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Prevalence of Glaucoma and Cardiovascular Comorbidities in the Hamburg City Health Study (HCHS)

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Abbreviation

HSHC	Hamburg City Health Study
POAG	Primary open-angle glaucoma
PACG	Primary angle-closure glaucoma
OAG	Open-angle glaucoma
ACG	Angle-closure glaucoma
IOP	Intraocular pressure
M	Mean
SD	Standard deviation
N	Number

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1. Introduction

1.1. General Introduction: Glaucoma and Research Stand

Glaucoma describes a group of eye diseases with optic nerve damage caused by progressive degeneration of retinal ganglion cells and characterized by excavation or cupping of the optic disc (Weinreb, Aung and Medeiros, 2014; McMonnies, 2017). The degenerative nerve damage may eventually lead to irreversible loss of visual function and in advanced stadium even to blindness (Choplin and Traverso, 2014; Weinreb, Aung and Medeiros, 2014; McMonnies, 2017). Primary open-angle glaucoma (POAG) is the most common type of glaucoma with more than 80% of total cases, followed by primary angle-closure glaucoma (PACG) representing about 10% of all glaucoma cases (Bonomi, Marchini, Marraffa, Bernardi, de Franco, et al., 2000; Weinreb, Aung and Medeiros, 2014). The global prevalence of glaucoma in adults aged from 40 to 80 years is estimated 3.54% and about 76 million people are estimated to be affected by glaucoma in 2020 (Kang and Tanna, 2021). Approximately 10% of them become bilaterally blind, making glaucoma the leading cause of irreversible blindness, and causing a big burden to society and medical system (Weinreb, Aung and Medeiros, 2014; Kang and Tanna, 2021). Though glaucomatous vision loss is irreversible, it is preventable. Early diagnosis and adequate treatment can halt or slow disease development, thereby preventing morbidity (Kang and Tanna, 2021). Clinical symptoms of glaucoma can vary from mild to severe, depending on each type of glaucoma and its pathophysiology. In most cases, particularly POAG, the disease tends to develop slowly over years and only the peripheral vision gets affected first, that most patients do not even realize it (Choplin and Traverso, 2014). It is also reported that only 10-50% of people with glaucoma are aware of this disease. For this reason, glaucoma is often accidentally detected during a routine eye test, or at a late stage, when the disease is severe (Weinreb, Aung and Medeiros, 2014).

Therefore, early detection of glaucoma through screening and identification of high-risk patients as well as identification of risk factors plays a significant role in preventing disease progression to advanced stage and irreversible blindness. Although research about glaucoma is increasing in recent years, the pathophysiology of this multifactorial disease still stays incompletely understood (Kang and Tanna, 2021), and a study including potential multifactorial togethers is shorted. Beside focusing on the role of intraocular pressure as in many studies till now, other risk factors, such as age, gender, and cardiovascular comorbidities, also need to be paid attention and to be detected. The aim of this study is to estimate prevalence of glaucoma and whether cardiovascular comorbidities have an influence on this disease.

1.2. Prevalence of Glaucoma and Previous Diagnosis Rate

In the scientific literature, there have been various reports on the prevalence of glaucoma. These differences can be attributed to several factors, including the age and ethnicity of the study population as well as the geographic region in which the research was conducted. Furthermore, the definition used to identify glaucoma patients in these studies also contributes to the variations observed. Several systematic reviews and meta-analyses have reported varying estimates of glaucoma prevalence, with particular emphasis on primary POAG due to its high occurrence.

Tham et al. (2014) reported a global prevalence of glaucoma of approximately 3.54% in adults aged 40 to 80 years, with POAG being the most prevalent form (3.05%) and PACG accounting for 0.5% of cases. This study further predicted that the number of adults aged over 40 years with glaucoma worldwide would increase by 18.3%, from 64.3 million in 2013 to 76 million in 2020, and then by 74% to 111.8 million in 2040 (Tham et al., 2014). Other systemic reviews have reported similarly low global prevalence rates of POAG in adults, ranging from 2.2% to 2.4% (Kapetanakis et al., 2016; Allison, Patel and Alabi, 2020; Zhang et al., 2021). In contrast, the prevalence of POAG in Europe was estimated to range from 2.1% to 2.51% (Kapetanakis et al., 2016; Allison, Patel and Alabi, 2020).

Several population-based studies have been established to estimate the prevalence of glaucoma. In this article, not only prevalence of glaucoma in the world, but also in Europe, is to be concerned, because our study is a population-based study in Germany, which is the most populous European country. An US study has estimated the prevalence of glaucoma of 2.1% in Caucasians aged over 40 years (Gupta et al., 2016). In Greece, the prevalence of OAG among people aged above 60 years was approximately from 3.8-5.5%, and that of POAG was from 2.7-3.8% depending on define criteria of glaucoma (Topouzis et al., 2007). The prevalence of glaucoma in population aged over 50 years in Northern Ireland was reported to be 2.83% and the age-weighted prevalence in 2017 was 3.24% (McCann et al., 2020). In wider age range of German population from 35-74 years, the Gutenberg Health Study has recently reported a lower glaucoma prevalence of 1.34% (Höhn et al., 2018).

Some population-based surveys have shown that around 50% of people with glaucoma are unaware of their diagnosis, this is even true in developed nations (Kang and Tanna, 2021). According to the Thessaloniki Eye Study (Topouzis et al., 2008), 50.4-52.1% patients with OAG in Greece were previously undiagnosed and this undiagnosed patients with POAG is even higher 57.1%, since this subtype of glaucoma often progresses slowly over years and stay asymptomatic until severe stage. The undiagnosed ratios of glaucoma in the USA and Northern Ireland are also similar high 56.3% and 50% (Gupta et al., 2016; McCann et al., 2020). Meanwhile Germany and Singapore have an extremely high undiagnosed rate of 81.9% and 72.1% (Höhn et al., 2018; McCann et al., 2020), the UK in EPIC-Norfolk study has a much lower previously undiagnosed rate of 33.3% (Chan et al., 2017). Generally, the undiagnosed rate of glaucoma in all countries stay very high, or it also means the previous diagnosis rate is very low and depending on countries. A systematic review has also reported that the previous diagnosis rate of OAG and ACG in developed countries was 34% and 67%, while this rate in developing countries was 8% and 0.1% (Quigley and Broman, 2006; Kim et al., 2016).

1.3. Risk Factors: Age, Gender, and Cardiovascular Comorbidities

In addition to ocular hypertension there are other risk factors playing an important role in the pathogenesis of POAG or even a predominant role in certain cases (Bonomi, Marchini, Marraffa, Bernardi, Morbio, et al., 2000). Age and frailty consistently appear as a risk factor for the diagnosis of glaucoma. Moreover, gender is also going in discussion, though there are conflicting between information from different studies. In addition, several studies have identified cardiovascular disease to be also a risk factor

for diagnosis of POAG (Marshall et al., 2021). To be mentioned are systemic hypertension, atherosclerosis and dyslipidemia, cerebral stroke, diabetes mellitus, smoke status and other vascular diseases (Bonomi, Marchini, Marraffa, Bernardi, Morbio, et al., 2000; Zhou et al., 2014; Kim et al., 2016; McMonnies, 2017; Kang and Tanna, 2021; Nislawati et al., 2021). Beside cardiovascular diseases, antihypertensive, aspirin and statins, and corticosteroid usages are also detected as risk factors for getting glaucoma (McMonnies, 2017; Marshall et al., 2021).

1.3.1. Age and Glaucoma

Glaucoma is more prevalent in the aging population, as age is the strongest risk factor for developing glaucoma (Chan et al., 2017), which may be affected by a variety of medical conditions including arterial hypertension and diabetes mellitus. This fact is demonstrated in many different glaucoma studies, whose results showed that the glaucoma prevalence varied significantly by age and increased steeply with age. In the Blue Mountains Eye Study from Australia, the prevalence of glaucoma was 0,4% for people under 60, 1.3% for people from age 60-69, 4.7% for the age group of 70-79, and 11.4% for people over 80, and there was an exponential relationship between glaucoma prevalence and age (Mitchell et al., 1996). With prevalence of 0.6% in age group of 50-59, 2.8% in 60-69, 8% in 70-79, and 12.8% in people over 80 years of age, the prevalence of OAG in the Reykjavik Eye study in Iceland also showed the effect of aging on developing glaucoma (Jonasson et al., 2003). With 8623 participants aged 48-92 from the city of Norwich and the eastern English county of Norfolk, the EPIC-Norfolk study has reported the prevalence of glaucoma, which also increases with age (Chan et al., 2017). With majority of African population, the glaucoma prevalence in the Barbados Eye study also increased steeply with age, reaching 14.8% at age group of 70-79 and 23.2% at older ages (Cristina Leske et al., 1994). In Asia, the prevalence of POAG, which increased significantly with age, was also reported in the Korea National Health and Nutrition Examination Survey, an increase from 2.8% to 8.9% were noted for the POAG prevalence of different age groups from 40-49 years to 80 years or older (Kim et al., 2016). Through listed studies above, glaucoma strongly correlated with age, older age consistently appears to be risk for having glaucoma in different races and geographic regions. No exception in German population, the Gutenberg Health study has also shown that the glaucoma prevalence gradually increased with each decade of age, and the rise especially increased exponentially above the age of 65 years (Höhn et al., 2018).

1.3.2. Gender and Glaucoma

The risk for glaucoma development between genders haven been reported in multiple epidemiologic and population-based studies with conflicting results, which may lay on multiple factors including the variable definition of glaucoma, the bias of researchers, the predominant type of glaucoma and the genetic variability in the study population (Tehrani, 2015). Multiple studies, such as Baltimore Eye Survey, the Framingham Eye Study, the Beaver Dam Eye Study and the Los Angeles Latino Eye Study, have found that there was no significant difference at risk for glaucoma development between genders (Vajaranant et al., 2010; Tehrani, 2015). On the other hand, gender differences in glaucoma are detected in several studies as well. A literature review from the USA has reported that the prevalence of glaucoma in males is 36% higher than in

females (Allison, Patel and Alabi, 2020). Furthermore, a higher prevalence of glaucoma among men is also noted in the Barbados Eye Study and the Rotterdam Study (Tehrani, 2015). However, the Blue Mountain Eye Study has found that the prevalence of glaucoma is higher in women after adjusting for age (Tehrani, 2015). Current evidence has identified that older women are particularly at higher risk for glaucoma and glaucoma blindness, not only because of their tendency to live longer, but also of their dominant number in the population (Vajaranant et al., 2010). Lastly, men are noted to be at higher risk for POAG (Tham et al., 2014; Allison, Patel and Alabi, 2020), meanwhile women are described in numerous studies for being at risk for PACG (Vajaranant et al., 2010; Tehrani, 2015; Allison, Patel and Alabi, 2020). In Germany, a more frequent occurrence of glaucoma in women has been reported in the Gutenberg Health Study (Höhn et al., 2018).

1.3.3. Cardiovascular and Systemic Risk Factors and Glaucoma

Beside age and gender, multiple potential contributing factors for diagnostic of glaucoma, including cardiovascular and relevant factors and medication interactions, have been reported. To be mentioned in this article are systemic arterial hypertension and other cardiovascular diseases and risk factors, such as carotid artery stenosis, diabetes, and smoking. Associations between glaucoma and taking medications, such as glucocorticoid and antihypertensive medication, are also to be concerned.

While description of systemic hypertension as a potential risk factor for glaucoma has been repeated in multiple studies, several studies have reported association between low diastolic pressure and higher prevalence of glaucoma (Memarzadeh et al., 2010; McMonnies, 2017; Tham and Cheng, 2017). According to the vascular hypothesis, high blood pressure can increase intraocular pressure (IOP) and increase therefore the risk of glaucoma diagnosis through two mechanisms, which are increase in the production of aqueous humor caused by increasing the in intravascular pressure and IOP gradient by rising capillary pressure in the ciliary body and decreasing of the aqueous humor absorption due to an increase in episcleral venous pressure (Nislawati et al., 2021). However, a conflicting result has also been reported in Chennai Eye Study, that hypertension is protective for the development of POAG after adjusting for age, gender, and habitation type (Vijaya et al., 2014; Tham and Cheng, 2017). This protective effect of hypertension can also be explained by increasing ocular perfusion pressure in hypertensive patients (Nislawati et al., 2021). The association between low blood pressure and glaucoma has also been explained by the vascular hypothesis. A Low systemic blood pressure, especially when combined with elevated IOP, will lower the ocular perfusion pressure, and can lead to ischemic and reperfusion oxidative stress damage to the axons (McMonnies, 2017). Therefore, antihypertensive treatments, such as antihypertensive medication, and associated lower blood pressure could increase the risk of glaucoma by this mechanism.

Not only in case of low ocular perfusion pressure, but retinal ischemia is also detected under certain conditions, such as diabetic retinopathy and carotid artery stenosis. The resultant neovascularization developing in the ocular anterior segment and over the iridocorneal angle can cause aqueous humor outflow obstruction (Zhou et al., 2014; Kang and Tanna, 2021). Therefore, diabetic mellitus and carotid artery stenosis are also listed as risk factors for developing diagnosis of glaucoma.

Systemic corticosteroid therapy has been mentioned in some studies as a risk factor for IOP elevation characterized in steroid responders, which is caused by increased resistance to outflow through the trabecular meshwork. Though the elevation of IOP is typically reversible after cessation of steroid exposure, corticosteroid usage is still a potential risk factor for glaucoma (Roberti et al., 2020; Kang and Tanna, 2021).

1.4. Medication Treatment of Glaucoma

All treatment methods of glaucoma are aimed to reduce the IOP, which is the only effective way that has been proven so far and generally accepted for the prevention of disease progression (Schuster et al., 2020; Kang and Tanna, 2021). Because glaucoma is not a single, but a group of diseases, treatment methods and the goal of IOP to achieve through the therapy stay individual (Schuster et al., 2020). Beside invasive treatments, such as laser therapy or glaucoma surgery, medication treatment offers a less invasive therapy option with diverse variations of substance classes, which are most in form of topical therapy. The main classes of glaucoma medication treatment are carbonic anhydrase inhibitor, beta-blocker, prostaglandin analogue, cholinergic and alpha-2 agonist (figure 1) (Kang and Tanna, 2021; Pharma Stulin GmbH, 2021). All these medication classes have different mechanisms to increase the outflow or to reduce the production of aqueous humor. The most frequently used substance class that has been reported is prostaglandin analogue, which activates matrix metalloproteases and degrades collagen in the ciliary body, that allows unconventional aqueous humor outflow through this tissue (Kang and Tanna, 2021). In individual consideration of current IOP, structural and functional progression, risk factors and potential side effects, it will be decided which and how many medication classes are applied to the treatment of glaucoma (Schuster et al., 2020). Approximately half of glaucoma patients require more than one medication to reach their goal of IOP (Kang and Tanna, 2021). For this reason, various combined preparations are existing.

Figure 1: Medication classes in glaucoma treatment (Schuster et al., 2020; Kang and Tanna, 2021)

Prostaglandin Analogue	ß-Blocker	Carbonic Anhydrase Inhibitor	Cholinergic Agonist	Alpha-2 Agonist
• Substances: Latanoprost, Travoprost, Bimatoprost, Tafluprost • Mechanism: aqueous humor outflow ↑ • Side effects: conjuntival hyperemia, eyelash growth, pigmentation change in iris and periocular skin • Contraindication: active uveitis, asthma, severe cardiovascular conditions, liver/kidney diseases	• Substances: Timolol, Levonunolol • Mechanism: aqueous humor production ↓ • Side effects: dry eye disease and other cardiac side effects (bradycardia, hypotension,...) • Contraindication: asthma/COPD, AV-Block II-III°, cerebral hypoperfusion, bradycardia, decompen-sated congestive heart failure	• Substances: Actetazolamid, Dorzol-amid, Brinzolamid • Mechanism: aqueous humor production ↓ • Side effects: ocular irritation, allergic dermatitis, metallic taste, corneal edema • Contraindication: Sickle cell disease, sulfa allergy	• Substances: Pilocarpine • Mechanism: aqueous humor outflow ↑ • Side effects: blurred vision, headache, retinal tear, paradoxic angle closure • Contraindication: ocular inflammation	• Substances: Brimonidin, apraclonidine, clonidine • Mechanism: aqueous humor outflow ↑, aqueous humor production ↓ • Side effects: conjunctiv-itis, lid retraction, dry mouth, fatigue, systemic hypotension • Contraindication: infant and children under 12, bradcardia,hypotension, arteriosclerosis, impair-ed hepatic and renal funtion

1.5. Hamburg City Health Study (HCHS)

The Hamburg City Health Study (HCHS) is a prospective, population-based cohort study that aims to investigate major risk factors for numerous symptoms and diseases and detect associations between different illnesses in patients with multimorbidity. With a design that randomly selects 45,000 participants aged between 45 and 74 years from the general population of Hamburg, the second biggest city in Germany, HCHS becomes the largest local health study in the world (Homepage Hamburg City Health Study, 2022). This simgle-center study was established in the University Medical Center Hamburg-Eppendorf with interdisciplinary cooperation of physicians and scientists from over 30 departments and institutes. The enrollment began on February 08, 2016 and is expected to be finished on November 30, 2022.

The participants were contacted and invited by post and underwent a 7-hour examination, which includes validated examination of different organ systems such as anthropometric measures, measurements of resting blood pressure, electrocardiogram, and further validated physical examinations. The study is extraordinary by examining multiple organs, ranging from detailed cardiovascular, cognitive, and oral health phenotyping, pulmonary function test over skin screening and muscle tests to optical coherence tomography. In addition, the study also analyzes extended laboratory parameters and collects biobanking samples. Validated self-reports via questionnaires about lifestyle, food patterns, professional life, quality of life, physical and sexual dysfunction, as well as psychosocial problems, are also filled out during the appointment.

Personal information such as age, gender, race, anthropometric measures, and registration of medical history and premedication from the participants are gathered to estimate the prevalence of glaucoma and detect cardiovascular comorbidities. After the baseline examination, participants are asked to report any major medical event and changes in medication, lifestyle, physical, as well as mental health. This follow-up is performed annually for 5 years, and after 6 years, participants are invited to the study center to undergo the whole procedures and examinations like in the baseline visit (Jagodzinski et al., 2020).

With its high number of examinations of different organ systems, extensive annual follow-up, expanded laboratory and biobanking analyses, and high number of probands, HCHS enables cause-effect analyses investigating major risk factors for numerous symptoms and diseases as well as detecting associations between different illnesses in patients with multimorbidity. The study also secures that even relatively rare outcomes may be explored, providing a rich and promising data source for advanced analyses and has a high potential and meaning for research.

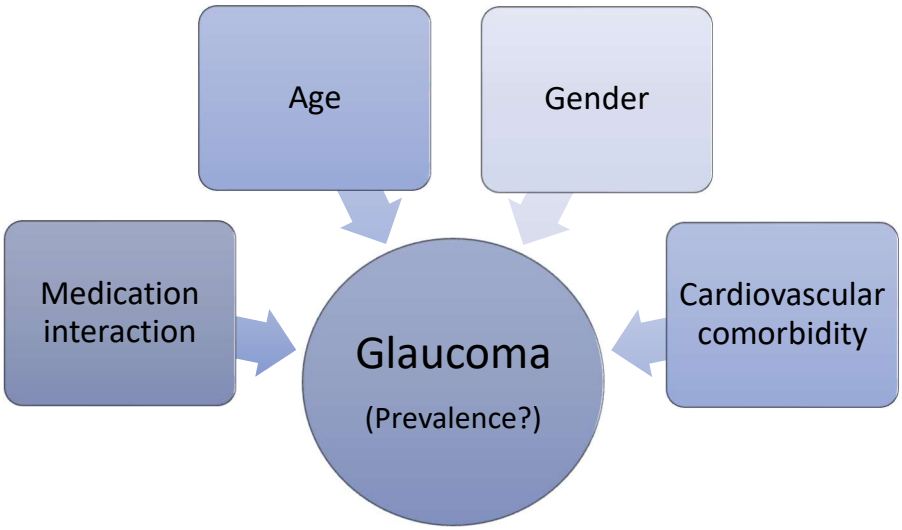
For this project, we have selected information from existing data of the first 10,000 participants, which allows us to estimate the prevalence of glaucoma and its association with different cardiovascular diseases and risk factors. This includes information such as age, gender, BMI, self-reported medical history regarding glaucoma, cardiovascular diseases, and other systemic illnesses such as diabetes mellitus. The premedication lists are also important to define what kind of medication a test person has and whether a test person uses antiglaucoma medication, which

defines that person as a glaucoma patient. The process of defining a sample with glaucoma and detecting the association between glaucoma prevalence and other cardiovascular risk factors will be described in detail in the upcoming section of the methods in this article.

1.6. Research Questions and Hypotheses

The primary objective of this thesis is to estimate the prevalence of glaucoma in the European population, with a particular focus on Germany. The secondary objective is to investigate the risk factors associated with glaucoma, including demographics such as age, gender, and body mass index, as well as cardiovascular comorbidities and medication use, Given the considerable impact of glaucoma on quality of life and the associated socioeconomic burden, it is critical to identify and understand these risk factors. To achieve these objectives, several research questions were formulated: What is glaucoma's prevalence in Germany? Is there an association between glaucoma and age or gender, and if so, what is the nature of this association? What is the effect of cardiovascular diseases and related risk factors on the development of glaucoma? Finally, is there any interaction between medication use and glaucoma? The findings to address these research questions will be presented in the subsequent sections of this thesis.

Figure 2: Glaucoma and concerned risk factors



2. Methods

2.1. Participants enclosure and data extraction

This study aims to recruit a random sample of 45,000 adults aged 45-74 years from the general population of Hamburg within the framework of HCHS. The recruitment process began on February 08, 2016 and is expected to be completed on November 30, 2022. Participants will be invited by post to the test center at University Clinic Hamburg Eppendorf and will be required to complete validated self-report questionnaires about their age, gender, health status, including glaucoma, cardiovascular and relevant comorbidities, during their 7-hour appointment at the center. In addition, participants will be requested to bring a list or packages of their current medication to the test center for recording an updated list of medication for the study.

Data have been collected from the first 10,000 participants and include their medical history regarding glaucoma, cardiovascular and relevant diseases, and a list of premedication. The data have been extracted and compressed into Excel tables and saved in a USB drive, which has been provided to the Clinic and Polyclinic for Ophthalmology of University Clinic Hamburg-Eppendorf. The document files are password protected and can only be read and extracted by software named VeraCrypt. After extraction, the data are displayed in their original form in three full-sized Excel tables, namely Projekt_197_data_20211206, Projekt_197_medicamentation_20211206, and VM_Projekt_197, which contain coded answers of relevant questionnaires from 10,000 participants, a list of their current medication, and a decoding table of relevant questionnaires and answers.

The collection of demographic data including Age, Gender, and BMI, as well as the assessment of comorbidities and substance use, was conducted through self-report, medication lists, and the application of specific criteria. The definition of comorbidities and usage of substances in this study is presented in Table 1 below.

Table 1: Disclosure's information Definition and Decoding from data pool

Category	Definition	Decoding
Age	Self-reported	Unit of years, Answer in number
Gender	Self-reported	'0' = male; '1'= female
BMI	Calculated	Answer in number = Weight/Height^2
Glaucoma	Self-reported	'0' = no; '1' = yes others than 0, 1 = NA
Antiglaucoma drug	List of medication with ATC-code S01E	'0' = no; '1' = yes; data missing = NA
Cataract	Self-reported	'0' = no; '1' = yes

		others than 0, 1 = NA
Macular Degeneration	Self-reported	'0' = no; '1' = yes others than 0, 1 = NA
Arterial hypertension	List of medication with ATC-code C09A, C09C, C07A, C03C, C03A, C03D, C08C, C02D, C02A, C09X, C01D or systolic blood pressure > 140mmHg or diastolic blood pressure > 90mmHg or self-reported yes	'0' = no; '1' = yes; data missing = NA
Diabetes mellitus	Self-reported	'0' = no; '1' = yes others than 0, 1 = NA
Carotid artery stenosis	Self-reported	'0' = no; '1' = yes others than 0, 1 = NA
Peripheral arterial disease	Self-reported	'0' = no; '1' = yes others than 0, 1 = NA
Dyslipidemia	Self-reported	'0' = no; '1' = yes others than 0, 1 = NA
Angina pectoris	Self-reported	'0' = no; '1' = yes others than 0, 1 = NA
Metabolic Syndrome	Presence of any 3 of 5 following risk factors: 1. Male & waist size ≥ 94 cm OR Female & waist size ≥ 80 cm 2. Triglycerides ≥ 150 mg/dL OR drug treatment for elevated triglycerides 3. HDL< 40 for men/ HDL < 50 for women OR drug treatment for reduced HDL-Cholesterol 4. Blood pressure systolic ≥ 130 mmHg OR diastolic ≥ 85 mmHg OR antihypertensive drug treatment 5. Fasting blood glucose ≥ 100 mg/dl OR drug treatment for elevated glucose	"0" = no when: • 3 Statements FALSE and the other 2 = TRUE/missing • 4 or 5 Statements FALSE and rest =TRUE/missing "1" = yes when: • 4 or 5 Statements TRUE and rest =FALSE/missing • 3 Statements TRUE and the other 2 = FALSE/missing "missing" = NA when: • 2 Statements = TRUE and 2 Statements = FALSE And 1 Statement = missing • 3 or 4 or 5 Statements = missing and rest = TRUE/FALSE

Coronary artery disease	Self-reported	'0' = no; '1' = yes others than 0, 1 = NA
Antihypertensive drug	List of medication with ATC-codes: C09A, C09C, C07A, C03C, C03A, C03D, C08C, C02D, C02A, C09X, C01D	'0' = no; '1' = yes data missing = NA
ß-Blocker	List of medications with ATC-Code of C07	'0' = no; '1' = yes data missing = NA
Glucocorticoid	List of medications with ATC-Code of H02AB	'0' = no; '1' = yes; data missing = NA
Drug Treatment for elevated Glucose	List of medications with ATC-Code of A10A, A10B, A10X	'0' = no; '1' = yes data missing = NA
Drug Treatment for elevated Triglycerides	List of medications with ATC-Code of C10AB, C10BB, C10AX06, C10AA,C10BA, C10BX, C10AX09, C10AX13,C10AX14	'0' = no; '1' = yes data missing = NA
Smoking	Self-reported: current smoking or quit within last than 6 months	'0' = no; '1' = yes others than 0, 1 = NA

2.2. Data analysis and statistical methods

The study defines glaucoma patients as subjects who take antiglaucoma drugs, which can be filtered from the registered premedication list as described in a previously mentioned table. This enables the estimation of the prevalence of glaucoma in the total sample as well as in specific groups of people with different comorbidities and substances. Statistical methods can be used to analyze the association between glaucoma and different cardiovascular diseases and risk factors.

Descriptive analysis will be conducted to compare glaucoma and non-glaucoma participants regarding age, sex, and comorbidities using appropriate tests such as Chi-2 test, t-test, or two-factor ANOVA-test. Numeric data such as age will be presented as means and standard deviations for normally distributed variables or as median and interquartile range for non-normally distributed variables. Categorical and binary data will be presented in absolute numbers and percentages. Logistic regression analysis will be used to analyze the correlation of age, sex, and selected comorbidities with the prevalence of glaucoma using a complete case approach. Adequate post-hoc correlation will be applied to address multiple testing.

The relevant columns from the HCHS data table will be selected, decoded, and copied into a new Excel table. This includes columns for disclosure ID, age, gender, BMI, interested diseases such as glaucoma, arterial hypertension, diabetes mellitus, carotid artery stenosis, and medications and substances such as antiglaucoma drugs, antihypertensive medications, beta-blockers, glucocorticoids, and smoking. Each

column about diseases and medications will have information possibilities of yes, no, or not available (NA, 8888, 9999), while age and BMI columns will be displayed as numbers.

The first step in the data analysis process involved importing the data from the Excel table into SPSS, a statistical software package. The variables were set up in the "Variable View" tab, where the level of measurement (metric, ordinal, or nominal) and type of variable (numeric or string), as well as missing values, were defined for each column. Invalid data, such as "NA", "8888", and "9999" from the dataset were removed by utilizing the "Transform" function and then the "Recode Into Different Variables" option. The missing values were excluded from analysis by checking the "Exclude cases listwise" option in "Descriptive Statistics". Descriptive statistics were performed for numeric data, such as age and BMI, and the output displayed the means, standard deviations, medians, and interquartile ranges for the numeric data. To compare glaucoma and non-glaucoma participants with respect to age, sex, and comorbidities, appropriate statistical tests such as Chi-2-test, t-test, or two-factor ANOVA test were used. For analyzing the correlation between age, sex, and selected comorbidities with the prevalence of glaucoma, logistic regression analysis was utilized. The output displayed the odds ratios, confidence intervals, and p-values for the logistic regression analysis. The results were presented in tables and various types of graphics, such as histograms, scatter plots, or bar charts. Table 2 provided an overview of the statistical analysis plan for various research questions.

Table 2: Overview method plan for research questions

Research question	Method
Prevalence of glaucoma in total sample, each gender, in different groups with different comorbidities and substances	Descriptive statistic: rate of people taking antiglaucoma drug in that group
Effect of age on prevalence of glaucoma	Two-tailed t-test for independent samples
Effect of gender, different comorbidities, and substances on prevalence of glaucoma	Chi-Square test + Interpretation of observed frequencies and expected frequencies for perfectly independent variables
Influence of gender, different comorbidities, and substances on relationship between age and prevalence of glaucoma	Two-factor ANOVA without repeated measures

In order to gain an understanding of the distribution of the data, descriptive statistics were applied to different samples including the entire sample (N=10,000) and samples stratified by different comorbidities and substances such as arterial hypertension, diabetes, antihypertensive drugs, corticoid therapy, etc. The prevalence of glaucoma in each sample was estimated as the rate of individuals taking antiglaucoma drugs within that sample.

To determine if there were differences in age and BMI between individuals taking antiglaucoma drugs and those who were not, a two-tailed t-test for independent samples was conducted. The null hypotheses were that there was no significant difference between the two groups with respect to age and BMI. If a statistically significant difference was found, a point-biserial correlation was conducted to determine the relationship between the continuous variables of age and BMI and the naturally binary variable of antiglaucoma drug use. Graphs of descriptive statistics were then created to visually represent any correlation relationships found.

To determine if the use of antiglaucoma drugs was influenced by gender or other factors such as specific diseases or medication use, a Chi-square test was performed. The test assessed the independence of two nominal variables: gender (female, male) and antiglaucoma drug use (yes, no). The same test was also used to study the relationship between different diseases and medication use and the use of antiglaucoma drugs. The Chi-square test results were displayed in tables containing the Chi-square value, degrees of freedom (df), and p-value. A significance level of 5% and a df-level of 1 were used to assess statistical significance. The effect strength was calculated using Cramer's V, which reflects the strength and significance of the association between the variables.

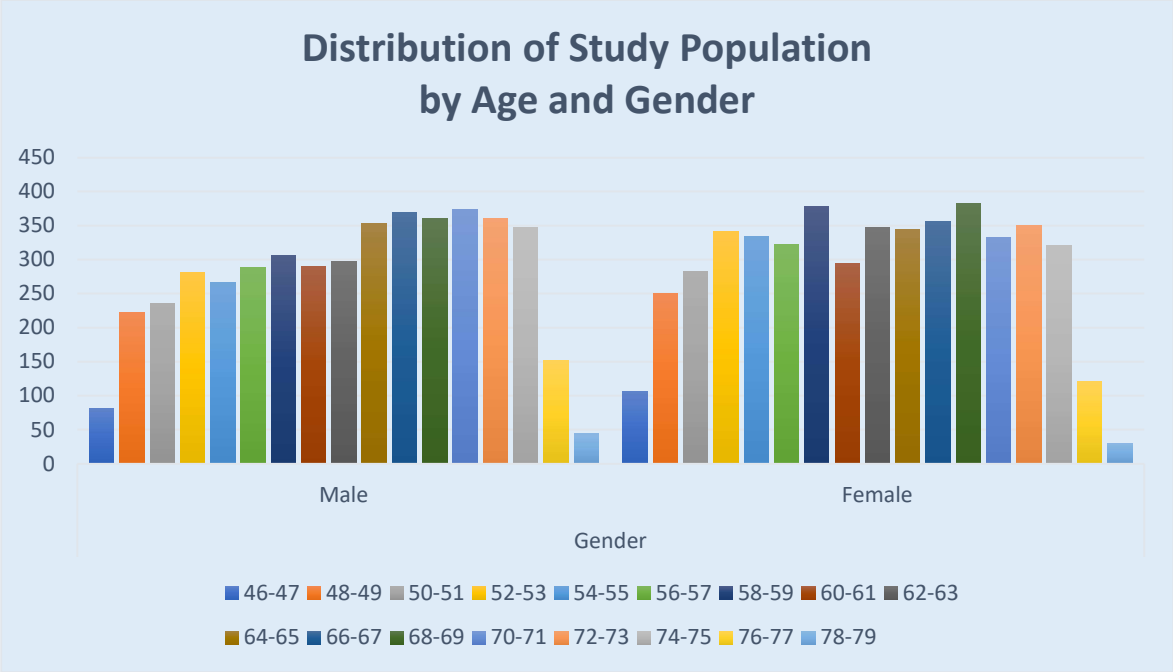
A two-factor analysis of variance (ANOVA) without repeated measures was conducted to assess the interaction between the variable of antiglaucoma drug use and another factor such as gender, arterial hypertension, diabetes mellitus, carotid artery stenosis, antihypertensive drug use, ß-blocker use, glucocorticoid use, or smoking in relation to the dependent variable of age. Levene's test was used to assess the equality of variances across groups. The null hypothesis was that there was no significant interaction between the variable of antiglaucoma drug use and another factor in relation to age. If the calculated p-value was below the significance level of 5%, the null hypothesis was rejected, and if the calculated p-value was above this level, the null hypothesis was retained. An interaction plot was used to analyze any interactions that were found.

3. Results

3.1. Description of the study population

In this study, participants with valid premedication data were included for statistical analysis, resulting in a study population of 9532 participants (M=62.5, SD=8.42), comprising 4898 women (51.38%) and 4634 men (48.62%). Other 468 subjects were excluded from statistical analysis due to the lack of valid premedication data. The age range of the valid participants was 46 to 78 years old, with males having a slightly higher mean age (M=62.97, SD=8.43) than females (M=62.06, SD=8.4). The age distributions for both gender groups were normal (Figure 3). The study analyzed the prevalence of glaucoma in the entire sample, as well as specific populations, and examined the relationship between glaucoma and potential influence factors such as age, gender, cardiovascular comorbidities, and medication interactions. The intriguing findings from the study are presented in the following sections.

Figure 3: Distribution of Study Population by Age and Gender



3.2. Prevalence of Glaucoma

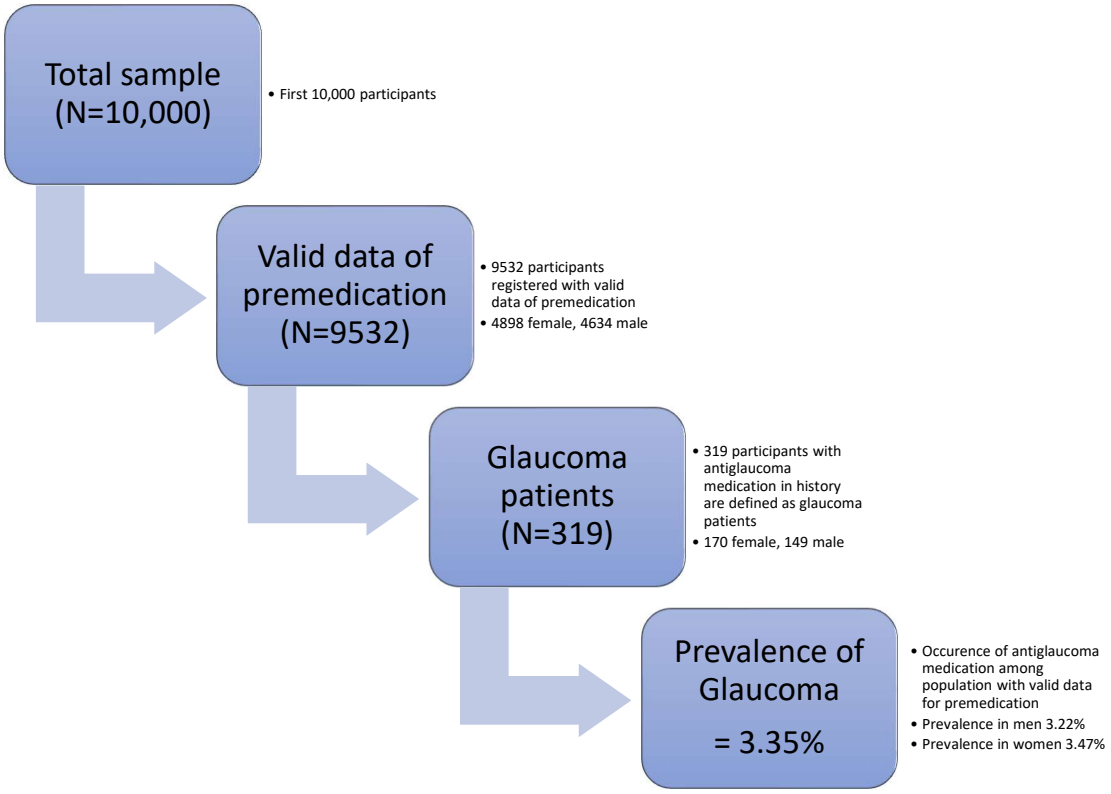
3.2.1 Prevalence of glaucoma in the general study population

Among the study population with valid data of premedication (N=9532), 319 subjects (M=67.09, SD=7.57) were identified as glaucoma patients based on their use of antiglaucoma medication (Figure 4), resulting in a prevalence of glaucoma of 3.35% (95% CI: 3.00%-3.70%). It is worth noting that the population with antiglaucoma medication or glaucoma (M=67.09, SD=7.57) had a higher mean age than the general study population (M=62.5, SD=8.42) and the population without antiglaucoma medication (M=62.34, SD=8.41). Further analysis revealed that only 214 out of 319 participants who reported taking antiglaucoma medication were aware of their glaucoma diagnosis, according to their responses on the questionnaires. The remaining one-third either denied having a diagnosis of glaucoma or were unsure. This

suggests that a significant proportion of individuals taking antiglaucoma medication may not fully understand the purpose of their medication. These results highlight the importance of patient education and communication in the management of glaucoma.

Among 319 glaucoma patients, women outnumbered men (53.29% female vs. 46.71% male), although men had a slightly higher mean age than women (M=67.22, SD=7.39 for males vs. M=66.97, SD=7.74 for females). The estimated prevalence of glaucoma in the male and female populations, based on the prevalence of taking antiglaucoma medication, was approximately 3.22% and 3.47%, respectively.

Figure 4: Overview from Data to Prevalence of Glaucoma in the Study Population

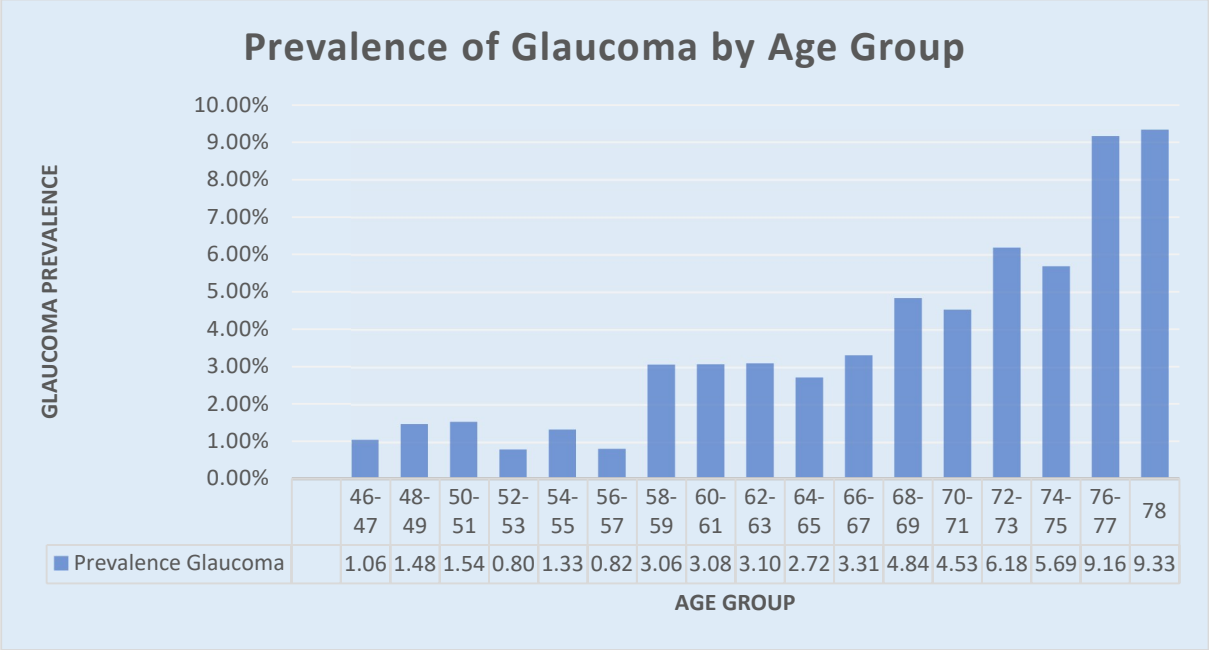


While the difference in glaucoma prevalence between genders was not significant, there were clear differences between age groups. A figure (Figure 5) visually displayed the prevalence differences between age groups and the relationship between age and glaucoma prevalence. The figure indicated that most people develop glaucoma after reaching an average age or at higher ages and that glaucoma prevalence increases with age. The older the population, the higher the prevalence of glaucoma. The highest prevalence of glaucoma was found in the age group of 76-78 years (9.16%-9.33%), while the lowest was found in the age groups of 52-53 and 56-57 years (less than 1%). Moreover, the figure also showed two age peaks for glaucoma prevalence: ages 58-59 and 76-78 years.

The rapid increase in glaucoma prevalence at ages 58-59 and 76-78 years may be explained by the fact that age has the greatest impact on developing glaucoma at these ages. In contrast, there was an observable drop in glaucoma prevalence at the age group of 52-56 years compared to previous age groups of 46-51 years. This could be attributed to a recession of potential genetic disposition for the disease, but this may be less likely after reaching an average age like 52-57 years. Overall, these findings

highlight the importance of age as a significant factor in developing glaucoma. The results indicate that the prevalence of glaucoma increases with age and that certain age groups are at higher risk for developing the disease. Further investigation is needed to identify the underlying mechanisms of age-related glaucoma development and to develop effective strategies for early detection and prevention.

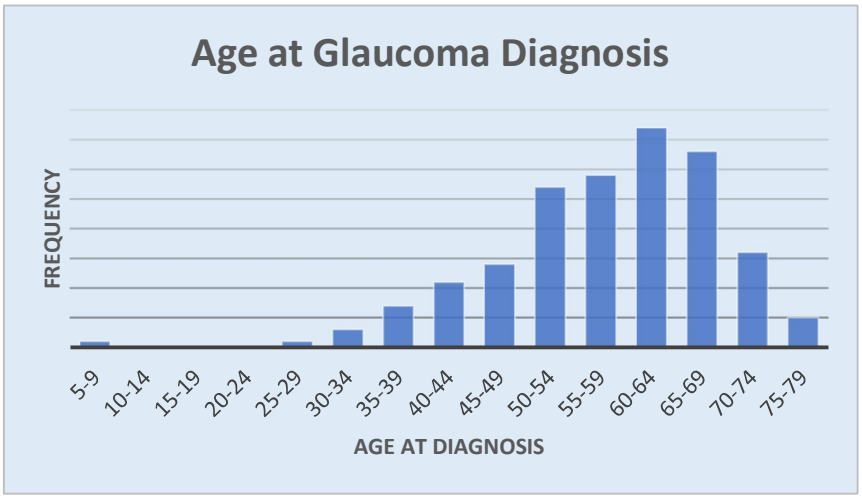
Figure 5: Prevalence of Glaucoma by Age Group



The age at which individuals receive their first diagnosis of glaucoma is an important factor in understanding the disease. In this study, out of the 319 glaucoma patients who were identified as taking antiglaucoma medication, only 184 participants have valid answers to questions about their age at first diagnosis of glaucoma. The mean age at first diagnosis was found to be 57.32 years (SD=11.16), with a wide range of ages reported (see Figure 6). The highest age at first diagnosis was 76 years and the lowest was 8 years. It is notable that only one patient reported receiving their first diagnosis of glaucoma at the age of 5-9 years, indicating the presence of congenital glaucoma in the study population. The majority of participants reported receiving their first diagnosis between the ages of 50 and 69 years, with the highest peak occurring at the age of 60-64 years. Although glaucoma diagnosis at young ages (25-39 years) was also reported, the prevalence of this was relatively low.

A visual field examination is an important measure for assessing the severity of glaucoma. In this study, only 5704 participants completed the visual field examination, including 189 participants with antiglaucoma medication and 5515 without. Among the group of glaucoma participants, nine were found to have a visual field loss (4.76%), including eight with partial hemianopia and one with complete hemianopia. In comparison, the percentage of participants with visual field problems in the non-glaucoma group was 2.05%. This indicates that the risk of visual field loss in the glaucoma population is double that in the non-glaucoma population, with a ratio of about 2.2:1. These findings highlight the importance of regular visual field examinations for glaucoma patients in order to monitor the progression of the disease and prevent further visual impairment.

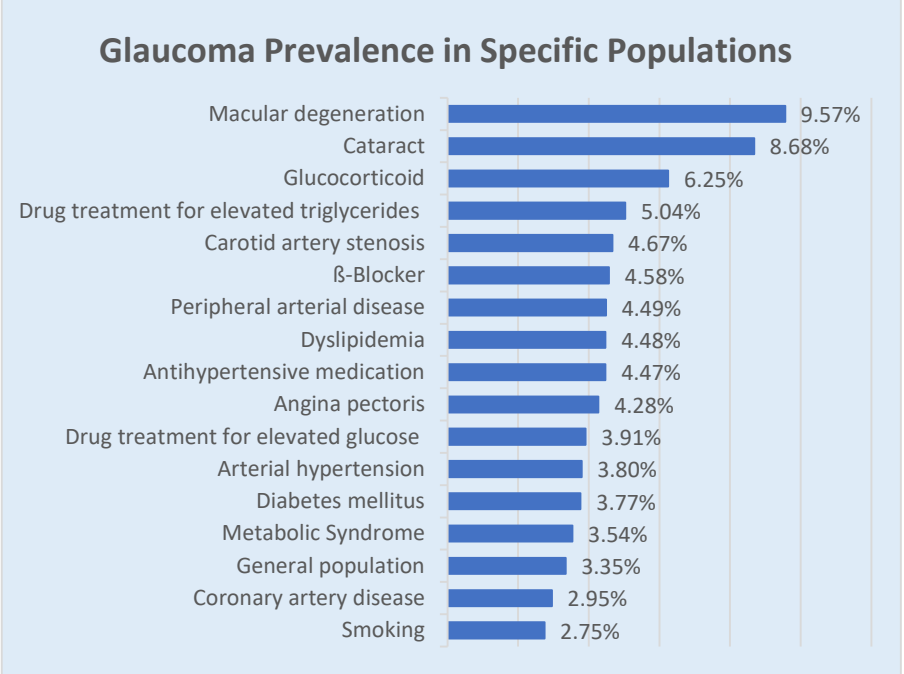
Figure 6: Age at Glaucoma Diagnosis



3.2.2. Prevalence of glaucoma in specific groups of the population

The prevalence of glaucoma in various populations with different cardiovascular and ocular diseases, along with related premedication substance classes, is depicted in Figure 7. It is observed that most population groups have higher glaucoma prevalence than the general population (3.35%). However, the population of smokers and those with coronary artery disease have a lower prevalence. Among the populations with higher glaucoma prevalence, those with other ocular diseases and under glucocorticoid treatment stand out. The prevalence of glaucoma in populations with macular degeneration (9.57%) and cataract (8.68%) is nearly three times as high as that in the general population. Similarly, populations with carotid artery

Figure 7: Glaucoma Prevalence in Specific Populations



stenosis, peripheral arterial disease, dyslipidemia, antihypertensive medication, ß-blockers, and drug treatment for elevated triglycerides also have a high prevalence. The populations with arterial hypertension, diabetes, and drug treatment for elevated glucose follow next. Overall, glaucoma is more prevalent in populations with ocular and cardiovascular comorbidities and those under related medication treatments. The statistical significance of these differences is presented in the subsequent results section.

The mean age of glaucoma patients varies across different population groups. The mean age of glaucoma patients was found to be highest in the population with cataracts (M=70.01, SD=5.56) and lowest in the population with dyslipidemia (M=66.49, SD=8.06). The population with macular degeneration had a mean age of 69.41 (SD=7.1), while the population under glucocorticoid therapy had a mean age of 70.1 (SD=7.09). Similarly, the mean age of glaucoma patients in populations with drug treatment for elevated triglycerides, carotid artery stenosis, and ß-blockers was found to be 68.99 (SD=5.95), 68.05 (SD=4.44), and 69.01 (SD=6.77), respectively. Furthermore, the mean age of glaucoma patients in the general population was 67.09 (SD=7.57), while populations with other cardiovascular and ocular comorbidities had higher mean ages. For instance, the mean age of glaucoma patients in populations with arterial hypertension, antihypertensive medication, angina pectoris, and diabetes mellitus was found to be 68.32 (SD=6.98), 68.58 (SD=6.67), 68.15 (SD=4.14), and 68.41 (SD=6.43), respectively. The descriptive analysis also showed that the mean age of glaucoma patients in the population with metabolic syndrome was 68.19 (SD=6.75), while the mean age in the population with peripheral arterial disease was 67.64 (SD=5.56). Finally, the population with coronary artery disease had the highest mean age of glaucoma patients, at 70.85 (SD=4.32). These findings suggest that age may be a factor in the development of glaucoma, with higher mean ages observed in populations with certain cardiovascular and ocular diseases. Further statistical tests may be able to determine the exact relationship between age and glaucoma, as well as the underlying mechanisms that may contribute to these associations.

3.3. Statistic relation between glaucoma and other population characters

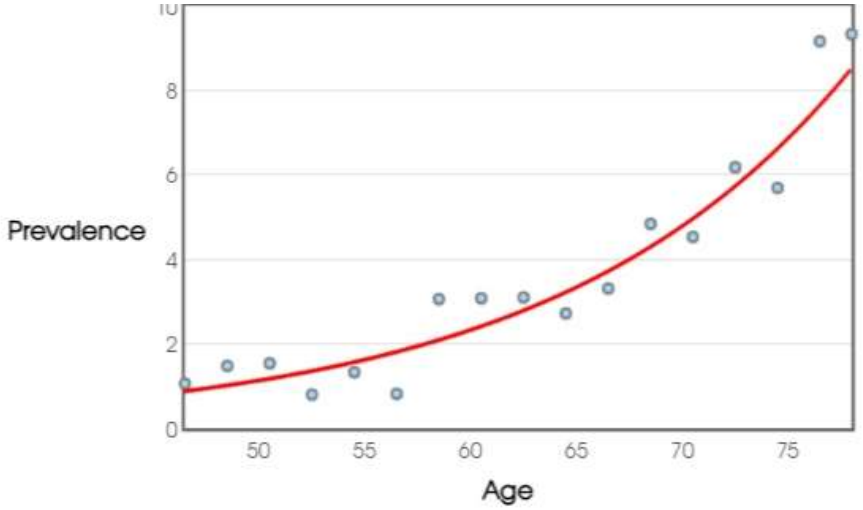
3.3.1. Relationship between Age and Glaucoma

The results of descriptive statistics revealed that the mean age of participants with antiglaucoma medication was 67.09 years with a standard deviation of 7.57, whereas the mean age of those without this medication was 62.34 years with a standard deviation of 8.41. These findings suggest that the group with antiglaucoma medication had a higher average age than the group without this medication. To determine whether this difference in age was statistically significant, a two-tailed t-test for independent samples was conducted, assuming unequal variances. The results of the t-test indicated a significant difference in age between the groups, $t(345.73)=-10.96$, $p=<0.001$, 95% confidence interval [-5.6, -3.89]. This indicates that the null hypothesis can be rejected, and there is a statistically significant difference in age between glaucoma and non-glaucoma populations. Overall, these results suggest that the use of antiglaucoma medication is associated with older age in individuals with glaucoma. These findings may have important implications for the management and treatment of glaucoma, as older age is a known risk factor for the disease. These results may inform

future research examining the relationship between age and the effectiveness of antiglaucoma medication.

The point-biserial correlation test conducted on the relationship between age and antiglaucoma drug reveals that there is a positive correlation between the two variables. This indicates that the two variables tend to move in the same direction. Specifically, as age increases, the number of participants with antiglaucoma medication also increases, and vice versa. Given that the group with antiglaucoma medication is defined as glaucoma patients, it can be inferred that the risk of developing glaucoma increases with age. The correlation coefficient, rpb, was found to be 0.1, which indicates a moderate positive correlation between age and antiglaucoma drug. Furthermore, the statistical significance of this relationship was established with a p-value of less than 0.001, indicating that the observed correlation

Figure 8: Correlation between Prevalence of Glaucoma and Age



is unlikely to have occurred by chance. The sample size for the analysis was 9532 participants. These findings suggest that age is an important factor in determining the likelihood of developing glaucoma and that medical interventions such as antiglaucoma medication may become more necessary as individuals age.

Results of this study indicate a clear exponential relationship between glaucoma prevalence and age in the studied population, as evidenced by the continuously increasing prevalence of the disease with age (Figure 8) and the detected regression equation:

$$\text{Prevalence} = 0.031 \times 1.0747^{\text{Age}}$$

This finding suggests that there is a strong relationship between age and the prevalence of glaucoma in the study population, with glaucoma prevalence increasing exponentially with age. The exponential function, as decried by the regression equation above, shows that for every unit increase in age, the prevalence of glaucoma increases by a factor of 1.0747. However, it is important to note that this exponential relationship may be only applicable to a specific age range, such as the adult age range of 45-80 years in this study. It is predicted that in an older population (≥ 80 years old), the prevalence of glaucoma may not continue to increase exponentially, but instead may reach a plateau or even decline. Further research is needed to investigate the

relationship between age and glaucoma prevalence in different age ranges and populations.

Table 3: Results of Statistic Analysis

Factor	Effect on glaucoma prevalence	Influence correlation between age and glaucoma prevalence
ß-Blocker	yes	yes
Macular degeneration	yes	yes
Dyslipidemia	yes	yes
Drug treatment for elevated triglycerides	yes	yes
Cataract	yes	yes
Antihypertensive medication	yes	yes
Glucocorticoid	yes	no
Arterial hypertension	yes	no
Carotid artery stenosis	no	yes
Smoking status	no	no
Peripheral arterial disease	no	no
Metabolic syndrome	no	no
Gender	no	no
Drug treatment for elevated glucose	no	no
Diabetes mellitus	no	no
Coronary artery disease	no	no
Angina pectoris	no	no

3.3.2. Relationship between BMI and Glaucoma

The results of the present study revealed the values for the dependent variable BMI in the group with antiglaucoma medication ($M = 26.49$, $SD = 4.48$) did not differ significantly from the group without this medication ($M = 26.8$, $SD = 4.72$). A two-tailed t-test for independent samples (equal variances assumed) confirmed that there was no statistically significant difference between the two groups with respect to BMI, $t(9{,}013) = 1.13$, $p = .26$, 95% confidence interval [-0.23, 0.86]. Therefore, it could be inferred that BMI had no significant effect on the prevalence of glaucoma in this study population. The null hypothesis that there is no difference in BMI between the two groups was retained. This finding suggests that other factors may be more important in determining the prevalence of glaucoma in this population. However, it is important to note that this analysis only showed an association between BMI and glaucoma prevalence and does not prove causation. Other factors, such as genetics, age, and lifestyle choices, may play a role in the development of glaucoma. Therefore, further research is necessary to fully understand the relationship between BMI and glaucoma prevalence.

3.3.3. Relationship between glaucoma and cardiovascular comorbidities and medication treatments

The present study utilized a Chi-Square test (Appendix 4) to investigate the relationship between glaucoma and various factors such as gender, metabolic syndrome, diabetes mellitus, coronary artery disease, angina pectoris, peripheral arterial stenosis, carotid stenosis, smoking status, and drug treatment for elevated glucose. The results of this analysis revealed that there was no statistically significant relationship between these factors and the presence of glaucoma. However, other factors such as cataract, macular degeneration, arterial hypertension, dyslipidemia, antihypertensive medication, ß-blocker, glucocorticoid, and drug treatment for elevated triglycerides were found to be significantly associated with the occurrence of glaucoma.

The results of the two-factor ANOVA without repeated measures (see Appendix 4) indicated that certain factors exhibit interactions with glaucoma concerning age, despite their indirect influence on the prevalence of glaucoma. Conversely, some factors do not interact with the relationship between age and glaucoma, despite their impact on glaucoma frequency. Specifically, factors such as gender, metabolic syndrome, diabetes mellitus, coronary artery disease, angina pectoris, peripheral arterial disease, smoking status, and drug treatment for elevated glucose have no interaction with glaucoma, nor do they affect glaucoma prevalence or influence the correlation between age and glaucoma frequency. On the other hand, the prevalence of glaucoma and its relationship with age is influenced by dyslipidemia, antihypertensive medication, ß-blocker, drug treatment for elevated triglycerides, cataract, and macular degeneration. While arterial hypertension and glucocorticoid affect the prevalence of glaucoma, they do not influence the correlation between age and the frequency of glaucoma. Furthermore, only carotid artery stenosis exhibits interaction with glaucoma concerning age, although it does not influence the prevalence of glaucoma. The significant effects between glaucoma and these factors, and their interactions with age, are interpreted in detail. These findings indicate that several factors can impact the prevalence of glaucoma and its relationship with age. Therefore, it is important to consider these factors when diagnosing and treating patients with glaucoma, as their management may differ based on these underlying factors.

3.3.3.1. Cardiovascular comorbidities (arterial hypertension, dyslipidemia, carotid artery stenosis)

Both arterial hypertension and dyslipidemia have been found to have an impact on the incidence of glaucoma, influencing the likelihood of an individual developing the condition. The frequency of glaucoma occurrence within a given population can be affected by the presence of these two risk factors. To examine this relationship, Table 4 displays the observed frequencies of both glaucoma and non-glaucoma cases across groups with varying degrees of arterial hypertension and dyslipidemia. Additionally, expected frequencies and Chi-square values $\chi 2$ are presented for instances where perfect independence exists between the two factors, arterial hypertension, and dyslipidemia, and the occurrence of glaucoma. By analyzing these data, it is possible to predict the direction of the correlation between these risk factors and the likelihood of developing glaucoma. Specifically, a Chi-square value greater

than 0.99 indicates that a significant difference exists between the observed and expected frequencies in the cell field, which is primarily influenced by the relationship between glaucoma and other variables.

Table 4: Observed and expected frequencies for perfect independence.

		Observed frequency		Expected frequency for independence	
		Glaucoma	No glaucoma	Glaucoma	No glaucoma
Arterial hypertension	**yes**	231	5847	205.74 (χ2 = 3.101)	5872.26 (χ2 = 0.109)
	no	84	3144	109.26 (χ2 = 5.840)	3118.74 (χ2 = 0.205)
Dyslipidemia	**yes**	100	2134	74.37 (χ2 = 8.833)	2159.63 (χ2 = 0.304)
	no	208	6810	233.63 (χ2 = 2.812)	6784.37 (χ2 = 0.097)
Glucocorticoid	**yes**	10	150	5.35 (χ2 = 4.042)	154.65 (χ2 = 0.140)
	no	309	9063	313.65 (χ2 = 0.069)	9058.35 (χ2 = 0.002)
Antihypertensive medication	**yes**	144	3075	107.73 (χ2 = 12.211)	3111.27 (χ2 = 0.423)
	no	175	6138	211.27 (χ2 = 6.227)	6101.73 (χ2 = 0.216)
ß-Blocker	**yes**	76	1585	55.59 (χ2 = 7.494)	1605.41 (χ2 = 0.259)
	no	243	7628	263.41 (χ2 = 1.581)	7607.59 (χ2 = 0.055)
Elvt. Triglycerides drug treatment	**yes**	86	1622	57.16 (χ2 = 14.551)	1650.82 (χ2 = 0.504)
	no	233	7591	261.84 (χ2 = 3.177)	7562.16 (χ2 = 0.110)
Macular degeneration	**yes**	22	208	7.39 (χ2 = 28.884)	222.61 (χ2 = 0.959)
	no	218	7023	232.61 (χ2 = 0.918)	7008.39 (χ2 = 0.030)
Cataract	**yes**	120	1262	44.82 (χ2 = 126.105)	1337.18 (χ2 = 4.227)
	no	142	6555	217.18 (χ2 = 26.025)	6479.82 (χ2 = 0.872)

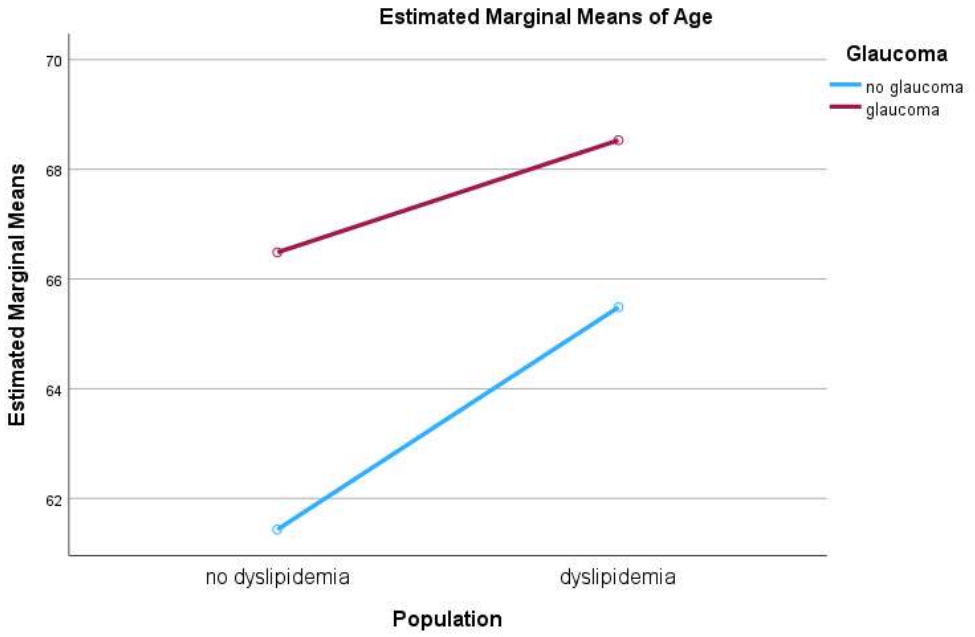
The present study demonstrates the existence of a statistically significant relationship between arterial hypertension and glaucoma. The obtained results reveal a Chi-square value of 9.258 and a p-value of 0.002, indicating the presence of a significant association between these two variables. The magnitude of the relationship is

considered weak, as evidenced by a Cramer's V value of 0.032. This finding is expected, as glaucoma diagnosis is only partially dependent on the presence of arterial hypertension. The study indicates that individuals with arterial hypertension are at a higher risk of developing glaucoma than those without this condition. Hence, arterial hypertension can be considered a significant risk factor for glaucoma diagnosis.

Similarly, a statistically significant relationship is observed between dyslipidemia and glaucoma. The obtained results reveal a Chi-square value of 12.045 and a p-value of less than 0.001, indicating a significant association between these two variables. The magnitude of the relationship is considered weak, as evidenced by a Cramer's V value of 0.036. This finding is also expected, as glaucoma is a multifactorial disease that only partially depends on the presence of dyslipidemia. The study suggests that the frequency of glaucoma is higher in populations with dyslipidemia and lower in those without this condition. Together with arterial hypertension, dyslipidemia can be considered a risk factor for glaucoma.

The study also found a significant interaction effect between dyslipidemia and glaucoma in relation to age, suggesting that the presence of dyslipidemia may affect the relationship between glaucoma and age (p=0.049). The interaction plot in Figure 9 visualizes the relationship between dyslipidemia, glaucoma, and age. The x-axis shows two groups of dyslipidemia (present and absent), the y-axis shows mean age, and the connecting lines show two groups of glaucoma (present and absent) with different colors. The plot shows that the mean age is higher in the group with glaucoma than the group without, regardless of whether they have dyslipidemia or not. However, the difference in mean age between the two groups is more pronounced in individuals without dyslipidemia, where the distance between the two slops is bigger. In contrast, the slopes are closer to each other in individuals with dyslipidemia, indicating a smaller difference in mean age between the groups with and without glaucoma. Overall, the findings suggest that dyslipidemia may attenuate the correlation between glaucoma and age. In other words, individuals with dyslipidemia have a smaller difference in mean age between groups with and without glaucoma compared to individuals without dyslipidemia. This result has important

Figure 9: Interaction plot dyslipidemia, glaucoma, and age



implications for understanding and management of both dyslipidemia and glaucoma, as they suggest that dyslipidemia may affect the progression and severity of glaucoma in older individuals. Further research is needed to confirm and expand on these findings.

Table 5: Two-factor ANOVA without repeated measures: dyslipidemia, glaucoma, age

Tests of Between-Subjects Effects

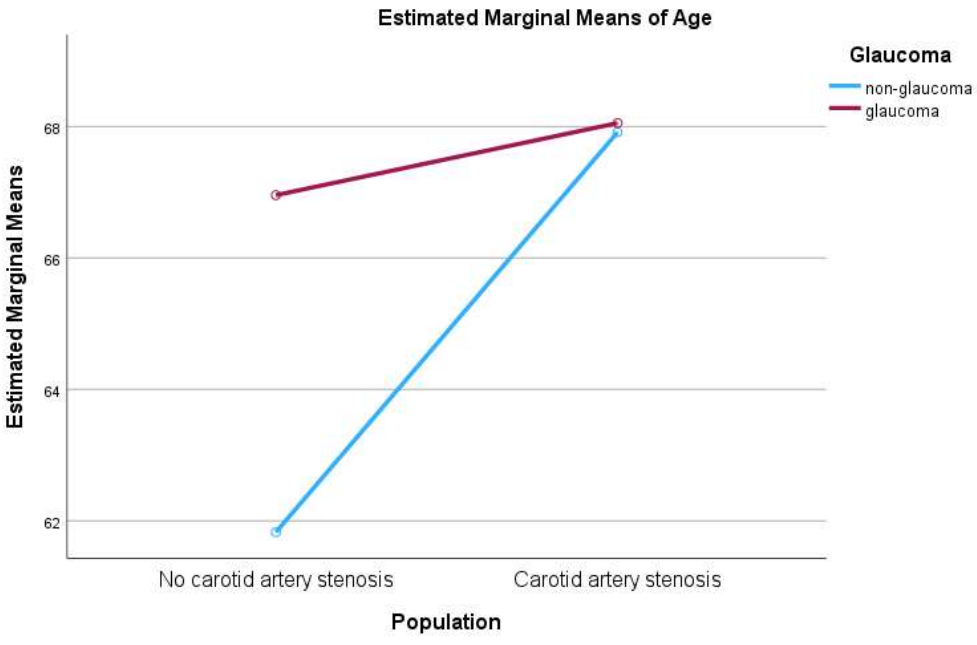
Dependent Variable: Age

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	33699.952[a]	3	11233.317	166.613	<.001	.051
Intercept	4448436.414	1	4448436.414	65979.200	<.001	.877
Dyslipidemia	2411.052	1	2411.052	35.761	<.001	.004
Antiglaucoma Med	4252.148	1	4252.148	63.068	<.001	.007
Dyslipidemia * Antiglaucoma Med	261.738	1	261.738	3.882	.049	.000
Error	623516.802	9248	67.422			
Total	36863997.000	9252				
Corrected Total	657216.753	9251				

a. R Squared = .051 (Adjusted R Squared = .051)

The study found no correlation between carotid artery stenosis and glaucoma prevalence but a significant interaction effect in relation to age (p=0.013). The interaction plot in Figure 10 shows that participants with glaucoma have generally higher mean age than participants without glaucoma, regardless of whether they have carotid artery stenosis or not. However, the population without carotid artery stenosis showed a large age difference

Figure 10: Relationship carotid artery stenosis, glaucoma, and age



between participants with glaucoma and without glaucoma, while in the population with carotid artery stenosis, there was almost no age difference between participants with and without glaucoma. These findings suggest that carotid artery stenosis may be a confounding variable that influences the relationship between glaucoma and age. In the absence of carotid artery stenosis, age appears to be a significant factor in the development of glaucoma. However, in the presence of carotid artery stenosis, age does not appear to differentiate between the two groups, likely due to the fact that carotid stenosis patients are generally older. Overall, these results suggest that the presence of carotid artery stenosis may affect the relationship between age and glaucoma. This highlights the importance of considering confounding variables when studying the relationship between glaucoma and other diseases or factors. Further research is needed to confirm and expand on these findings.

Table 6: Two-factor ANOVA without repeated measures: carotid artery stenosis, glaucoma, age

Tests of Between-Subjects Effects

Dependent Variable: Age

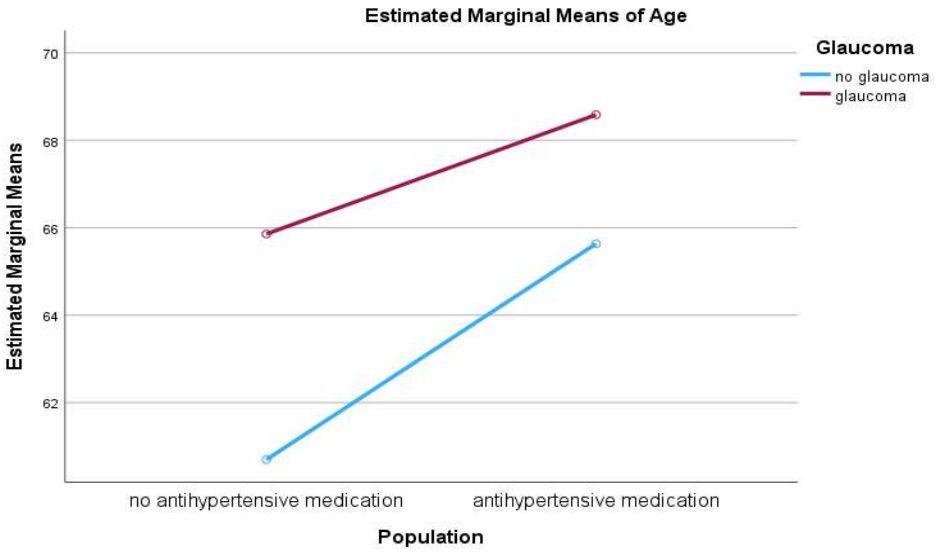
Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	20507.295[a]	3	6835.765	99.452	<.001	.033
Intercept	1187512.521	1	1187512.521	17276.785	<.001	.666
Antiglaucoma Med.	470.302	1	470.302	6.842	.009	.001
Carotid Artery Stenosis	873.900	1	873.900	12.714	<.001	.001
Antiglaucoma Med * Carotid Artery Stenosis	421.555	1	421.555	6.133	.013	.001
Error	596753.589	8682	68.735			
Total	34300647.000	8686				
Corrected Total	617260.884	8685				

a. R Squared = .033 (Adjusted R Squared = .033)

3.3.3.2. Medication interaction (cardiovascular drug treatment, glucocorticoid)

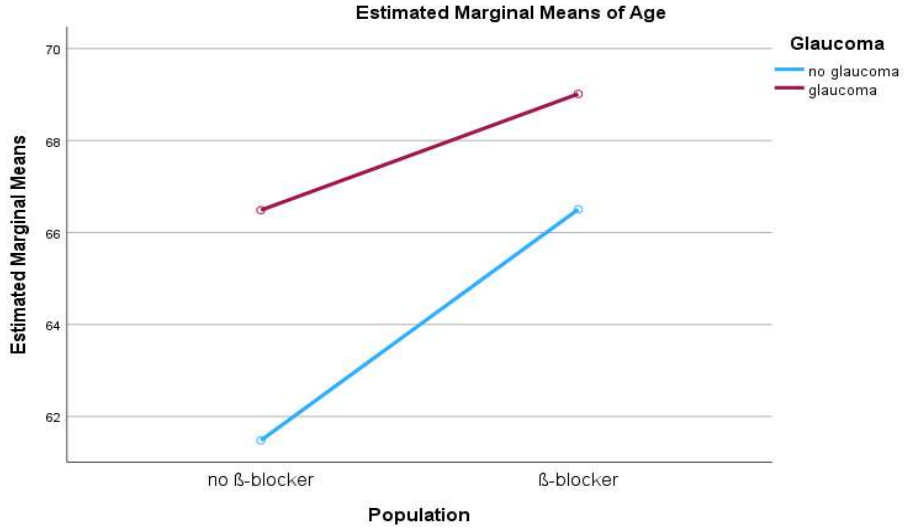
The prevalence of glaucoma diagnosis is influenced by certain medication interactions, such as the use of glucocorticoids and cardiovascular drugs including antihypertensive medication, ß-blockers, and treatment for elevated triglycerides. Additionally, there is an interaction between these cardiovascular medications and glaucoma diagnosis in relation to age.

Figure 11: Relationship antihypertensive medication, glaucoma, age



The statistical analysis has confirmed a significant relationship between the use of glucocorticoids and the incidence of glaucoma, as indicated by a Chi-square value of $\chi^2(1) = 4.241$, $p = 0.039$, and a weak effect size represented by Cramer's V of 0.021. Specifically, the population receiving glucocorticoid therapy showed a higher number of cases of glaucoma than expected, as reported in Table 4. Conversely, the absence of this medication did not appear to reduce the likelihood of developing glaucoma. Thus, it can be concluded that glucocorticoid use is a risk factor for the development of glaucoma, but its discontinuation alone may not necessarily reduce the risk.

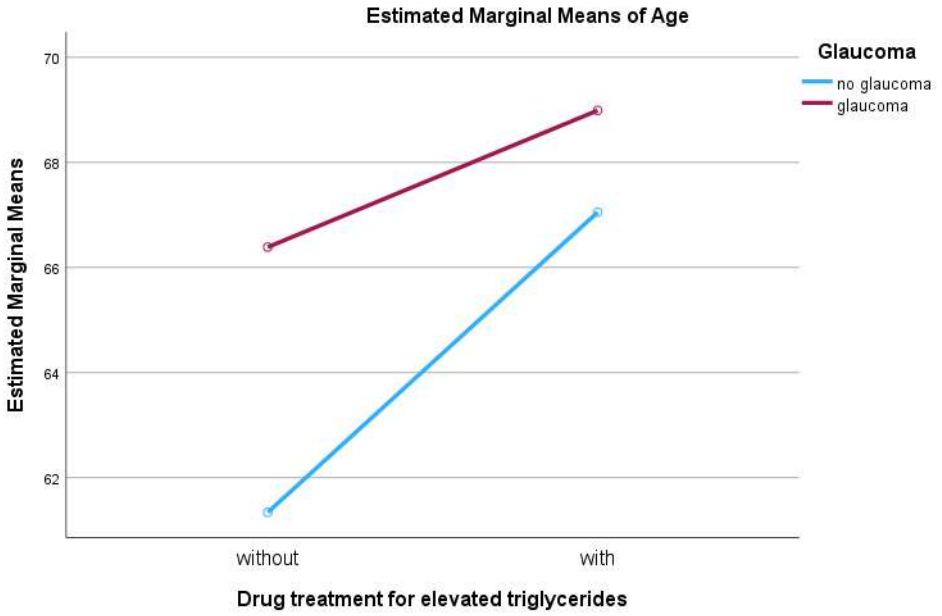
Figure 12: Relationship ß-blocker, glaucoma, age



The statistical analysis also indicates a weak but significant interaction between glaucoma and several classes of cardiovascular medication, including antihypertensive medication ($\chi^2(1) = 19.079$, $p = < 0.001$, Cramer's V = 0.045), ß-blockers ($\chi^2(1) = 9.329$, $p = 0.002$, Cramer's V = 0.031), and medications for the treatment of elevated triglycerides ($\chi^2(1) = 18.341$, $p = < 0.001$, Cramer's V = 0.044). Furthermore, the frequency of glaucoma diagnoses is much higher than expected in populations receiving these drug treatments and lower than expected in populations without them (Table 4). Therefore, the use of antihypertensive medication, ß-blockers, and medications for elevated triglycerides should be considered as risk factors for developing a glaucoma diagnosis.

In relation to age, there is an interaction between cardiovascular medications and glaucoma. The strength of the correlation between glaucoma and age is dependent on the use of specific medications, including

Figure 13: Relationship drug treatment for elevated triglycerides, glaucoma, age



antihypertensive medication, ß-blockers, and medication for elevated triglycerides treatment. This association was statistically significant (p=0.017, p=0.023, p=0.003, respectively). Notably, individuals with glaucoma generally have a higher mean age than those without glaucoma. However, the mean age difference between these two groups varies depending on medication use. Specifically, in the population taking antihypertensive medication, ß-blockers, and medication for elevated triglycerides treatment, the mean age difference becomes smaller in comparison to the population not taking these medications. This effect is demonstrated by different slops in Figures 11, 12 and 13. Indeed, the findings suggest that the use of specific medications, including antihypertensive medication, ß-blockers, and medication for elevated triglycerides treatment, may have a moderating effect on the relationship between glaucoma and age. Specifically, individuals taking these medications and having glaucoma have a smaller difference in mean age compared to individuals without these medications and glaucoma. This suggests that these medications may potentially mitigate the age-related effects on glaucoma.

Table 7: Two-factor ANOVA without repeated measures: Elevated triglycerides medication, glaucoma, age

Tests of Between-Subjects Effects

Dependent Variable: Age

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	50980.909[a]	3	16993.636	258.924	<.001	.075

Intercept	4173917.515	1	4173917.515	63595.937	<.001	.870
Antiglaucoma Med	2928.280	1	2928.280	44.617	<.001	.005
Elevated Triglycerides Medication	4147.912	1	4147.912	63.200	<.001	.007
Antiglaucoma Med * Elevated Triglycerides Medication	580.533	1	580.533	8.845	.003	.001
Error	625340.041	9528	65.632			
Total	37913446.000	9532				
Corrected Total	676320.949	9531				

a. R Squared = .075 (Adjusted R Squared = .075)

Table 8: Two-factor ANOVA without repeated measures: antihypertensive medication, glaucoma, age

Tests of Between-Subjects Effects

Dependent Variable: Age

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	57474.408[a]	3	19158.136	294.966	<.001
Intercept	5172382.329	1	5172382.329	79635.993	<.001
Antiglaucoma Med	5005.101	1	5005.101	77.060	<.001
Antihypertensive Med	4467.588	1	4467.588	68.785	<.001
Antiglaucoma Med * Antihypertensive Med	372.000	1	372.000	5.727	.017
Error	618846.541	9528	64.950		
Total	37913446.000	9532			
Corrected Total	676320.949	9531			

a. R Squared = .085 (Adjusted R Squared = .085)

Table 9: Two-factor ANOVA without repeated measures: ß-blocker, glaucoma, age

Tests of Between-Subjects Effects

Dependent Variable: Age

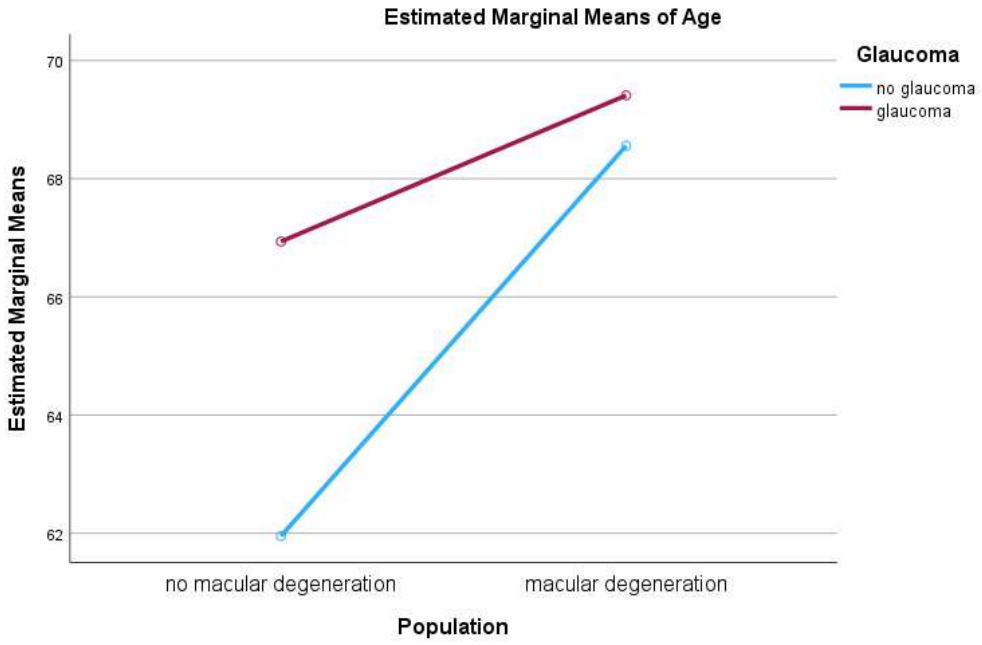
Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	40437.346[a]	3	13479.115	201.969	<.001
Intercept	3849289.172	1	3849289.172	57677.265	<.001
Antiglaucoma Med	3132.342	1	3132.342	46.935	<.001
ß-Blocker	3162.207	1	3162.207	47.382	<.001
Antiglaucoma Med * ß-Blocker	345.646	1	345.646	5.179	.023
Error	635883.603	9528	66.738		
Total	37913446.000	9532			
Corrected Total	676320.949	9531			

a. R Squared = .060 (Adjusted R Squared = .059)

3.3.3.3. Ocular comorbidities (macular degeneration, cataract)

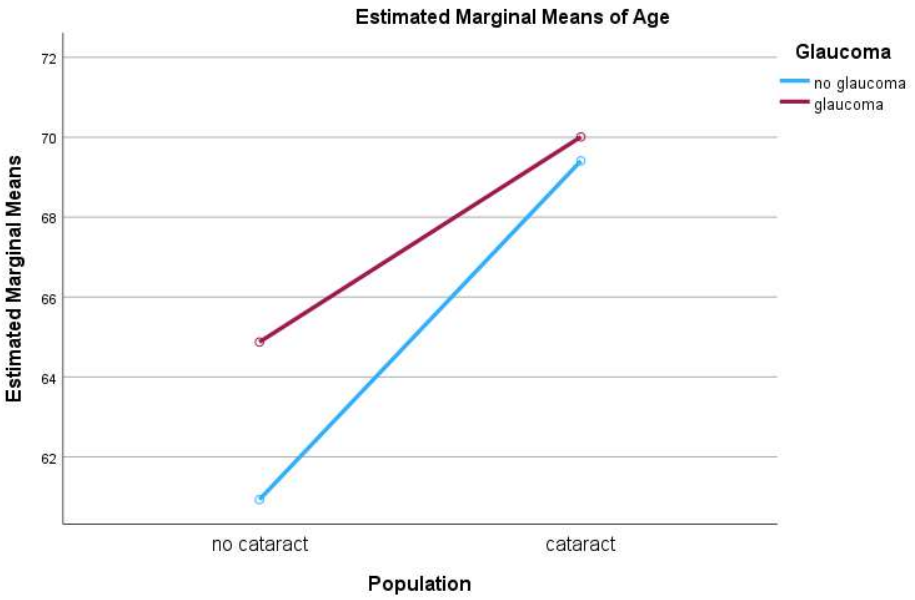
The prevalence of glaucoma is also affected by other progressive ocular diseases. Specifically, there are statistically significant relationships between glaucoma and macular degeneration ($\chi^2(1) = 30.802$, $p = < 0.001$, Cramer's V = 0.064) as well as cataract ($\chi^2(1) = 157.243$, $p = < 0.001$, Cramer's V = 0.140). Notably, the influence of cataracts on glaucoma is stronger than the influence of macular degeneration because the Cramer's V value for cataract is greater than that value for macular degeneration. Observations indicate that there are more cases of glaucoma among individuals with both macular degeneration and cataract than expected (as shown in Table 4). Moreover, individuals without cataract tend to have a lower incidence of glaucoma diagnosis. Therefore, macular degeneration and cataract represent strong risk factors for developing glaucoma.

Figure 14: Relationship macular degeneration, glaucoma, age



In relation to age, both macular degeneration (p=0.034) and cataract (p=<0.001) interact with glaucoma.

Figure 15: Relationship cataract, glaucoma, age



These findings are supported by interaction plots in Figures 14 and 15, which suggest that both macular degeneration and cataract have a similar effect on the relationship between glaucoma and age. Specifically, the mean age difference between individuals with and without glaucoma is smaller in the population with macular degeneration and cataract, while the difference in the population without these two ocular diseases is relatively large. This suggests that both macular degeneration and cataract are associated with a weaker age-related effect on the development of glaucoma.

Table 10: Two-factor ANOVA without repeated measures: cataract, glaucoma, age

Tests of Between-Subjects Effects

Dependent Variable: Age

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	83921.183[a]	3	27973.728	461.300	<.001	.146
Intercept	4310016.568	1	4310016.568	71074.170	<.001	.898
Antiglaucoma Med	1264.540	1	1264.540	20.853	<.001	.003
Cataract	11353.952	1	11353.952	187.232	<.001	.023
Antiglaucoma Med * Cataract	684.515	1	684.515	11.288	<.001	.001
Error	489676.965	8075	60.641			
Total	32090768.000	8079				
Corrected Total	573598.148	8078				

a. R Squared = .146 (Adjusted R Squared = .146)

Table 11: Two-factor ANOVA without repeated measures: macular degeneration, glaucoma, age

Tests of Between-Subjects Effects

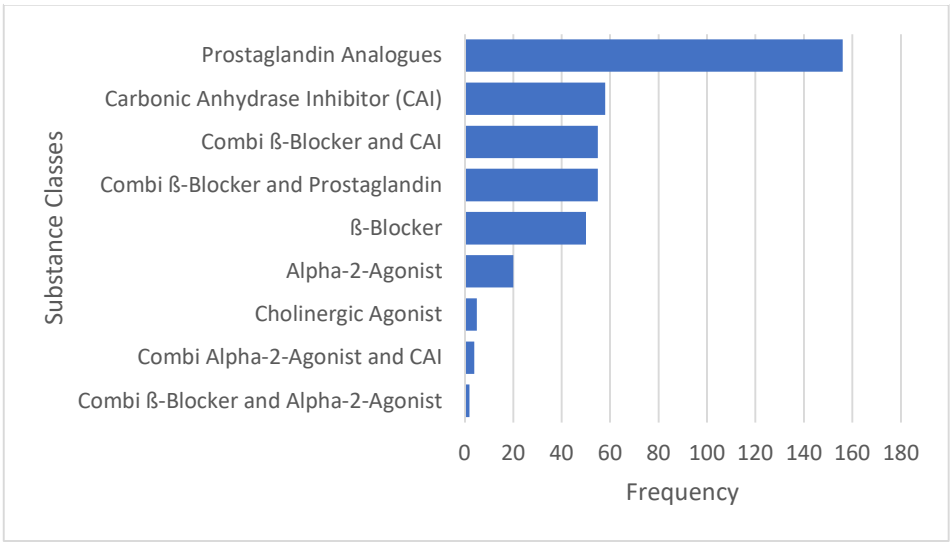
Dependent Variable: Age

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	14796.368[a]	3	4932.123	71.396	<.001	.028
Intercept	1294937.277	1	1294937.277	18745.196	<.001	.715
Antiglaucoma Med	619.349	1	619.349	8.966	.003	.001
Macular Degeneration	1499.198	1	1499.198	21.702	<.001	.003
Antiglaucoma Med * Macular Degeneration	310.656	1	310.656	4.497	.034	.001
Error	515827.975	7467	69.081			
Total	29530072.000	7471				
Corrected Total	530624.343	7470				

a. R Squared = .028 (Adjusted R Squared = .027)

3.4. Medication Treatments for Glaucoma

Figure 16: Frequency of antiglaucoma substance classes



The medication with the code value starting with S01E is known to be used for the treatment of glaucoma. In this study, a separate excel table was created to filter out disclosures that used medication with these code values. After removing 409 duplicate values, 405 unique values remained. Among the remaining disclosures, 319 reported the use of antiglaucoma medication. Out of these 319 disclosures, 8 reported the use of three different antiglaucoma preparations, 70 reported the use of two preparations, and 241 reported the use of one preparation. The frequency and percentage of each antiglaucoma substance class were represented in

Table 12 and Figure 16. The most used substance class was prostaglandin analogs, with 156 usages accounting for 38,52% of the total applications. This was followed by carbon anhydrase inhibitor (CAI), ß-blocker, and combination preparations from ß-blocker and CAI, ß-blocker, and prostaglandin, with similar usage frequencies ranging from 50 to 58 items, accounting for 12.35% to 14.35% of the total applications. The least used single and combined preparations were cholinergic agonists, with 1.23% usage, and a combination of ß-blocker and α_2-agonist, with only 0.49% usage.

Among all the antiglaucoma substance classes, Latanoprost was found to be the most prescribed substance for glaucoma medication treatment, accounting for 22.47% of the total applications. This was not only within the most applied substance class, prostaglandin analogs, but also across all antiglaucoma substance classes (see Appendix 1).

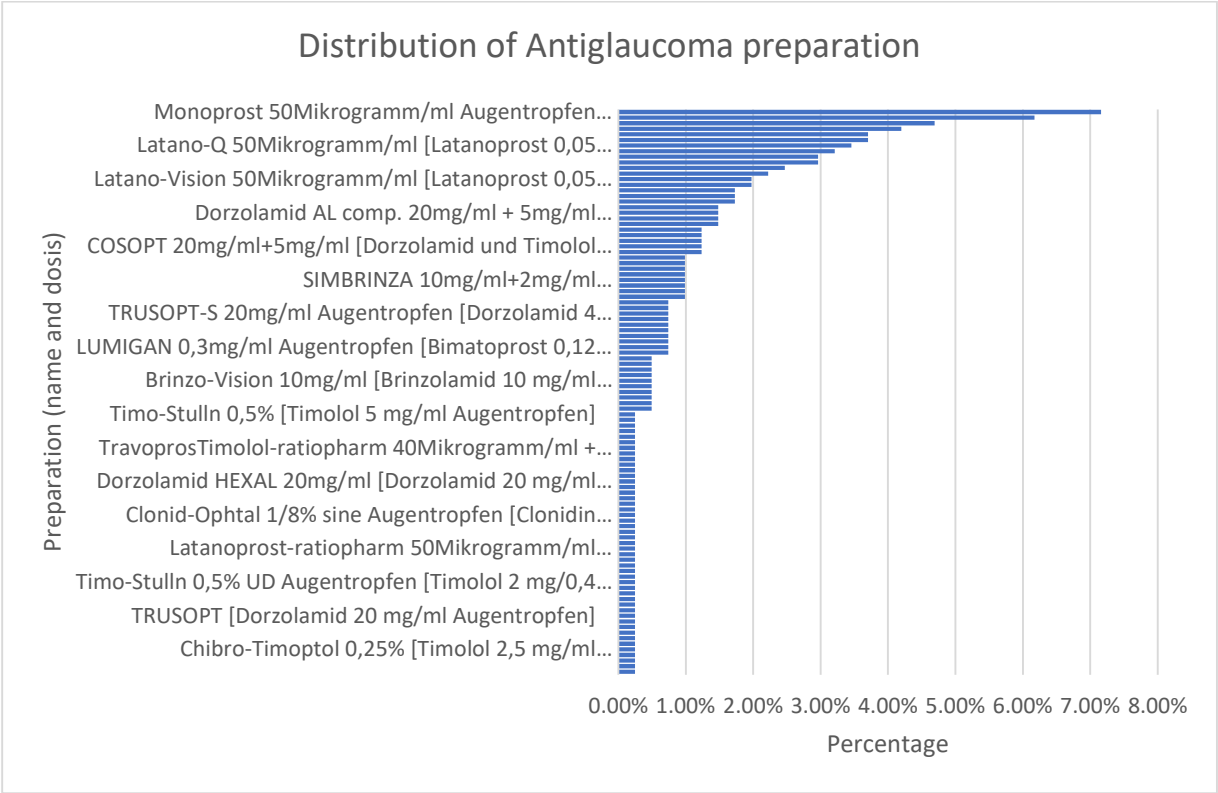
Table 12: Frequency and percentage of antiglaucoma substance classes

Antiglaucoma substance class	Frequency	Percentage
Prostaglandin Analogues	156	38.52%
Carbonic Anhydrase Inhibitor (CAI)	58	14.32%
Combi ß-Blocker and CAI	55	13.58%
Combi ß-Blocker and Prostaglandin	55	13.58%
ß-Blocker	50	12.35%
Alpha-2-Agonist	20	4.94%
Cholinergic Agonist	5	1.23%
Combi Alpha-2-Agonist and CAI	4	0.99%
Combi ß-Blocker and α_2-Agonist	2	0.49%
Total	**405**	**100.00%**

The study included a total of 101 antiglaucoma preparations that differed in doses and application forms. These preparations were produced by various pharmaceutical companies and had different labels. Figure 17 displays the distribution of the usage of these preparations in decreasing order, along with some typical preparations.

The most preferred antiglaucoma preparation was Monoprost 50µg/ml in the form of single-dose pipettes, accounting for 7.16% of the total usage. The next most commonly used preparation was Azopt 10mg/ml eye drop, with a usage rate of 6.17%. Almost all of the preparations were in the form of eye drops, either as pipettes or suspensions for topical treatment. Only one preparation, Glaupax, was in tablet form for oral use. This preparation had the lowest usage rate in our study population, with only one application, making up 0.25% of the total usage. Appendix 2 contains further details about usage distribution of all preparations.

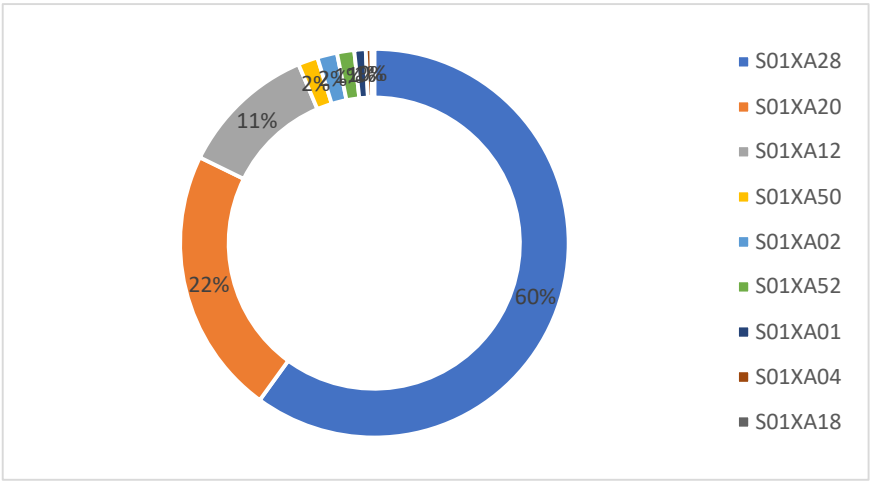
Figure 17: Distribution of antiglaucoma preparation



3.5. Artificial Tear Substitutes

The study focused on the usage of artificial tears with a code value that starts with S01XA. After removing 338 duplicate values, 432 unique values remained. The study population consisted of 384 disclosures (4.03% of the population) that used artificial tear substitutes. Of these, two disclosures used three different preparations, 35 used two different preparations, and the remaining used only one preparation.

Figure 18: Distribution of ophthalmologic moisturizing treatments



There was a total of nine substance classes used in ophthalmologic moisturizing treatment, with Hyaluronic Acid (code value S01XA28) being the most commonly used substance class, followed by Hypromellose (S01XA20) and Dexpanthenol (S01XA12). Details about the frequency and percentage of usage for each substance class are provided in Table 13 and Figure 18.

Artificial tear substances were applied in various forms, including eye drops (pipettes or suspension), ointment, and gel. Eye drops were the most commonly used form.

Among the various artificial tear substances, Hyaluronic Acid under the trade names Hylo-Comod and Hylo-Gel was the most commonly prescribed, with nearly 22% and 8% of the total application in the study population, respectively. The third most commonly used preparation was the one marketed under the trade name Bepanthen, accounting for approximately 6% of the total usage. Additional information on the distribution of artificial tears is provided in Appendix 3.

Of the 319 disclosures related to antiglaucoma medication, 21 disclosed the use of artificial tear preparations, which corresponds to 6.6% of the glaucoma population in the study. This is higher than the percentage of artificial tear usage in the general population (approximately 2.5%). This result suggests that individuals with glaucoma may be more likely to experience dry eye symptoms, which could explain the higher percentage of artificial tear usage in this population compared to the general population. It may also indicate that the use of antiglaucoma medication could be contributing to dry eye symptoms in this population. Further research would be needed to explore these potential relationships and to better understand the factors contributing to the higher percentage of artificial tear usage in individuals with glaucoma.

Table 13: Distribution of ophthalmologic moisturizing treatments

Code Value	Substance Class	Frequency
S01XA28	Hyaluronic Acid	254
S01XA20	Hypromellose	94
S01XA12	Dexpanthenol	48
S01XA50	Others	7
S01XA02	Retinol	7
S01XA52	Retinol combination	6
S01XA01	Guaiazulene	4
S01XA04	Potassium iodide	2
S01XA18	Ciclosporin	1
Total		**423**

4. Discussion

4.1. Important findings from the study

The aim of this study was to estimate the prevalence of glaucoma in a population-based German sample aged 45-78 years based on the rate of taking antiglaucoma medication. The study found that the prevalence of glaucoma in the sample was 3.35%, which is higher than the prevalence reported in the Gutenberg Health Study in Germany (1.34%) (Höhn et al., 2018). This difference in prevalence could be due to the fact that the study population in this study was older than that in the Gutenberg Health Study (aged 35-74 years).

The study also found that the prevalence of glaucoma in the sample was similar to the global prevalence of glaucoma reported in the systemic review and meta-analysis of Tham (Tham et al., 2014), which was 3.54%. However, the prevalence reported in other systematic reviews was lower than that in this study, in which the global and European prevalence of POAG were 2.2-2.4% and 2.1-2.51% (Kapetanakis et al., 2016; Allison, Patel and Alabi, 2020; Zhang et al., 2021). This difference in results could be explained by the fact that these reviews only reported the prevalence of the most common type of glaucoma, POAG, whereas the prevalence in this study was estimated for all types of glaucoma. One more explanation, which is also a limitation of this study, is that the definition of a glaucoma patient was only based on the use of antiglaucoma medication, which may over- or underestimate the real prevalence of glaucoma in the population.

Moreover, the previous undiagnosed glaucoma rate in Germany, which was recently reported in the Gutenberg Health Study, was found to be 81.9% (Höhn et al., 2018), which is much higher than rates reported in other studies worldwide, ranging from 50-57% (Topouzis et al., 2008; Gupta et al., 2016; McCann et al., 2020). This suggests that the prevalence of glaucoma in the population could be higher than reported in this sample, as this study only accounts for the prevalence of diagnosed glaucoma based on the use of antiglaucoma medication. These findings emphasize the importance of regular eye examinations to detect glaucoma at an early stage and lower the rate of undiagnosed cases. Early detection and treatment of glaucoma can prevent or delay vision loss and improve the prognosis of the disease. Therefore, public health efforts should focus on increasing awareness of glaucoma and promoting regular eye exams, especially for people aged over 45 years, who are at higher risk of developing the disease. Additionally, healthcare providers should educate their patients about the importance of eye exams and encourage them to attend regular screenings to identify any potential eye problems. By taking these steps, the undiagnosed rate of glaucoma in the population can be reduced, leading to better outcomes for patients and a healthier population overall.

Another interesting finding in this study was that only 67% of people using antiglaucoma had self-reported a diagnosis of glaucoma and knew the aim of antiglaucoma medication usage, indicating that about 33% of people did not understand exactly why they were taking the medication. Since medication adherence plays an important role in preventing the irreversible progression of glaucoma (Kang and Tanna, 2021), this result is a warning sign for unsatisfactory success in the medical

treatment of glaucoma and calls for an improvement in physician-patient communication as well as an optimization in educating patients about their health and illness insight.

The findings highlight several important points regarding glaucoma prevalence and diagnosis in the studied population. Firstly, while women outnumbered men in the total number of glaucoma patients, the prevalence of taking antiglaucoma medication among male and female participants was similar, with the prevalence of glaucoma being slightly higher in females. Additionally, while there was no distinctive difference in glaucoma prevalence between genders, the differences between age groups were significant, with glaucoma prevalence increasing with age. The highest prevalence of glaucoma was observed in the 52-53 and 56-57 age groups. Moreover, the study found that the age at first diagnosis of glaucoma ranged widely, with a mean age of 57.32 years and the majority of participants being diagnosed between the ages of 50 and 68. The highest peak of glaucoma diagnosis was observed in the 60-64 age group. Finally, the risk of visual field loss in the glaucoma population was found to be double that in the non-glaucoma population. These findings provide valuable insights into the epidemiology of glaucoma and have important implications for the prevention and management of the disease.

There is a significant usage of antiglaucoma medication in the study population, with a total of 319 disclosures related to its use. Prostaglandins were the most applied substance class, accounting for 38,52% of total applications, followed by carbonic anhydrase inhibitors, ß-blockers, and combination preparations from ß-blocker and carbonic anhydrase inhibitors, ß-blocker, and prostaglandin, with similar usage frequencies ranging from 12.35% to 14.35% of total applications. These findings suggest that there is a diverse range of antiglaucoma medications available, and clinicians have multiple options for managing the condition. Prostaglandin analogs are widely considered to be the first-line treatment for glaucoma due to their efficacy, favorable side effect profile, and convenient once-daily dosing regimen. This is supported by previous literature (Kang and Tanna, 2021), which recommended prostaglandin analogs as the initial treatment for most cases of glaucoma. Therefore, it is not surprising that prostaglandin analogs were found to be the most used substance class among the antiglaucoma medications in the study population.

The study findings suggest that some factors have a direct impact on the development of glaucoma, while others do not have any significant association with the disease. Age, cataracts, macular degeneration, arterial hypertension, antihypertensive medication, dyslipidemia, drug treatment for elevated triglycerides, and treatment with glucocorticoids were identified as direct risk factors for glaucoma, although the correlation was weak. This suggests that these factors only partially contribute to the risk of developing glaucoma, which is a multifactorial disease. Conversely, gender, angina pectoris, coronary artery disease, carotid stenosis and peripheral arterial disease, diabetes, metabolic syndrome, drug treatment for elevated glucose, and smoking status were not found to be major risk factors for glaucoma. Healthcare professionals need to consider all potential risk factors when evaluating patients for glaucoma, but further research is necessary to understand the interplay between these factors.

The study revealed that some factors, such as carotid stenosis, may not directly impact the development of glaucoma but can affect the relationship between age and glaucoma. Furthermore, certain factors, including cataract, macular degeneration, dyslipidemia, drug treatment for elevated triglycerides, and antihypertensive substances, were found to have both direct and indirect effects on glaucoma. The statistical analyses conducted in this study showed that these factors can modulate the age-related effects on glaucoma by altering blood pressure or lipid levels. The positive correlation between age and glaucoma was significantly weakened by these factors, highlighting their importance in mitigating the age-related effects on glaucoma.

The study findings have important implications for the management and treatment of glaucoma, as older age is a known risk factor for the disease. The use of antiglaucoma medication was found to be associated with older age in individuals with glaucoma, which could impact the effectiveness of the medication. Therefore, future research should examine the relationship between age and the effectiveness of the antiglaucoma medication. It is possible that the efficacy of antiglaucoma medication may differ in older individuals compared to younger individuals, and further research could help to identify potential differences and optimize treatment strategies accordingly. Overall, this study contributes to our understanding of the complex relationship between risk factors and glaucoma, but further research is necessary to determine how best to incorporate these factors into risk assessment and management strategies for the disease.

4.2. Causal arguments and comparison with prior studies

The findings from our study are consistent with those of previous literature. Age has been repeatedly identified as the strongest known risk factor for glaucoma in various studies, as it is more prevalent in older population (Chan et al., 2017; McMonnies, 2017; Zhang et al., 2021). Our results on arterial hypertension and antihypertensive medication treatment as risk factors for developing glaucoma are also in line with most previous. However, the usage of antihypertensive medication consistently appears as a risk factor for developing glaucoma (Klein, Klein and Knudtson, 2005), and there are conflicting results on the effect of arterial hypertension on glaucoma development. The vascular hypothesis for glaucoma has been mentioned in some literatures, suggesting that better ocular perfusion, which adapts gradually to the condition of persistent high systemic blood pressure in people with arterial hypertension, may explain the protective effect of arterial hypertension on glaucoma (Memarzadeh et al., 2010; Nislawati et al., 2021). However, other studies disagree with the protective effect of systemic arterial hypertension on glaucoma and consider hypertension and higher systolic blood pressure as predictive factors for specific structural and functional progression on glaucoma patients (Marshall et al., 2021). This discrepancy in results leaves the effect of arterial hypertension on glaucoma development in further discussion. Our study provides additional evidence on the association between this cardiovascular disease and glaucoma and adds to the growing body of literature on this topic.

Although the prevalence of glaucoma in women was found to be slightly higher than in men in this study, there was no significant gender difference observed. The relationship between gender and glaucoma remains a controversial topic in the literature. Our

findings are consistent with those reported in the Blue Mountain Eye Study, which found a higher prevalence of glaucoma in women after adjusting for age (odds ratio 1.55) (Mitchell et al., 1996). Similarly, the Gutenberg Health Study, another German population-based study, also found a higher occurrence of glaucoma in women (Höhn et al., 2018). On the other hand, the Barbados Eye Study and the Rotterdam Eye Study reported a higher prevalence of glaucoma in men, while no gender difference was observed in the Beaver Dam Eye Study and the NICOLA Study (Klein et al., 1992; Cristina Leske et al., 1994; Wolfs et al., 2000; McCann et al., 2020). The protective effect of female sex hormones against glaucoma has been suggested, as higher intraocular pressure was found in women after menopause, and women with early menopause or shorter estrogen exposure are at a higher risk for developing glaucoma (Vajaranant et al., 2010). This indicates that the development of glaucoma is especially rapid in rapid in women around the age of menopause. Given the growing aging population and the dominance of glaucoma cases and blindness worldwide among this population (Vajaranant et al., 2010), older women are at high risk for glaucoma and therefore require improved care from the healthcare system.

The relationship between diabetes mellitus and glaucoma is an area of ongoing debate in the literature. In our study, we found no significant association between the two conditions. This finding is consistent with some of the previously reported studies, while others have found evidence of an increased risk of POAG in individuals with diabetes. A systematic review by Song (Song, Aiello and Pasquale, 2016) reported an increased risk of POAG in individuals with diabetes based on the majority of the review evidence. However, a recently published meta-analysis by Li (Li et al., 2021) found a range of controversial results. While some studies have reported no association between diabetes and glaucoma, several have only found a positive correlation between diabetes and elevated IOP, but not with glaucoma. Interestingly, some studies have even reported diabetes as a protective factor against glaucoma. The discrepancy in findings among studies could be attributed to differences in study design, population characteristics, and diagnostic criteria for glaucoma and diabetes. It is possible that the relationship between diabetes and glaucoma is complex and multifactorial, involving other factors such as age, gender, and race. Further research is needed to clarify this relationship and identify potential mechanisms underlying the association, which could ultimately inform glaucoma prevention and management strategies in individuals with diabetes.

In contrast to previous studies that have suggested carotid artery stenosis as a potential risk factor for glaucoma development (Moore et al., 2008), our findings do not support such an association. This is consistent with some studies that have reported no significant relationship between carotid artery stenosis and glaucoma (De Voogd et al., 2006; Tham and Cheng, 2017). However, other studies have reported a positive association between carotid artery stenosis and glaucoma (Havens and Gulati, 2015; Kim, Sung and Park, 2017; Chou et al., 2018). Our study did confirm an effect of carotid artery stenosis on the interaction between age and glaucoma, which may suggest that carotid artery stenosis may play a role in glaucoma development in older individuals. Further studies are needed to clarify the potential relationship between carotid artery stenosis and glaucoma, especially in the context of age-related changes in ocular blood perfusion.

Our finding of a positive correlation between glucocorticoid and glaucoma is consistent with previous literature. Several studies have reported this correlation between glucocorticoid use and glaucoma risk (McMonnies, 2017; Allison, Patel and Alabi, 2020; Roberti et al., 2020), particularly in individuals who are steroid responders (Roberti et al., 2020). This means that these individuals are more predisposed to developing high IOP, which is a major risk factor for glaucoma. Although the risk of elevated IOP is higher with topical, intraocular, and periocular glucocorticoid treatment, systemic glucocorticoid treatment can also increase the risk of glaucoma over time. Therefore, it is important to carefully monitor individuals who are treated with systemic glucocorticoids for any signs of elevated IOP or glaucoma. Early detection and treatment of these conditions can prevent or limit damage to the optic nerve and preserve vision. Healthcare professionals should be aware of the potential risks associated with glucocorticoid use and take appropriate measures to minimize these risks.

Our study reveals a positive correlation between glaucoma and risk factors such as cataract (Marchini et al., 2017) and macular degeneration (Cuellar-Partida et al., 2016). This finding aligns with previous literature documenting the coexistence of glaucoma with cataract and macular degeneration. The underlying mechanisms for these associations are not fully understood, but several hypotheses have been proposed. The age-related nature of both conditions, potential lens modifications promoting glaucoma development, correlation between certain glaucoma types and cataract onset, and the impact of hypotensive eyedrops on lens opacity have been suggested to explain the association with cataract (Marchini et al., 2017). For the association between glaucoma and macular degeneration, heritable inflammatory mechanisms and genetic correlation haven reported (Cuellar-Partida et al., 2016). Further investigation is required to gain a deeper understanding of these relationships.

4.3. Strengths and Limitations of this work

Population-based studies can be inconsistent due to various factors such as criteria, sample size, and characteristics of the population, among others. Our study also has its own strengths and limitations. One of the major strengths of our study is its population-based design, which included a large number of participants from a wide age range of adults (45-78 years). Our study also collected data on various human organs and body systems, allowing for comprehensive interdisciplinary analysis. Furthermore, the use of strict criteria for inclusion and exclusion can enhance the validity of the statistical results.

However, our study also has limitations, such as defined criteria for glaucoma, which were primarily based on medication plans and subjective self-reported information from patients. Additionally, some participants were excluded due to insufficient data or not bringing their medication plans to the appointment, which may have affected the analyses related to medication and glaucoma prevalence. Participants who answered “I don’t know” were also excluded from statistical analyses, which may have led to an underestimation or overestimation of glaucoma prevalence in the population. While these criteria were strictly considered, they also led to numerous participants being excluded, which is a limitation of our study.

It is also important to note that the severity of cardiovascular comorbidities was not described in our study sample, which is a limitation of our study. This is because the association between glaucoma and cardiovascular risk factors may only be present in individuals with extreme levels of these risk factors. Without information on the severity of these conditions, it is difficult to draw definitive conclusions about the relationship between cardiovascular risk factors and glaucoma in our study population. Future studies with more detailed information on the severity and duration of cardiovascular diseases may provide more insight into this potential association.

Another limitation of our study is the lack of ophthalmologic examinations in the first 10,000 participants, as the study was not initially designed to estimate the prevalence of glaucoma. However, we recognized the potential for a large population-based study like HCHS to advance research in glaucoma and ophthalmology. To address this limitation, further ophthalmologic examinations were added to the HCHS examination program, which has paved the way of more adequate research in this field.

In future studies, it would be beneficial to examine the relationship between age and the effectiveness of antiglaucoma medication, as this was not explored in our present study. Additionally, including more objective measures for diagnosing glaucoma, such as visual filed tests and optic nerve imaging, could improve the accuracy of glaucoma prevalence estimates.

4.4. Outlook and future directions

The present study has shed light on the prevalence and associated factors of glaucoma in a large population-based sample of adults aged 45-78 years. This study provides a foundation for future research in the field of glaucoma epidemiology, prevention, and treatment. Several important directions for future research are suggested by the findings of this study.

Firstly, a possible future direction is to conduct further investigations into the relationship between age and the effectiveness of the antiglaucoma medication. This could involve designing a randomized clinical trial to test the efficacy of various treatments in different age groups and assessing the impact of age on treatment outcomes. This would help to clarify the optimal treatment strategies for older patients with glaucoma and could inform the development of tailored treatment plans based on age. Secondly, future studies should investigate the role of lifestyle factors, such as physical activity, diet, smoking, and alcohol consumption in the development and progression of glaucoma. and the prevalence of glaucoma. Identifying modifiable risk factors could lead to the development of interventions to prevent or slow the onset of the disease and could improve outcomes for patients with glaucoma. Thirdly, future studies should investigate the prevalence of glaucoma according to added eye examinations. The present study only used self-reported data to define glaucoma, but there are promising publications from the Hamburg City Health Study in the future, which use additional data to better diagnose and confirm glaucoma cases. Fourthly, as advances in imaging technology continue to improve our ability to detect and monitor glaucoma, it will be important to explore the potential of new imaging techniques to improve early detection and diagnosis. This could include developing new imaging modalities that can detect early signs of glaucoma or refining existing

techniques to improve their accuracy and reliability. Lastly, the HCHS also promises impactful results in further publications. The large dataset collected in this study offers ample opportunities to explore the relationship between glaucoma and other factors such as genetics, environmental exposures, and comorbidities. These future studies may provide a more comprehensive understanding of the pathophysiology of glaucoma and lead to the development of new prevention and treatment strategies.

Overall, the findings of this study represent an important step forward in our understanding of glaucoma and its risk factors and provide a solid foundation for future research to build to on. By continuing to investigate the complex interplay of factors that contribute to the development and progression of this disease, we can hope to improve outcomes for patients with glaucoma and ultimately work toward a cure.

5. Conclusion

In conclusion, this study provided important information on the prevalence of glaucoma in a German population-based sample aged 45-78 years. The results highlighted the high prevalence of glaucoma among the adult population and the association between some cardiovascular diseases and glaucoma.

Based on these results, it is important to consider regular eye exams for patients with hypertension, diabetes, and other cardiovascular diseases. The findings suggested that early detection and treatment of these conditions may also have a positive impact on reducing the risk of developing glaucoma. Furthermore, the study highlighted the need for standardized criteria and methods for defining and diagnosing glaucoma, as well as the importance of ophthalmologic examinations in large population-based studies. Future research should continue to investigate the relationship between age and the effectiveness of the antiglaucoma medication, as well as the impact of lifestyle factors and additional eye examinations on the prevalence and incidence of glaucoma. The study also pointed out the need for better physician-patient communication and patient education to improve medication adherence and prevent the irreversible progression of glaucoma.

Overall, the results of this study provide valuable insights into the epidemiology of glaucoma and its association with various demographic, lifestyle, and cardiovascular factors. These findings can inform public health policies and interventions aimed at preventing and managing this condition, which can have significant impacts on individual and population health.

6. Abstract

Introduction: Glaucoma is a group of eye diseases that can lead to irreversible visual loss due to progressive degeneration of retinal ganglion cells and optic nerve damage. It is a major cause of blindness worldwide, and understanding its prevalence, risk factors, and association with cardiovascular diseases is crucial. Despite this, research in this area is limited. The Hamburg City Health Study (HCHS), which involves 45,000 participants, is the largest local health study in the world and presents an opportunity to estimate the prevalence of glaucoma and address important questions.

Methods: The HCHS is a prospective, long-term, population-based cohort study that includes a random sample of 45,000 participants aged between 45 and 74 years from the general population of Hamburg, Germany. In this project, data from the 10,000 participants were used. The data included premedication, questionnaires of medical history regarding glaucoma and cardiovascular illnesses, and validated self-reports. The prevalence of glaucoma was detected through antiglaucoma premedication. Descriptive analysis and logistic regression analysis were performed to analyze the data.

Results: The prevalence of glaucoma in the study was found to be 3.35%. Age, cataracts, macular degeneration, arterial hypertension, dyslipidemia, antihypertensive medication, ß-blocker, glucocorticoid, and drug treatment for elevated triglycerides were significantly associated with the occurrence of glaucoma. Dyslipidemia, antihypertensive medication, ß-blocker, drug treatment for elevated triglycerides, cataracts, macular degeneration, and carotid artery stenosis were found to have an influence on the relationship between the prevalence of glaucoma and age.

Discussion: The study results suggest that the prevalence of glaucoma is influenced by a combination of factors. Age, cataracts, macular degeneration, arterial hypertension, antihypertensive medication, dyslipidemia, drug treatment for elevated triglycerides, and treatment with glucocorticoids are all significant factors. However, the weak correlation between these factors and glaucoma suggests that the disease is multifactorial and not solely dependent on any one factor. Therefore, a combination of factors should be considered when assessing the risk of glaucoma in patients.

7. Zusammenfassung

Einführung: Glaukom beschreibt eine Gruppe von Augenerkrankungen, die durch einen fortschreitenden Verlust der retinalen Ganglienzellen und einer daraus resultierenden Schädigung des Sehnervs zu irreversiblen Sehverlusten führen können. Glaukom ist weltweit eine der führenden Ursachen für Blindheit und zählt somit zu den wichtigsten ophthalmologischen Erkrankungen, die erforscht werden müssen. Bisher gibt es jedoch nicht ausreichend Forschung, um die Prävalenz von Glaukom, die relevanten Risikofaktoren sowie die Assoziation mit kardiovaskulären Erkrankungen zu bestimmen. Die Hamburg City Health Study (HCHS) mit 45.000 Probanden ist die größte lokale Gesundheitsstudie der Welt und findet anfangs im Universitätsklinikum Hamburg-Eppendorf (UKE) statt. Die Studie hat somit ein hohes Potenzial, um die Prävalenz von Glaukom zu schätzen und die relevanten Fragen zu beantworten.

Methoden: Die HCHS ist eine prospektive, langfristige, bevölkerungsbasierte Kohortenstudie, die eine zufällige Stichprobe von 45,000 Teilnehmern im Alter zwischen 45 und 74 Jahren aus der allgemeinen Bevölkerung von Hamburg, Deutschland, einschließt. In diesem Projekt wurden Daten von 10,000 Teilnehmern verwendet. Die Daten umfassten Vorbehandlungen, Fragebögen zur medizinischen Vorgeschichte bezüglich Glaukoms und kardiovaskulären Erkrankungen sowie validierte Selbstberichte. Die Prävalenz von Glaukom wurde durch die Vorbehandlung mit Antiglaukomatosa ermittelt. Deskriptive Analysen und logistische Regressionsanalysen wurden durchgeführt, um die Daten zu analysieren.

Ergebnisse: Die Prävalenz von Glaukom in dieser Studie beträgt 3,35%. Alter, Katarakt, Makuladegeneration, arterielle Hypertonie, Dyslipidämie, antihypertensive Medikation, ß-Blocker, Glukokortikoid und Medikamentenbehandlung bei erhöhten Triglyceriden wurden signifikant mit dem Auftreten von Glaukom assoziiert. Darüber hinaus wird die Beziehung zwischen der Prävalenz von Glaukom und dem Alter durch Faktoren wie Dyslipidämie, antihypertensive Medikation, ß-Blocker, Medikamentenbehandlung bei erhöhten Triglyceriden, Katarakt, Makuladegeneration und Karotisstenose beeinflusst.

Diskussion: Die Ergebnisse dieser Studie legen nahe, dass die Prävalenz von Glaukom von einer Kombination von Faktoren beeinflusst wird, einschließlich Alter, Katarakt, Makuladegeneration, arterieller Hypertonie, antihypertensiver Medikation, Dyslipidämie, Medikamentenbehandlung bei erhöhten Triglyceriden und Behandlung mit Glukokortikoid. Diese Faktoren sind statistisch signifikant und haben einen direkten Einfluss auf die Diagnose von Glaukom- Die schwache Korrelation zwischen diesen Faktoren und Glaukom legt jedoch nahe, dass die Krankheit multifaktoriell und nicht allein von einem Faktor abhängig ist. Daher ist es wichtig, eine Kombination von Faktoren zu berücksichtigen, wenn das Risiko von Glaukom bei Patienten bewertet wird.

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9. Appendix

Appendix 1: Distribution of Antiglaucoma Substances in the Study Sample

Group of Substance	N	%	Substance	Code	N	%
α2-Agonist	20	4.94%	Clonidin	S01EA04	4	0.99%
			Brimonidin	S01EA05	16	3.95%
Cholinergic Agonist	5	1.23%	Pilocarpin	S01EB01	5	1.23%
Carbonic Anhydrase Inhibitor (CAI)	58	14.32%	Actetazolamid	S01EC01	1	0.25%
			Dorzolamid	S01EC03	27	6.67%
			Brinzolamid	S01EC04	30	7.41%
Combi CAI and α2-Agonist	4	0.99%	Brinzolamid and Brimonidin	S01EC24	4	0.99%
Beta-Blocker	50	12.35%	Timolol	S01ED01	49	12.10%
			Levobunolol	S01ED03	1	0.25%
Combi ß-Blocker and Prostaglandin	55	13.58%	Timolol and Latanoprost	S01ED61	25	6.17%
			Timolol and Bimatoprost	S01ED62	23	5.68%
			Timolol and Travoprost	S01ED63	7	1.73%
Combi ß-Blocker and CAI	55	13.58%	Timolol and Dorzolamid	S01ED66	39	9.63%
			Timolol and Brinzolamid	S01ED67	16	3.95%
Combi ß-Blocker and α2-Agonist	2	0.49%	Timolol and Brimonidin	S01ED69	2	0.49%
Prostaglindin Analogues	156	38.52%	Latanoprost	S01EE01	91	22.47%
			Bimatoprost	S01EE03	24	5.93%
			Travoprost	S01EE04	10	2.47%
			Tafluprost	S01EE05	31	7.65%
Total	**405**	**100.00 %**			**405**	**100.00 %**

Appendix 2: Percentage Distribution of Antiglaucoma Preparation

Antiglaucoma Preparation (N=101)	Percentage
Monoprost 50Mikrogramm/ml Augentropfen [Latanoprost 0,01 mg/0,2 ml Einzeldosispipetten]	7.16%
Azopt 10mg/ml [Brinzolamid 10 mg/ml Augentropfen]	6.17%
TAFLOTAN 15Mikrogramm/ml [Tafluprost 15 µg/ml Augentropfen]	4.69%
LUMIGAN 0,1mg/ml [Bimatoprost 0,1 mg/ml Augentropfen]	4.20%
Latanoprost Pfizer 50Mikrogramm/ml [Latanoprost 0,05 mg/ml Augentropfen]	3.70%
AZARGA 10mg/ml+5mg/ml Augentropfensuspension [Brinzolamid und Timolol 10 mg/ml + 5 mg/ml Augentropfen]	3.70%
Latano-Q 50Mikrogramm/ml [Latanoprost 0,05 mg/ml Augentropfen]	3.46%
GANFORT 0,3mg/ml + 5mg/ml [Bimatoprost und Timolol 0,3 mg/ml + 5 mg/ml Augentropfen]	3.21%
Taflotan sine 15Mikrogramm/ml Augentropfen [Tafluprost 4,5 µg/0,3 ml Einzeldosispipetten]	2.96%
DorzoComp-Vision 20mg/ml + 5mg/ml [Dorzolamid und Timolol 20 mg/ml + 5 mg/ml Augentropfen]	2.96%
Tim-Ophtal 0,25% [Timolol 2,5 mg/ml Augentropfen]	2.47%
TRAVATAN 40Mikrogramm/ml [Travoprost 0,04 mg/ml Augentropfen]	2.22%
Latano-Vision 50Mikrogramm/ml [Latanoprost 0,05 mg/ml Augentropfen]	1.98%
Xalatan 0,005% (Raumtemperatur) [Latanoprost 0,05 mg/ml Augentropfen]	1.98%
GANFORT 0,3mg/ml + 5mg/ml Augentropfen [Bimatoprost und Timolol 0,12 mg/0,4 ml + 2 mg/0,4 ml Augentropfen]	1.73%
LatanoTim-Vision 50Mikrogramm/ml + 5mg/ml [Timolol und Latanoprost 5 mg/ml + 0,05 mg/ml Augentropfen]	1.73%
TRUSOPT-S 20mg/ml Augentropfen [Dorzolamid 4 mg/0,2 ml Augentropfen]	1.73%

TRUSOPT 20mg/ml [Dorzolamid 20 mg/ml Augentropfen]	1.48%
Dorzolamid AL comp. 20mg/ml + 5mg/ml [Dorzolamid und Timolol 20 mg/ml + 5 mg/ml Augentropfen]	1.48%
Latanoprost-1A Pharma 0,05mg/ml [Latanoprost 0,05 mg/ml Augentropfen]	1.48%
Timo-COMOD 0,5% [Timolol 5 mg/ml Augentropfen]	1.48%
Brimonidin-AL 2mg/ml [Brimonidin(R,R)-tartrat 2 mg/ml Augentropfen]	1.23%
Brimo-Vision 2mg/ml [Brimonidin(R,R)-tartrat 2 mg/ml Augentropfen]	1.23%
Tim-Ophtal 0,5% [Timolol 5 mg/ml Augentropfen]	1.23%
COSOPT 20mg/ml+5mg/ml [Dorzolamid und Timolol 20 mg/ml + 5 mg/ml Augentropfen]	1.23%
DuoTrav 40Mikrogramm/ml + 5mg/ml [Travoprost und Timolol 0,04 mg/ml + 5 mg/ml Augentropfen]	1.23%
Brinzolamid AL 10mg/ml [Brinzolamid 10 mg/ml Augentropfen]	0.99%
Tavu 50Mikrogramm Latanoprost + 5mg Timolol pro 1ml [Timolol und Latanoprost 5 mg/ml + 0,05 mg/ml Augentropfen]	0.99%
Duokopt 20mg/ml + 5mg/ml [Dorzolamid und Timolol 20 mg/ml + 5 mg/ml Augentropfen]	0.99%
Xalacom [Timolol und Latanoprost 5 mg/ml + 0,05 mg/ml Augentropfen]	0.99%
SIMBRINZA 10mg/ml+2mg/ml Augentropfensuspension [Brinzolamid und Brimonidin(R,R)-tartrat 10 mg/ml + 2 mg/ml Augentropfen]	0.99%
COSOPT-S 20mg/ml+5mg/ml Augentropfen [Dorzolamid und Timolol 4 mg/0,2 ml + 1 mg/0,2 ml Einzeldosispipetten]	0.99%
Xalatan 50Mikrogramm/ml [Latanoprost 0,05 mg/ml Augentropfen]	0.99%
Latano-Q comp. 50Mikrogramm/ml + 5mg/ml [Timolol und Latanoprost 5 mg/ml + 0,05 mg/ml Augentropfen]	0.99%
DorzoComp-Vision sine 20mg/ml + 5mg/ml [Dorzolamid und Timolol 4 mg/0,2 ml + 1 mg/0,2 ml Einzeldosispipetten]	0.74%
Dorzolamid-1A Pharma 20mg/ml [Dorzolamid 20 mg/ml Augentropfen]	0.74%

TRUSOPT-S 20mg/ml Augentropfen [Dorzolamid 4 mg/0,2 ml Einzeldosispipetten]	0.74%
GANFORT 0,3mg/ml + 5mg/ml Augentropfen [Bimatoprost und Timolol 0,12 mg/0,4 ml + 2 mg/0,4 ml Einzeldosispipetten]	0.74%
Tim-Ophtal 0,5% sine Augentropfen 0,5ml [Timolol 2,5 mg/0,5 ml Augentropfen]	0.74%
Timo-COMOD 0,25% [Timolol 2,5 mg/ml Augentropfen]	0.74%
Alphagan 0,2% m/V (2mg/ml) [Brimonidin(R,R)-tartrat 2 mg/ml Augentropfen]	0.74%
Dorzolamid Heumann 20mg/ml [Dorzolamid 20 mg/ml Augentropfen]	0.74%
LUMIGAN 0,3mg/ml Augentropfen [Bimatoprost 0,12 mg/0,4 ml Einzeldosispipetten]	0.74%
Timolol 0,5% AT-1A Pharma [Timolol 5 mg/ml Augentropfen]	0.74%
Dorzolamid comp-1A Pharma 20mg/ml + 5mg/ml [Dorzolamid und Timolol 20 mg/ml + 5 mg/ml Augentropfen]	0.49%
TimoHEXAL 0,1% [Timolol 1 mg/ml Augentropfen]	0.49%
Combigan 2mg/ml+5mg/ml [Brimonidin(R,R)-tartrat und Timolol 2 mg/ml + 5 mg/ml Augentropfen]	0.49%
Clonid-Ophtal 1/8% [Clonidin hydrochlorid 1,25 mg/ml Augentropfen]	0.49%
Brinzo-Vision 10mg/ml [Brinzolamid 10 mg/ml Augentropfen]	0.49%
Latanelb 50Mikrogramm/ml [Latanoprost 0,05 mg/ml Augentropfen]	0.49%
Brimonidin-HEXAL 2mg/ml [Brimonidin(R,R)-tartrat 2 mg/ml Augentropfen]	0.49%
Timo-Vision 0,5% [Timolol 5 mg/ml Augentropfen]	0.49%
Tim-Ophtal 0,1% [Timolol 1 mg/ml Augentropfen]	0.49%
LUMIGAN 0,3mg/ml [Bimatoprost 0,3 mg/ml Augentropfen]	0.49%
Timo-Stulln 0,5% [Timolol 5 mg/ml Augentropfen]	0.25%

Cosopt 4mg/0,2 ml + 1mg/0,2ml Dorzolamida/Timolol	0.25%
Dispatim 0,25% sine Augentropfen [Timolol 1 mg/0,4 ml Augentropfen]	0.25%
Monopost 50mg (Latanoprot)	0.25%
Tim-Ophtal 0,25% sine Augentropfen 0,5ml [Timolol 1,25 mg/0,5 ml Augentropfen]	0.25%
MONOPOST 50Mikrogramm/ml Augentropfen [Latanoprost 0,01 mg/0,2 ml Einzeldosispipetten]	0.25%
TravoprosTimolol-ratiopharm 40Mikrogramm/ml + 5mg/ml [Travoprost und Timolol 0,04 mg/ml + 5 mg/ml Augentropfen]	0.25%
Dorzolamid AL 20mg/ml [Dorzolamid 20 mg/ml Augentropfen]	0.25%
Bimatoprost HEXAL 0,3mg/ml [Bimatoprost 0,3 mg/ml Augentropfen]	0.25%
Monoprost Tropfen	0.25%
Tim-Ophtal 0,1% sine Augentropfen 0,5ml [Timolol 0,5 mg/0,5 ml Einzeldosispipetten]	0.25%
Pilomann 0,5% [Pilocarpin hydrochlorid 5 mg/g Augentropfen]	0.25%
Dorzolamid HEXAL 20mg/ml [Dorzolamid 20 mg/ml Augentropfen]	0.25%
Pilomann 1% [Pilocarpin hydrochlorid 10 mg/g Augentropfen]	0.25%
Clonid-Ophtal 1/8% sine Augentropfen [Clonidin hydrochlorid 0,625 mg/0,5 ml Augentropfen]	0.25%
Pilomann 2% [Pilocarpin hydrochlorid 20 mg/g Augentropfen]	0.25%
TravoTim-Vision 40Mikrogramm/ml + 5mg/ml [Travoprost und Timolol 0,04 mg/ml + 5 mg/ml Augentropfen]	0.25%
Glaupax 250mg [Acetazolamid 250 mg Tabletten]	0.25%
Clonid-Ophtal 1/8% sine Augentropfen [Clonidin hydrochlorid 0,625 mg/0,5 ml Einzeldosispipetten]	0.25%
Spersacarpin 0,5% [Pilocarpin hydrochlorid 5 mg/ml Augentropfen]	0.25%

Xalatan 0,005% (Raumtemperatur) [Latanoprost 0,05 mg/ml Lösung]	0.25%
Spersacarpin 2% [Pilocarpin hydrochlorid 20 mg/ml Augentropfen]	0.25%
Cosopt Santen 20mg/ml+5mh/ml	0.25%
Arutidor 20mg/ml+5mg/ml [Dorzolamid und Timolol 20 mg/ml + 5 mg/ml Augentropfen]	0.25%
Latanoprost-ratiopharm 50Mikrogramm/ml [Latanoprost 0,05 mg/ml Augentropfen]	0.25%
Brimozept 2mg/ml [Brimonidin(R,R)-tartrat 2 mg/ml Augentropfen]	0.25%
Latanoprost-ratiopharm comp. [Timolol und Latanoprost 5 mg/ml + 0,05 mg/ml Augentropfen]	0.25%
Latano Q Icta Pharma	0.25%
Tim-Ophtal 0,5% sine Augentropfen 0,5ml [Timolol 2,5 mg/0,5 ml Einzeldosispipetten]	0.25%
Timo-COMOD 0,1% [Timolol 1 mg/ml Augentropfen]	0.25%
Timo-Stulln 0,5% UD Augentropfen [Timolol 2 mg/0,4 ml Einzeldosispipetten]	0.25%
Latanoprost + Timolol TRB 50Mikrogramm/ml+ 5mg/ml [Timolol und Latanoprost 5 mg/ml + 0,05 mg/ml Augentropfen]	0.25%
Dorzo-Vision 20mg/ml [Dorzolamid 20 mg/ml Augentropfen]	0.25%
Latanoprost comp. AbZ 50Mikrogramm/ml + 5mg/ml [Timolol und Latanoprost 5 mg/ml + 0,05 mg/ml Augentropfen]	0.25%
Travoprost-ratiopharm 40Mikrogramm/ml [Travoprost 0,04 mg/ml Augentropfen]	0.25%
TimoEDO 0,5% Augentropfen [Timolol 2,5 mg/0,5 ml Augentropfen]	0.25%
TRUSOPT [Dorzolamid 20 mg/ml Augentropfen]	0.25%
TimoEDO 0,5% Augentropfen [Timolol 2,5 mg/0,5 ml Einzeldosispipetten]	0.25%
Dorlazept 20mg/ml [Dorzolamid 20 mg/ml Augentropfen]	0.25%

Latanoprost HEXAL comp 0,05mg/ml + 5mg/ml [Timolol und Latanoprost 5 mg/ml + 0,05 mg/ml Augentropfen]	0.25%
VISTAGAN Liquifilm 0,5% [Levobunolol hydrochlorid 5 mg/ml Augentropfen]	0.25%
TimoHEXAL 0,25% [Timolol 2,5 mg/ml Augentropfen]	0.25%
Chibro-Timoptol 0,25% [Timolol 2,5 mg/ml Augentropfen]	0.25%
TimoHEXAL 0,5% [Timolol 5 mg/ml Augentropfen]	0.25%
Monopost 50 µg Augentropfen	0.25%
Timolol 0,25% AT-1A Pharma [Timolol 2,5 mg/ml Augentropfen]	0.25%
LUMIGAN 0,3mg/ml Augentropfen [Bimatoprost 0,12 mg/0,4 ml Augentropfen]	0.25%
Grand Total	**100.00%**

Appendix 3: Percentage Distribution of Artificial Tears

Trade name/Substance	Percentage of Application (N=423)
HYLO-COMOD	21.75%
HYLO-GEL	8.27%
Bepanthen	5.91%
Hylo-Vision HD	4.26%
Hyaluron-rationpharm Augentropfen	4.02%
Artelac Splash EDO	3.55%
Thealoz Duo	2.60%
Corneregel	2.13%
Hyabak 0,15%	2.13%
Hylo-Vision Gel multi 10ml	2.13%
Hylo-Vision sine Augentropfen 0,4ml	2.13%
Hylo-Vision HD plus	2.13%
HYLO-FRESH	2.13%
Corneregel Fluid	1.65%
VITA-POS	1.65%
HYLO-CARE	1.65%
Hylo-Vision Gel sine Augengel 0,35ml	1.65%
Artelac Rebalance	1.42%
Vit-A-Vision	1.42%
Bepanthen Augentropfen	1.42%
Artelac Splash MDO	1.18%
HYLO-PROTECT	1.18%
HYLO-PARIN	1.18%
CATIONORM SD sine	0.95%
SYSTANE ultra Benetzungstropfen für die Augen	0.95%
Hya-Ophtal sine	0.95%
Pan-Ophtal Gel	0.71%

Vitagel	0.71%
Taxofit Augen Kapseln	0.71%
Corneregel Fluid EDO Augentropfen	0.71%
Vismed multi Benetzungslösung	0.71%
Hylo-Vision SafeDrop 0,1%	0.71%
CATIONORM MD sine	0.71%
Tears Again Augenlidspray mit Liposomen	0.47%
SYSTANE Benetzungstropfen für die Augen	0.47%
Artelac Rebalance EDO 0,5ml	0.47%
EvoTears	0.47%
Corneregel EDO Augengel	0.47%
Hylo-Vision SafeDrop Gel	0.47%
Vismed Gel Multi	0.47%
Artelac Nighttime	0.47%
Opticalm BERUHIGENDE AUGENTROPFEN Plus 0,5ml	0.47%
Blink intensives tears PLUS Gel-Augentropfen	0.24%
COLIQUIFILM	0.24%
VisuXL	0.24%
GenTeal HA	0.24%
Artelac Splash (15ml Augentropfen)	0.24%
Biolan Augentropfen	0.24%
Vislube Benetzungslösung	0.24%
Herba-Vision Augentrost	0.24%
Systane Augentropfen (Alcon)	0.24%
Artelac Complete EDO 0,5ml	0.24%
Hyaluron-ratiopharm Augentropfen	0.24%
Blepha-Stulln soft Einmal-Augenkompressen	0.24%
Tears Again Gel Augentropfen	0.24%
IKERVIS 1mg/ml Augentropfen-Emulsion	0.24%
Thealoz Trehalose 3%	0.24%

Herba-Vision Blaubeere	0.24%
Vismed light	0.24%
Artelac Nighttime Gel	0.24%
Superlens Tears (mit reinem Hyaluron)	0.24%
Hyaluron Augentropfen	0.24%
SYSTANE Balance Benetzungstropfen für die Augen	0.24%
Lipospray comfort	0.24%
SYSTANE Hydration Benetzungstropfen für die Augen	0.24%
Oculotect	0.24%
SYSTANE ultra UD Benetzungstropfen für die Augen	0.24%
Oculsoft care sine 0,10 %	0.24%
Artelac EDO Augentropfen	0.24%
OmniMed Hya HD 0,2%	0.24%
Tears Again Sensitive Augenlidspray mit Liposomen	0.24%
OmniTears Lidspray N	0.24%
Thealoz Duo UD	0.24%
Hylan 0,015% Augentropfen	0.24%
Visiocomfort B5 i med	0.24%
Oxysept Comfort 90 Tage Premium Pack	0.24%
Hylo-Vision Gel multi 5 ml	0.24%
Artelac Splash MDO Augentropfen	0.24%
Hya-Ophtal system	0.24%
Siccaprotect	0.24%
Artelac	0.24%
SUPERLENS Tears	0.24%
Jodid 100 mikrogramm Tabletten	0.24%
Xailin Night	0.24%
Jodid 200	0.24%

Lipo Nit Augentropfen 0,1%	0.24%
Grand Total	**100.00%**

Appendix 4: Result of hypothesis tests between Antiglaucoma medication and other variables

Variable	Chi-Square	Two factor ANOVA without repeated measures
Gender	no statistically significant relationship $\chi^2(1) = 0.48$, $p = 0.488$, Cramer's V = 0.007	No significant interaction between the two variables in relation to the dependent variable Age (p=0.466)
Cataract	statistically significant relationship $\chi^2(1) = 157.243$, $p = < 0.001$, Cramer's V = 0.140	significant interaction between the two variables in relation to the dependent variable Age (p=0.001)
Macular degeneration	statistically significant relationship $\chi^2(1) = 30.802$, $p = < 0.001$, Cramer's V = 0.064	Significant interaction between the two variables in relation to the dependent variable Age (p=0.034)
Arterial hypertension	statistically significant relationship $\chi^2(1) = 9.258$, $p = 0.002$, Cramer's V = 0.032	No significant interaction between the two variables in relation to the dependent variable Age (p=0.267)
Dyslipidemia	statistically significant relationship $\chi^2(1) = 12.045$, $p = < 0.001$, Cramer's V = 0.036	Significant interaction between the two variables in relation to the dependent variable Age (p=0.049)
Metabolic syndrome	no statistically significant relationship $\chi^2(1) = 1.310$, $p = 0.252$, Cramer's V = 0.012	No significant interaction between the two variables in relation to the dependent variable Age (p=0.077)
Diabetes mellitus	no statistically significant relationship $\chi^2(1) = 0.467$, $p = 0.494$, Cramer's V = 0.007	No significant interaction between the two variables in relation to the dependent variable Age (p=0.199)
Coronary artery disease	no statistically significant relationship $\chi^2(1) = 0.219$, $p = 0.640$, Cramer's V = 0.005	No significant interaction between the two variables in relation to the dependent variable Age (p=0.359)

Angina pectoris	no statistically significant relationship $\chi^2(1) = 0.672$, $p = 0.412$, Cramer's V = 0.009	No significant interaction between the two variables in relation to the dependent variable Age (p=0.601)
Peripheral arterial disease	no statistically significant relationship $\chi^2(1) = 1.233$, $p = 0.267$, Cramer's V = 0.012	No significant interaction between the two variables in relation to the dependent variable Age (p=0.075)
Carotid artery stenosis	no statistically significant relationship $\chi^2(1) = 2.339$, $p = 0.126$, Cramer's V = 0.016	significant interaction between the two variables in relation to the dependent variable Age (p=0.013)
Smoking status	no statistically significant relationship $\chi^2(1) = 2.614$, $p = 0.106$, Cramer's V = 0.017	No significant interaction between the two variables in relation to the dependent variable Age (p=0.188)
Antihypertensive medication	statistically significant relationship $\chi^2(1) = 19.079$, $p = < 0.001$, Cramer's V = 0.045	significant interaction between the two variables in relation to the dependent variable Age (p=0.017)
ß-Blocker	statistically significant relationship $\chi^2(1) = 9.392$, $p = 0.002$, Cramer's V = 0.031	significant interaction between the two variables in relation to the dependent variable Age (p=0.023)
Glucocorticoid	statistically significant relationship $\chi^2(1) = 4.241$, $p = 0.039$, Cramer's V = 0.021	No significant interaction between the two variables in relation to the dependent variable Age (p=0.902)
Drug treatment for elevated triglycerides	statistically significant relationship $\chi^2(1) = 18.341$, $p = <0.001$, Cramer's V = 0.044	significant interaction between the two variables in relation to the dependent variable Age (p=0.03)
Drug treatment for elevated glucose	no statistically significant relationship $\chi^2(1) = 0.537$, $p = 0.464$, Cramer's V = 0.008	No significant interaction between the two variables in relation to the dependent variable Age (p=0.135)

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11. Curriculum vitae

Der Lebenslauf wurde aus datenschutzrechtlichen Gründen entfernt

12. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
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Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

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