CHAPTER 7

General discussion
In this thesis, I aimed to expand our knowledge on the genetics of glaucoma and the molecular mechanisms underlying glaucoma pathogenesis. I also explored the effect of novel risk factors on glaucoma. I have (1) reviewed and summarized the proportion of variance in glaucoma (and related endophenotypes) that can be explained by genetic factors, (2) prioritized the most likely causal genes and identified molecular mechanisms underlying glaucoma pathogenesis, and (3) assessed the role of autonomic dysfunction (represented by heart rate variability [HRV]) and blood pressure (BP) in glaucoma. Furthermore, in the last chapter, I have built and validated a proxy for myopia (another eye disease, and a glaucoma risk factor) and by applying this proxy among Lifelines participants, I have confirmed the well-known risk of education and genetic variants in myopia. In this section, I discuss the most important findings per chapter with their strengths and limitations. Besides, I reflect on a variety of methodological issues as well as future directions for research.

I confirmed the strong influence of genetic factors on glaucoma and its endophenotypes

Given that twin, family, and genome-wide association studies revealed substantial glaucoma heritability ($h^2$), I did a systematic review and meta-analysis by collecting all available $h^2$ estimates of glaucoma subtypes and related endophenotypes. The systematic review and meta-analysis provided accurate estimates of the proportion of variance due to genetic variation that can ultimately be explained by gene-finding studies. One previous publication attempted to review ocular trait $h^2$ studies in 2010, however, the review was not systematic and did not focus on glaucoma. Furthermore, the inclusion of endophenotypes, in addition to that of the $h^2$ of glaucoma itself, is a novel approach of this systematic review and meta-analysis.

Heritability studies of primary open-angle glaucoma (POAG) were heterogeneous in terms of design, disease definition, and diagnostic criteria, and because of this, a meta-analysis of glaucoma itself was not possible. On the other hand, a meta-analysis of glaucoma endophenotypes showed moderate to high heritability estimates, but the majority of genetic variants accounting for these estimates have not been discovered yet, hence further gene finding studies are needed. Furthermore, through subgroup and meta-regression analyses, I also identified age (higher $h^2$ in younger people), study design (higher $h^2$ in twin-based studies), and ethnicity (higher $h^2$ of anterior chamber size [ACS] in East Asians) as the major sources of heterogeneity in $h^2$ studies of glaucoma-related endophenotypes.
The change of $h^2$ with age is not well studied among glaucoma-related endophenotypes, but my meta-analysis finding highlights an increasing influence of non-genetic factors with age. After 40 years of age, a similar finding was observed in the UK Biobank, where they studied the variability of $h^2$ across different age groups in several traits. More specifically, of the included 50 physical measures (e.g., weight and body mass index [BMI]), 33 (66%) showed a significant decreases of $h^2$ by 3.5% per decade. In contrast, other meta-analysis studies reported an increasing trend of $h^2$ with age in behavioral traits, including intelligence quotient, depression, anxiety, and gambling behavior throughout life, whereas a stable $h^2$ was reported for C-reactive protein and blood pressure. These findings highlight that the relationship of $h^2$ with age depends on the type of phenotype, environmental factors, and interactions between genetic and environmental factors.

In the meta-analysis, I observed higher $h^2$ estimates among studies that used twin study designs. The same pattern was also observed in a previous meta-analysis study of personality traits. Several explanations have been proposed for the discrepancy between twin vs. family designs. One possible reason might be age differences within family-based studies, as opposed to the twin design. For example, a 10-year follow-up of 6,201 twins reported a decreasing genetic correlation ($r_G$) of C-reactive protein at visit 2 and 3, i.e., $r_G$ dropped from 0.82, in a pair-wise analysis of visit 1 vs. 2, to 0.66 at visit 1 vs. 3, which were both significantly different from 1. This highlights that some traits are influenced by different sets of genes at different ages. Furthermore, the contribution of genetic and environmental influence in a phenotype may vary by birth cohort. Because age-related environmental variables change between family members but not between age-matched twins, the age difference within families gives more power to detect the variance due to the shared environmental effects, resulting in lower $h^2$ estimates in family-based studies. For example, compared to twin design, more shared environmental influence was detected for myopia in variance component models in a family-based design. Another reason might be due to the violation of the underlying assumptions of twin designs. Most criticism has focused on the equal environment assumption, the most crucial assumption of the twin study design. This assumption presumes monozygotic and dizygotic twin pairs are exposed to the same amount of common environmental factors; violation of this assumption may lead to overestimation of $h^2$ if monozygotic twins share more similar environments. The validity of this assumption was tested in different traits and the results were inconsistent; violation of assumption was observed in bulimia; modest bias was detected in mental well-being and personality characteristics, but not for spatial ability and aggression or cardiac conduction.
I prioritized the most important genes and identified pathways underlying POAG pathogenesis

Using previously identified genetic variants from a large POAG genome-wide association study (GWAS) by Choquet et al. in a comprehensive bioinformatics pipeline, I systematically prioritized the most likely causal genes for glaucoma and identified the underlying biological processes involved in glaucoma pathogenesis. Furthermore, I also strengthened the already-known genetic overlap between POAG and its related endophenotypes using in-silico look-up and genetic correlation analyses.

Of the 142 most likely causal genes prioritized, 64 were novel for POAG. Of the 50 nearest genes identified in the POAG GWAS, less than half (46%) were prioritized in the bioinformatics analyses. This confirms the limitation of GWAS, i.e., due to the linkage disequilibrium structure of the genome, GWAS has a limited mapping resolution, and consequently, lead SNPs detected in GWASs are often not the causal functional variants. These findings show that post-GWAS bioinformatics analysis of POAG genes, based on different types of biological evidence, can be used to prioritize the most likely causal genes. Furthermore, this approach not only ranks known POAG genes but also simultaneously identifies novel POAG genes (not immediately implied by GWAS) and their underlying mechanisms, be it impact on coding or gene expression. Furthermore, I identified several novel DNA methylation sites for POAG, strengthening previous evidence that epigenetic mechanisms are also involved in POAG development.

Another important finding of this study is the identification of several pathways through which the prioritized causal genes act. Based on several lines of evidence, my findings pointed out that the extracellular matrix (ECM), transforming growth factor-beta (TGF-β) signaling, cardiovascular and blood vessel development, and the retinoic acid receptor signaling pathways are the most overrepresented pathways in POAG pathogenesis. This is in line with previous evidence showing elevated levels of TGF-β in aqueous humor of glaucoma patients, and high TGF-β has been shown to increase the synthesis of ECM in human trabecular meshwork cells. Other studies demonstrated that TGF-β prevents activation of matrix metalloproteinases (enzymes responsible for the degradation of most ECM proteins) thereby increasing the cross-linking of ECM components in trabecular meshwork cells. Additional studies are needed to investigate how abnormalities in the ECM pathway may lead to POAG, other than through increasing the aqueous humor flow resistance, which leads to elevated IOP. Overrepresentation of heart and blood vessel development pathways is partly in line with the vascular theory of glaucoma, which proposes insufficient blood supply as a potential risk factor for damage to the optic nerve.
Overall, the overrepresentation of the pathways identified in this thesis generally agreed with two previous comparable studies. However, I could not find the importance of inflammation-related factors, perhaps because no gene prioritization analysis was performed in these two previous studies.

**Low heart rate variability and high blood pressure are associated with glaucoma in the general population**

I used data from Lifelines, a multidisciplinary population-based cohort study of the Northern Netherlands, to determine the relationship of HRV, a proxy measure of autonomic nervous system regulation, and BP with glaucoma. In this study, glaucoma was defined using a previously described algorithm developed in Lifelines. Previous studies hypothesized that the optic nerve head is more susceptible to damage in individuals with low HRV. For example, in a five-year follow-up study, a faster rate of central visual field damage was observed among 48 normal-tension glaucoma (NTG) patients (glaucoma without elevated IOP) with lower HRV. I expected that low HRV associates with glaucoma in the general population. My finding has strengthened previous evidence; after adjustment for the effects of age, age squared, sex, and BMI, I found a negative relationship between glaucoma and HRV.

Regarding the effect of BP, previous studies reported both positive and negative relationships with glaucoma risk. Furthermore, two US studies (National Health and Nutrition Examination Survey [NHANES] and The Los Angeles Latino Eye Study [LALES]) that recruited 40-year or older participants found a J- or U-shaped relationship, suggesting that those with either low or high BP may be at greater risk for glaucoma. This J- or U-shaped relationship drew my attention and to test this hypothesis, I did a regression analysis of glaucoma on continuous BP as well as quartiles of the BP distribution to accommodate potential nonlinear effects. Without an indication of J- or U-shaped relationship, my findings showed an increasing trend of glaucoma risk with increasing SBP and PP. Furthermore, an increasing trend of glaucoma was observed among hypertensive individuals. Several factors, including differences in glaucoma definition, model building, and ethnicity may have contributed to the apparent discrepancy between my study and NHANES and LALES. For example, NHANES and LALES defined glaucoma based on fundus photographs and on a combination of fundus photographs and a visual field test, respectively, whereas Lifelines glaucoma definition was based on a questionnaire-based proxy including self-reported glaucoma; glaucoma with elevated IOP is more frequent among self-reported glaucoma cases.
Like BP, the effect of antihypertensive medications on glaucoma development and progression is controversial. My findings showed that individuals, who were using angiotensin-converting enzyme (ACE) inhibitors and calcium-channel blockers, were more likely to develop glaucoma. The same findings were observed for ACE inhibitors and calcium-channel blocker users in a case-control study from the UK. In the longitudinal Rotterdam study, a higher incidence of glaucoma was observed among calcium-channel blocker users, but not for ACE inhibitors. On the other hand, in a 9-year follow-up study from Barbados, where antihypertensive medication use was simply modeled as “yes” or “no”, neither protective nor harmful effects were reported. In contrast, all classes of antihypertensive medications, but not vasodilators, were significantly associated with a lower risk of glaucoma, as reported by a nation-wide study in Denmark. Given that the association of glaucoma with antihypertensive medication use remains controversial even in prospective studies, it is difficult to explain why ACE inhibitors and calcium-channel blockers are harmful. Other study designs, such as clinical trials or Mendelian randomization are needed to investigate the association of antihypertensive medications reported by observational studies. Mendelian randomization uses genetic variants to test and estimate the causal effect of a modifiable risk factor on health and disease outcomes. It also offers a novel approach to predict the effects of drugs based on variation in the genes for the drug target proteins. Mendelian randomization is considered to be analogous to the randomized controlled trial study, as genotypes are segregated randomly from parent to offspring at conception.

In a large population-setting, a questionnaire-based proxy can be used to identify myopic individuals accurately

Myopia is a risk factor for glaucoma, and this evidence could have been investigated further, however, in this thesis, I created a myopia proxy and laid down the foundation for future myopia investigations in large population-based studies where myopic individuals can be captured without the need to perform an eye examination. The proxy yielded an age-standardized myopia (defined as mean spherical equivalent $<-0.5$ D) prevalence of 35%, essentially similar to the standardized prevalence of 30.6% for myopia defined as spherical equivalent $\leq -0.75$ D and reported by a meta-analysis study of the European Eye Epidemiology Consortium. The meta-analysis was based on refractive error data collected between 1990 and 2013 from fifteen European population-based studies. The crude prevalence in this study (34.8%) was similar to the crude prevalence reported in the UK biobank (33.5%), but clearly higher than the Blue Mountain Eye Study (15%). The
myopia definition in both UK Biobank and the Blue Mountain Eye Study were similar to my study (spherical equivalent ≤ -0.5), however, the data were collected in 2009 and between 1992-1994, respectively. Another difference between the current and these two studies was the age of study participants; adults (≥18 years or older) were included in my study, but data were collected from older people in the UK biobank (aged 40-69 years) and the Blue Mountain Eye Study (> 49 years) - the discrepancy in study results is expected as the burden of myopia is increasing globally in young people.46,47

Like glaucoma, myopia is a complex ocular disorder, where both environmental and genetic components are involved. I found a dose-response association of myopia with education and a polygenic risk score (PRS), conferring strong evidence that the current proxy is robust in the diagnosis of myopia. There is well-established evidence that higher education level is a strong indicator of myopia in the general population, and recently, two studies have confirmed its causality through Mendelian Randomization.48,49 The association with the PRS is in agreement with a previous study that performed PRS analysis on myopia.50 Based on genetic data, PRS enables prediction of the genetic liability of complex diseases, such as myopia.50 The PRS model is based on the assumption that instead of using single genes, a risk score in which all genes are integrated has more power for disease prediction.

Validated against the gold standard (measured spherical equivalent), the proxy accurately detected myopic cases; both specificity and sensitivity for myopia were > 90% and the area under the receiver operating characteristic (ROC) curve was 95%. Owing to differences in myopia definition thresholds (cut-off values) and gold standards used, direct comparison with various studies may not be possible. However, my work is the first to report a simultaneously high specificity and sensitivity compared to previous studies that investigated the validation of, at least partially, similar refractive error-related questions in detecting myopia.51-53 For example, although the sensitivity value (90%) in this thesis was similar to that of the UK biobank (89%),54 and a study by Ip et al. (88%),53 the specificity was significantly higher (92%) when compared to 84%, and 83% in the UK biobank,54 and Ip et al.,53 respectively.

The current work adds to the literature that the use of advanced statistical approaches, such as principal component analysis (PCA) in this case, maximizes the information that could be retrieved from the questions. Consequently, PCA showed the best performance (highest area under the ROC curve [AUC]) in detecting myopic cases when compared to individual questions or combinations thereof.
Methodology

I used multiple datasets and a wide range of data analysis approaches that were best suited for addressing the different research questions of each chapter. Here, I discuss these important methodological aspects of the thesis.

Data source

In Chapter 2, I prepared a peer-reviewed protocol for a systematic review and meta-analysis. It describes the objective, hypothesis, and planned methods for the review process. More specifically, the review protocol clearly defines the outcome data to be reviewed, outlines the method of data analysis, lists the inclusion and exclusion criteria, as well as the search strategies used to collect literature that fits pre-specified eligibility criteria. Aiming at minimizing review biases, the protocol also provides the quality control procedures that should be performed to evaluate the quality of selected articles, as well as to extract, synthesize, and report data.

In Chapter 3 (systematic review and meta-analysis), I did a comprehensive step-by-step systematic search in PubMed, EMBASE, Web of Science, and ScienceDirect. With more than 30 million records per database, PubMed and Embase are the two most popular, largest, and up-to-date biomedical and life science literature databases. I included studies of glaucoma and its related endophenotypes published until 31 December 2017. Furthermore, studies in which values were not reported but that could be re-estimated from intraclass correlations or linear coefficients were also included. To ensure that all relevant data were collected per study, I created a data extraction form, containing title and abstract, sample size, type of glaucoma or endophenotype, estimates, and other relevant variables.

I used the largest and most recent POAG GWAS-based summary statistics data for Chapter 4: this optimizes power for downstream gene prioritization and pathway analyses. The original GWAS analysis was performed by Choquet et al., and the summary statistics data are publicly available at the GWAS catalog (https://www.ebi.ac.uk/gwas/). The GWAS data were based on 12,315 glaucoma cases and 227,987 controls, of which 4,986 cases and 58,426 controls were from the multi-ethnic Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort, and 7,329 cases and 169,561 controls were from the UK Biobank. Of the 84 identified or replicated SNPs, 75 SNPs were selected for further analysis. Next, these 75 SNPs were clumped at Linkage Disequilibrium (LD) $r^2 < 0.1$ and a physical distance of 1 Mb using PLINK (v1.9). The resulting 50 nearest SNPs were used as input for
identifying variants that are located in coding regions and resulting in amino acid change, whereas, a full set of POAG GWAS summary statistics data were used for prioritizing the most likely causal genes using co-functionality, gene expression or summary statistics-based SMR. For exploring enriched functional pathways, I used DEPICT, GeneMANIA, and IPA (www.ingenuity.com) databases. These databases use different approaches to predict functional pathways associated with a set of input genes - a description for each of the databases is given in Chapter 4.

For Chapters 5 and 6, I used data from the Lifelines Cohort Study and Biobank, a multi-generational, prospective cohort study that includes over 167,000 participants (10%) from the northern population of the Netherlands. The LifeLines cohort employs a broad range of investigative procedures to assess the sociodemographic, biomedical, physical, behavioral, and psychological factors that contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. The large number of participants enables the detection of natural variations in risk factors and diseases. Lifelines participants were asked to invite their family members (i.e., partners, parents, and children), resulting in the formation of a three-generation family study.

Participants complete a follow-up questionnaire and visit a Lifelines research site every ~ 5 years. During the visits, biomaterials are collected and several tests and measurements are conducted. Both baseline and first follow-up data were available for BP measurements, but for antihypertensive medication use, only baseline data were collected. Similarly, follow-up eye questionnaire data, but not baseline, were available from all Lifelines participants (n = 110,759, 18 years of age and older); the data were collected between 2014 and 2017, after a median period of 3.8 years from baseline. Therefore, I investigated the association of baseline BP, HRV, and medication use with glaucoma at follow-up. Similarly, I investigated the association of education at baseline with myopia at follow-up. However, my analyses cannot be considered to be prospective as no information on eye conditions was available at baseline. As such, limitations in the interpretation of results are similar to those of cross-sectional study designs.

Data analysis

Meta-analysis of glaucoma heritability studies

Only a few glaucoma $h^2$ studies were reported; three for POAG, one for angle-closure glaucoma (PACG), and two studies for “unspecified” glaucoma. Within the POAG studies, the authors used different inclusion criteria to define individuals as having glaucoma. For
example, of the several inclusion criteria, vertical cup-to-disc ratio ≥ 0.7 was used to define POAG in the Charlesworth et al study, whereas, in the Cuellar-Partida et al study, cup-to-disc ratio > 0.95 was used. Because of these issues, no meta-analysis was performed for any of the glaucoma $h^2$ studies - studies were reviewed separately.

Random-effects meta-analyses were performed for 10 glaucoma-related endophenotype clusters (intraocular pressure, anterior chamber size, central corneal thickness, cup-to-disc ratio, disc size, cup size, corneal hysteresis, retinal nerve fiber layer thickness, cup shape, and peripapillary atrophy). A substantial degree of heterogeneity ($I^2 > 75\%$) was observed between studies of each cluster, but not for peripapillary atrophy ($I^2 = 58\%$). Therefore, for clusters with more than ten studies, I did additional subgroup and meta-regression analyses. Outcomes of both analyses showed consistent results, i.e., mean age (higher $h^2$ in younger people), study design (higher $h^2$ in twin-based studies), ethnicity (higher $h^2$ of anterior chamber size in East Asians), and method of data analyses (higher $h^2$ for the variance component) were identified to be the major sources of heterogeneity.

Post-GWAS bioinformatics of POAG

Danford et al and Janssen et al pioneered to determine the functional characteristics of POAG candidate genes. However, in these papers, no gene prioritization analysis was performed, i.e., input genes used for functional enrichment analyses were directly based on significant findings of previous genome-wide linkage- or association studies. In the current study, by combining genomic, transcriptomic, and epigenomic data from different sources, I did a comprehensive post-GWAS bioinformatics analysis on POAG. To identify genes whose expression or methylation levels are associated with POAG, I used publicly available expression Quantitative Trait Loci (eQTL) and methylation Quantitative Trait Loci (mQTL) data from blood and brain tissues. This has led to the identification of 142 genes relevant for POAG, of which 64 were novel. These 142 prioritized genes were then used as input data for functional enrichment analysis. This makes the current study unique, i.e., genes that may have a role through different mechanisms, including coding consequence, gene expression, co-regulation, or epigenetic regulation, were identified and used as input data for exploring overrepresented functional pathways and related tissues in POAG pathogenesis. On the other hand, the use of expression data from blood and brain tissues may have biased my findings towards previous knowledge. However, we used agnostic methods by including data from large-scale studies while simultaneously avoiding false interpretations by using conservative significance cut-offs adjusted for multiple testing.
Association of low HRV and high blood pressure with glaucoma

I used a glaucoma definition based on a previously defined algorithm in Lifelines. To build the glaucoma proxy, the algorithm used a self-reported questionnaire on diagnosis and treatment of eye conditions in combination with a standard visual function questionnaire from the National Eye Institute. As such, participants were categorized as have definite (who had incisional surgery for glaucoma), probable (who self-reported glaucoma or used IOP-lowering medication together with glaucoma-specific complaints above a certain threshold), or possible (who either self-reported glaucoma or had glaucoma-specific complaints) glaucoma cases, or were classified as having no glaucoma. This might have introduced an ascertainment bias on glaucoma classification, which could also affect the precision of association analyses. Obviously, with the proxy, it is not possible to disentangle normal tension (NTG) from high tension glaucoma (HTG) precisely. However, by leveraging Lifelines eye-questionnaire data, I made the best possible effort to address this issue.

The Lifelines algorithm included data on awareness of glaucoma status, i.e., participants were categorized into aware (definite, probable, and possible glaucoma by self-report) and unaware (possible glaucoma by complaint). Interestingly, based on the following reasoning, this information was used to identify NTG and HTG surrogates. Clinical glaucoma cases differ from glaucoma cases captured during glaucoma screening; HTG dominates in the former and NTG in the latter. For example, of the newly detected glaucoma cases during the baseline of the Rotterdam Study, only 10% had an IOP above 21 mmHg. As such, those cases who did not self-report their glaucoma but were classified based on their visual complaints (category “possible glaucoma by complaint”) could be considered as the best possible approximation of NTG cases. I repeated the analysis (glaucoma vs. HRV and BP) with these unaware cases and compared this group to cases who already knew their status (definite, probable, and possible glaucoma by self-report; a surrogate for HTG cases - inevitably significantly contaminated with NTG cases). Despite the fact that the aware group (HTG surrogate) contains the more clear cases (definite and probable), the effect of (low) HRV was essentially similar in the two groups. On the other hand, the effect of (high) blood pressure was only significant in the aware group. This suggests that either a high blood pressure is not related to NTG but only to HTG, or that indeed ascertainment bias plays a role. Phenotyping Lifelines participants or additional studies, with clinically defined glaucoma cases, is needed to investigate whether the role of HRV and BP is dependent on glaucoma subtype; NTG vs. HTG.
Future perspectives

Future glaucoma genetic studies

One of the main goals in this thesis was to estimate the proportion of variance of glaucoma (and closely related endophenotypes) due to genetic factors ($h^2$) through meta-analysis. The $h^2$ of POAG derived from twin or family-based studies ranges from 71% to 81% and that of PACG was 65%. However, when compared to glaucoma $h^2$ estimates observed within families, the $h^2$ explained by all SNPs on the genotyping array or by a collection of GWAS-significant variants is much smaller ($h^2 26\%$). Future genetic studies that combine POAG and different POAG-related endophenotypes will likely improve power and give rise to the identification of more genetic loci that may explain a substantial $h^2$.

Publicly available eQTL data from blood and brain tissues were used in the post-GWAS bioinformatics analyses of POAG, which may have introduced a bias, such as false positives. Therefore, future post-GWAS studies that incorporate eQTL data from eye-related tissues (e.g., trabecular meshwork), may improve the power to identify genes and functional pathways driving POAG development. Further in vitro and in vivo studies are needed for the most likely POAG causal genes identified in this thesis, particularly those with multiple lines of evidence. Furthermore, of the 142 prioritized genetic loci, 64 were novel for POAG, which means that there is no literature showing their roles and underlying mechanisms; future studies may focus on the functional characterization of these novel genes.

Causal inference

Despite extensive human and animal studies, the exact cause of glaucoma is not well understood. In this thesis, I have demonstrated the risk of low HRV, high BP, and antihypertensive medication use (especially ACE inhibitors and calcium-channel blockers) in glaucoma. Exposure-outcome associations detected in classical epidemiology often suffer from confounding potentially deriving from factors such as socio-economic status or lifestyle, or from reverse causation and measurement error. This calls for further studies to provide unbiased evidence on the causal inference of previously reported glaucoma risk factors, including HRV and BP. Mendelian randomization is an alternative approach to overcoming these limitations of classical epidemiological studies: - unmeasured confounding and reverse causation. Therefore, Mendelian randomization studies are required to elucidate whether HRV, BP, and antihypertensive medications have a causal association with glaucoma.
Towards myopia research in large-scale population-based settings

Utilizing five-item refractive error-related questions, I created and validated a myopia proxy for use in large population-based surveys. Compared to previous population-based validation studies, the current proxy was robust with a reasonably high accuracy for identifying myopia cases. The proxy not only provided a realistic myopia prevalence estimate, but the effects of educational attainment and PRS on myopia were also consistent with the results of previous studies that used directly measured refractive error data. Being cost-effective and less time-consuming, the current proxy provides more power for future myopia research aiming to develop novel prevention or treatment approaches.

Conclusions

In Part I of this thesis, I found a strong influence of genetic factors on glaucoma and its endophenotypes and provided the most accurate heritability estimates to date. Besides, I also identified 142 likely causal genes for glaucoma and their functional pathways leading to glaucoma pathogenesis. In Part II, I found an association of glaucoma with low heart rate variability and high blood pressure, which could be studied further using population-based prospective studies. Finally, in Part III, I developed and validated a questionnaire-based myopia proxy. The findings of this thesis may improve further glaucoma gene finding studies, ultimately aiming for efficient screening and personalized health care based on genetic profiles before irreversible blindness occurs. Similarly, the biological pathways identified in this thesis may highlight candidate drug targets guiding development of future novel therapies. The proxy can be used to describe myopia status accurately in large population-based cohorts, in which direct refraction measurement is costly and challenging.
References


