Toward Genetic Screening for Glaucoma

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CHAPTER1

Introduction

Classifying Glaucoma

Glaucoma is an umbrella term for a group of progressive optic neuropathies. Structural losses include damage to the optic nerve and permanent loss of retinal ganglion cells (RGCs), and functional consequences include irreversible visual field (VF) loss. As a result, a person with glaucoma will experience slow, albeit progressive vision loss, typically originating in the periphery and ultimately leading to irreversible blindness.

There are two main variants of glaucoma; primary and secondary. Secondary glaucoma arises as a complication of other medical conditions or injury.[1,2] Alternatively, primary glaucoma is defined as glaucomatous damage with no alternative reason, i.e. a differential diagnosis is made.[3]

There are different subtypes of primary glaucoma, see Figure 1. The first subtype is primary childhood glaucoma; it tends to run in consanguineous families and encompasses both congenital glaucoma, which is a disorder affecting infants up to two years of age and is characterized by increased intrauterine intraocular pressure (IOP), as well as juvenile glaucoma, an inherited form of glaucoma affecting youths up to 18 years of age.[4] The second subtype is primary angle closure glaucoma (PACG); it is characterised by the presence of iridotrabecular contact which inhibits outflow of aqueous humour, leading to increased IOP in combination with glaucomatous optic neuropathy.[5] Pathological elevation of IOP impedes axonal transport at the optic nerve head (ONH), coinciding structurally to the lamina cribrosa, where axonal damage and subsequent visual field loss in glaucoma corresponds to this structure.[6–8] Primary angle closure glaucoma occurs more frequently in women, those at an older age, those with small or hyperopic eyes, and those of East Asian ethnicity.[5] The third, and most common subtype of glaucoma, is adult-onset primary open-angle glaucoma (POAG). Here the anterior chamber drainage angle remains open, yet glaucomatous damage still occurs (Figure 1). Adult-onset POAG is the most common subtype in Caucasian populations, and is the focus of this thesis; therefore, the term glaucoma will be in reference to adult-onset POAG.

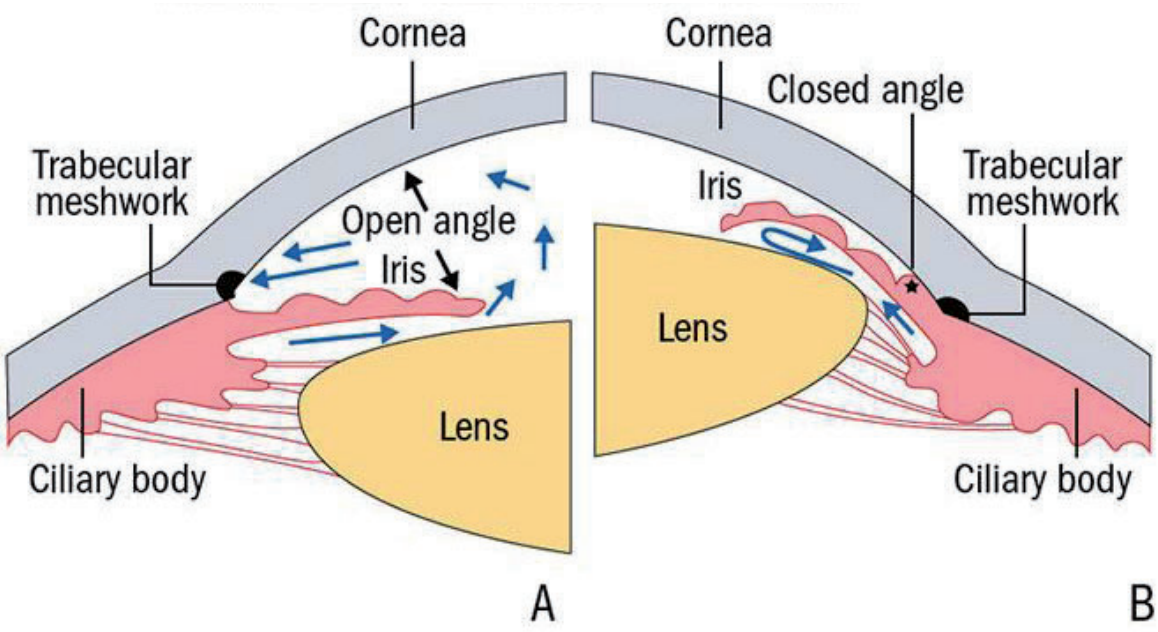

Figure 1. Variants of Glaucoma. A) Open-angle glaucoma (OAG), the iridocorneal angle is physiologically open, however drainage of aqueous humor may still be impeded, leading to increased intraocular pressure. B) Angle-closure glaucoma (ACG), the iridocorneal angle is closed, prohibiting aqueous humor from draining. Source:https://www.opticianonline.net/cet-archive/4744, *permission for use granted (February 24th 2021)*

Epidemiology

Risk Factors

Risk factors, or continuous, heritable traits that are associated with disease risk but not part of the disease definition, are classified as endophenotypes. Intraocular pressure is currently the only modifiable risk factor for glaucoma. However, in populations screened for glaucoma, only 30-60% of newly diagnosed patients presented with IOP outside normal range at the time of screening.[9,10] Intrinsic IOP fluctuations may partially explain why glaucoma patients may have IOP within the bounds of normality, but glaucoma may also develop in those with IOP consistently within normal limits, a condition termed 'normal tension glaucoma'. Medications that lower IOP are also effective in these cases, therefore anatomical vulnerabilities of the optic disc have been hypothesized to account for why some with high IOP are unaffected by glaucoma, a condition called ocular hypertension (OHT), while others with relatively normal IOP develop glaucomatous damage.[11–13] Additionally, IOP measurement accuracy can be influenced by the central corneal thickness (CCT), another glaucoma endophenotype.[14] Doughty and Zaman reported that thicker CCTs are associated with higher IOP,[15] and the Los Angeles Latino Eye Study reported that thinner CCTs were associated with significantly higher prevalences of glaucoma than those with normal or thick CCT.[16]

With respect to non-endophenotypic glaucoma risk factors, old age is the most well-known;[17–19] an initial glaucoma diagnosis is usually made in the sixth decade of life,[20] and beginning in middle age, the increased odds of developing glaucoma is 1.71 per decade.[21] Family history is another well-known risk factor; those with first-degree relatives with glaucoma are at a 9-fold increase in risk, with a lifetime glaucoma risk of 22%, while those with second-degree affected relatives are at a 1.5-fold increased risk to develop glaucoma.[22,23] Another risk factor for glaucoma is ethnicity; those with African and Hispanic ethnicity are at a higher risk of developing glaucoma,[20] see Figure 2 for ethnicity-stratified glaucoma prevalence. Next, individuals with myopia, specifically high myopia (defined as a spherical equivalent < -6.00 diopters) are at a higher risk of glaucoma; it is hypothesized the longer axial length in myopic eyes, defined as the distance between the anterior surface of the eye and the foveal centre, weakens scleral support to the optic nerve, leaving it vulnerable to IOP-induced damage.[24,25] Finally, single gene mutations are a major risk factor for congenital/juvenile glaucoma, like

myocilin (*MYOC*), optineurin (*OPTN*), and TANK binding kinase 1 (*TBK1*). However, these mutation-induced forms of glaucoma are rare and account for <5% of glaucoma cases.[26,27]

Prevalence

Glaucoma is the second-leading cause of irreversible blindness in the world after age-related macular degeneration (AMD), and current projections report 111.8 million people to be affected by the year 2040.[21] Due to the asymptomatic and insidious nature of glaucoma, up to 50% of patients are unaware of their disease status, which is why glaucoma is called the "sneak thief of sight".[28] Active disease management will slow disease progression, however a retrospective multicentre data review reported that higher initial mean deviation (MD), an increased age at diagnosis, and higher IOP as significant predictors for glaucoma-induced blindness, with an incidence of 1% conversion to blindness per year.[29]

The prevalence of glaucoma increases exponentially per decade beginning in middle age, with notable ethnicity-based differences. From ages 55-95, glaucoma prevalence of people from Caucasian, African, and Hispanic ethnicity increases from 1 to 14%, 4 to 22%, and 2 to 34%, respectively (Figure 2).[20] The focus of this thesis is glaucoma in Dutch Caucasian populations, where the total glaucoma prevalence in people 55 years of age or older is approximately 3.2%.[30] Therefore the findings and inferences based on this research should be made in the context of Western European Caucasian populations, where screening, socio-demographic, and treatment approaches with respect to glaucoma may differ from the the rest of the world.

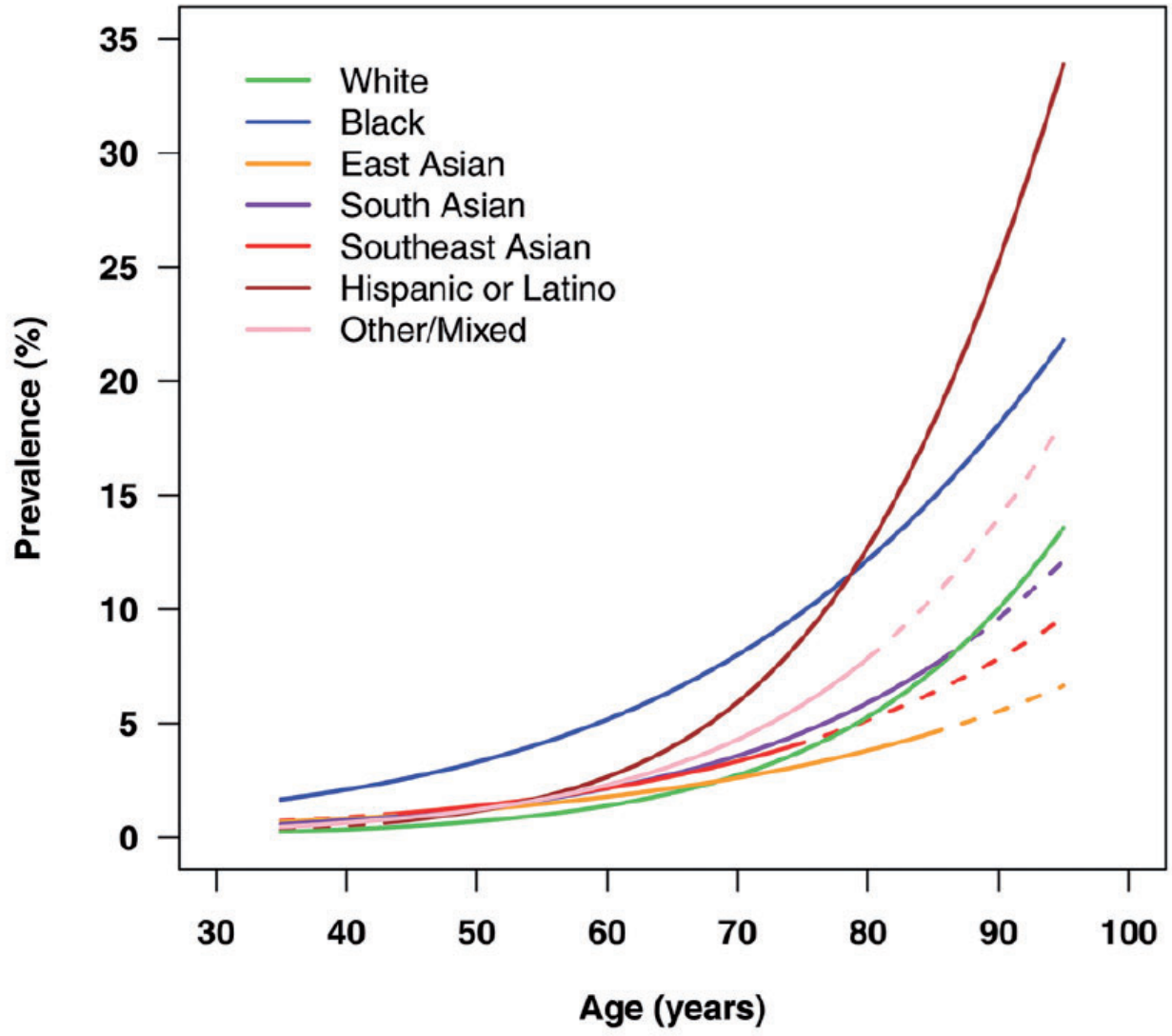

Figure 2: Estimated percentage prevalence by ethnicity. Solid lines derived from regression models of available data and dashed lines are predicted values, fitted separately per ethnic group, White (green), Black (blue), East Asian (orange), South Asian (purple), Southeast Asian (red), Hispanic/Latino (brown), and mixed/other ethnicity (pink). Source: Kapetanakis VV, *et al. Br J Ophthalmol* 2016;100:86–93.

Population-based epidemiological studies provide insight into not only the prevalence of complex adult-onset disorders like glaucoma, but also biological and lifestyle factors that may be implicated with disease risk. The longitudinal nature of these cohorts are representative of the population at-large, and one of the major benefits of these studies is the abundance of data they create. This data can be utilized to obtain population-wide observations, i.e., data-driven analyses. Medical, questionnaire, and biological data is created from these cohorts, and inferences made with large cohort analyses can be further used for clinical guidance.

Screening

The later the initial diagnosis of glaucoma, the poorer the patients' prognosis, driving the need for effective population-based case-detection, i.e., screening. Glaucoma screening on known risk factors such as IOP have been implemented in the past, where tonometry-based screening protocols utilized a population-wide IOP threshold of 21 mmHg; the resulting specificity of this screening approach was 92.4% with an associated sensitivity of 47.1%. [31] The ineffectiveness of IOP-based screening stems from two major reasons. First, only up to 50% of glaucoma cases have chronic IOP >22 mmHg, or an IOP of >22 mmHg at a single screening.[32,33] Second, most individuals with high IOP at a single screening never develop functional glaucomatous damage.[33]

Another popular screening approach for glaucoma is to evaluate visual fields (VF), as glaucomatous VF loss usually begins in the periphery. The frequency doubling technique (FDT) can be briefly described as when an achromatic sinusoidal grating of low spatial frequency (Figure 4, left) undergoes counterphased flickering at a high temporal frequency, the spatial frequency appears to be doubled (Figure 4, right).[34] This apparent flicker is useful in glaucoma screening because loss of motion and flicker detection may be an early sign of glaucoma, this is due to preferential cell loss in the magnocellular ganglion cell pathway.[35] This visual phenomenon has thus been exploited for use in the FDT device. Although the FDT is a fast VF screening device, it is more promising for moderate to late glaucoma, general VF testing alone may not be sufficiently sensitive for early glaucoma screening.[36] A commonly used FDT test is the C-20-5, where the central 20 degrees is tested with targets at a contrast level that 95% of age-matched healthy subjects are expected to detect. There are a total of 17 stimulus locations made up of four 10-degree targets per quadrant and one 5-degree central target.[37] In a masked case-control study, the sensitivity, specificity, and positive

predictive power of the C-20-5 test as a glaucoma screening device was 58%, 99%, and 13% (assuming a 0.5% prevalence), respectively.[38] However, in a prospective community-based screening program in Australia, the sensitivity, specificity, and positive predictive power of the C-20-5 algorithm alone as a glaucoma detection method was 84%, 55%, and 13% for one missed test location.[39] This decrease in specificity may be due to differences in technician training, as VF abnormalities may be also due to small pupils, participant inexperience, eyelid overhang (especially in older individuals), or the presence of multiple ocular pathologies affecting the VF.[39]

In terms of ocular structure, optical coherence tomography (OCT) is used for evaluating and monitoring glaucoma in a clinical setting. OCT is a non-invasive optical technique allowing for real-time cross-sectional imaging of the optic nerve head and retina.[40] The retinal nerve fiber layer (RNFL) thickness is a clinically useful parameter in detecting glaucoma, however utilizing the RNFL thickness as a screening test for glaucoma remains limited. One study reported a sensitivity and specificity of 98% and 87% to discriminate between glaucomatous versus non-glaucomatous eyes, respectively, when using an average RNFL thickness at the 5% level compared to the normative database (corresponding to yellow of the RNFL deviation map).[41] A 2017 meta-analysis of diagnostic accuracy of imaging devices concluded that although OCT can differentiate between normal and glaucomatous eyes, it is more equipped to do so in moderate to severe glaucoma, rather than screening for early glaucoma.[42]

Finally, questionnaires have been developed to identify demographic characteristics associated with a higher risk for glaucoma, but the low sensitivity (20-49%) and specificity (29-69%) for glaucoma screening limits the utility of this approach.[43]

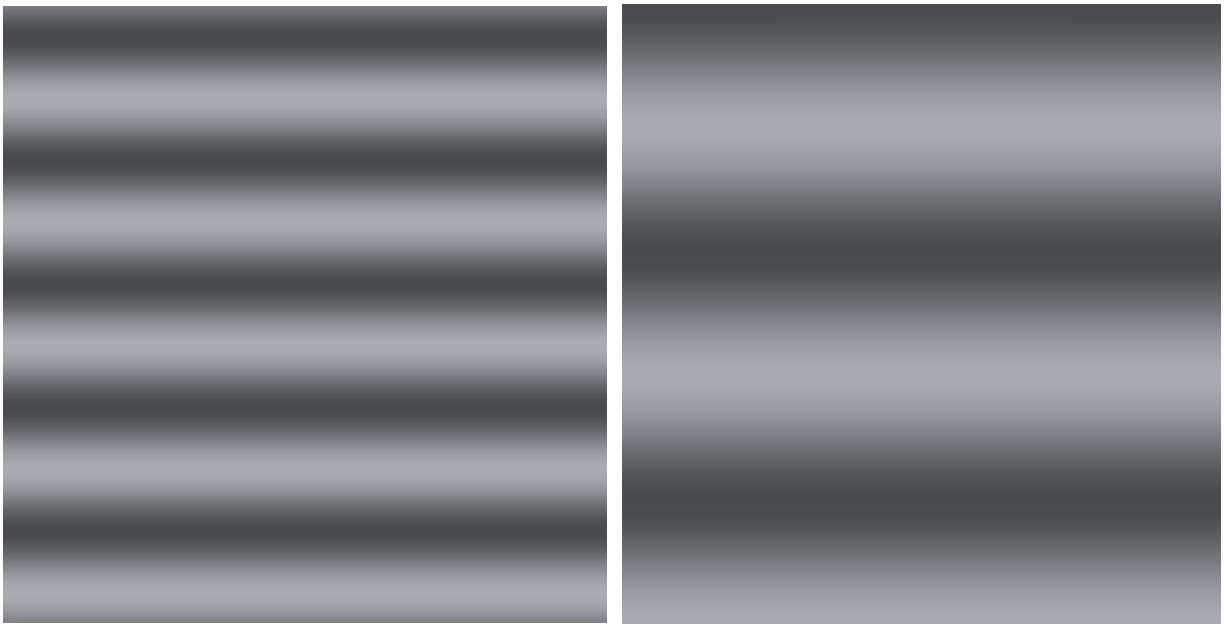

Figure 4: Sinusoidal grating pattern, shown with low spatial frequency (SF), left and high SF, right. Briefly, when low SF gratings undergo counterphased flickering, the frequency of the stimuli appears to be doubled. In glaucoma there is a preferential loss of cells in the magnocellular ganglion cellular pathway, partially responsible for flicker detection. This method is then exploited for functional vision assessment in glaucoma (Sharma et al. 2008). Image designed by Lorenzo Scanferla, 2021.

At this time, approximately half of incident glaucoma cases are obtained via regular ophthalmic care and is the basis of the argument for population-based screening.[44] However, currently population-based screening for glaucoma is not cost-effective in Caucasian populations, due to the relatively low prevalence, late age of onset, and a lack of screening tests with a sufficiently high specificity (at least 95-97.5%) at an acceptable sensitivity.[45,46] The benefit of a screening programme depends on, among other things, length time bias.[9] For example, if a screening programme based on questionnaire only detects elderly patients with slow progressing glaucoma, this screening programme is unlikely to be efficient for population-based blindness prevention.[9] Therefore, a screening programme should be targeted to the subset of the population it will benefit the most, i.e. middle aged people with early undetected glaucoma. In addition, a screening programme should utilize the most appropriate risk factors. Due to the multifaceted nature of glaucoma, a genetic pre-screening programme may be ideal in capturing this at-risk population.

Genetics of glaucoma and related traits

A phenotype is a measurable trait, such as IOP or glaucoma, and is a function of genes and the environment. Thus,

$$Phenotype(P) = Genotype(G) + Environment(E) \quad (1)$$

To further break this down, the variation, or variance of a phenotype V_P can be subdivided into two parts:[47]

$$V_P = V_G + V_E \quad (2)$$

where V_G is genetic variance and is environmental variance. At this generalized level, we assume no interaction between genetics and environment. The proportion of phenotypic variation (V_P) within a trait that is due to genetic variation is termed (broad sense) heritability (H^2).[48]

$$H^2 = \frac{V_G}{V_P} \quad (3)$$

In essence, heritability measures the fraction of variation between individuals in a population that is due to their genotypes. [49] The V_G can be further broken down to individual genetic components

$$V_G = V_A + V_D + V_I \ (4)$$

where V_A is defined as the additive effect of genes on a trait of interest resulting in a deviation of the mean of the phenotype. The dominance effects V_D defined as the dominant action of a gene on a phenotype, and the interaction effects (V_I) considers the variance of other allelic interactions. As only one copy of each gene is passed to offspring, most relatives share one or no gene copies that are identical by descent, save identical twins and full-siblings. That being said, dominance and other non-additive genetic effects that are based on sharing two gene copies do not contribute to phenotypic resemblance between parents and offspring.[49] This is why narrow-sense heritability (h^2) is used, where

$$h^2 = \frac{V_A}{V_P} \ (5)$$

At the population level, an h^2 estimate indicates what proportion of observed V_P is due to genetic differences between individuals. It is important to note that h^2 is a population-specific estimate, genetic variance depends on segregation in a population of the alleles that influence the trait(s) including allelic frequencies and effect sizes. Additionally, environmental variance can vary across populations.[49] Given this, the heritability in one population theoretically does not predict the heritability of the same trait in another population, however they may be similar especially in morphometric traits.[49]

With complex traits, h^2 estimates are a prerequisite for gene-finding studies such as genome-wide association studies (GWAS). The first successful GWAS was a 2005 study of 96 age-related macular degeneration (AMD) cases and 50 controls; it reported that individuals with at least one C (risk-bearing) allele of the Complement H Factor (*CHF*) gene were at a 2.7-fold increased risk to have AMD risk.[50] More recent studies have reported individuals carrying the rare *Arg1210Cys* variant within the *CHF* gene are at a 47 times higher risk of developing AMD.[51] Due to the complex and polygenic nature of glaucoma, current GWAS findings have not been as successful.[52] Currently uncovered genetic variants have small effect sizes, and individually have little

value in terms of predicting an individuals' risk.[53] However, these uncovered variants bring us closer to a) explaining the functional deficits of ocular cells, and b) increasing the ability of genetic prediction, i.e. population screening for glaucoma based on genetic risk, i.e. a genetic risk score (GRS).

Scope of this thesis

Glaucoma is a complex ocular disorder and is the second-leading cause of permanent vision loss in Dutch Caucasians; up to 50% of those affected are unaware they have the disease.[21] Currently, periodically screening a population for glaucoma is not cost-effective due to the low prevalence of the disease (~3% in those aged 55 and older) and the lack of a single screening test containing sufficiently high specificity of at least 95% with an acceptable sensitivity. In addition, the subtle subjective visual problems, the associations with other systemic disorders, and the complex genetic inheritance underlying the multifactorial nature of glaucoma contribute to the puzzle of early glaucoma detection.

The primary aim of this thesis is to explore the value of genetic pre-screening for glaucoma in a population-based setting. The secondary aim is to improve the measurements of self-reported ocular disease status in population-based cohorts by questionnaire data.

First, in **Chapter 2** we collated all reports of heritability for glaucoma and related endophenotypes and performed a systematic review and meta-analysis to update the heritability estimates of glaucoma and related endophenotypes. For endophenotype clusters with $n \geq 10$ h^2 estimates, we also performed subgroup and meta-regression analyses and identified mean age, ethnicity, and study design as major sources of heterogeneity.

Next, in **Chapter 3** we investigated the utility of genetic pre-screening for glaucoma in a population-based setting, by adopting a double-blind prospective design with contrasting genetic groups. We obtained a highly curated list of genetic variants from the literature to obtain each participants' genetic risk for glaucoma. Participants undergo comprehensive ophthalmic screening including glaucoma classification via an ophthalmologist. The primary outcome is the relative risk of glaucoma given a high genetic risk compared to a low genetic risk. Data collection is ongoing at the time of publication.

Further, we improved upon self-reported glaucoma status in population-based cohorts by developing a questionnaire-based proxy in **Chapter 4**. Because glaucoma is often undiagnosed, and ocular hypertension, where someone has high IOP without damage to the visual system, is sometimes confused with glaucoma, therefore

we combined self-reported glaucoma status with the presence of glaucoma-specific visual complaints to define glaucoma as accurately as possible with a questionnaire. For the assessment of visual complaints, we used the National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25). We established four glaucoma classifications, definite, probable, possible (by self-report and by complaint), and unaffected. Standardised prevalences are in line with other population-based cohort studies where ocular/glaucoma phenotyping had occurred. We also assessed our proxy as an outcome in two cross-sectional questionnaire-based association studies. In **Chapter 5** we applied it to investigate the relationship between tinnitus and glaucoma in both a clinic-based cross-sectional questionnaire study alongside a population-based cohort, and in **Chapter 6** we investigated the relationship of the glaucoma proxy with aspects of autonomic dysfunction, including heart rate variability and blood pressure.

Then, in **Chapter 7** we used the above approaches in developing a questionnaire-based proxy for AMD. The standardized prevalence of definite and possible AMD for participants 55+ was 12.3%. To confirm the findings of the proxy, AMD GRS were created for both late and early AMD and case-controls comparisons were made. Self-reported status proved to be more accurate in terms of AMD and associated genetic risk.

Finally, in **Chapter 8** I conclude with a summary of the work within this thesis. This is followed by a critical discussion of the contents of this work as well as direction for future research.

References

1. Bai, H.-Q., Yao, L., Wang, D.-B., Jin, R. & Wang, Y.-X. Causes and treatments of traumatic secondary glaucoma. *Eur. J. Ophthalmol.* **19**, 201–206 (2009).
2. Foster, C. S., Havrlikova, K., Baltatzis, S., Christen, W. G. & Merayo-Lloves, J. Secondary glaucoma in patients with juvenile rheumatoid arthritis-associated iridocyclitis. *Acta Ophthalmol. Scand.* **78**, 576–579 (2000).
3. Prum, B. E., Jr *et al.* Primary Open-Angle Glaucoma Preferred Practice Pattern(®) Guidelines. *Ophthalmology* **123**, P41–P111 (2016).
4. Yu Chan, J. Y., Choy, B. N., Ng, A. L. & Shum, J. W. Review on the Management of Primary Congenital Glaucoma. *J Curr Glaucoma Pract* **9**, 92–99 (2015).
5. Wright, C., Tawfik, M. A., Waisbourd, M. & Katz, L. J. Primary angle-closure glaucoma: an update. *Acta Ophthalmol.* **94**, 217–225 (2016).
6. Quigley, H. A. & Addicks, E. M. Chronic experimental glaucoma in primates. II. Effect of extended intraocular pressure elevation on optic nerve head and axonal transport. *Invest. Ophthalmol. Vis. Sci.* **19**, 137–152 (1980).
7. Quigley, H. A. & Addicks, E. M. Regional differences in the structure of the lamina cribrosa and their relation to glaucomatous optic nerve damage. *Arch. Ophthalmol.* **99**, 137–143 (1981).
8. Morrison, J. C., Cepurna Ying Guo, W. O. & Johnson, E. C. Pathophysiology of human glaucomatous optic nerve damage: insights from rodent models of glaucoma. *Exp. Eye Res.* **93**, 156–164 (2011).
9. Stoutenbeek, R. *et al.* The additional yield of a periodic screening programme for open-angle glaucoma: a population-based comparison of incident glaucoma cases detected in regular ophthalmic care with cases detected during screening. *Br. J. Ophthalmol.* **92**, 1222–1226 (2008).
10. Chan, M. P. Y. *et al.* Glaucoma and intraocular pressure in EPIC-Norfolk Eye Study: cross sectional study. *BMJ* j3889 (2017) doi:10.1136/bmj.j3889.
11. Janssen, S. F. *et al.* The vast complexity of primary open angle glaucoma: disease genes, risks, molecular mechanisms and pathobiology. *Prog. Retin. Eye Res.* **37**, 31–67 (2013).
12. Mahmoudinezhad, G. *et al.* Rate of visual field decay in glaucomatous eyes with acquired pits of the optic nerve. *Br. J. Ophthalmol.* (2020) doi:10.1136/bjophthalmol-2020-315980.
13. Ha, A. *et al.* Baseline Lamina Cribrosa Curvature and Subsequent Visual Field Progression Rate in Primary Open-Angle Glaucoma. *Ophthalmology* **125**, 1898–1906 (2018).
14. Ehlers, N., Bramsen, T. & Sperling, S. Applanation tonometry and central corneal thickness. *Acta Ophthalmol.* **53**, 34–43 (1975).
15. Doughty, M. J. & Zaman, M. L. Human Corneal Thickness and Its Impact on Intraocular Pressure Measures. *Survey of Ophthalmology* vol. 44 367–408 (2000).
16. Francis, B. A. *et al.* Intraocular pressure, central corneal thickness, and prevalence of

open-angle glaucoma: the Los Angeles Latino Eye Study. *Am. J. Ophthalmol.* **146**, 741–746 (2008).

17. Gordon, M. O. *et al.* The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch. Ophthalmol.* **120**, 714–20; discussion 829–30 (2002).
18. Le, A., Mukesh, B. N., McCarty, C. A. & Taylor, H. R. Risk factors associated with the incidence of open-angle glaucoma: the visual impairment project. *Invest. Ophthalmol. Vis. Sci.* **44**, 3783–3789 (2003).
19. Armaly, M. F. *et al.* Biostatistical analysis of the collaborative glaucoma study. I. Summary report of the risk factors for glaucomatous visual-field defects. *Arch. Ophthalmol.* **98**, 2163–2171 (1980).
20. Kapetanakis, V. V. *et al.* Global variations and time trends in the prevalence of primary open angle glaucoma (POAG): a systematic review and meta-analysis. *Br. J. Ophthalmol.* **100**, 86–93 (2016).
21. Tham, Y.-C. *et al.* Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology* **121**, 2081–2090 (2014).
22. Wolfs, R. C. *et al.* Genetic risk of primary open-angle glaucoma. Population-based familial aggregation study. *Arch. Ophthalmol.* **116**, 1640–1645 (1998).
23. Wang, X. *et al.* Using the Utah Population Database to assess familial risk of primary open angle glaucoma. *Vision Res.* **50**, 2391–2395 (2010).
24. Marcus, M. W., de Vries, M. M., Junoy Montolio, F. G. & Jansonius, N. M. Myopia as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. *Ophthalmology* **118**, 1989–1994.e2 (2011).
25. Kuzin, A. A. *et al.* Ocular biometry and open-angle glaucoma: the Los Angeles Latino Eye Study. *Ophthalmology* **117**, 1713–1719 (2010).
26. Sears, N. C., Boese, E. A., Miller, M. A. & Fingert, J. H. Mendelian genes in primary open angle glaucoma. *Exp. Eye Res.* **186**, 107702 (2019).
27. Fingert, J. H. Primary open-angle glaucoma genes. *Eye* **25**, 587–595 (2011).
28. Patty, L., Wu, C., Torres, M., Azen, S. & Varma, R. Validity of Self-reported Eye Disease and Treatment in a Population-based Study: The Los Angeles Latino Eye Study. *Ophthalmology* vol. 119 1725–1730 (2012).
29. Rossetti, L. *et al.* Blindness and Glaucoma: A Multicenter Data Review from 7 Academic Eye Clinics. *PLoS One* **10**, e0136632 (2015).
30. Springelkamp, H. *et al.* Incidence of glaucomatous visual field loss after two decades of follow-up: the Rotterdam Study. *European Journal of Epidemiology* vol. 32 691–699 (2017).
31. Tielsch, J. M. *et al.* A population-based evaluation of glaucoma screening: the Baltimore Eye Survey. *Am. J. Epidemiol.* **134**, 1102–1110 (1991).
32. Dielemans, I. *et al.* The Prevalence of Primary Open-angle Glaucoma in a Population-based Study in The Netherlands. *Ophthalmology* vol. 101 1851–1855 (1994).

33. Sommer, A. *et al.* Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch. Ophthalmol.* **109**, 1090–1095 (1991).
34. Kelly, D. H. Frequency Doubling in Visual Responses*†. *J. Opt. Soc. Am., JOSA* **56**, 1628–1633 (1966).
35. Sharma, P., Sample, P. A., Zangwill, L. M. & Schuman, J. S. Diagnostic tools for glaucoma detection and management. *Surv. Ophthalmol.* **53 Suppl1**, S17–32 (2008).
36. Mowatt, G. *et al.* Screening Tests for Detecting Open-Angle Glaucoma: Systematic Review and Meta-analysis. *Investigative Opthalmology & Visual Science* vol. 49 5373 (2008).
37. Zeppieri, M. & Johnson, C. A. Frequency Doubling Technology (FDT) Perimetry. *Imaging and Perimetry Society* https://webeye.ophth.uiowa.edu/ips/PerimetryHistory/FDP/ (2008).
38. Salim, S., Netland, P. A., Fung, K. H., Smith, M. E. & Aldridge, A. Assessment of the Student Sight Savers Program methods for glaucoma screening. *Ophthalmic Epidemiol.* **16**, 238–242 (2009).
39. Robin, T. A. *et al.* Performance of community-based glaucoma screening using Frequency Doubling Technology and Heidelberg Retinal Tomography. *Ophthalmic Epidemiol.* **12**, 167–178 (2005).
40. Hee, M. R. *et al.* Optical coherence tomography of the human retina. *Arch. Ophthalmol.* **113**, 325–332 (1995).
41. Wu, H., de Boer, J. F. & Chen, T. C. Diagnostic capability of spectral-domain optical coherence tomography for glaucoma. *Am. J. Ophthalmol.* **153**, 815–826.e2 (2012).
42. Fallon, M., Valero, O., Pazos, M. & Antón, A. Diagnostic accuracy of imaging devices in glaucoma: A meta-analysis. *Surv. Ophthalmol.* **62**, 446–461 (2017).
43. McManus, J. R. & Netland, P. A. Screening for glaucoma: rationale and strategies. *Curr. Opin. Ophthalmol.* **24**, 144–149 (2013).
44. Wolfs, R. C. *et al.* Changing views on open-angle glaucoma: definitions and prevalences--The Rotterdam Study. *Invest. Ophthalmol. Vis. Sci.* **41**, 3309–3321 (2000).
45. Burr, J. M. *et al.* The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol. Assess.* **11**, iii–iv, ix–x, 1–190 (2007).
46. Principles and Practice of Screening for Disease. *Annals of Internal Medicine* vol. 69 1085 (1968).
47. Hill, W. G. & Mackay, T. F. C. D. S. Falconer and Introduction to quantitative genetics. *Genetics* **167**, 1529–1536 (2004).
48. Stoltenberg, S. F. Coming to terms with heritability. *Genetica* **99**, 89–96 (1997).
49. Visscher, P. M., Hill, W. G. & Wray, N. R. Heritability in the genomics era--concepts and misconceptions. *Nat. Rev. Genet.* **9**, 255–266 (2008).
50. Klein, R. J. Complement Factor H Polymorphism in Age-Related Macular Degeneration. *Science* vol. 308 385–389 (2005).
51. Fritsche, L. G. *et al.* A large genome-wide association study of age-related macular de-

generation highlights contributions of rare and common variants. *Nat. Genet.* **48**, 134–143 (2016).

52. Camp, N. J. & Aruna, B. Complex Multifactorial Genetic Diseases. *Encyclopaedia of Life Science* 5426–5430 (2009) doi:10.1002/9780470015902.a0001881.pub2.
53. Choquet, H. *et al.* A multiethnic genome-wide association study of primary open-angle glaucoma identifies novel risk loci. *Nat. Commun.* **9**, 2278 (2018).