78-point field screening test with a single-intensity light stimulus among elderly drivers demonstrated that the prevalence of VFL in the 55-59 yr age group was 3% and rose to 13% in 65+ year olds.[4] Another study using a single-intensity stimulus found that the number of points missed in the central 60 degrees tripled with increasing age.[8] Though all surveys found an increasing prevalence with age, differences in measuring techniques and population sampling prevent a reliable comparison.

Two thirds of all cases with VFL were unilateral, which points out that random unilateral screening would underestimate the prevalence with 33%. This is of practical relevance for determining the cost-effectiveness of future glaucoma screening programs.

In the absence of other available population-based data, comparisons of the relative contribution of retinal vascular occlusive disease is only possible if one assumes that venous occlusions make up the largest part of retinal vascular occlusive disease. The overall prevalence in our study of 0.65% did not differ from a previous epidemiologic study on venous occlusions, that found a prevalence of 0.54% among elderly aged 65 years and over.[16] However, our prevalence differed twofold from another study that observed retinal branch and central vein occlusion in 1.4% (55/3875).[17] This study based its diagnosis on ophthalmoscopy and grading of photographs, which may account for the difference. We found no significant sex difference after adjusting for age, which is in keeping with another population based study,[17] but conflicts with clinical series.[18]

Previous reports showed that elderly progressively rely on visual feedback to maintain balance with increasing age, because proprioceptive feedback, musculoskeletal strength and often also vestibular function decline with age.[19] It is well known that low visual acuity is associated with a greater risk of falling, hip fractures and mortality among elderly.[20,21] Contrastingly, only one study has

focused on the association between field loss and falling: missing at least 5 points on suprathreshold testing doubled the chance of having fallen before.[6] Because it was a cross-sectional study among community-dwelling elderly, it could not be excluded that multiple fallers with field loss were more likely to be non-participants. However, this is likely since 2% of all accidental falls lead to hip fractures,[22] that, in turn, lead to institutionalization in 30% or death in 15-30% of hip fracture cases.[23] This non-participation bias may explain why subjects with bilateral VFL in our study less frequently had a history of falling and hip fractures than subjects without VFL. This underestimation from history data underscores the importance of prospective data when associations with VFL are investigated and explains why we prospectively found a higher risk for falling than a previous study.[6] We found that both unilateral and bilateral field loss were associated with a sixfold increased risk of frequent falling in the two years after the eye exam. This association remained after subjects with impaired vision were excluded and adjustment for disability (e.g. walking problems) was made. This strengthens the possibility that also VFL and not visual acuity only, are causally related to fall risk. Those with bilateral VFL tended to have a higher fracture risk and a higher risk of fracture if they had a fall accident. Paradoxically, the hip fracture incidence was low in persons with VFL. It has been pointed out that fall characteristics, such as fall direction[24] and outdoor mobility,[25] may shift fracture location from hip to other bones. This could explain our findings, but remains speculative since the number of fracture cases was low.

In conclusion, this population-based study showed that VFL was present in both eyes in one out of fifty elderly. Regardless of visual acuity, VFL was associated with absence of enjoyment of reading and watching TV, moderate disability in daily life activities, and, more importantly, accidental falling.

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CHAPTER 4

GENETIC RISK OF OPEN-ANGLE GLAUCOMA

A POPULATION-BASED FAMILIAL AGGREGATION STUDY

ABSTRACT

Objective: To study familial aggregation of primary open-angle glaucoma in a general population, and to determine the absolute and relative risks for first-degrees relatives.

Methods: First degree relatives of glaucoma cases (n=48) and of controls (n=155) from the population-based Rotterdam Study underwent a standardized examination, including perimetry.

Main outcome measures: Intraocular pressure; vertical cup-disc ratio; presence of glaucoma, defined as visual field defect with a cup-disc ratio ≥ 0.7, or asymmetry ≥ 0.3 between both eyes.

Results: Among relatives of cases, glaucoma prevalence was 10.4% among siblings and 1.1% among offspring, while this was 0.7% and 0% among relatives of controls. Lifetime risk of elevated intraocular pressure was 42.5% in relatives of cases versus 6.7% in relatives of controls; of enlarged cup-disc ratio 62.2% versus 16.6%; and of glaucoma 22.0% versus 2.3%, yielding a risk ratio of 9.2 (95% CI 1.2, 73.9). The population attributable risk of family history to glaucoma was 16.4%.

Conclusions: In a general population, relatives of glaucoma cases have a strongly increased risk of glaucoma. Not intraocular pressure, but enlarged cup-disc ratio was the earliest and most prominent feature of familial aggregation. Further studies are needed to disentangle the genetic components of the increased familial risk.

The etiology of primary open-angle glaucoma, in this paper further referred to as glaucoma, is as yet unknown. This disorder is the second most prevalent cause of incurable blindness in the elderly.[1] Findings from epidemiologic studies indicate that apart from high intraocular pressure[2, 3] and age[4], ethnic origin[2], diabetes mellitus[5] and familial history[6, 7] are associated risk factors. Evidence for genetic factors has been found for juvenile-onset glaucoma[8-11] and for selected families with adult-onset glaucoma.[12-14]

As early as 1869, Von Graefe[15] mentioned hereditary glaucoma, and in 1941, Duke-Elder described a type of glaucoma, which was inherited in a dominant manner and was called familial glaucoma.[16] Since then many studies have been performed in selected families, in which the familial aggregation, inheritance and mode of transmission of glaucoma were studied.[6, 7, 11, 17, 18] These studies differed significantly in methodology and in criteria for the diagnosis glaucoma, resulting in different conclusions regarding the inheritance. Often only family history was taken into account, or a limited number of family members was actually ophthalmologically examined. Moreover, most studies were clinic-based, which opens the possibility of selection bias related to family history and severity of disease. Although in several studies there was evidence of autosomal dominant inheritance and familial aggregation [6, 7], it is not clear whether this accounts for all glaucoma cases.

The purpose of this study was to study whether glaucoma aggregates in families of a general population. We thereto selected probands from the population-based Rotterdam Study, and determined presence of glaucoma in their relatives by actual examination using a standardized protocol. We calculated the absolute and relative risk of glaucoma for first degree relatives, and estimated to what extent genetic factors attribute to the overall occurrence of glaucoma.

METHODS

Study Population

The present study was performed as a part of the Rotterdam Study, a prospective population-based study of determinants and prognosis of chronic

disabling ophthalmic, cardiovascular, neurologic, and locomotor diseases.[4, 19] The study has been approved by the Medical Ethics Committee of Erasmus University and a written informed consent was obtained from all participants.

At the start of our study, all known cases with glaucoma (n=48) from the baseline phase of the Rotterdam Study[4] were asked to participate in the family study (see measurement section for criteria glaucoma). In addition, a random sample of all participants without glaucoma (no visual field defect, normal optic discs) was asked to serve as a control group (n=155). This group was frequency-matched for age (in 5 years strata) and gender. Probands were contacted by letter and by telephone, and subsequently visited at their homes. When informed consent was obtained, first degree relatives were contacted for an examination. Eligible for this study were all first degree relatives living in the Netherlands or Belgium.

Response

The overall response among probands was 89.5% (188 subjects participated of the 210 eligible subjects). Among glaucoma cases, 45 of the 48 eligible probands participated (93.8%), compared to 135 of the 155 probands (87.1%) among controls. In siblings, the overall response was 80.1% (209 / 261). Of the 83 eligible siblings of glaucoma cases, 67 (80.7%) participated, as did 142 of the 178 eligible siblings of control subjects (79.8%). Overall response in offspring was 84.2% (288 / 342); 88 of the 95 (92.6%) eligible children of glaucoma cases participated, compared to 200 of the 247 (81.0%) of controls. Overall response for all relatives was 82.7%. Not motivated, too old, too busy, and privacy reasons were the most important reasons of non-response, which did not differ between groups.

Measurements

Most family members were examined in the research center of the Rotterdam Study. Participants who were homebound were examined at their homes using portable examination equipment, including a "portable" perimeter (Humphrey

Visual Field Analyzer II, model 750). Family members of glaucoma cases and of controls underwent exactly the same examinations.

The intraocular pressure was measured three times (Goldmann applanation tonometer), and the median of these three consecutive measurements was taken.[20] An intraocular pressure > 21 mmHg was considered to be an elevated intraocular pressure, as was intraocular pressure lowering therapy. The visual field was examined with the Humphrey Visual Field Analyzer, using the central 24-2 full-threshold program. After mydriatic eyedrops, stereo fundus transparencies (Topcon TRC-SS2, Topcon Optical Company, Tokyo, Japan) were made from the optic disc, and ophthalmoscopy was performed to examine the optic nerve head.

All stereoscopic optic disc transparencies were used for automated assessment of the optic nerve head characteristics with a digital image analyzer (Topcon Imagenet 2000 system). This system measured three-dimensional topography data based on parallax shifts between both pictures on the stereoscopic slide. The use of the Imagenet system enhanced the standardization and precision of the optic disc measurements and reduced interobserver variability and measurement bias.[21, 22] The vertical cup-to-disc ratio (further referred to as cup-disc ratio) as measured by Imagenet was used in our study. Subjects with a cup-disc ratio ≥ 0.7 in at least one eye or asymmetry in cup-disc ratio ≥ 0.3 between both eyes were considered as having an enlarged cup-disc ratio.

All visual field charts were graded in a masked way by two independent graders, using all available data calculated by the statistical software of the perimeter to eliminate visual field defects caused by media opacities.[23-25] The graders were masked for all clinical characteristics including the cup-disc ratio, intraocular pressure, and familial relationship. Possible glaucomatous visual field defects were defined as field defects not explainable by other abnormalities, such as retinal (e.g. chorioretinal scars, macular degeneration, vascular obstructions), optic disc (e.g. optic disc drusen, optic disc pit, tilted disc), or neurologic (e.g. cerebrovascular accidents) disorders. Unreliable visual field tests were discarded in the analyses.

The diagnosis of primary open-angle glaucoma was based on the presence of a glaucomatous visual field defect in combination with a cup-disc ratio ≥ 0.7 in the affected eye or an asymmetry in cup-disc ratio ≥ 0.3 between both eyes.

Other Risk Factors

Diabetes mellitus is a known risk factor for primary open-angle glaucoma.[5, 26] Also, a relation between elevated intraocular pressure and hypertension has been shown before.[27] To investigate whether clustering of these concurrent disorders could account for familial aggregation of primary open-angle glaucoma, we evaluated presence of diabetes mellitus, and presence of hypertension as risk factors. Diabetes mellitus was defined as the use of anti-diabetic medication, which was assessed using a questionnaire. Hypertension was defined as a systolic bloodpressure of 160 mmHg or over, or a diastolic bloodpressure of 95 mmHg or over, or use of bloodpressure lowering drugs.

Statistical Analyses

Prevalence of glaucoma was compared between siblings and offspring of glaucoma cases and siblings and offspring of controls. Prevalence figures were adjusted for age and gender. Multiple logistic regression analysis was used to estimate the risk of glaucoma for siblings and offspring, with the odds ratio serving as an approximation of relative risk. Odds ratios were adjusted for age and gender, and in addition analyses also for presence of diabetes mellitus and hypertension. Interaction between genetic factors and diabetes and hypertension was studied by performing stratified analyses, as well as performing analyses on the full data set including product terms for diabetes and proband status (case or control), and hypertension and proband status.

Survival analyses (Kaplan-Meier product-limit survival analysis) were performed to calculate cumulative risks of glaucoma, elevated intraocular pressure and enlarged cup-disc ratio. These cumulative risks are estimations of the absolute lifetime risk. Subjects above 80 years were pooled to maintain unbiased estimates. [28] The log-rank test was used to compare survival curves of

relatives of glaucoma cases and of controls. All analyses were performed with the BMDP statistical package.[29]

The attributable risk of genetic factors to the occurrence of primary open-angle glaucoma in the exposed and general population was estimated using the formulas developed by Miettinen.[30] The attributable proportion for genetically exposed (Ape) was calculated with the formula

$$Ape = \frac{RR - 1}{RR}$$

where RR is the relative risk. The attributable proportion for the total population (App) was calculated with

$$App = Ape * Pe$$

where Pe is the proportion genetically exposed in the cases.

Table 1. ***Characteristics of Siblings of Glaucoma Cases and of Controls***

	Siblings of Cases (n=61)	Siblings of Controls (n=142)	Difference	95% CI
Age in years	72.3 (1.1)	75.4 (0.8)	-3.0 *	-5.7, -0.3
Women (%)	52.8 (6.3)	57.9 (4.2)	-5.1	-19.9, 9.7
Hypertension (%)	38.0 (6.0)	34.3 (4.0)	+3.7	-10.5, 17.9
Diabetes mellitus (%)	11.9 (3.0)	3.8 (2.0)	+8.1 *	0.9, 15.3
Mean intraocular pressure (mmHg_	14.7 (0.4)	13.1 (0.3)	+1.6 *	0.6, 2.5
Intraocular pressure > 21 mmHg † (%)	4.1 (1.9)	0.7 (1.2)	+3.4	-1.0, 7.8
Intraocular pressure lowering therapy (%)	15.0 (2.9)	1.4 (2.0)	13.5 *	6.6, 20.5
Mean cup-disc ratio	0.54 (0.02)	0.46 (0.01)	+0.08 *	0.04, 0.12
Cup-disc ratio ≥ 0.7 or asymmetry ≥ 0.3 (%)	32.8 (4.5)	6.5 (3.0)	+26.3 *	15.8, 36.8
Visual field defect‡ (%)	33.7 (4.8)	10.8 (3.4)	+22.8 *	11.3, 34.4
Prevalence of glaucoma§ (%)	10.4 (2.5)	0.7 (1.7)	+9.7 *	3.8, 15.6

All figures are, if appropriate, adjusted for age and gender. Values in parentheses are standard errors of the mean.

* Statistically significant difference ($p < 0.05$)

† Subjects with intraocular pressure lowering therapy were excluded.

‡ All visual field defects caused by retinal abnormalities, optic disc abnormalities (except glaucoma), or neurologic disorders were excluded.

§ Glaucoma was defined as the presence of a visual field defect, with no other causes, in combination with a cup-disc ratio ≥ 0.7 or asymmetry ≥ 0.3.

RESULTS

The mean age of the siblings of the glaucoma cases was 72.3 years (Table 1). The siblings of the control subjects were on average 3.0 years older (95% CI 0.3, 5.7; adjusted for gender). The mean age of the offspring of the glaucoma cases was 42.2 years, whereas the offspring of the control subjects were 3.5 years older (95% CI 1.3, 5.7; Table 2).

Table 2. ***Characteristics of Offspring of Glaucoma Cases and of Controls***

	Offspring of Cases (N=86)	Offspring of Controls (n=201)	Difference		95% CI
Age in years	42.2 (0.9)	48.7 (0.6)	-3.5	*	-5.7, -1.3
Women (%)	43.8 (5.5)	45.7 (3.6)	-1.9		-14.7, 11.0
Hypertension (%)	7.3 (2.9)	7.9 (1.9)	-0.6		-7.4, 6.2
Diabetes mellitus (%)	1.2 (0.6)	0.0 (0.0)	+1.2		-0.4, 2.7
Mean intraocular pressure (mmHg)	14.7 (0.3)	13.6 (0.2)	+1.2	*	0.5, 1.9
Intraocular pressure > 21 mmHg † (%)	1.3 (1.0)	0.5 (0.6)	-0.8		-1.5, 3.1
Intraocular pressure lowering therapy (%)	0.0 (0.0)	1.5 (0.7)	1.5		-4.2, 1,2
Mean cup-disc ratio	0.52 (0.01)	0.49 (0.01)	+0.03		0.0, 0.06
Cup-disc ratio ≥ 0.7 or asymmetry ≥ 0.3 (%)	11.9 (3.4)	9.2 (2.2)	+2.7		-5.3, 10.8
Visual field defect‡ (%)	3.6 (1.3)	0.5 (0.9)	+3.1	*	0.01, 6.3
Prevalence of glaucoma§ (%)	1.1 (0.7)	0.0 (0.0)	+1.1		-0.4, 2.7

All figures are, if appropriate, adjusted for age and gender. Values in parentheses are standard errors of the mean.

* Statistically significant difference ($p < 0.05$)

† Subjects with intraocular pressure lowering therapy were excluded.

‡ All visual field defects caused by retinal abnormalities, optic disc abnormalities (except glaucoma), or neurologic disorders were excluded.

§ Glaucoma was defined as the presence of a visual field defect, with no other causes, in combination with a cup-disc ratio ≥ 0.7 or asymmetry ≥ 0.3.

Siblings of glaucoma cases had a significantly higher intraocular pressure and cup-disc ratio than siblings of controls. Intraocular pressure lowering therapy occurred statistically significant more often in siblings of cases. In offspring, similar trends were found for mean intraocular pressure and cup-disc ratio, but differences were smaller and only statistically significant for intraocular pressure. There was no statistical significant difference in

intraocular pressure lowering therapy. The prevalence of glaucoma in the siblings of glaucoma cases was 10.4% (n=6) compared to 0.7% (n=1) in the siblings of controls (Table 3; prevalence odds ratio 14.7; 95% CI 1.7, 130; adjusted for age and gender). In offspring of cases, glaucoma prevalence was 1.1% (n=1), while this was not present among offspring of controls. The higher frequencies were independent of presence of diabetes mellitus or hypertension (Table 3). We found no statistical evidence for interaction between familial risk and diabetes mellitus or hypertension (data not shown).

Table 3. ***Odds Ratios of Glaucoma Features for First Degree Relatives***

	Intraocular pressure > 21 mmHg[‡]				Cup-disc ratio ≥ 0.7 or asymmetry ≥ 0.3			
	+	-	OR*	OR†	+	-	OR*	OR†
Siblings								
of cases	11	48	10.5	9.8	21	41	8.6	9.2
of controls	3	121	(2.7, 41.0)	(2.5, 38.9)	7	135	(3.4, 21.9)	(3.5, 24.1)
Offspring								
of cases	1	81	0.6	0.6	9	76	1.3	1.3
of controls	4	187	(0.1, 6.1)	(0.1, 5.5)	18	181	(0.5, 3.1)	(0.5, 3.1)
	Visual field defect[§]				Diagnosis of glaucoma[¶]			
	+	-	OR*	OR†	+	-	OR*	OR†
Siblings								
of cases	19	40	4.8	5.1	6	55	14.7	16.6
of controls	14	107	(2.1, 11.1)	(2.2, 12.2)	1	123	(1.7, 130)	(1.9, 147)
Offspring								
of cases	3	82	7.5	7.5	1	84	-	-
of controls	4	188	(0.7, 76.9)	(0.7, 76.5)	0	194		

The relative risks of family members in the control group are set to 1.0.

OR= Odds ratio, with 95% confidence interval between parenthesis.

* adjusted for age and gender

† adjusted for age, gender, and presence of hypertension or diabetes mellitus

‡ or intraocular pressure lowering treatment.

§ Visual field defects caused by retinal or optic disc abnormalities (except glaucoma), or neurologic disorders were excluded.

¶ Glaucoma was defined as a visual field defect in combination with a cup-disc ratio ≥ 0.7 or asymmetry in cup-disc ratio ≥ 0.3.

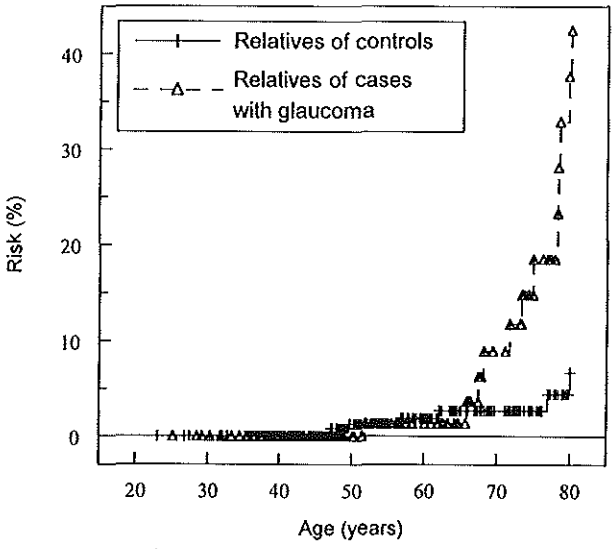

Figure 1. *Lifetime risk of elevated intraocular pressure (IOP > 21 mmHg) or therapy to lower the IOP.*

Figures 1 and 2 show the lifetime risks of elevated intraocular pressure and enlarged cup-disc ratio in relatives of glaucoma cases and controls. Lifetime risk of elevated intraocular pressure was 42.5% in relatives of glaucoma cases compared to 6.7% in relatives of controls (risk ratio 6.3, 95% CI 2.1, 19.2; log-rank test p=0.0003). Lifetime risk of enlarged cup-disc ratio was 62.2% in relatives of glaucoma cases compared to 16.6% in relatives of controls (risk ratio 3.8, 95% CI 2.3, 6.1; log-rank test p<0.0001). Figure 3 shows the Kaplan-Meier lifetime risks of glaucoma. The lifetime absolute risk of glaucoma at the age of 80 years was 22.0% for relatives of cases compared to 2.4% for relatives of controls (risk ratio 9.2, 95% CI 1.2, 73.9; log-rank test p=0.0002).

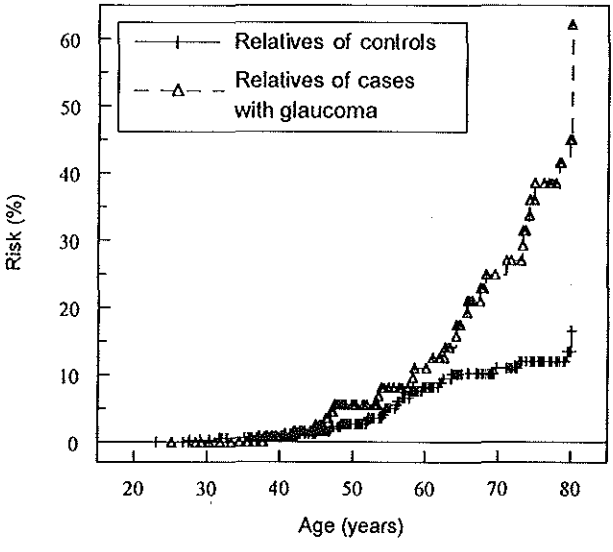

Figure 2. *Lifetime risk of VCDR ≥ 0.7 or asymmetry in VCDR between both eyes ≥ 0.3*

The attributable proportion was calculated using the ratio of the lifetime cumulative risks of glaucoma in relatives as the best approximation of the true relative risk for genetic factors (RR=9.2) in the Ape and App formulas (see methods). The attributable proportion among the genetically exposed (Ape) was 89%, indicating that 89% of the familial occurrence is genetically determined. The proportion exposed cases (Pe) was calculated as the ratio of case probands with affected relatives (n=7) divided by the total number of case probands (n=38) with relatives who were at least 44 years of age (minimum age of glaucoma in our study). The attributable proportion of genetic factors to the overall occurrence of glaucoma in the general population (App) was calculated to be 16.4%.

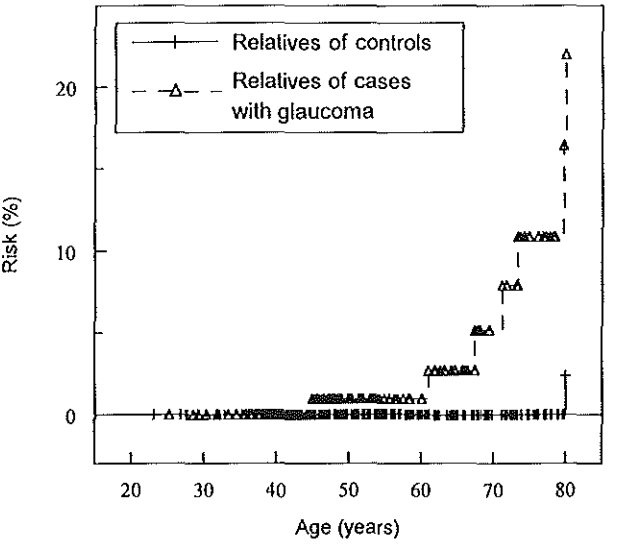

Figure 3. *Lifetime risk of glaucoma, defined as a visual field defect in combination with a VCDR ≥ 0.7 or asymmetry in VCDR between both eyes ≥ 0.3.*

DISCUSSION

The main finding of this study is that the prevalence of glaucoma, enlarged cup-disc ratio, and of elevated intraocular pressure is much higher in siblings and offspring of glaucoma cases than in relatives of non-affected subjects. The lifetime risk of glaucoma was 22% in relatives of glaucoma cases, almost 10 times higher than in controls. Our findings suggest that at least one sixth of all glaucoma in the general population may be due to a genetic component. Enlarged cup-disc ratio was the earliest feature of glaucoma in relatives.

Former family studies were limited to clinic-based families or glaucomatous disorders, which are nowadays not regarded as adult-onset primary open-angle glaucoma. Often data from a large number of ophthalmologists were used, which may have introduced non-standardized diagnosis. Advantages of our study were that we ascertained glaucoma cases and controls from the same population-based cohort, minimizing selection bias. We did not rely on history data, but examined all first-degree relatives, and assessed each feature of glaucoma separately in a masked fashion to ensure an unbiased diagnosis. We aimed at full ascertainment, and approached all glaucoma cases of our source population. Ascertainment in our study was high, and was very similar among both groups. Therefore, it is unlikely that selective participation explains our results. Unfortunately, the number of case probands was relatively low, which limited the statistical power of our study. Although confidence intervals were wide, the risk estimates reached statistical significance.

Glaucoma is a disease which develops slowly and only becomes manifest at an older age. As a result, genetically exposed relatives may not have expressed the disease yet at the time of investigation. By censoring these individuals in the survival analyses, the true absolute lifetime risks for relatives are approximated.[28] For simple genetic disorders, an absolute risk of 50% is compatible with autosomal dominant inheritance, and 25% with autosomal recessive inheritance[28]. For complex disorders as glaucoma, the interpretation of these proportions for mode of inheritance is not as straight forward. Different genes are likely to be involved, each with their own mode of inheritance and interaction with environmental factors.

In general, magnitude of any exposure in the etiology of disease may be quantified by its relative and attributable risks. We found a relative risk of 9.2 for genetic factors, which is higher than the effect of any other risk factor known. In contrast, the population attributable risk was approximately 16%, which was rather low. This suggests that other, non-genetic, factors determine the overall occurrence of glaucoma to a great extent.

Unlike former family studies, we investigated each feature of glaucoma separately. We found that relatives of glaucoma cases had a higher frequency of

enlarged cup-disc ratio, but even in the "normal" cup-disc range their ratio was on average higher. From Figures 1 and 2 it can be concluded that enlarged cup-disc ratio was the earliest manifestation of familial aggregation. As expected, elevated intraocular pressure or pressure lowering therapy occurred more often in relatives of glaucoma cases. Yet, the majority of relatives who had been newly diagnosed with glaucoma had normal intraocular pressures. The high prevalence of glaucoma therapy among relatives of cases may be a result of the selective treatment by ophthalmologists of patients with positive family history.

In summary, we have demonstrated that relatives of glaucoma cases are at a 10 times increased risk of developing glaucoma. Not intraocular pressure, but enlarged cup-disc ratio was the earliest expression of genetic exposure. Whether this is caused only by genetic factors, or also by gene-environmental interactions has to be further investigated. Other, yet unknown, non-genetic factors seem to play a major role in the overall occurrence of glaucoma in the general population.

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CHAPTER 5

CUP-TO-DISC RATIO

OPHTHALMOSCOPY
VERSUS
SEMI-AUTOMATED MEASUREMENT

ABSTRACT

Objective: To determine the correlations between ophthalmoscopic estimations and the measurements with a semi-automated image-analysis device of the vertical cup-to-disk ratio (VCDR) in the human optic disk.

Participants: All subjects aged 55 years or older from the population-based sample of 6777 ophthalmologically examined subjects from The Rotterdam Study of whom gradable optic disk transparencies of at least one eye and ophthalmoscopy data of the same eye were available.

Methods: Indirect as well as direct ophthalmoscopy were performed in mydriasis to assess the VCDR. Optic disk transparencies made with a simultaneous stereoscopic telecentric fundus camera were analyzed with a semi-automated measurement system (Topcon Imagenet).

Results: In 5143 subjects the mean ophthalmoscopic VCDR was 0.30 (SE 0.0021; range 0.00, 1.00) compared to a semi-automatically measured VCDR of 0.49 (SE 0.0019; range 0.04, 0.86; difference 0.19; $p<0.0001$). The overall correlation between both methods was moderate (correlation coefficient 0.61 (SE 0.11)), and lower in small optic disks. Semi-automated optic disk measurements correctly identified 76% of the glaucoma cases (as defined using visual field data and ophthalmoscopic data about the optic disk).

Conclusion: Semi-automated measurements of the VCDR are larger than the ophthalmoscopic VCDR estimate with a moderate correlation. The inter-observer variability using Imagenet was smaller, compared to the ophthalmoscopic assessments, and Imagenet was better standardized, which is important for epidemiological surveys and follow-up studies.

Reliable assessment of the vertical cup-to-disk ratio (VCDR) is essential for the diagnosis and monitoring of primary open-angle glaucoma (POAG). Unfortunately, ophthalmoscopic estimation of the VCDR has a low interobserver agreement (kappa 0.57[1], correlation coefficient 0.65[2]). The more favorable interobserver agreement (coefficient of variability 3-28%[3]) of recently introduced semi-automated systems may be advantageous for glaucoma research. These systems were shown to detect morphometric optic disk changes as small as 50-100 μm.[4] Yet, the question may rise to what extent results of previous studies using ophthalmoscopy are interchangeable with more recent studies using semi-automated systems. In addition, it is uncertain whether semi-automated measurements have better diagnostic accuracy than ophthalmoscopic estimates.

Semi-automated measurement of the VCDR with Imagenet involves three-dimensional topographic mapping of the optic disk surface, using digital images of the optic disk. The cup is outlined using strict criteria, based on topographic data, and not on pallor. There is no intrinsic measurement variability; however, operator input in outlining the disk may account for small measurement variability (1-12%).[3]

Previous studies on the correlation between semi-automated measurement and ophthalmoscopy are lacking. A study on 35 eyes showed an only moderate correlation (weighted kappas 0.45-0.52) between clinicians estimating VCDR from stereo-photographs and semi-automated measurements.[5] Vertical cup-disk ratio estimations from photographs are known to be larger than ophthalmoscopic ones.[6] Using ophthalmoscopic VCDR estimations, the presence or absence of POAG could be correctly identified in 90% of the subjects.[6] However, these figures are not yet known for semi-automated measurements.

Though proven to be less reproducible, ophthalmoscopy still is the major screening tool for the detection of POAG. Therefore we aimed at answering the following questions: do ophthalmoscopy and semi-automated measurement give the same VCDR estimate? If not, what is the extent of the difference? What is the linearity of the relationship, given that there is a difference in means? In

addition, we determined the diagnostic accuracy of semi-automated measurements for the presence of POAG according to ophthalmoscopic criteria.

METHODS

The present study was performed as part of the baseline phase of The Rotterdam Study, a population based cohort study among residents, aged 55 years and over.[7] The study has been approved by the Medical Ethics Committee of the Erasmus University and written informed consent was obtained from all participants.

Of all 10,275 eligible persons, 69% (n=6777) underwent an ophthalmological examination performed by three medical doctors (MDs). The examination included measurement of best corrected visual acuity and corneal curvatures. Pupils were dilated with tropicamide 0.5% and phenylephrine 5%. Monocular indirect and direct ophthalmoscopy (Zeiss, Germany) were performed to assess VCDR. The optic cup was defined based on its contour and on the course of small blood vessels on the disk and not on pallor. The border of the optic disk was defined as the inner border of the peripapillary scleral ring. Next, optic disk transparencies were made with a simultaneous stereoscopic, telecentric fundus camera (Topcon TRC-SS2, Topcon Optical Company, Tokyo, Japan). Of all 6777 examined subjects in the Rotterdam Study, on 5143 subjects both ophthalmoscopic and semi-automated VCDR measurements on at least one optic disk were available.

Stereo transparencies from both eyes of all individuals were digitized and analyzed by two technicians with the Topcon Imagenet, using the module for the retinal nerve fiber layer height. The system's hardware, its software modules and reproducibility of measurements have previously been described.[3] The technician marked four points on the disk margin, defined as the inner border of the peripapillary scleral ring of Elschnig or the outer border of the neural rim if the scleral ring was not visible. Next, the program fitted the best ellipse around the four points to outline the disk margin. The technician subsequently marked five to eight corresponding points along retinal landmarks as blood vessels on both members of a stereo pair. These points were equally spaced outside the

disk's perimeter at 0.5 to 0.75 disk diameters from the disk margin. Imagenet used these points to define a retinal zero-reference plane and the parallax between corresponding points on the image pair to determine the topography of 600 to 800 points within the optic disk relative to this zero-reference plane. To determine the margin of the cup, 36 vertical planes were established, perpendicular to the zero-reference plane and radially extending from the center of the disk to the disk margin at 10-degree intervals. At the intersection of the disk surface and each vertical plane, the most elevated point on the disk margin was determined. Relative to this point, more centrally located points that were ≥ 150 µm lower, were by convention [8] considered to be within the cup margin (Figure 1). The disk area, VCDR, and neural rim ratio (neural rim width divided by disk diameter at 36 equally spaced points along the disk circumference; Figure 1) were automatically calculated from the topographic data. If topographic information from an image point was unreliable due to low image quality, topographic information was interpolated from surrounding reliable image points. Disks in which more than 10% of the image points were unreliable, were excluded from this study. Disk measurements were corrected for magnification by the eye and camera system to obtain measurements in absolute size units using a modified Littmann correction factor calculated from spherical refractive equivalents and corneal curvatures.[9]

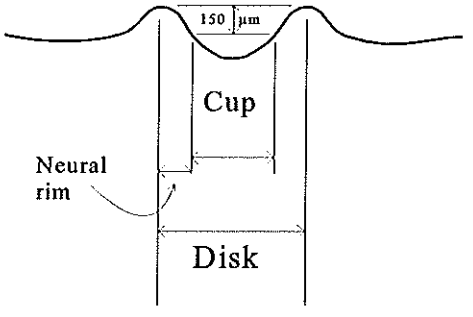

Figure 1. *Schematical drawing of optic disc characteristics as calculated by the semi-automated measurement device. Vertical cup-to-disc ratio = Cup diameter / Disc diameter. Neural rim ratio = Rim width / Disc diameter.*

All subjects that had reliable semi-automated measurements and ophthalmoscopy data of at least one optic disk were included in this study.

The diagnosis POAG was made on the presence of a visual field defect (after other causes had been excluded), in combination with an ophthalmoscopic VCDR ≥ 0.5 or asymmetry in this VCDR between both eyes ≥ 0.3, and no evidence of

secondary glaucoma. Methods have been described in detail before.[10] Briefly, visual fields were screened with a suprathreshold screening test (Humhrey Visual Field Analyzer, Zeiss, Germany). Confirmatory kinetic Goldmann perimetry was performed if defects persisted on a repeated suprathreshold test. Monocular indirect and direct ophthalmoscopy was performed to assess the VCDR. Intraocular pressure was not used as a criterion for POAG.

Glaucomatous disks on semi-automated measurements were defined as disks with a VCDR $\geq$ 0.7, or asymmetry in VCDR $\geq$ 0.3 between both eyes, or a minimal neural rim width $\leq$ 0.15. These criteria were based on the mean shift in distribution of semi-automated measurements to larger VCDRs compared to ophthalmoscopic assessments, and on available data on stereoscopic grading of disk photographs.[11, 12]

Data analysis.

In our analyses we included one eye per person and selected the eye which had the stereo transparency with the highest photographic quality. A weighted kappa was calculated to compare ophthalmoscopic estimates with the categorized semi-automated Imagenet measurements. Means for semi-automated measurements and ophthalmoscopic VCDR estimations were compared with the paired Student's t-test and linear regression analysis. Pearson correlation coefficients were calculated for all subjects together. To study differences in ophthalmoscopy between observers we calculated the correlation coefficients for each of the three physicians. Furthermore, we studied whether the disk area calculated with Imagenet had an influence on the estimation of the VCDR by stratifying in tertiles of disk area. The percentage of interpolated points was taken as a measure of photographic quality, and was adjusted for in all analyses.

In order to determine the diagnostic accuracy of Imagenet measurements, the sensitivity was calculated as the proportion of all subjects with POAG (using ophthalmoscopic disk assessment) who had a glaucomatous disk on semi-automated measurement. The specificity was defined as the proportion of correctly identified subjects without POAG.

To estimate within- and between-technician variation of semi-automated measurements, two technicians measured the same set of 25 at random selected transparencies at two, four, and nine months after the start of the 12-month measuring period. Weighted kappa values for within- and between technician variation were calculated. As the respondents were seen only once by one MD at a time, we could not calculate intra- and interobserver differences on ophthalmoscopy.

Table 1. ***Influence of different physicians on the linear association between ophthalmoscopic estimates and semi-automated measurements of VCDR.***

	Correlation coefficient
MD 1	0.632 (0.106)
MD 2	0.629 (0.108)
MD 3	0.655 (0.106)

Figures between parentheses are standard errors of the mean.

RESULTS

Figure 2 shows a scatter plot of ophthalmoscopic estimations and semi-automated measurements. For the separate MDs the weighted kappas were 0.14, 0.22, and 0.23, respectively. The weighted kappa for all MDs together was 0.18.

The mean ophthalmoscopically estimated VCDR was 0.30 (SE 0.0021; range 0.00, 1.00) compared to a VCDR of 0.49 (SE 0.0019; range 0.04, 0.86) measured with the image-analyzer (difference 0.19; 95% CI 0.186 - 0.194; $p<0.0001$). The cumulative frequencies of ophthalmoscopic estimations and semi-automated measurements are shown in Figure 3; a clear shift to the right is visible for Imagenet measurements compared to ophthalmoscopic estimates.

The two methods showed a moderate correlation (coefficient 0.61 (SE 0.11; $p<0.001$). The correlation between ophthalmoscopic VCDR assessment and Imagenet assessment of VCDR varied little and not significantly between each of the three MDs (Table 1). To determine whether a MD was influenced by disk dimensions, the correlation between both measurements by tertile of disk area (measured with Imagenet) is given in Table 2. The correlation between both

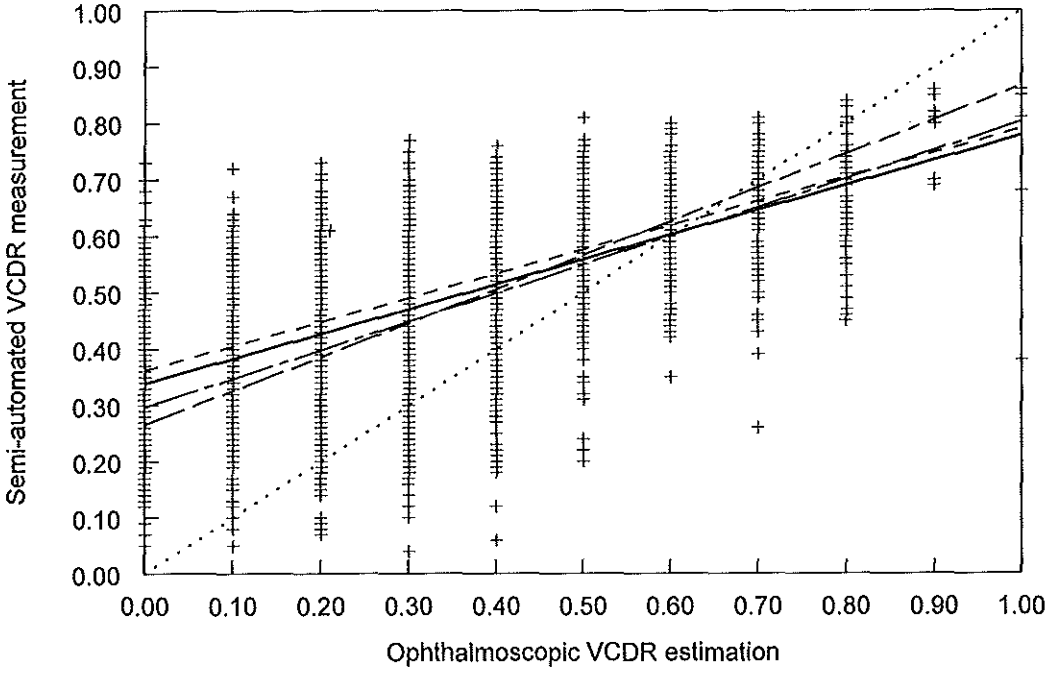

Figure 2. *Comparison between ophthalmoscopic estimates of VCDR and semi-automated measurements. Each mark represents the measurements of one eye. The solid line is the linear regression line, calculated for all the measurements (correlation 0.64). Also regression lines for each of the three MDs are shown (dotted and dashed lines).*

methods was higher in large disks (disk area > 2.56 mm^2) than in small disks (disk area < 2.17 mm^2; test for trend: p = 0.02). Regression lines for the separate MDs and for all MDs together are shown in Figure 2.

In this study, 37 persons had POAG according to our ophthalmoscopic criteria (see methods). Of these, 28 subjects had on Imagenet a VCDR ≥ 0.7, or asymmetry ≥ 0.3 or a minimal neural rim width ≤ 0.15, yielding a sensitivity of 75.7% (28/37) for detecting POAG. The specificity of the semi-automated measurements was 72.7% (3712/5106). We did not perform these calculations for ophthalmoscopic VCDR estimations, because we used these as a reference for the POAG diagnosis in our study.

The optic disk transparencies were digitized and analyzed by two technicians. The weighted kappa for inter-technician variability was 0.85. The

weighted kappa for intra-technician variability was 0.92 for technician 1 and 0.88 for technician 2.

Because of logistic reasons it was only possible for one MD to evaluate each subject. This made it impossible to evaluate the inter- and intra-observer reliability of the VCDR estimates of the different MDs.

Table 2. ***Influence of disk area as measured with Imagenet on the linear association between ophthalmoscopic estimates and Imagenet measurements of VCDR.***

Disk area (tertiles)	Correlation coefficient	Difference between ophthalmoscopy and Imagenet measurements
< 2.17 mm^2	0.523 (SE 0.145)	0.21 (SE 0.004)
2.17 - 2.56 mm^2	0.562 (SE 0.142)	0.19 (SE 0.004)
> 2.56 mm^2	0.617 (SE 0.152)	0.17 (SE 0.004)
Test for trend:	p=0.02	$p < 0.0001$

The correlation coefficient shows the strength of linear association between the ophthalmoscopic VCDR and its Imagenet counterpart. The strength of this association increased with disk size (statistically significant, p=0.02), while the difference between the ophthalmoscopic VCDR and Imagenet decreased with increasing disk size (statistically significant, $p< 0.0001$).

DISCUSSION

We found that Imagenet measurements of VCDR were moderately correlated (r=0.63) with ophthalmoscopic estimates. Differences between methods were more pronounced both in disks with ophthalmoscopic small and large VCDRs. Furthermore, differences were largest in larger disks.

The low weighted kappa is in contrast with the finding of a study (kappa ranging from 0.45 to 0.52 for different observers [5]) in which Imagenet measurements were compared with visual gradings of optic disk transparencies. This partly can be explained by the difference in method used to estimate the VCDR (because ophthalmoscopy is often less accurate than grading of fundus abnormalities). Furthermore, we saw a shift to the right in the distribution of semi-automated VCDR measurements compared to the ophthalmoscopic

VCDRs. This 'systematic' difference can result in a marked decrease of a kappa. In addition, as is usual in daily practice, we used different MDs for ophthalmoscopy.

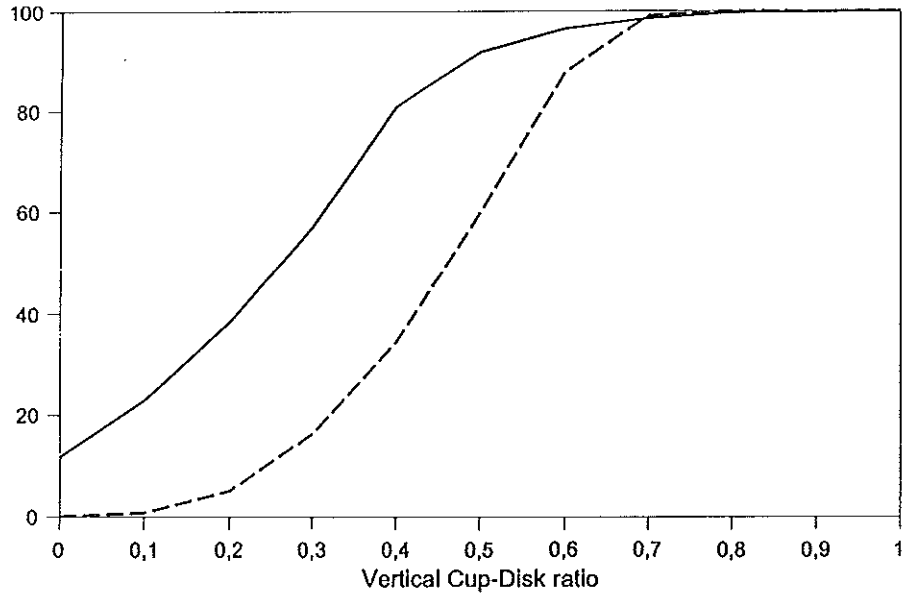

Figure 3. *Cumulative prevalences of ophthalmoscopic estimates of the VCDR (solid line) and of Imagenet measurements (dashed line) in one eye of 5134 subjects.*

Differences between semi-automated VCDR measurements and ophthalmoscopic estimates of the VCDR can be explained by several factors. In our study, monocular ophthalmoscopy was performed, while Imagenet measurements are based on stereoscopic transparencies. Monocular assessment differs from the stereoscopic counterpart, because frequently the point at which the cup starts has to be inferred and cannot be perceived. It has been found that stereoscopic estimations yield larger estimates.[6] This may partly explain why the mean of semi-automated VCDR measurements was higher than its ophthalmoscopic counterpart. Furthermore, it can not be excluded that the observer has been biased by the area of pallor and peripapillary atrophy on ophthalmoscopy. Contrastingly, semi-automated measurement disregards color

differences of the optic disk, and has strict criteria for defining the cup. Ultimately, the issue which of both methods most accurately reflects reality might only be resolved using histopathological data.

Unfortunately, no other studies were found that compared ophthalmoscopy with other disk measuring methods. Studies that correlated manual stereoscopic disk planimetry with semi-automated measurements also found moderate correlations of 0.67[13] and of 0.77. [14] Since planimetry, grading of stereoscopic transparencies of the optic disk, and semi-automated VCDR measurement all correlate moderately with ophthalmoscopic VCDR estimations, all are equally eligible to be an alternative to ophthalmoscopic estimations. Additional characteristics, such as measurement variability, interobserver agreement, and costs determine therefore their usefulness. In the ophthalmoscopic lower VCDR range, semi-automated measurements were lower than the ophthalmoscopic estimates, while this was reversed in the upper VCDR range (Figure 2). Furthermore, we found a lower correlation between both methods in small optic disks. A possible explanation may be that semi-automated systems cannot distinguish between the entrance of the blood vessels in the disk and the neural tissue lining the cup. Therefore, the central depression caused by the entering blood vessels is regarded as the cup, and thus may be overestimated. Since small optic disks are known to have on average also smaller cups, this overestimation will particularly affect semi-automated measurements in small disks, and not in larger disks. The lower correlation in smaller disks is in keeping with our findings that the automated measurements were higher in disks with ophthalmoscopic low VCDRs.

One advantage of our study is that we avoided selection on optic disk characteristics, and therefore our results can be generalized to daily practice. Former studies on applicability of semi-automated measurement systems chose cases and controls [15, 16] based on contrasting health status of the optic disk. This may have overestimated diagnostic accuracy and correlation between both methods. The present study is the first that reports sensitivity and specificity of Imagenet measurements of VCDR for the diagnosis POAG in a general population.

At present there is no gold standard for assessment of the VCDR. Most methods differ in the way they define or detect the cup and optic disk border. No method has the ideal sensitivity and specificity for detecting POAG. To define POAG in this study only ophthalmoscopic VCDR data were used, no semi-automated measurements. First reason for this was that ophthalmoscopic VCDR estimates are the usual estimates used in clinical practice at this moment and in the past, and we wanted to compare the newer semi-automated measurements with the 'old' method as reference. Secondly, we wanted to examine to which amount the semi-automated measurements were able to separate POAG cases from non-POAG cases. By choosing the ophthalmoscopic estimates for use in POAG diagnosis the possibility exists that some POAG cases were missed because of inaccurate ophthalmoscopic VCDR estimates. This can also have its effect on the sensitivity and specificity values of the new method which is being tested. Furthermore, clinical measurements, often performed by several examiners, can introduce extra variation in these measurements and result in noise, decreasing the strength of the association between the two measurement methods.

The sensitivity and specificity figures were not very high, suggesting that Imagenet measurements of the VCDR are not as good as ophthalmoscopic evaluation of the optic disk in identifying POAG. A possible explanation could be that with ophthalmoscopy the observer, when estimating the VCDR, also takes other characteristics of the optic disk into account, such as eccentric location of the cup, irregular cupping and notching. In this way a better discrimination between glaucomatous and not-glaucomatous optic disks may be achieved.

The intertechnician agreement of Imagenet measurements in our study was higher than previously reported values of interobserver agreement on ophthalmoscopy. This is of benefit in epidemiological follow-up studies with different observers, apart from the advantage that pictures can be kept while ophthalmoscopy never can be checked again after some time. In addition, semi-automated devices have been proven to detect longitudinal optic disk changes more sensitively than clinical assessment of stereoscopic photographs.[17]

However, cooperation of the subjects, and media opacities can be a more distorting factor for the semi-automated measurement than for ophthalmoscopic assessment by an experienced observer. In the absence of available comparison data on the performance of ophthalmoscopic and semi-automated measurements in follow-up studies, there is no scientifically based preference possible. To date, it seems that ophthalmoscopic assessment has a higher diagnostic value in cross-sectional research, while semi-automated measurements may prove to be superior in longitudinal studies.

In conclusion, we found that Imagenet measurement of the VCDR shows moderate correlation with ophthalmoscopic VCDR assessment. The methods use different criteria for defining the cup and maybe also the disk. Most importantly, inter-observer variability of semi-automated measurements is smaller, and the measurements are better standardized compared to the ophthalmoscopic assessments, which is essential in follow-up studies.

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CHAPTER 6

CENTRAL CORNEAL THICKNESS

DISTRIBUTION AND ASSOCIATION WITH INTRAOCULAR PRESSURE

ABSTRACT

Purpose: To perform a cross-sectional study on the distribution of central corneal thickness in an elderly population, and its association with intraocular pressure (IOP).

Methods: In 395 subjects (352 control subjects, 13 subjects with ocular hypertension and 30 cases with primary open-angle glaucoma (POAG)) of 55 years and over from the population-based Rotterdam Study, central corneal thickness was measured with ultrasonic pachymetry (Allergan Humphrey 850) and the IOP with the Goldmann applanation tonometer.

Results: Mean central corneal thickness in the 352 control subjects was 537.4 μm (95% Confidence Interval (CI) 533.8, 540.9; range 427-620 μm). It was similar between right and left eyes, with a maximal difference of 42 μm. There were no gender differences and there was no significant association with age. Linear regression analysis of central corneal thickness against IOP showed an increase of 0.19 mmHg in IOP with each 10 μm increase in central corneal thickness (95% CI 0.09, 0.28). This association was similar in both eyes and in both sexes. The 13 subjects with ocular hypertension had a 16.0 μm (95% CI -2.6, +34.6) thicker cornea than controls (P=0.093), whereas the 30 cases with POAG had a 21.5 μm (95% CI 8.8, 34.1) thinner cornea compared to controls (P=0.001).

Conclusion: Mean central corneal thickness was similar to that found in clinical studies and was slightly higher in subjects with ocular hypertension and significantly lower in POAG cases. The IOP was positively related with central corneal thickness. Central corneal thickness may influence the division between normal and elevated IOP when using a simple cut-off point of 21 mmHg.

The intraocular pressure (IOP) is used for diagnosis and management of many eye diseases, including several types of glaucoma. Goldmann applanation tonometry is the gold standard, but provides only an estimate of the real IOP. The accuracy of this estimate is dependent on many factors.[1] To a large extent errors can be avoided by a correct measurement technique.[2] However, errors caused by other factors, notably central corneal thickness which influences the rigidity of the cornea, cannot be avoided. On the other hand on statistical grounds a cut-off value of 21 mmHg is widely used to differentiate between normal and abnormal IOP. When calibrating his tonometer, Goldmann assumed central corneal thickness to be 0.5 mm and he stressed that variation in thickness could theoretically affect the measurement.[3] Information on differences in corneal thickness from in vivo measurements has subsequently become available.[4-7]

Central corneal thickness can be measured with an optical method and with ultrasound, the latter being more reliable.[8] Ultrasonic pachymetry has been proven to be very accurate and reproducible with a lower inter- and intraobserver variability than optical pachymetry.[8-10] Most studies on central corneal thickness have been performed in clinic-based populations. We set out to study in a cross-sectional way the distribution of central corneal thickness in an elderly population-based cohort and the association between central corneal thickness and IOP.

Subjects and Methods

This study was performed as part of the Rotterdam Study, a population based cohort study of 7983 residents, aged 55 years and over, of a suburb of Rotterdam, The Netherlands. The Rotterdam Study aims at investigating determinants of chronic disabling ophthalmologic, cardiovascular, neurogeriatric, and locomotor diseases.[11] The study has been approved by the Medical Ethics Committee of the Erasmus University and a written informed consent was obtained from all participants. The baseline measurements were performed between 1990 and 1993. This baseline phase consisted of an extensive home interview, registration of used medication and a medical

examination, including a complete ophthalmological examination, as described in detail before.[12] Overall response was 77.7%.

The first follow-up part of the Rotterdam Study, including a medical and ophthalmological examination, was performed in 1993 and 1994. During two months in this follow-up study, central corneal thickness was measured with ultrasound pachymetry (Allergan Humphrey 850) in all subsequent, at random (using postal codes) invited, participants (n=408) visiting the examination center for routine follow-up. Only persons with normal corneae on slit-lamp examination and no eye surgery within the last year were included in this study (n=365, 89.5%). Of these 365 participants, 352 subjects had no ocular abnormalities (we call them here control subjects); 13 subjects were diagnosed as ocular hypertension cases, of whom eight were treated to lower the IOP. In addition to the at random participating subjects, as many cases with POAG from the first phase of the Rotterdam Study as possible were reinvited to take part in the present study. In total 30 cases with POAG participated, all under treatment for their glaucoma at the moment of this study. In a pilot study we found no influence on IOP of the ultrasound measurements. Thus prior to the IOP measurements five consecutive measurements of the central corneal thickness were taken on both eyes, and the mean of the middle three (in terms of numerical value) measurement values was used in the analyses. For the POAG cases the examiner was masked with regard to the category in which the participants belonged.

Ocular hypertension was defined as an IOP greater than 21 mmHg, or use of IOP lowering medication, with a cup/disc ratio of less than 0.5 and no glaucomatous visual field defect in the baseline phase of the Rotterdam Study.

The diagnosis POAG was based on the presence of a glaucomatous visual field defect on kinetic Goldmann perimetry in the same baseline phase, combined with either a vertical cup/disc ratio of 0.5 or greater, or a difference in cup/disc ratio of 0.2 or more between both eyes, or an IOP greater than 21 mmHg, or use of IOP lowering medication, with open and normal anterior chamber angles, without any other abnormality that could explain the visual field defect.[12]

Only one eye per person was used in the analyses. In subjects without POAG and in bilaterally affected subjects with POAG, a random choice was made between the right and left eye. In monocular POAG, the affected eye was used in the analysis. Mean central corneal thickness was calculated for the entire group and also for right and left eyes separately in men and women. Student's t-test and linear regression was used for comparing means between groups. The effect of central corneal thickness on IOP was evaluated with linear regression analysis. All analyses were performed with the BMDP statistical package.[13]

Table 1. ***Characteristics of the study population***

	Control subjects	Subjects with ocular hypertension	POAG cases
N	352	13	30
Age (years)	72.0 [1.21]	65.1 [2.34]	64.7 [0.35]
Age range (years)	55.1 - 90.2	64.7 - 72.1	69.7 - 88.5
Women (%)	43.4	37.5	51.1
Body mass index (kg/m^2)	25.7 [0.60]	27.1 [1.13]	26.1 [0.17]
Systolic blood pressure (mmHg)	137.2 [4.10]	158.9 [7.64]	139.2 [1.16]
Diastolic blood pressure (mmHg)	72.2 [2.12]	79.9 [3.96]	73.8 [0.60]
Left eyes (%)	63.8	36.9	51.1

All figures (when appropriate) are adjusted for age and/or gender.
Numbers between square brackets are standard errors of the mean.

* See methods for description of groups.

RESULTS

In Table 1, the general characteristics of the 395 subjects are given. The controls had a significantly higher age than the other groups. Other characteristics were comparable. The mean central corneal thickness in the control subjects was 537.4 µm (95% CI 533.9, 540.9; it ranged from 427 till

620 µm). In Figure 1 the distribution of the central corneal thickness in the 365 random selected subjects (controls and ocular hypertension cases) is shown.

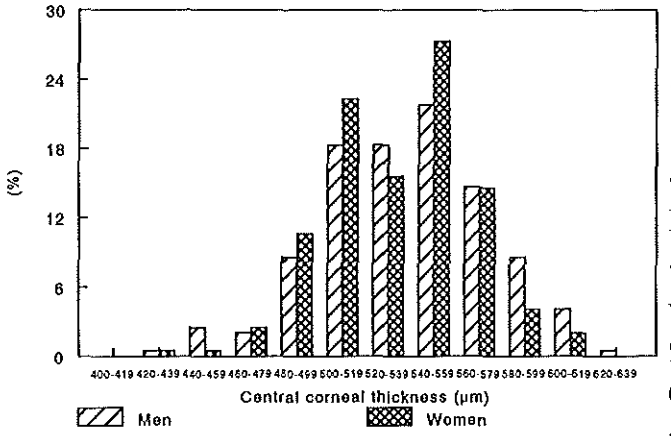

Figure 1. *Distribution of central corneal thickness in the 365 random selected subjects (controls and ocular hypertension cases).*

There was no significant difference in corneal thickness between right and left eyes (mean difference 4.22 µm; 95% CI -2.68, 11.3; P=0.23; maximum difference 42 µm) nor between men and women (difference 4.39 µm; 95% CI -2.52, 11.3; P=0.21). Central corneal thickness did not change significantly with age (0.061 µm/year; 95% CI -0.46, 0.58; P=0.82), similarly for right and left eyes, and for men and women. All corneal thickness measurements were performed during daytime (8.30 - 16.00 hour), and there was no association between central corneal thickness and time of examination.

The mean central corneal thickness in the subgroups, and the differences in corneal thickness with the controls, are given in Table 2. In the ocular hypertension group we saw a slightly, although not significantly, higher central corneal thickness than in the controls (+16.0 µm, 95% CI -2.6, +34.6; P=0.093). In the POAG group the mean central corneal thickness was significantly lower than in the controls (-21.5 µm, 95% CI -34.1, -8.8; P=0.001). Past surgical or different medical treatments in the POAG group had no effect on the central corneal thickness.

The association between IOP and central corneal thickness was examined only in the subjects without IOP lowering treatment. The IOP rose with increasing central corneal thickness (0.19 mmHg/10 µm; 95% CI 0.09, 0.28; P=0.0001; Figure 2). This regression coefficient did not change after adjustment for age and gender. Conversely, the corneal thickness increased with 2.23 µm/1.0 mmHg increase in IOP (95% CI 1.13, 3.34; P=0.0001).

Table 2. ***Central corneal thickness and intraocular pressure of one eye per subject in the different subgroups***

	N	Mean CCT* (μm)	SE†	95% CI‡	Difference with controls (μm)	*p* value	Mean IOP§ (mmHg)	SE†	95% CI‡	Difference with controls (mmHg)	*p* value
Control subjects	352	537.4	1.80	533.8, 540.9	-	-	14.6	0.16	14.3, 15.0	-	-
Ocular hypertension cases	13	553.4	8.50	534.8, 571.9	+16.0	0.093	18.7	1.26	16.0, 21.4	+4.05	0.000
* Without IOP§ lowering treatment	5	562.3	9.08	537.1, 587.5	+25.0	0.100	23.6	0.51	22.2, 25.0	+8.96	0.000
* With IOP§ lowering treatment	8	547.8	12.6	517.8, 577.7	+10.4	0.390	15.6	0.91	13.5, 17.8	+0.98	0.347
POAG	30	515.9	6.70	502.2, 529.6	-21.5	0.001	14.3	0.75	12.8, 15.8	-0.35	0.549
All subjects	395	536.3	1.73	532.9, 539.7			14.8	0.16	14.4, 15.1		

All subjects with POAG were monitored and under treatment at the time of this study.

*CCT = Central corneal thickness
†SE = Standard error of the mean
‡95% CI = 95 percent confidence interval
§IOP = Intraocular pressure.

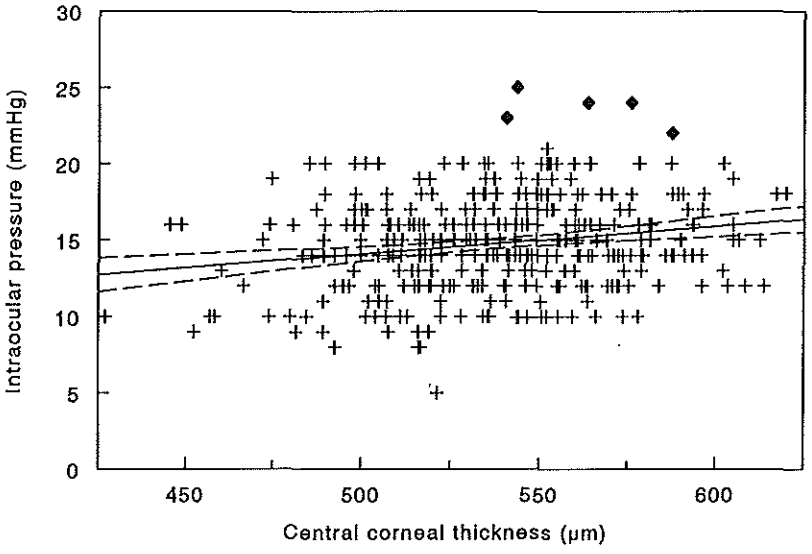

Figure 2. *Association between central corneal thickness and intraocular pressure, in 352 control subjects and 5 subjects with ocular hypertension, all without IOP-lowering treatment. The black solid line represents the linear regression line, the dashed lines represent the borders of the 95% confidence interval.* ◆ *= subject with ocular hypertension.*

DISCUSSION

The main findings in our population-based study are that the mean central corneal thickness in normal eyes with 537.4 µm is similar as in clinic-based studies and that it is positively associated with IOP. In clinical studies the mean central corneal thickness varied from about 520 µm, using optical pachymetry [4,6,7,18] to 540 µm with ultrasound.[9,19] Subjects with ocular hypertension had in this study a slightly higher corneal thickness than controls; on the other hand, POAG cases had a significantly lower central corneal thickness than the controls. Age had only a small and non-significant inverse relation to corneal thickness, in agreement with other studies [6,7,19] and similarly there were no sex differences.[6,7]

Central corneal thickness was similar in right and left eyes. Previous studies with optical pachymetry [6,20] did show a systematic right-left difference. This may be due to a measurement error in the optical method when the measurement is not perpendicular to the cornea. Such a measurement error does not occur with the ultrasound pachymeter used here, as this gives only a reading when the probe is perpendicular to the cornea. Indeed, other studies using ultrasound pachymetry could also not find a right-left difference.[9,10]

In the ocular hypertension group central corneal thickness was slightly higher than in controls, which has also been found by others.[15-17] In the POAG group, however, the central corneal thickness was significantly lower than in the controls, in contrast to the findings in other studies, possibly because of a too low power or the use of the less accurate optical pachymetry in those studies.[7,14,16,17]

As expected from the literature [6,21] we found that central corneal thickness and IOP were positively related. On the other hand a negative relation between central corneal thickness and IOP was found in a study on 45 subjects with unilateral retinal detachment.[5] However, eyes with a retinal detachment often show flare in the anterior chamber and vitreous pointing to a breakdown of the blood retina barrier and to release of inflammatory mediators. These may have influenced the corneal thickness in that study[5], as also was confirmed in another one.[22]

It is still not clear whether the relation between IOP and corneal thickness is artifactual rather than real. It may be caused by a measurement error in applanation tonometry due to differences in corneal thickness, as already suggested by Goldmann himself.[3] Another possible explanation is a physiological effect of IOP on the cornea, resulting, for example, in an increase of collagen fibers or rigidity in the cornea or a combination of both. Based on our data, we cannot prove or reject any of the possibilities. To examine this, invasive measurement of the IOP is necessary.[21]

The diagnosis ocular hypertension, and high-tension and low-tension POAG is usually made on an arbitrary IOP cut-off point of 21 mmHg, based on statistical grounds and convention rather than on causative factors. Our findings

on central corneal thickness, showing a definite relation with IOP values, may have an impact on values around the "magic" 21 mmHg. Many patients with an elevated IOP, but without other glaucomatous features, might merely have a thicker cornea but not a higher risk for glaucoma.

In conclusion, the mean central corneal thickness in normal eyes of this elderly population was 537.4 μm and it showed a maximal difference between eyes of 193 μm. Within a person the maximum difference between the right and left eye was 42 μm. Mean central corneal thickness was slightly higher in subjects with ocular hypertension and significantly lower in POAG cases. The IOP as measured by applanation tonometry is positively related to central corneal thickness. From these experiments it cannot be concluded if this is only due to measurement errors or also to a direct effect of the IOP on the corneal thickness. Due to the variation in central corneal thickness in the population the measured IOP can be an underestimation or an overestimation of the real hydrostatic IOP, and thus can be a confounder in the subdivision between normal and elevated IOP, and therefore also between normal-pressure and hypertensive POAG, when using an absolute cut-off point of 21 mmHg.

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CHAPTER 7

RISK OF ACUTE ANGLE-CLOSURE GLAUCOMA AFTER DIAGNOSTIC MYDRIASIS

ABSTRACT

Purpose. To report the incidence of acute angle-closure glaucoma (AACG) after diagnostic mydriasis in non-selected subjects aged 55 years and over.

Methods. Of all subjects in the population-based Rotterdam Study (n=7,983), 6,760 participated in the ophthalmological examination and received tropicamide 0.5% and phenylephrine 5% eyedrops for diagnostic mydriasis. No selection was made such as on intraocular pressure, presence of narrow anterior chamber angles or history of glaucoma. After the ophthalmological examination all participants received thymoxamine 0.5% drops in both eyes and were warned for the symptoms of AACG.

Results. In two subjects an attack of AACG developed in one eye. Both cases were initially treated with thymoxamine 0.5% eyedrops and oral acetazolamide 0.500. Subsequently peripheral iridotomies were performed with a Nd-YAG-laser, and both eyes healed without other sequelae.

Conclusion. In non-selected (Caucasian) subjects of 55 years of age or older the incidence of AACG after this type of diagnostic mydriasis is 0.03%.

Diagnostic mydriatics are very widely used in ophthalmological clinical practice. In most cases they are essential for an adequate examination of the ocular media and fundus, especially by non-ophthalmologists.[1] However, the use of mydriatic agents can provoke an attack of acute angle-closure glaucoma (AACG), with rise of the intra-ocular pressure (IOP) up to 80 mmHg within a few hours, and with a risk of permanent damage to the optic nerve.[2,3] Only early recognition of the, in most cases substantially, elevated IOP and subsequent reduction of the pressure, can save the visual capacity of the eye involved.

The risk of inducing an AACG attack might be a reason why many general practitioners, internists and other non-ophthalmologic physicians are reluctant to dilate pupils for ocular examination. Also when an (ophthalmic) epidemiological study is started, the question will rise, whether it is safe to use mydriatics in all participants. Participants in an ophthalmic epidemiological study may be selected based on an inclusion criterion that requires an inspection of the anterior chamber angle (e.g. using the van Herick method[6]). On the other hand this may create bias. From the literature no data could be obtained on the risk of AACG when, with or without prior examination, all subjects in a population-based study received mydriatic drops. Thus, in The Rotterdam Study all participants were scheduled to receive mydriatic eyedrops for fundus examination and photography. The purpose of this paper is to report the incidence of AACG after diagnostic mydriasis in non-selected subjects in a population aged 55 years and over.

Methods

The Rotterdam Study is a large population-based follow-up study in which 7,983 subjects participated. Of these 97% were of Caucasian origin. This study aims at investigating chronic disabling ophthalmologic, cardiovascular, neurogeriatric, and locomotor diseases in subjects aged 55 years and over.[4] The ophthalmological part focussed on primary open-angle glaucoma and age-related macular degeneration. The study has been approved by the Medical Ethics Committee of the Erasmus University and a written informed consent was obtained from all participants. The baseline phase (1990-1993) consisted of

an extensive home interview, followed by a medical and complete ophthalmological examination in the research center.[5] The ophthalmological examination included an estimation of the width of the anterior chamber angle, by comparing the thickness of the cornea with the distance between cornea and iris (method of van Herick [6]) The anterior chamber angles were roughly divided in normal open angles (grade 4 or 3) or narrow angles (grade 2 or 1). In order not to create unacceptable bias all participants received tropicamide 0.5% and phenylephrine 5% mydriatic eye drops, regardless of the presence of a shallow anterior chamber angle or a history of angle-closure or primary open angle glaucoma. After the examination, all received as a miotic one drop of thymoxamine 0.5% in each eye. Every participant was warned to notify the investigator immediately, when blurred vision, pain or redness around the eye was noted. In those cases, the intraocular pressure was re-measured (in mydriasis) at the end of the ophthalmological examination. In case these symptoms started later on at home the participants were told to warn the investigator or their general practitioner.

Table 1. ***Participants and refusal of mydriatics in the ophthalmological part of the Rotterdam Study.***

Age-category (years)	Men	% refusal of mydriatics	Women	% refusal of mydriatics	Total	% refusal of mydriatics
55-64	1,098	1.1 (n=12)	1,463	0.5 (n=8)	2,561	0.8 (n=20)
65-74	1,051	1.3 (n=14)	1,349	1.0 (n=13)	2,400	1.1 (n=27)
75-84	503	1.2 (n=6)	887	1.6 (n=14)	1,390	1.4 (n=20)
85+	89	3.4 (n=3)	320	3.4 (n=11)	409	3.4 (n=14)
Total	2,741	1.3 (n=35)	4,019	1.1 (n=46)	6,760	1.2 (n=81)

Prevalence figures were calculated in the whole group of participants (prevalence of AACG) and in subgroups of gender and age (prevalence figures of narrow chamber angle). Linear regression analysis was used for calculating the effect of age and refraction on the prevalence of narrow chamber angles.

Logistic regression analysis was used to estimate the risk of having narrow chamber angles in women versus men, with the odds ratio serving as an approximation of relative risk. All analyses were adjusted for age and gender when appropriate. All analyses were performed with the BMDP statistical package. [13]

RESULTS

Of the 7,983 participants in the baseline phase, 6,760 (84.7%) subjects underwent an ophthalmological examination, and 6,679 (98.8%) of these received mydriatic drops for ophthalmoscopy and fundus photographs (Table 1). A small part (1.2%) of the participants refused the mydriatics. This refusal was only significantly dependent on age and not on gender or presence of narrow chamber angles or to eye-complaints in the past (Table 2). Subjects with a history of ophthalmological examinations did not refuse more frequently.

Table 2. ***Relative risks for refusal of mydriatics.***

		Odds Ratio*	95% Confidence interval
Age†	65-74	2.14	1.04, 4.44
	75-84	3.27	1.56, 6.91
	85+	8.02	3.53, 18.2
Gender‡		0.82	0.49, 1.35
Narrow angle§		1.22	0.29, 5.11
Visit to ophthalmologist¶		0.96	0.59, 1.58

* Odds ratio from multiple logistic regression with age, gender, presence of narrow chamber angle, and eye-complaints in past in the model.
† Reference: age-category 55-64 years
‡ Gender: females versus males
§ Presence versus absence of narrow chamber angle (method of van Herick)
¶ Visits versus no visits to ophthalmologist for examination (other than for prescription of glasses) in the past.

The overall-prevalence of narrow anterior chamber angles was 2.2 %. The prevalence rates in the different age and gender categories are given in Table 3. With increasing age the chance on having a narrow angle increased with 3.0 percent/year (Odds ratio 1.03; 95% CI 1.01, 1.04; p=0.0043); after adjustment for refraction this effect of age disappeared (Odds ratio 1.01; 95% CI 0.99, 1.03;

p=0.32). Women had a two times higher chance of having a narrow anterior chamber angle than men (Odds ratio 2.0, 95% CI 1.4, 3.0; adjusted for age and refraction).

Table 3. ***Prevalence of narrow anterior chamber angles.***

Age-category (years)	Men %	Women %	Total %
55-64	1.2 (0.33)	2.4 (0.40)	1.9 (0.27)
65-74	1.4 (0.37)	2.4 (0.42)	2.0 (0.29)
75-84	1.4 (0.52)	2.8 (0.55)	2.3 (0.40)
85+	1.1 (1.11)	5.7 (1.31)	4.7 (1.05)
Total	1.3 (0.22)	2.8 (0.26)	2.2 (0.18)

Figures between parentheses are standard errors of the mean.

Of the 6,679 subjects who received mydriatic eye-drops, two participants (0.03%; 95% CI 0.01-0.04; Table 4) developed an AACG attack after mydriasis. They both were initially treated medically (thymoxamine 0.5% and acetazolamide 0.500), and subsequently were referred to the Department of Ophthalmology of the University Hospital Rotterdam. In both cases peripheral iridotomies were performed with a Nd-YAG-laser, and both cases had no sequelae of the AACG attack.

Discussion

The results of this study show that only about 1 in 3000 unselected persons aged 55 years and over will develop AACG after the use of tropicamide 0.5% and phenylephrine 5% eyedrops. The number of cases which developed AACG in our study is too low to perform (reliable) statistical analyses on risk factors for AACG.

Table 4. ***Characteristics of respondents with acute angle-closure glaucoma after instilling diagnostic mydriatics***

		right eye	left eye
Case 1:	Female, 64 years of age		
	Visual acuity	1.00	1.00
	Refraction*	+4.87	+5.13
	Slitlamp examination	both eyes narrow chamber angle (van Herick grade 1-2), no cataract	
	Applanation tonometry	25 mmHg	24 mmHg
	Pressure rise till	69 mmHg	35 mmHg
		after 1 hour. Normalized after 2 hours with medical treatment, after which in both eyes peripheral iridotomies were performed with a Nd-YAG-laser.	
Case 2:	Male, 63 years of age		
	Visual acuity	1.00	1.00
	Refraction*	+3.87	+3.75
	Slitlamp examination	both eyes normal chamber angle (van Herick grade 3-4), cortical cataract	
	Applanation tonometry	19 mmHg	21 mmHg
	Pressure rise till	unknown	66 mmHg
		after 2-3 hours. With medical treatment pressure was lowered to 16 mmHg OD and 18 mmHg OS. In both eyes peripheral iridotomies were performed with a Nd-YAG-laser.	

* Spherical equivalent (spherical value plus half cylinder value)

Narrow anterior chamber angles were present in 2.2% of the subjects, when estimated with the method of van Herick. In the literature no data could be found on the distribution of narrow chamber angles in the general population. The higher risk of women of having a narrow chamber angle was in agreement of a study using gonioscopy. [8] The effect of age on the presence of narrow anterior chamber angles as described in the literature [8] was in agreement with our findings. However, after adjustment for refraction this effect disappeared. A possible explanation for this is the swelling of the lens with increasing age.

Both tropicamide and phenylephrine are seen as relatively safe mydriatics. [9, 10] Phenylephrine affects IOP and the anterior chamber depth only little and is rapidly reversed in action by thymoxamine.[9, 10] Also tropicamide does not cause a significant rise in IOP and the effects of tropicamide can be quickly counteracted by acetazolamide.[10]

Recently the absence of AACG after mydriatic drops in a population based survey on 4,870 subjects has been reported.[9] However, all subjects were previously selected on the absence of a shallow anterior chamber. Exclusion of subjects from a study, based on the size of the anterior chamber angle of the eye, determined by gonioscopy or with van Herick's method [6], can introduce unwanted bias. It is known that eyes with open anterior chamber angles on gonioscopy still can develop an AACG after mydriasis.[11] Even an elevation of the IOP after mydriasis is compatible with normal open anterior-chamber angle and also a gonioscopically closed anterior angle chamber is compatible with no rise in IOP after mydriasis. [10] Therefore, gonioscopy seems of limited value to predict which eyes will develop angle-closure glaucoma in response to pupillary dilatation.

In mydriasis the sensitivity of funduscopy in the detection of diabetic retinopathy is considerably improved.[1] The same holds for macular and peripheral retinal disorders. The advantage of a more sensitive fundus examination in mydriasis outbalances in our view the risk of luxating AACG. Moreover, in 8% of the cases at risk [2], AACG would have occurred within 2 years, usually late in the evening without prior knowledge and without medical supervision. This may lead to a higher chance of permanent loss of visual

capacity in the affected eye. Therefore, we consider mydriasis with the mentioned mydriatics to be a relatively safe procedure, provided that everybody has been thoroughly informed about related complaints and that a physician is available for re-examination of the subjects. Good contact with eye care facilities in the neighbourhood is necessary in order to reduce the risk of permanent damage to the eye.

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CHAPTER 8

GENERAL DISCUSSION

In this thesis several cross-sectional studies are described, which were based on a general population of about 7000 subjects aged 55 and older, on a subset of this population, or on their relatives. The aim of the open-angle glaucoma (OAG) research in the Rotterdam Study is to increase our knowledge of its etiology and risk factors. Despite the many studies performed in the past, still very little is known about these two.

This thesis focuses on the prevalences of OAG or its determinants in a general population. I define in this thesis open-angle glaucoma as all forms of idiopathic glaucoma from which especially congenital, (acute) angle-closure, pupillary-block, and secondary glaucomas found on examination or by history taking, have been excluded. Among others, these secondary glaucomas include traumatic glaucomas, post-inflammatory and neovascular glaucoma. The idiopathic form of glaucoma is often called primary open-angle glaucoma (POAG) or simple chronic glaucoma. Because we felt that during baseline pseudoexfoliation glaucoma - a secondary form of glaucoma with open anterior chamber angles - has not sufficiently been excluded, we write in some articles about OAG instead of POAG. The familial or hereditary aspects of OAG were studied by examining first-degree relatives of OAG cases from the Rotterdam Study and comparing them with first-degree relatives of age and gender matched controls from the same study population. Relative and absolute life-time risks were calculated to quantify the risks.

This is the first large population-based study that used semi-automated measurements of the optic nerve head to diagnose glaucoma. Semi-automated measurements give more objective results of optic disc characteristics. These semi-automated measurements were compared with the funduscopic estimates.

Prevalence of OAG

Several large population-based studies on POAG have been performed in recent years in different parts of the world. Most showed prevalence figures of about 1% (Framingham Study [1] 1.2%, The Baltimore Eye Survey [2] 1.1%, Barbados Eye Study [3] 0.8% in white subjects). These findings are comparable with the 0.9% found in the Rotterdam Study. Only the Beaver Dam Eye Study and the

Blue Mountains Eye Study found a higher overall prevalence (2.1% [4] and 3.0% [5] respectively). However, despite the similar prevalence figures reported by the different studies, almost all studies used different criteria for diagnosing OAG and different algorithms for examination and classification of the subjects. This raises the question, whether all those study results are actually comparable. It could well be that, when the criteria and algorithms of one study (e.g. the Baltimore Eye Survey) were applied on another population (e.g. in the Netherlands or in Australia), very different prevalence figures would be found, giving evidence for regional differences in the prevalence of OAG. In order to test this, I applied the criteria of other population-based studies on our study-population. This showed 12-fold differences in prevalence, when comparing the resulting prevalence figures. The real differences will probably be smaller, because only the criteria were used and not also the examination algorithms, which would be unfeasible. It might mean that regional differences in OAG prevalence do exist. To study these, and to really compare studies, criteria for diagnosing OAG and examination algorithms should be standardized, to reduce the amount of noise when pooling data of studies on glaucoma. We recently resumed trying to formulate criteria for OAG in epidemiologic studies (International Working Group on Defining Glaucoma in Eye Examination Surveys - personal communication). Standardizing diagnostic methods and definitions could be of much benefit for future epidemiologic glaucoma research and might result in actual progress in the understanding of the glaucoma etiology. As time of the respondents and of the examiners often is the limiting factor in these studies, I would propose in future studies as minimum examination algorithm:

- Optic disc characteristics measurements (e.g. vertical cup/disc ratio, neuroretinal rim, disc and rim area) should be either captured on (stereo) transparencies or recorded digitally, so that they may be examined at a later time with (semi) automated image analysis systems. These systems have to be compared to each other, and need to have a good correlation for the used parameters. Automated analysis improves objectivity of the measurements, especially in follow-up studies. One system for automated optic disc

analysis would be preferable, but due to technological innovations new systems and techniques will be developed in the future. Therefore, criteria for optic disc characteristics should be reviewed regularly and when needed adapted.

- Visual field testing has to be performed in all subjects who are physically and mentally able to perform a reliable visual field test, and not in a (selected) subset. The gold standard for visual field testing at this moment is the Humphrey full-threshold static perimetry of the central 24 or 30 degrees of the visual field. However, one single field test that shows a defect, although reliable performed, is not enough to conclude that there really is a visual field defect. The Humphrey test is known about its learning effects. [6] This means that in case of abnormalities or unreliable tests at least two visual field tests should be performed, before one can conclude that there is a visual field defect. A disadvantage of this system is the relatively large amount of time needed to perform the tests, also resulting in fatigue especially in older subjects, often resulting in less reliable and false-positive tests. [7] New full-threshold testing algorithms (SITA, frequency doubling perimetry) are being developed and tested at this moment, all trying to reduce testing time and improving accuracy of the test. [8-11] It is too early to select one for the epidemiologic screening algorithm. Perhaps a suprathreshold screening test is at this moment the most realistic, feasible, and accepted visual field screening test in a (large) population-based epidemiologic study, eventually followed by a repetition of the same test when the first test was abnormal or unreliable to eliminate or minimize learning effects. All abnormal screening tests should be confirmed with full threshold perimetry for definite diagnosis of visual field defects. Kinetic Goldmann perimetry in the hands of an experienced perimetrist is a good, although less sensitive [12], alternative for subjects in which automated testing cannot be performed reliably, especially in the elderly.
- Ophthalmoscopy has to be performed in mydriasis in all subjects, regardless of the presence or history of glaucoma or status of anterior chamber angle.

This is necessary to detect other causes of visual field defects or other forms of glaucoma than POAG.

- The anterior chamber angle has to be assessed with gonioscopy in all subjects with visual field defects and in subjects with evident glaucomatous damage to the optic nerve head.

As definition of definite OAG, I would propose the presence a visual field defect not due to retinal or neuro-ophthalmic causes, in combination with a VCDR ≥ 0.7, or a minimal neuroretinal rim width of less than 0.10, or an asymmetry in VCDR ≥ 0.3 between both eyes, with open anterior chamber angles. Optic disc characteristics should ideally be assessed using (semi) automated measurements. When a visual field can not reliably be performed, a VCDR ≥ 0.9 could be regarded as enough evidence for presence of definite glaucoma. These cut-off points for optic disc characteristics are based on statistical 97.5th percentiles of their distribution.

Probable OAG could be defined as the presence of a visual field defect not due to retinal or neuro-ophthalmic causes, but without optic disc abnormalities suspect for OAG. Because of the large variation in optic disc characteristics, one could argue whether optic disc abnormalities suspect for OAG, but without visual field defect also should be classified as probable OAG.

Visual field defects

Techniques to examine the visual field of a patient underwent a rapid change over the last decade with the introduction of computerized automated perimetry. Although the technique has improved, not much is known about the prevalence of visual field abnormalities in the general population. Only few studies on the prevalence of field defects and their causes were performed in the past. In the Rotterdam Study perimetry was performed in all participants to screen for OAG. We demonstrated a sharp rise in prevalence of field defects from 3% in the 55-64 year old subjects to 19% above 85 years of age. The large amount of available data on the health status of all participants in the Rotterdam Study also made it possible to study the causes of field defects. Furthermore, because of

the large size of our study we had the opportunity to also detect more rare causes of visual field defects. Unfortunately no other studies are available for comparison of our data. Glaucoma and age-related macular degeneration were the main causes of visual field loss in the studied age categories. The importance of an intact visual field is shown by the association of visual field defects with the increased risk of falling and hip fractures. Not only visual acuity, but also visual field loss was related with a higher risk. In OAG the visual field can be considerably damaged before a patient notices any complaints. The early detection and treatment of OAG therefore also is important for elderly subjects to maintain their independence in the society.

Familial/genetic risk

Since many years a genetic influence on OAG has been known, given various published pedigrees [13-23], and only recently specific genes/gene locations were identified. [24-29] However, actual risk estimates never were calculated to quantify that risk in a general population. Studies in selected families showed impressive pedigrees, with different types of inheritance of glaucoma (or related disorders). Most studies suggested that genetic factors played an important role in the etiology of OAG, at least in the examined subgroup. However, very few studies used (matched) control groups for comparison. Also, often only family history data were used, and not actual examination data, giving rise to recall bias.

We designed a study using both OAG cases and controls from the same population to study the familial risks. Subjects from both groups were ascertained using the same examination methods, minimizing selection bias. We actually examined all first-degree relatives of OAG cases and controls, and studied all determinants of OAG separately. In order to deal with the age-dependent expression of the disease we used a special statistical analysis technique, survival analysis, to compare both groups of relatives. [30, 31]

This study showed that the prevalence of the separate glaucoma features (IOP, vertical cup/disc ratio (VCDR) and visual field defects) were all more prevalent in the relatives of OAG cases. The lifetime risk of OAG for relatives of OAG cases was 22%, almost 10 times higher than in relatives of controls.

The enlargement of the cup-disc ratio was the first sign of increased familial risk. In contrast, the population attributable risk, which is the proportion of OAG cases in the general population attributable to genetic factors, was approximately 16%, which was rather low. This suggests that other, non-genetic, factors determine to a great extent the overall occurrence of OAG. Which factors are of importance has to be further studied. Further research into the genetic background of OAG can lead to new clues in its etiology, and maybe more important, in new and maybe better treatment possibilities.

Optic nerve head measurements

For a long time, drawings of the optic nerve head were the only way of documenting optic disc characteristics. These ophthalmoscopic estimations are characterized by their large inter- and intra-observer variations. [32, 33] Even photography of the optic disc, and subsequent estimation or grading of the VCDR has been shown to be subject to considerable inter-observer variation. [32, 33] Many older population-based studies [34-37] on OAG depended on ophthalmoscopic evaluation of the optic discs, often estimated by several different examiners, or grading of photographs. [2-5] Recently, new techniques and methods became available for objective measurement of optic disc characteristics. Computerized analysis of conventional stereoscopic optic disc photographs has been shown to be accurate and reproducible. [32, 38, 39] Also newer techniques, as laser scanning tomography of the optic disc, have shown promising results. These newer techniques can provide new insights in the pathogenesis of OAG when they are more accurate and reproducible than the ophthalmoscopic estimates. Their advantage, especially for follow-up studies, in which examiners often change, or differences in optic disc characteristics are small, will be clear.

In the Rotterdam Study we performed ophthalmoscopy to estimate the VCDR in all participants. Also simultaneous stereoscopic photographs of the optic discs were made, which were later on analyzed with a semi-automated image analyzer (Imagenet, Topcon, Japan). We compared the ophthalmoscopic estimations with their semi-automated counterparts, and found an only

moderate correlation between both estimates. Different reasons for this are possible. In our study, monocular ophthalmoscopy was performed, while Imagenet measurements are based on stereoscopic transparencies, which often yield larger estimates. [22] Also, because the examiner was aware of other subject characteristics (as visual field status, IOP), a measurement bias can not be excluded. Furthermore, the observer could be biased by the area of pallor and peripapillary atrophy on ophthalmoscopy; this is disregarded by the semi-automated measurements, which only take three-dimensional topographic data into account to calculate the VCDR and other optic disc characteristics.

Our study differs from other large population-based studies, because we used semi-automated optic disk measurements to assess evidence of optic nerve damage (enlargement of VCDR, narrow neuroretinal rim, asymmetry in cupping between both eyes). These measurements were unbiased by knowledge of visual field status or IOP of the subjects. Furthermore, the semi-automated system used strict criteria for defining the cup margins, based only on topographic data, therefore reducing variation due to different observers, and is particularly interesting for follow-up studies. [40] Differences in techniques and criteria for defining the cup margins play an important role in the varying results of different studies. Even interpretation of photographs is subject to interobserver variation. [41]

In our population-based study we found the 97.5th percentiles of semi-automated measurements of the VCDR were 0.70, similar to ophthalmoscopy. This means that both for measurement methods a cut-off point of 0.7 can be used, although for the ophthalmoscopic estimates interobserver variation can play a disturbing role.

Central corneal thickness

Intraocular pressure has for long been an important criterium for the diagnosis OAG. As already pointed out by Goldmann himself, the thickness and rigidity of the central cornea influence the accuracy of the IOP estimate, when measuring the IOP with an applanation tonometer. [42, 43] With this equipment the force necessary to flatten the cornea over a given area is measured in dynes

(marked on tonometer scale), which multiplied by ten equals the intraocular pressure in mmHg. [44] The corneal thickness is related to the rigidity of the cornea, and partly determines the amount of force necessary to flatten this area of the cornea. In the past several studies were performed, which showed different distributions of central corneal thickness (CCT) in various populations. However, mostly optical measurements were used, which are not always very accurate. The newer ultrasound technique gives more accurate measurements of the CCT. Using this technique in a general population, we confirmed that the mean CCT was about 540 µm, and that there were no significant differences between right and left eyes [45, 46], nor between both sexes. [47, 48] There was no relation between CCT and age. We found a slightly higher CCT in ocular hypertension cases, and a significantly lower CCT in OAG cases. A higher CCT in cases with ocular hypertension, subjects with an IOP > 21 mmHg without visual field loss or abnormal optic discs, has been found in more studies. [49-52] One might hypothesize that cases with ocular hypertension, who do not develop OAG over many years, have no elevated IOP, but just abnormal corneal thickness or rigidity leading to false IOP readings. Also the positive relation between IOP and CCT was confirmed by our study. A study in a Mongolian population showed a strikingly similar effect of CCT on IOP. [53] However, due to study design and feasibility, we were not able to study or prove any causal relationships between CCT and IOP. It is plausible, that both a large and small CCT cause a measurement error in applanation tonometry. On the other hand, we can not reject that there is a physiological effect of IOP on the cornea. To study such a causal relation, invasive measurement of the IOP is necessary. [54] For glaucoma diagnosis, this study shows again that the simple cut-off point of 21 mmHg for IOP is not always applicable to everyone.

Acute angle-closure glaucoma

Studies on the incidence of acute angle-closure glaucoma in the past were hampered by a selection of subjects with open anterior chamber angles. [55] This selection often was performed to prevent the risk of inducing angle-closure glaucoma in participants with narrow angles, due to diagnostic mydriasis. Also,

in clinical practice often no mydriatics are given to subjects with narrow anterior chamber angles, because of the fear for resulting high IOP and damage of the visual function of the eye. However, even on gonioscopy open anterior chamber angles ('non-occludable' angles) are capable of causing a rise in IOP in mydriasis. [56, 57] On the other hand, some subjects with gonioscopically closed anterior angle chambers show no rise in IOP in mydriasis. [56] Furthermore, subjects who respond to diagnostic mydriasis with a rise of IOP will probably also get high IOP's when they are at home in the evening or at night (physiologic mydriasis). They might not notice the elevation of IOP until pain arises or wait too long before going to a doctor with their complaints. In the Rotterdam Study, we gave all participants mydriatic eyedrops, regardless of their anterior chamber angle depth or history of glaucoma to prevent selection bias. As a precaution, we warned all participants for possible complaints associated with acute angle closure. In only two of 6679 participants receiving mydriatics acute angle closure glaucoma developed. Both were sent to the outpatient department of the University Hospital Rotterdam, and were treated with Nd-YAG laser iridotomies. Both recovered without visual acuity or visual field loss. In our experience, both tropicamide 0.5% and phenylephrine 5.0% are relatively safe mydriatics; the mydriasis and the pressure rise can respectively be counteracted by thymoxamine and acetazolamide. [55, 56] In our view, the benefits of a more sensitive fundus examination through dilated pupils outbalance the small increase in risk of inducing angle closure glaucoma after diagnostic mydriasis and the selection bias. It provides a way for an accurate retinal examination, and can serve as a selection method for subjects at risk for angle closure glaucoma, which with proper facilities can be treated before permanent damage to the eye occurs.

With our studies we showed that there is an urgent need for standardized criteria for OAG in epidemiologic research. Discussion on these criteria was started a few years ago by us, and hopefully future studies will be more structured according to 'new' criteria and algorithms that have to be developed. Only in this way a reliable pooling of different population-based studies is possible, and more insight in the etiology and risk factors for OAG can be

gained. In the familial aggregation study we quantified the risk for first-degree relatives of OAG cases, and concluded that there is a 'familial' factor. However, whether this factor is a genetic one, or an environmental or a combination of both has to be further studied. The semi-automated measurements of the optic disc are an important tool to get more objective and standardized measurements of optic disc characteristics related to OAG, and also improve comparison and pooling of data of different studies. When future (population-based) studies are using the same algorithms and criteria for OAG, smaller risk factors can be identified, and OAG cases of different studies can be pooled for more extensive research to genetic factors in the OAG etiology. Future research on OAG will probably mostly be on a genetic base, in order to find more clues in its etiology and pathogenesis, thereby also giving more starting-points for better therapeutic possibilities (e.g. neuroprotection).

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CHAPTER 9

SUMMARY

The eye disease "glaucoma" has been known for a long time and the history of its concept is shortly described in chapter 1. In time the definitions and our understanding of the disease underwent a major change. Intraocular pressure, visual fields and optic disc characteristics were recognized as important determinants in the course of the disease. Although new methods for examining the eye became available, still very little is known about its etiology.

The early detection of glaucoma is an important public health concern. Glaucomatous blindness may be prevented if the disease is diagnosed in time and treated adequately. However, once vision has been lost, it cannot be restored at present time by any form of treatment. Because most patients with early glaucoma are asymptomatic, much (peripheral) visual field can be lost before the patient notices visual impairment. This means that routine screening of asymptomatic people is necessary to detect early glaucoma cases.

There are many types of glaucoma. Primary open angle glaucoma (POAG) is the most prevalent type of glaucoma in Western countries. This thesis focuses on (primary) open-angle glaucoma (OAG). We could not sufficiently exclude pseudoexfoliation as a cause of glaucoma and that is why we use OAG instead of POAG in some chapters. All studies were performed based on data from examinations of subjects from the Rotterdam Study, a population-based cohort study of subjects aged 55 years and over.

An important problem in quite a few studies on OAG in the past was the difference in criteria and methods used to diagnose and classify OAG. These differences can result in different findings and make comparisons between studies difficult. Today glaucoma may be defined as a disease causing an optic neuropathy characterized by cupping of the optic disc with an associated visual field defect. In chapter 2 we present the prevalence figures of OAG in the Rotterdam Study. These figures are based on ophthalmic examinations in 6781 subjects aged 55 years or over (6293 independently living subjects and 488 living in nursing homes). The criteria for diagnosis of OAG were based on semi-automated measurements of the optic disc, such as vertical cup-to-disc ratio (VCDR), minimal width of neural rim, or asymmetry in VCDR between both eyes, and visual field testing with kinetic Goldmann perimetry. Intraocular

pressure (IOP) was measured with Goldmann applanation tonometry. All separate criteria for the diagnosis of OAG were assessed independently of each other. Also different criteria for OAG as used in other large population-based studies were applied on the data of the Rotterdam Study. Although the prevalence figures as reported by most population-based studies are more or less comparable, their criteria for OAG when applied on our population resulted in a 12-fold difference in prevalence figures (ranging from 0.1% to 1.2%). That is why we presented as proposal for uniform OAG criteria: a VCDR $\geq$ 0.7, asymmetry in VCDR between both eyes $\geq$ 0.3 or a minimal rim width $<$ 0.10 using (semi-)automated measurements, in combination with a visual field defect not due to retinal or neuro-ophthalmic causes. With these criteria we found an overall prevalence of OAG in the independently living subjects of 0.9% (95% CI 0.6, 1.1; 56 cases). Prevalence of OAG was two times higher in men than in women (Odds ratio 2.3, 95%CI 1.2, 4.5). The risk of OAG increased with 8% per year of age (95% CI 4.0%, 13.0%). Standardization of criteria and diagnostic algorithms will improve the comparability of different studies, to study regional differences, and also gives the opportunity of pooling data from different studies to study (smaller) risk factors.

In chapter 3 we describe our estimates of the prevalence and causes of visual field loss (VFL) and the association with impairment in daily life. Prevalences and causes were measured cross-sectionally in the Rotterdam Study cohort. Indicators of impairment were measured both cross-sectionally and prospectively. Visual fields were tested with a Humphrey suprathreshold test of the central 48 degrees. When a defect was present the test was repeated. Goldmann kinetic perimetry was performed when a defect was present after retesting. Data from the ophthalmological examinations, from the neurological examinations as well as history data from ophthalmologists and general practitioners was used to determine the cause of visual field defect. Interview data on disability in daily life, reading, use of walking aids, falling and fractures was used to assess impairment. The overall prevalence of visual field defects was 5.5%, ranging from 1.9% in the youngest age-category to 17.0% in the oldest age-group. Glaucoma was the leading cause of a visual field defect at all

ages. Optic disc disease (other than glaucoma) and stroke were the second and third most common causes. After 75 years of age, age-related macular degeneration and retinal vascular occlusions were the second and third ranking causes. VFL was, independent from impaired visual acuity, associated with disability and a higher risk of falling and fractures. In 28% of all subjects with VFL, the subjects were unaware of the defect and had never visited an ophthalmologist except for glasses.

About the genetic background of OAG still little is known, although genetic factors were already assumed to be of importance since 1869 by von Graefe. Many pedigrees were published since that time and studies in selected populations showed different hereditary patterns. Often in these studies only family history data was used and family members were not actually examined. In chapter 4 we describe a study in which we evaluated whether glaucoma aggregates in families drawn from of a general population. We thereto selected all probands with OAG and a random selection of controls from the population-based Rotterdam Study. From these subjects all first-degree relatives were examined using a standardized protocol. Among relatives of cases, OAG prevalence was 10.4% among siblings and 1.1% among offspring, while this was 0.7% and 0% among relatives of controls. Lifetime risk of elevated IOP was 42.5% in relatives of cases versus 6.7% in relatives of controls; of enlarged cup-disc ratio 62.2% versus 16.6%; and of OAG 22.0% versus 2.3%, yielding a risk ratio of 9.2 (95% CI 1.2, 73.9). The population attributable risk of OAG was 16.4%. We concluded that in a general population, relatives of OAG cases have a strongly increased risk of OAG. Surprisingly not intraocular pressure but enlarged cup-disc ratio was the earliest and most prominent feature of familial aggregation. Further studies are needed to disentangle the genetic components of the increased familial risk.

Reliable assessment of the vertical cup-to-disk ratio (VCDR) is essential for the diagnosis and monitoring of OAG. Unfortunately, ophthalmoscopic estimation of the VCDR has a low interobserver agreement. The recently introduced semi-automated image analyzers have been shown to be more reproducible and able to detect very small changes over time. At this time,

though proven to be less reproducible, ophthalmoscopy still is the major screening tool for the detection of OAG. In chapter 5 we compared the ophthalmoscopic VCDR estimates with their semi-automated counterparts. In 5143 subjects the mean ophthalmoscopic VCDR was 0.30 (SE 0.0021; range 0.00, 1.00) compared to a semi-automatically measured VCDR of 0.49 (SE 0.0019; range 0.04, 0.86; difference 0.19; $p<0.0001$). The overall correlation between both methods was moderate (correlation coefficient 0.61 (SE 0.11)), and lower in small optic disks. Semi-automated optic disk measurements correctly identified 76% of the OAG cases (as defined using visual field data and ophthalmoscopic data about the optic disk). Semi-automated measurements of the VCDR are larger than the ophthalmoscopic VCDR estimate with a moderate correlation. The inter-observer variability using semi-automated measurements was smaller, compared to the ophthalmoscopic assessments, and semi-automated measurements are better standardized, which is important for epidemiological surveys and follow-up studies. The 97.5th percentiles of the VCDR distributions in our study-population was 0.70, both for semi-automated measurements and for ophthalmoscopic VCDR estimates.

Also IOP is used for diagnosis and management of OAG. Goldmann applanation tonometry is the gold standard, but provides only an estimate of the real IOP. The accuracy of this estimate is dependent on many factors. To a large extent errors can be avoided by a correct measurement technique. However, errors caused by other factors, notably central corneal thickness which influences the rigidity of the cornea, cannot be avoided. Central corneal thickness can be measured with an optical method and with ultrasound, the latter being more reliable. Ultrasonic pachymetry has been proven to be very accurate and reproducible with a lower inter- and intraobserver variability than optical pachymetry. In chapter 6 we present data on the central corneal thickness in a randomly selected subset of subjects from the Rotterdam Study. In 395 subjects (352 control subjects, 13 subjects with ocular hypertension and 30 cases with POAG) of 55 years and over, central corneal thickness was measured with ultrasonic pachymetry (Allergan Humphrey 850) and the IOP with the Goldmann applanation tonometer. Mean central corneal thickness in

the 352 control subjects was 537.4 µm (95% Confidence Interval (CI) 533.8, 540.9; range 427-620 µm). It was similar between right and left eyes, with a maximal difference of 42 µm. There were no gender differences and there was no significant association with age. Linear regression analysis of central corneal thickness against IOP showed an increase of 0.19 mmHg in IOP with each 10 µm increase in central corneal thickness (95% CI 0.09, 0.28). This association was similar in both eyes and in both sexes. The 13 subjects with ocular hypertension had a 16.0 µm (95% CI -2.6, +34.6) thicker cornea than controls (P=0.093), whereas the 30 cases with POAG had a 21.5 µm (95% CI 8.8, 34.1) thinner cornea compared to controls (P=0.001). In conclusion, the IOP as measured by applanation tonometry is positively related to central corneal thickness. From these experiments it cannot be concluded if this is only due to measurement errors or also to a direct effect of the IOP on the corneal thickness. Due to the variation in central corneal thickness in the population the measured IOP can be an underestimation or an overestimation of the real hydrostatic IOP. Thus central corneal thickness can be a confounder in the subdivision between normal and elevated IOP, and therefore also between normal-pressure and hypertensive POAG, when using an absolute cut-off point of 21 mmHg.

Diagnostic mydriatics are very widely used in ophthalmic clinical practice. In most cases they are essential for an adequate examination of the ocular media and fundus, especially by non-ophthalmologists. However, the use of mydriatic agents can provoke an attack of acute angle-closure glaucoma (AACG), with rise of the IOP up to 80 mmHg within a few hours, and with a risk of permanent damage to the optic nerve. This risk of inducing an AACG attack might be a reason why many general practitioners, internists and other non-ophthalmologic physicians are reluctant to dilate pupils for ocular examination. Also, in an ophthalmic epidemiological study participants may be selected based on an inclusion criterion that requires an inspection of the anterior chamber angle, which may create bias. In chapter 7 we describe the risk of inducing AACG in a screening protocol for OAG. In total 6,760 subjects participated in the ophthalmic examination and 6,679 (98.8%) of them received tropicamide 0.5%

and phenylephrine 5% eyedrops for diagnostic mydriasis. No selection was made such as on intraocular pressure, presence of narrow anterior chamber angles or history of glaucoma. After the ophthalmic examination all participants received thymoxamine 0.5% drops in both eyes and were warned for the symptoms of AACG. In two subjects an attack of AACG developed in one eye. Both cases were initially treated with thymoxamine 0.5% eyedrops and oral acetazolamide 0.500. Subsequently peripheral iridotomies were performed with a Nd-YAG-laser, and both eyes healed without other sequelae. This study shows that in non-selected (Caucasian) subjects of 55 years of age or older the risk of AACG after this type of diagnostic mydriasis is as low as 0.03%. Therefore, we consider mydriasis with the mentioned mydriatics to be a relatively safe procedure, provided that everybody has been thoroughly informed about related complaints and that medical care is available for re-examination of the subjects in case of complaints.

In chapter 8 all results are placed in a larger perspective. A proposal for standardizing OAG diagnosis and classification in epidemiologic studies is given. Standardized examination algorithms and definitions make pooling of data from different studies possible, and give more insight in regional differences across the world. Also it creates more power to identify smaller risk factors, including genetic factors. Future research on OAG will probably mostly be on a genetic base, in order to find more clues in its etiology and pathogenesis, thereby also giving more starting-points for better therapeutic possibilities.

CHAPTER 10

SAMENVATTING

De oogaandoening "glaucoom" werd reeds lang geleden voor het eerst beschreven en de verdere ontwikkelingen in de geschiedenis van deze aandoening worden kort belicht in hoofdstuk 1. Gedurende de laatste decades zijn de definities van de aandoening en ons begrip ervan fors veranderd. Intraoculaire druk, gezichtsvelden en papil kenmerken werden onderkend als belangrijke factoren in het beloop van de aandoening. Alhoewel er steeds nieuwe onderzoeksmethoden ontwikkeld worden is er nog steeds weinig bekend met betrekking tot de etiologie.

Het vroeg opsporen van de aandoening is een belangrijk algemeen gezondheidsprobleem. Het ontstaan van blindheid ten gevolge van glaucoom kan voorkómen worden als de aandoening vroegtijdig gediagnostiseerd en adequaat behandeld wordt. Wanneer echter gezichtsveld verlies is ontstaan, is er geen herstel meer mogelijk met de huidige therapeutische methoden. Omdat de meeste glaucoompatiënten aanvankelijk lange tijd asymptomatisch zijn, kan er al veel gezichtsveld verloren zijn op het moment dat de patiënt klachten ontwikkelt. Dit betekent dat routinematige screeningen bij asymptomatische personen nodig zijn om de aandoening in een vroeg stadium op te sporen.

Er zijn veel verschillende soorten glaucoom. Primair open-kamerhoek glaucoom (POAG) is de meest voorkomende vorm in Westerse landen. Dit proefschrift richt zich op (primair) open-kamerhoek glaucoom (OAG). Omdat we pseudoexfoliatie als oorzaak van glaucoom niet voldoende konden uitsluiten, spreken we in sommige artikelen over OAG in plaats van POAG. Alle studies waren gebaseerd op data van onderzoeken in het ERGO onderzoek, een bevolkingsonderzoek bij personen van 55 jaar en ouder.

Een belangrijk probleem bij een aantal studies naar OAG in het verleden was de verschillen in criteria en methoden die gebruikt waren om glaucoom op te sporen en te classificeren. Deze verschillen kunnen resulteren in de verschillende bevindingen van deze studies en maken vergelijkingen moeilijk. Op dit moment wordt glaucoom gedefinieerd als een aandoening die een opticopathie veroorzaakt die gekarakteriseerd wordt door het uithollen van de oogzenuw (de papil) met een bijbehorend gezichtsveld defect. In hoofdstuk 2 beschrijven we de prevalentiecijfers van OAG in het ERGO onderzoek. Deze getallen zijn gebaseerd op oogheelkundige onderzoeken bij 6781 respondenten van 55 jaar of ouder (6293

zelfstandig wonende respondenten en 488 wonend in verzorgingshuizen). De criteria voor OAG die gebruikt werden, waren gebaseerd op semi-automatische metingen van de papil, zoals verticale cup-disk ratio (VCDR), minimale neuroretinale rand dikte, of asymmetrie van de VCDR tussen beide ogen. en gezichtsveld onderzoeken met kinetische Goldmann perimetrie. De oogdruk (IOP) werd gemeten met een Goldmann applanatie tonometer. Alle aparte criteria voor de diagnose OAG werden onafhankelijk van elkaar beoordeeld. Ook werden verschillende andere definities voor de diagnose OAG, zoals gebruikt in andere grote bevolkingsonderzoeken, toegepast op de data van het ERGO onderzoek. Alhoewel de prevalentiecijfers, zoals deze gerapporteerd worden door de verschillende studies, min of meer vergelijkbaar zijn, resulteerden de verschillende definities toegepast op onze data in 12-voudig verschillende prevalentie cijfers (variërend van 0.1 tot 1.2%). Daarom presenteren wij het volgende voorstel voor uniforme definiëring en classificering van OAG in epidemiologische studies: een VCDR $\geq$ 0.7, asymmetrie van VCDR tussen beide ogen $\geq$ 0.3 of een minimale neuroretinale rand dikte $<$ 0.10 gebruik makend van (semi-)automatische metingen, in combinatie met een gezichtsveld defect dat niet veroorzaakt wordt door retinale of neuro-ophthalmologische oorzaken. Met deze criteria vonden we een prevalentie van OAG van 0.9% (95% betrouwbaarheidsinterval (BI) 0.6, 1.1; 56 cases). De prevalentie van OAG is twee maal hoger bij mannen in vergelijking tot vrouwen (Odds ratio 2.3, 95% BI 1.2, 4.5). Het risico voor OAG steeg met 8% per levensjaar (95% BI 4.0%, 13.0%). Standaardisatie van criteria en diagnostische methoden zal de vergelijkbaarheid van verschillende epidemiologische studies verbeteren, en biedt de mogelijkheid om regionale verschillen op te sporen en om data van verschillende studies te combineren.

In hoofdstuk 3 beschrijven we onze bevindingen met betrekking tot de prevalentie van gezichtsveld defecten oorzaken hiervan, en de associatie met beperkingen hierdoor in het dagelijkse leven. De prevalentie en oorzaken van gezichtsveld defecten werden cross-sectioneel bepaald. Indicatoren voor beperkingen in het dagelijkse leven werden zowel cross-sectioneel als prospectief gemeten. Gezichtsvelden werden getest met een bovendrempelige screeningstest van de centrale 48 graden met de Humphrey perimeter. Wanneer een defect

aanwezig was, dan werd de test herhaald. Kinetische Goldmann perimetrie werd verricht wanneer ook bij herhaling de screeningstest afwijkend was. Gegevens van de oogheelkundige onderzoeken, van de neurologische onderzoeken en gegevens van oogartsen en huisartsen werden gebruikt om de oorzaken van afwijkende gezichtsvelden te bepalen. Interviewgegevens met betrekking tot problemen in het dagelijkse leven, bij lezen, gebruik van loop hulpmiddelen, vallen en botfracturen werden gebruikt om de mate van beperkingen te bepalen. De prevalentie van gezichtsvelddefecten was 5.5%, variërend van 1.9% in de jongste leeftijdscategorie tot 17.0% in de oudste leeftijdscategorie. Glaucoom was de belangrijkste oorzaak voor gezichtsvelddefecten in alle leeftijdsgroepen. Andere oogzenuwpathologie en cerebrovasculaire aandoeningen stonden op de tweede en derde plaats. Na het 75ste levensjaar waren stonden leeftijdsgebonden maculadegeneratie en retinale vasculaire occlusies op de tweede en derde plaats. Gezichtsveldverlies was, onafhankelijk van een verminderde gezichtsscherpte, geassocieerd met beperkingen in het dagelijkse leven en een hogere kans op vallen en bot fracturen. In 28% van alle personen met gezichtsveld verlies waren deze personen hiervan niet op de hoogte en hadden ze nog nooit een oogarts bezocht behalve voor een bril.

Over de genetische achtergrond van OAG is nog steeds zeer weinig bekend, alhoewel genetische faktoren al van belang werden geacht sinds 1869 door von Graefe. Veel uitgebreide stambomen zijn gepubliceerd sinds die tijd, meestal in geselecteerde populaties, en resulterend in verschillende inzichten met betrekking tot overeving. Vaak werd in deze studies alleen anamnestische familieanamnese data gebruikt en werden de familieleden niet echt onderzocht. In hoofdstuk 4 beschrijven we een studie waarin we bepaalden of OAG aggregeert in families in de algemene bevolking. Hiervoor selecteerden we alle OAG cases en een random selectie van controle personen uit het ERGO bevolkingsonderzoek. Van deze personen werden de eerstegraads familieleden onderzocht volgens een gestandaardiseerd protocol. Bij broers en zusters van OAG cases vonden we een OAG prevalentie van 10.4% en bij kinderen van OAG cases was de prevalentie 1.1%. In de controlegroep waren deze prevalentiecijfers respectievelijk 0.7% en 0%. Het lifetime risico voor een verhoogde IOP was 42.5% bij familieleden van

OAG cases ten opzichte van 6.7% bij familieleden van controles; voor een grote VCDR 62.2% versus 16.6%; en voor OAG 22.0% versus 2.3%, resulterend in een relatief risico van 9.2 (95% BI 1.2, 73.9). Het populatie-attributief risico voor OAG was 16.4%. Concluderend hebben familieleden van OAG cases een sterk verhoogd risico voor OAG. Verrassend genoeg was niet IOP maar een vergroting van de VCDR het eerste en meest prominente teken van familie aggregatie. Verder onderzoek is nodig om de genetische achtergrond van het verhoogde familierisico van OAG te ontrafelen.

Een betrouwbare bepaling van de verticale cup-disc ratio (VCDR) is noodzakelijk voor de diagnose en behandeling van OAG. Echter, funduscopische VCDR bepalingen zijn bekend om hun lage interobserver overeenkomst. De recent geintroduceerde semi-automatische beeld analyse apparatuur heeft een betere reproduceerbaarheid en kan kleine veranderingen in de tijd eerder detecteren. Op dit moment is funduscopie, ondanks de lagere reproduceerbaarheid, nog steeds de belangrijkste screeningsmethode voor het opsporen van OAG. In hoofdstuk 5 vergelijken we de funduscopische met de semi-automatische VCDR metingen. De gemiddelde funduscopische VCDR van 5143 respondenten was 0.30 (SE 0.0021; range 0.00, 1.00); de gemiddelde semi-automatisch gemeten VCDR was 0.49 (SE 0.0019; range 0.04, 0.86; verschil 0.19; $p<0.0001$). De correlatie tussen beide methoden was matig (correlatie coefficient 0.61, SE 0.11), en was lager bij kleine papillen. Met de semi-automatische VCDR metingen werd 76% van de OAG cases correct geidentificeerd (waarbij gezichtsveld gegevens en funduscopische papil karakteristieken werden gebruikt om OAG te definieren). Bij de semi-automatische metingen was er een kleinere variabiliteit in vergelijking met funduscopie. Verder zijn de semi-automatische metingen beter gestandardiseerd, hetgeen van belang is bij epidemiologische studies en follow-up onderzoeken. De 97.5de percentiel van de VCDR distributie was zowel voor de semi-automatische metingen als voor oogspiegelen 0.70.

De IOP wordt gebruikt voor de diagnostiek en behandeling van OAG. Goldmann applanatie tonometrie is de gouden standaard, maar deze geeft slechts een schatting van de echte IOP. De nauwkeurigheid van deze schatting is afhankelijk van vele factoren. Tot op zekere hoogte kunnen fouten voorkomen

worden door een juiste meettechniek. Maar fouten veroorzaakt door andere factoren, zoals met name centrale cornea dikte die de stugheid van de cornea beinvloedt, kunnen niet voorkomen worden. Centrale corneadikte kan gemeten worden door middel van een optische methode en met behulp van ultrageluid. Deze laatste methode is betrouwbaarder. Het is gebleken dat ultrasone pachymetrie zeer nauwkeurig is en reproduceerbaar met een lagere inter- en intra-observer variabiliteit dan optische pachymetrie. In hoofdstuk 6 presenteren we gegevens over de centrale corneadikte bij een gerandomiseerd geselecteerde subgroep van personen van het ERGO onderzoek. Bij 395 personen (352 controles, 13 personen met oculaire hypertensie en 30 cases met POAG) van 55 jaar en ouder, werd de centrale corneadikte gemeten met behulp van ultrasone pachymetrie (Allergan Humphrey 850) en de IOP met de Goldmann applanatie tonometer. De gemiddelde centrale corneadikte van de controlegroep was 537.4 µm (95% Betrouwbaarheids Interval (BI) 533.8, 540.9; bereik 427-620 µm). Dit was nagenoeg hetzelfde voor zowel het linker als het rechter oog, met een maximaal verschil van 42 µm. Er was geen verschil tussen de geslachten en er was geen significant verband met leeftijd. Lineaire regressie analyse van de centrale corneadikte ten opzichte van IOP liet een toename van 0.19 mmHg in de IOP zien bij iedere 10 µm toename van de centrale corneadikte (95% BI 0.09, 0.28). Dit verband was gelijk voor beide ogen en voor beide geslachten. De 13 personen met oculaire hypertensie hadden een 16.0 µm (95% BI –2.6, +34.6) dikkere cornea dan de controlegroep (P=0.093), terwijl daarentegen de 30 personen met POAG een 21.5 µm (95% BI 8.8, 34.1) dunnere cornea hadden in vergelijking tot de controlegroep (P=0.001). Concluderend kan gezegd worden dat de IOP gemeten door middel van applanatie tonometrie positief gerelateerd is aan de centrale corneadikte. Door dit onderzoek kan niet uitgesloten worden of dit alleen door meetfouten wordt veroorzaakt, of mede wordt veroorzaakt door een direct effect van de IOP op de corneadikte. Als gevolg van de variatie in de centrale corneadikte in de populatie kan de gemeten IOP een onder- of een overschatting van de echte hydrostatische IOP zijn. Dus: de centrale corneadikte kan een confounder zijn bij het onderscheid tussen een normale en een verhoogde IOP, en daardoor ook tussen normotensief en een hypertensief POAG, wanneer een absoluut afkappunt van 21 mmHg gehanteerd wordt.

Diagnostische mydriatica worden veel gebruikt in de klinische oogheelkundige praktijk. In de meeste gevallen zijn ze essentieel voor een adequaat onderzoek van de oculaire media en de fundus, met name bij niet-oogartsen. Echter het gebruik van pupilverwijdende middelen kan een aanval van acuut kamerhoek-afsluitings glaucoom (acute angle-closure glaucoma, AACG) uitlokken, met een stijging van de IOP tot 80 mmHg binnen enkele uren, met het bijkomend risico van blijvende schade aan de oogzenuw. Dit gevaar een AACG-aanval te veroorzaken kan een reden zijn waarom veel huisartsen, internisten en andere (niet-oog)artsen niet graag pupillen verwijden voor oogonderzoek. Tevens kan dit bias veroorzaken bij het selecteren van deelnemers aan een oogheelkundig epidemiologisch onderzoek. In hoofdstuk 7 beschrijven we het risico op het uitlokken van AACG bij een screeningsprotocol voor OAG. In totaal 6760 personen namen deel aan het oogheelkundig onderzoek en 6679 (98,8%) van hen kregen tropicamide 0,5% en phenylephrine 5% oogdruppels toegediend voor diagnostische pupilverwijding. Er was geen selectie gemaakt op basis van bijvoorbeeld oogdruk, aanwezigheid van een nauwe voorste oogkamer, of de aanwezigheid van glaucoom in de voorgeschiedenis. Na het oogheelkundig onderzoek kregen alle deelnemers thymoxamine 0,5% druppels in beide ogen toegediend en werden ze gewaarschuwd voor de symptomen van AACG. In twee gevallen ontwikkelde zich een aanval van AACG in een oog. Beide cases werden om te beginnen behandeld met thymoxamine 0,5% oogdruppels en oraal acetazolamide 0.500. Vervolgens werd een perifere iridotomie verricht met een Nd-YAG-laser, en beide ogen genazen zonder restverschijnselen. Deze studie toont aan dat, bij niet-geselecteerde (Kaukasische) personen van 55 jaar of ouder, het risico op AACG na dit soort diagnostische pupilverwijding slechts 0,03% is. Daarom beschouwen wij pupilverwijding met bovengenoemde mydriatica als een relatief veilige procedure, vooropgesteld dat iedereen vooraf grondig geinformeerd is over de gerelateerde klachten en dat medische zorg beschikbaar is voor her-onderzoek van de personen in geval van klachten.

In hoofdstuk 8 worden alle resultaten in een groter perspectief bekeken. Er wordt een voorstel gedaan tot standaardisatie van OAG-diagnostiek en classificatie in epidemiologische studies. Gestandaardiseerde onderzoeks algoritmen en

definities maakt het vergelijken en samenvoegen van gegevens uit verschillende onderzoeken mogelijk, en geeft meer inzicht in regionale verschillen over de hele wereld. Ook kunnen zo beter kleinere risicofactoren geïdentificeerd worden, inclusief genetische factoren. Toekomstig onderzoek naar OAG zal waarschijnlijk voornamelijk op genetische grondslagen gericht zijn, om zo meer aanwijzingen over etiologie en pathogenese te krijgen, en daarbij ook meer aangrijpingspunten voor betere behandelingsmogelijkheden.

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Curriculum vitae

Roger Wolfs was born on April 20th, 1966 in Reymerstok, the Netherlands. He graduated in 1984 at the "Sophianum" (secondary school) in Gulpen. In 1984 he started his medical study at Maastricht University in Maastricht, where he obtained his Medical Degree in June 1991. During his medical study he worked as research assistant at the Instituut voor Geneesmiddelen, Veiligheid en Gedrag, assisting in a study investigating the effects of some (sedative) anti-allergic medication on actual driving performances, and sleep medication of flying performances of airway pilots. After his medical study he worked, from 1991 to 1993, as medical doctor at the Algemeen Burgerlijk Pensioen Fonds in Heerlen where he medically and juridically evaluated insurance claims.

On January 1st, 1993 he started the work described in this thesis at the Department of Ophthalmology (Prof. Dr. P.T.V.M. de Jong) and the Department of Epidemiology and Biostatistics (Prof. Dr. A. Hofman) of the Erasmus University Rotterdam. In April 1997, he started his specialty training in ophthalmology at the University Hospital Rotterdam-Dijkzigt (Prof. Dr. G. van Rij).

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