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The KORA Eye Study: A Population-Based Study on Eye Diseases in Southern Germany (KORA F4)

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Purpose. The population-based KORA (Cooperative Health Research in the Region of Augsburg [Germany]) study was used to evaluate the prevalence of eye diseases and potential interactions with general health status, laboratory data, medication, and genetic background.

Methods. In all, 2593 probands, ranging in age from 32 to 71 years (mean: 52 years), were asked in a standardized interview for the presence of cataracts, glaucoma, and corneal or retinal disorders; positive answers were validated and specified by treating ophthalmologists. Additional data came from a questionnaire or from laboratory data.

Results. We validated 10 probands with corneal diseases (validation rate: 32%), 26 with retinal diseases (validation rate: 60%), 40 with glaucoma (validation rate: 75%), and 100 participants with cataracts (validation rate: 88%). Glaucoma was significantly associated with increasing age, diabetes and its treatment, and the use of drugs in airway diseases. Cataracts were significantly associated with increasing age, female sex, hypertension, and diabetes. In females, cataracts were particularly associated with the use of ophthalmological corticosteroids, some antihypertensives, and antidiabetics. In contrast, cataracts in males were associated only with the use of angiotensin-converting enzyme inhibitors. We also tested some polymorphic markers; two (*GJA8*, *CRYBB3*) were significantly associated with cataracts.

Conclusions. Self-reported ocular diagnoses by questionnaire showed varying degrees of accuracy; this method of data collection is valid, providing confirmation is obtained from treating ophthalmologists. It revealed a similar profile of major risk factors for cataracts (age, female sex, and diabetes) in Germany like that of other international studies. The reported associations between medical treatment and genetic polymorphisms in early-onset cataract merit further functional study. (*Invest Ophthalmol Vis Sci.* 2011;52:7778–7786) DOI:10.1167/iovs.10-7113

Visual impairment is one of the leading disabilities in the elderly. If it cannot be cured by glasses, the loss of vision leads to a significant loss of quality of life comparable to that of a stroke[1] and is associated with a shorter lifespan.[2] The general estimates for blindness give a total number of 50 million people worldwide. Recent data from the World Health Organization indicate that cataracts represent the most frequent reason for blindness in the world (39%), followed by uncorrected refractive error (18%, excluding presbyopia), glaucoma (10%), and age-related macular degeneration (AMD; 7%). The proportion of blindness due to cataracts among all eye diseases ranges from 5% in Western Europe, North America, and the Western Pacific region up to 65% in poorer regions.[3]

For Germany, age-related prevalence data for blindness do not exist. Data from the German Statistical Federal Office give a total number of 348,442 blind or partially sighted people in Germany for the year 2007.[4] In the next 20 years, this number will increase by 12,000 to 16,000 persons per year. Due to clinical intervention, the relative contribution to the incidence of blindness in Germany will differ from that of the global scenario: just 5% cataracts, 7% optic atrophy, 11% glaucoma, 14% diabetic retinopathy, and 34% macular degeneration (29% others or of unknown origin).[5]

Based on previous epidemiologic studies in Australia (The Blue Mountains Eye Study, Attebo et al.[6]), in the United States (The Baltimore Eye Survey, Tielsch et al.[7]; The Beaver Dam Eye Study, Knudtson et al.[2]), and in The Netherlands (Borger et al.[8]), several risk factors for different eye diseases have been identified. Diabetes (types 1 and 2)[9] and increased blood pressure[10] are among the major causes for retinal disorders and cataracts; for isolated cataracts, corticosteroids, female sex, and myopia are risk factors.[11] For glaucoma, an association with arterial hypertension, electrocardiographic alterations, headache and migraine, platelet aggregation, blood viscosity, and thyroid-associated disorders is likely and an association with neurodegenerative disorders such as Alzheimer and Parkinson is possible (for a review, see Pache and Flammer[12]).

Similarly, it has been shown that lung diseases and impaired respiratory functions are associated with several systemic diseases such as cardiovascular diseases, arterial stiffness, meta-

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bolic syndrome, insulin resistance, and diabetes.[13,14] In addition, the association with eye diseases (i.e., AMD) was recently raised.[15] Although the potential mechanisms for these associations are poorly understood, low-grade systemic inflammation, oxidative stress, and accelerated aging are currently being discussed.[16,17] Eventually, these mechanisms result in a progressive decline of cellular homeostasis. Therefore, we wondered whether impaired respiratory function might also be associated with eye diseases. Moreover, as recently raised by Gonzalez and colleagues,[18] we addressed the question whether topical medication of lung diseases, including steroids, β-agonists, and anticholinergic drugs, promotes eye diseases.

In a global and genomewide perspective, data concerning the genetic susceptibility of age-related ocular disorders are missing. For age-related cataracts, there have been assumptions (based on twin studies) that the heritability for nuclear and cortical cataracts is approximately 50%.[19,20] For diabetic retinopathies some candidate genes are being tested in studies with small sample sizes (for a recent review, see Uhlmann et al.[9]).

Here, we report for the first time the prevalence and risk factors for eye disorders in a population-based study in Germany: the KORA (Cooperative Health Research in the Region of Augsburg [Germany]) Eye Study. KORA is a regional research platform for population-based surveys and subsequent follow-up studies in the fields of epidemiology, health economics, and health care research.[21] Since the most frequent eye disease in our study is cataracts, we could analyze cataracts in more detail than other eye diseases. We studied the association of eye disorders with other diseases such as diabetes, lung and cardiovascular diseases and their medication, with the general health status and lifestyle parameters. Moreover, we also tested the hypothesis, whether SNPs (single nucleotide polymorphisms) of those genes, which previously have been shown to be involved in the formation of congenital cataracts,[22] are involved in the formation of age-related cataracts.

METHODS

The KORA Eye Study was performed within the framework of KORA-F4,[23] which is a follow-up of the KORA S4 study, a population-based health survey conducted in the city of Augsburg and two surrounding counties between 1999 and 2001. A total sample of 6640 subjects was drawn from the target population consisting of all German residents within the region, ranging in age from 25 to 74 years. Of all 4261 participants of the S4 baseline study, 3080 also participated in the 7-year follow-up F4 study (2006/2008). Persons were considered ineligible for F4 if they had died in the meantime (n = 176, 4%), lived outside the study region, or were completely lost to follow-up (n = 206, 5%), or had demanded deletion of their address data (n = 12, 0.2%). Of the remaining 3867 eligible persons, 174 could not be contacted, 218 were unable to participate either because of illness or time constraints, and 395 were not willing to participate in this follow-up, giving a response rate of 79.6%.

The investigations were carried out in accordance with the Declaration of Helsinki, including written informed consent of all participants. All study methods were approved by the ethics committee of the Bavarian Medical Association, Munich.

Eye Disorders

In the actual KORA F4 study, a subgroup of 2593 participants, ranging in age from 32 to 71 years, were asked in a newly developed, self-administered standardized questionnaire for the presence of eye disorders, subdivided into the sections of cornea disorders, lens opacities (cataracts), glaucoma, and retinal disorders. For those that gave written consent we could refer to the treating ophthalmologists for confirmation and further specification. In all calculations reported here only validated data have been used. In addition to the participant's personal data, family information about eye diseases was also recorded; however, these replies were not cross-checked with ophthalmologists.

General Health Status

Procedures within the KORA studies have been described elsewhere.[21] Information about medical history (including diabetes and hypertension), alcohol consumption, smoking habits, and physical activity was gathered in a structured face-to-face interview. Hypertension (blood pressure: $\geq$140/90 mm Hg) and its treatment were defined according to Meisinger et al.[24]

General Medication

The participants were asked to bring all medications along with them, which they had taken during the past 7 days preceding the interview. The medical staff registered the medication data online using a noncommercial software tool (IDOM).[25] The drugs were categorized according to the Anatomic Therapeutical Chemical classification index. Composite variables for local or systemic use of corticoids, insulin and oral antidiabetics, antihypertensives, diuretics, beta-blocking agents, calcium antagonists, angiotensin-II–enzyme antagonists, angiotensin antagonists, calcium homeostasis, and endocrine therapy were defined. Additionally, medications were assigned as hypertensive medication, if the compounds taken were classified as antihypertensively active by the most recent guidelines of the German Hypertension Society.[24]

Clinical Laboratory

Blood was collected without stasis after a fasting period of at least 8 hours; after blood withdrawal the blood samples were centrifuged and kept cool (4°C) until analyzed in the central laboratory. Analysis was performed within a maximum of 6 hours after withdrawal. In blood, concentrations of glucose, cholesterol, uric acid, creatinine, and ions were determined. Similarly, activities of some key enzymes were measured and blood count was performed; diagnoses of diabetes were performed essentially as described previously.[26]

Lung Function

Lung function tests were performed in a subsample of the KORA F4 cohort corresponding to a random population sample of subjects born between 1946 and 1965 (age range: 41–63 years). A total of 1321 individuals (618 males, 703 females) were studied. Age was 51.6 $\pm$ 5.7 years (mean $\pm$ SD), weight was 79.2 $\pm$ 16.8 kg, and height was 1.70 $\pm$ 0.09 m. Spirometry was performed using a pneumotachograph-type spirometer (Masterscreen PC, CardinalHealth, Würzburg, Germany) before and after inhalation of 200 μg salbutamol. The spirometer was calibrated daily using a 1-L calibration pump (CardinalHealth). Additionally, an internal control was used to ensure constant instrumental conditions. Measurements were performed in line with the American Thoracic Society/European Respiratory Society recommendations.[27] At least two acceptable and reproducible measurements were required. Percentage predicted values were based on the reference values provided by the European Community for Coal and Steel.[28] The best vital capacity (VC) was determined and used as a measure for lung size. The best value of forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) were selected and used to determine the Tiffeneau index (FEV1/FVC) before and after bronchodilation as a measure for airway obstruction. The presence of acute or chronic respiratory diseases as well as medication was assessed by a standardized questionnaire. The severity of chronic obstructive pulmonary diseases (COPD) was classified according to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) standards.[29]

Analysis of SNPs

For SNP analysis, we selected age- and sex-matched controls in a 2:1 ratio to the cataract cases. SNPs have been analyzed of the coding

region of genes, which have been previously shown to be involved in congenital cataracts (for an overview of the genetics of congenital cataracts, see Graw[22]). Genomic DNA was prepared from blood according to standard methods. The SNP samples were genotyped by PCR, allele-specific primer extension followed by mass spectrometry analysis (Sequenom, San Diego, CA). Primer extension products were loaded onto a 384-element chip using a nanoliter pipetting system (SpectroCHIP, SpectroPOINT Spotter, Sequenom). The samples were analyzed in a MALDI-TOF MS (matrix-assisted laser desorption ionization time-of-flight mass spectrometer; Bruker Daltonik GmbH, Leipzig, Germany). The resulting mass spectra were analyzed automatically for peak identification using analytical software (SpectroTYPER RT 3.4 software; Sequenom). Genotyping was done with an SNP genotyping sequenom (MassARRAY, using the iPLEX assay), which uses a primer extension reaction chemistry designed to detect sequence differences at the single nucleotide level. Each sample was amplified in a multiplexed reaction and a specific primer, dependent on the template sequence, was extended. MALDI-TOF mass spectrometry detects the mass difference that differentiates between SNP alleles. For quality reasons 10% of the spectra were checked by two independent trained persons. Cases and controls were genotyped together on mixed plates.

To detect those polymorphisms, which could not be analyzed using the SNP genotyping system (MassARRAY), we used the ARMS (amplification refractory mutation system[30]) assay. Primers (Table 1) were designed using Primer3 v.0.4.0.[31] All the primers were analyzed using a nucleotide basic local alignment search tool (BLAST; National Center for Biotechnology Information) for their specificity and synthesizing capabilities (Life Science Technologies and Specialty Chemicals/Sigma-Aldrich [formerly Sigma-Genosys], Steinheim, Germany). PCR was performed as a standard method, using control primers (forward and reverse) and allele-specific primers for each of the SNPs. PCR products along with 100-bp ladder marker (Fermentas, St. Leon-Rot, Germany) were electrophoresed on 2% agarose gel, stained with ethidium bromide, and photographed using a bioimaging system (Argus XI Bioimaging system; Biostep, Jahnsdorf, Germany). Alleles were assigned on the basis of the presence or the absence of allele-specific bands. For validation of genotypes, samples were retyped.

Statistics

The statistical association models between disease outcome and risk factors were estimated by a multiple logistic regression adjusted for age and sex; variables have been selected and grouped for general health status (variables were age, body mass index [BMI], smoking, and alcohol consumption), general medication (variables included various forms of corticosteroids, antidiarrheals, vitamins, and medications used in calcium homeostasis or for endocrine therapy), diabetes (variables included diagnosis of diabetes, glucose concentration, and various forms of drugs used in treatment of diabetes), hypertension (variables included blood pressure and various forms of drugs used in treatment of hypertension), and lung function (variables included functional lung parameters and drugs used in airway diseases). This grouping was based on hypotheses of their probable participation in the formation of cataracts or glaucoma. Laboratory data contained a large data set (including concentrations of cholesterol, uric acid, creatinine, sodium and potassium ions; enzyme activities of γ-glutamyltransferase, glutamate pyruvate transaminase, glutamate oxalate transaminase, γ-glutamyltranspeptidase, and alkaline phosphatase, as well as a blood count). Therefore, the multivariate analysis has been performed based on a component-wise functional gradient boosting (R function glmboost in R-package mboost[32]; R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). The parameter mstop was selected by a cross-validation approach (repeated [$n = 20$] random subsampling). For continuous variables (e.g., laboratory data) standardized odds ratios (ORs) were calculated as the ratio of odds of cataracts or glaucoma based on the model when the variable considered is increased by 1SD of that variable within the data set under study, with the other variables held fixed.

Genotype, allele frequencies, and violations of Hardy–Weinberg equilibrium were computed routinely for each SNP in cases and controls, used for statistical analysis (SAS program packages; SAS Institute Inc., Cary, NC; S-PLUS; Insightful Corporation). Parts of the genetic analyses were computed with the open source statistical computing environment R,[32] with various contributed packages, such as the *genetics* package for basic genetic measures and the packages *haplo.score* and *hapassoc* for association analyses based on haplotypes. Binary data (e.g., SNPs in the dominant model) were examined with Fisher's exact test and *P* values were adjusted controlling for false discovery rate (FDR).[33] SNPs were selected if the adjusted FDR was <0.05. Moreover, we used conditional inference trees (ctree) and recursive partitioning and regression trees (rpart) for detecting interactions. Multiple test correction was done by the Monte Carlo method. All calculations were done with R (packages: mboost, ade4, rpart, party).[32]

Results

Study Population

In the current KORA Eye Study, 2593 participants, ranging in age from 32 to 71 years, were asked for the presence of any eye disorders; the mean age was 52.7 years for males and 52.1 years for females; there were 47% males and 53% females. The distribution among the age groups was very similar between both sexes.

Table 1. ARMS Primers for the Detection of SNPs

Gene and Primer	rs Number	Sequence	Ann. Temp. (°C)	Product Size (bp)
*CRYBB2-CF**	rs8140949	CCTTGGGAAGTGGCAATGGT	66	378
CRYBB2-CR†		CTGGGAGGTCTGGAGGGTTC		
CRYBB2-FG‡		TACCCCGGCTACCGTTGG	66	221
CRYBB2-FA‡		AGTACCCCGGCTACCGTTGA	66	221
*CRYGD-CF**	rs2242074	TCCAGAGAGAATGCGACCAA	63	646
CRYGD-CR†		TTGCTTGAAACCATCCAGTGA		
CRYGD-RT‡		GTGGTCGCTGCTGCATACA	63	401
CRYGD-RG‡		TGGTCGCTGCTGCATACG	63	401
*SIX5-CF**	rs2014377	CGGAGAGGGAGGGGCTGT	68	680
SIX5-CR†		CTCCTCCACAGGCACCGACT		
SIX5-FC‡		TCGTGACGGGTGTGGACC	68	557
SIX5-RG‡		AGGATGATCTTGCCCTGCTGAAC	68	259

* Control forward primers (CF).
† Control reverse primers (CR).
‡ Allele-specific primers (FN; RN).

TABLE 2. Validation of Eye Diseases in the Questionnaire

Factor	Corneal Disease	Cataract	Retinal Disease	Glaucoma
Self-reported	31	114	43	53
Validated	10	100	26	40
Validation rate (%)	32	88	60	75

In total, 252 participants (9.7%) reported the presence of cataracts, glaucoma, and corneal or retinal disorders. Of those, 212 (84.1%) questionnaires were sent to the respective ophthalmologists for further validation and specification. We received 197 replies (response rate: 92.9%). In the age range from 32 to 71 years, 10 cases of corneal diseases, 26 cases of retinal disorders, 40 cases of glaucoma, and 100 cases of cataracts could be validated (Table 2). Because of the low number of cases, corneal and retinal disorders were not analyzed further.

In general, it has to be considered that our findings of ocular disorders are restricted to clinically relevant cases, and less severe phenotypes may have remained in the control group. Such misclassification bias might have been greater in the younger ages where eye examination is less common. Moreover, it should be considered that patients suffering from chronic diseases such as diabetes or hypertension should undergo regular screening for side effects on the eye; they are, therefore, more likely to be examined by ophthalmologists and diagnosed with ocular disorders.

Glaucoma

Forty cases of glaucoma could be validated. Most glaucomas were open-angle glaucomas (75%), followed by optic nerve excavation (53%), visual field anomalies (30%), and closed-angle glaucomas (8%; combinations of various forms were possible). There was a slight, but statistically significant increase of glaucoma with age ($P > 0.001$; standardized OR 2.3 [1.6–3.5]; Fig. 1); there was no sex difference ($P = 0.987$). Using univariate analysis (adjusted for age), it turned out that glaucoma was significantly associated with the presence of diabetes ($P = 0.004$, OR 3.2 [1.4–6.9]). Moreover, using multivariate regression analysis, treatment of diabetes (Table 3) was statistically significantly associated with glaucoma. Similarly, glaucoma was statistically significantly associated with treatment of hypertension by angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin antagonists (Table 4) and drugs used for obstructive airway diseases, but not with airway diseases (Table 5). Because of the small numbers, a more detailed analysis was not possible.

Cataracts

A total of 100 participants had a confirmed diagnosis of cataract, 24% of whom had surgery in one or both lenses. Some of the participants with cataracts were additionally diagnosed with glaucoma and/or retinal diseases. In all, 34 participants had nuclear cataracts, followed by cortical cataracts (27 cases), subcapsular cataracts (12 probands), and posterior cataracts (11 cases; combinations of various forms were possible); 33 cases had no detailed diagnosis. There was a strong association of cataracts with increasing age ($P < 0.001$, standardized OR 4.3 [3.2–5.9]) and female sex ($P = 0.007$, OR 1.8 [1.2–2.8]; Figs. 1 and 2). Because of the strong gender effect, further cataract data were analyzed separately for males and females. Since the number of variables for lifestyle, blood count, clinical chemistry, and general medical treatment was high ($n = 23$), multivariate analysis was performed based on a component-

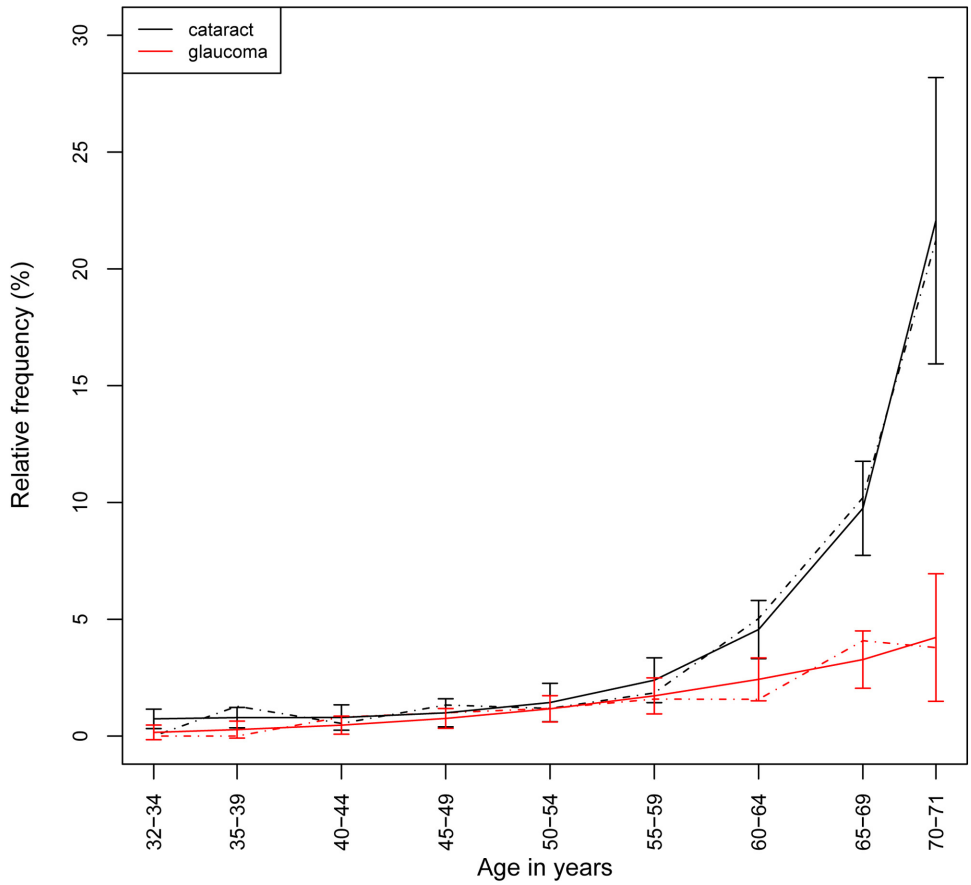

FIGURE 1. Age dependence of ocular disorders. The dependence on age is given for validated, self-reported cataracts and glaucoma between 32 and 71 years. *Black*: cataracts; *red*: glaucoma; *dotted line*: observed values; *solid line*: fitted values; *gray bars*: 95% confidence interval.

TABLE 3. Association of Eye Diseases with Treatment of Diabetes ($n = 2593$)

Variable	Cataract (Females, $n = 64$)		Cataract (Males, $n = 36$)		Glaucoma ($n = 40$)	
	P	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)
Diabetes without medication ($n = 29$; ♀ 16; ♂ 13)	0.404	2.0 (0.3–8.8)	0.989	(0–∞)	0.131	3.4 (0.5–13.4)
Diabetes treated only with oral antidiabetics ($n = 73$; ♀ 28; ♂ 45)	**0.012**	**4.3 (1.3–13.1)**	0.777	0.8 (0.1–3.6)	0.373	1.9 (0.4–6.8)
Diabetes treated with insulin and antidiabetics* ($n = 35$; ♀ 22; ♂ 13)	**<0.001**	**13.0 (3.8–46.0)**	0.263	2.9 (0.4–12.4)	**0.014**	**5.8 (1.3–21.8)**

Statistically significant associations ($P < 0.05$; OR ± 95% CI ≥ 1) are given in bold.

* The number of patients treated with insulin only was very small (in males, $n = 6$) and, thus, merged with the group of patients having the combined therapy by insulin and antidiabetics. Multiple logistic regression; OR (95% CI): odds ratio (95% confidence interval).

wise functional gradient boosting. We could not identify a significant association of cataracts with suggested risk factors such as smoking, alcohol consumption, or BMI. Concerning general health parameters, cataracts are significantly associated only with an increased thrombocyte concentration in females ($P < 0.001$; OR 1.6 [1.2–2.1]). It is also obvious that only in females the use of ophthalmologicals containing corticosteroids (plain or in combination with antiinfectives) was associated with cataracts ($P < 0.001$; OR 261.5 [33.0–2243.4]); such drugs are not used frequently: we observed 8 cases in females, but only one in males.

Moreover, univariate analysis (adjusted for age and sex) revealed that diabetes ($P = 0.001$, OR 2.6 [1.5–4.4]) and hypertension ($P = 0.001$, OR 2.2 [1.4–3.5]) were significantly associated with the presence of cataracts. Stratification for age and sex showed that in the age group older than 60 years, 36.4% of the diabetic females develop cataracts (OR = 4.6; 95% CI 2.1–9.8; $P = 0.000005$), but only 7.8% of the diabetic males of the same age group (OR = 1.3; 95% CI 0.3–4.2; $P = 0.5$).

Using multivariate testing, we saw a highly significant association with the use of insulin in female patients suffering from cataracts; a weaker association was found using oral antidiabetics or a combination of various antidiabetics. Using conditional interference tree calculation, any kind of treatment of diabetes was highly associated with cataracts in females older than 60 years. In contrast, no significant association of treatment in diabetes was found in males (Table 3).

Similarly, treatment of hypertension has been identified to be associated with cataracts. For both, females and males, treatment with ACE inhibitors or angiotensin antagonists was significantly associated with the formation of cataracts; however, hypertension, controlled by other hypertensives (e.g., Ca^{2+}-antagonists and β-blockers, with or without ACE inhibitors or angiotensin antagonists) were significantly associated with cataracts in females only (Table 4).

Since previous reports have demonstrated that corticosteroids used in the treatment of asthma and related disorders might play a role in cataract formation (for a recent review, see Weatherall et al.[34]), we also tested this association in the KORA Eye Study. Unfortunately, the subset of lung function analysis was very small and, thus, multivariate analysis did not reveal any significant result; there was no association with any treatment of airway diseases.

Since a genetic risk for age-related cataracts has to be considered,[22,34–36] we investigated the hypothesis that the age-related formation of cataracts might be associated with particular SNPs in the coding regions of genes, which have previously been shown to be involved in congenital or juvenile cataracts. Among the SNPs investigated, some were present with only one allele in the KORA population and cannot be considered as polymorphic (rs11549440, rs11549441, rs17850134, rs1801966, rs2234703, rs4252581, rs4252582, all *CRYAB*; rs1129658, *CRYBA1*; rs4277, rs12053788, rs28412604, all *CRYBA4*; rs5761634, *CRYBB1*; rs7291633, *CRYBB2*; rs4455261, *CRYBB3*; rs2241980, *CRYGB*; rs2242072, rs28931604, both *CRYGC*; rs1058372, rs80355685, both *EPHA2*; rs3751386, rs9578255, rs968566, all *GJA3*; rs11485706, *GJA8*; rs2547310, *LIM2*; rs12981796, *SIX5*). In contrast, 18 SNPs were polymorphic (i.e., more than one allele is present in the population), and the criterion of the Hardy–Weinberg equilibrium was fulfilled (Table 6). As is obvious from Table 6, in several SNPs no homozygotes are observed. Therefore, a multivariate analysis including a recessive model leads to an even smaller set of SNPs to be analyzed. Therefore,

TABLE 4. Association of Eye Diseases with Treatment of Hypertension ($n = 2593$)

Variable	Cataract (Females, $n = 64$)		Cataract (Males, $n = 36$)		Glaucoma ($n = 40$)	
	P	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)
Actual hypertension without medication ($n = 264$; ♀ 96; ♂ 168)	0.655	0.8 (0.2–2.3)	0.473	1.49 (0.5–4.2)	0.660	1.3 (0.4–3.7)
Treated hypertension (ACE inhibitors and/or angiotensin antagonists without other hypertensives*) ($n = 74$; ♀ 36; ♂ 38)	0.410	1.7 (0.4–5.8)	**0.006**	**5.2 (1.5–15.9)**	**0.025**	**3.8 (1.0–11.2)**
Treated hypertension (other antihypertensives*) ($n = 236$; ♀ 138; ♂ 98)	**0.046**	**2.1 (1.0–4.3)**	0.540	0.6 (0.1–2.5)	0.362	1.6 (0.5–4.2)
Treated hypertension (ACE inhibitors and/or angiontensin antagonists with other hypertensives*) ($n = 321$; ♀ 136; ♂ 185)	**0.003**	**2.8 (1.4–5.5)**	0.071	2.3 (0.9–5.7)	0.101	2.1 (0.9–4.8)

Statistically significant associations ($P < 0.05$; OR ± 95% CI ≥ 1) are given in bold.

* Other hypertensives included diuretics, β-blocking agents, Ca^{2+}-antagonists, and drugs involved in Ca^{2+}-homeostasis and endocrine therapy; this composite variable was defined because of the small numbers of the individual treatment groups. Multiple logistic regression; OR (95% CI): odds ratio (95% confidence interval).

TABLE 5. Association of Eye Diseases with Treatment of Airway Diseases

Treatment (n > 5)	Cataract (n = 100)		Glaucoma (n = 40)	
	P	OR (95% CI)	P	OR (95% CI)
Corticosteroids (nasal preparations) (n = 15)	0.208	3.9 (0.2–22.9)	0.988	— (0–∞)
Drugs for obstructive airway diseases (n = 16)	0.756	1.4 (0.1–8.0)	**0.004**	**10.5 (1.5–42.8)**
Glucocorticoids in airway diseases (n = 37)	0.972	1.0 (0.2–3.5)	0.659	1.6 (0.1–7.8)

Statistically significant associations ($P < 0.05$; OR ± 95% CI ≥ 1) are given in bold. Multiple logistic regression; OR (95% CI): odds ratio (95% confidence interval).

we report here only P value data of a Fisher's exact test controlling for the FDR. Using this approach, the SNP rs3766503 affecting the coding region of the *GJA8* gene was significantly associated with cataracts (Table 6). It is a synonymous exchange (Leu/Leu) of unknown biological function; homozygosity of the minor allele was reported neither in our study nor in the SNP database. However, in the absence of the minor allele of the *GJA8* SNP rs3766503, the minor allele of the *CRYBB3* SNP rs9608378 had a significant protective effect ($P = 0.022$; calculated using conditional interference tree with multiple test correction by the Monte Carlo method).

DISCUSSION

The KORA Eye Study

The KORA Eye Study is a population-based study reporting prevalence and risk factors for eye disorders in a large representative German sample. In contrast to many other countries, population-based studies on eye disorders in Germany are rare and have been focused only on particular aspects such as cataracts,[37] diabetic retinopathy,[38] or retinal disorders (in the Münster Aging and Retina Study [MARS][39]); only MARS has continued focusing on the association between age-dependent macular degeneration and smoking.[40] However, within the framework of KORA it is possible to analyze many aspects of eye diseases in a systemic way, that is, to associate eye disorders in an unbiased manner to a broad variety of parameters, allowing the development of new hypotheses for age-related ocular diseases and comorbid disorders. In the present study, we describe basic findings on this issue in the KORA F4 study (referred to as the KORA Eye Study).

The KORA Eye Study is based on a questionnaire with physician-validated diagnoses. Compared with direct ophthalmic investigation, it is fast and, in combination with a high

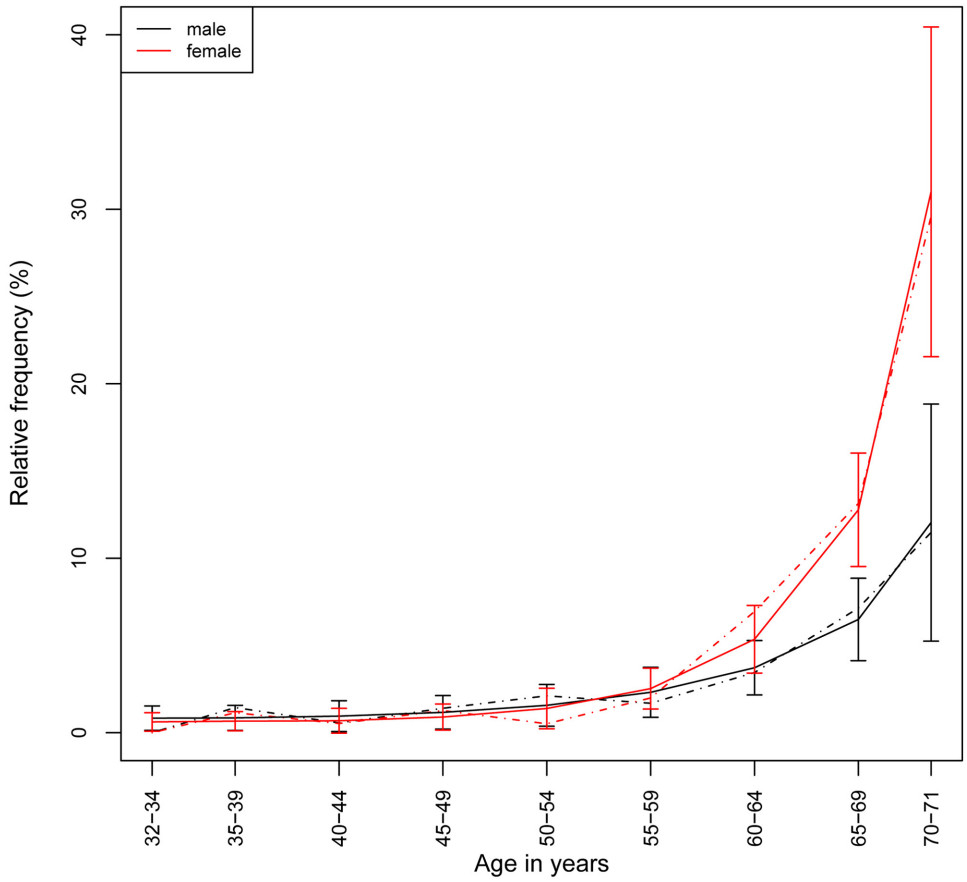

FIGURE 2. Sex-difference in age-related cataracts. Males (*black*) and females (*red*) are plotted separately for any cataract between 32 and 71 years. The frequency of cataracts increases slowly for both sexes until 59 years; after that age, females develop more cataracts than males. *Dotted line*: observed values; *solid line*: fitted values; *gray bars*: 95% confidence interval.

TABLE 6. Informative SNPs Analyzed in the KORA Eye Study

				Allele Distribution										
				dbSNP*			KORA (Control)			KORA (Cases)				
Gene	SNP	Allele	Amino Acid	XX	XY	YY	XX	XY	YY	XX	XY	YY	HWE†	*P*‡	OR (± CI)‡
CRYAA	rs872331	C→T	Asp→Asp	32	48	20	38	42	18	43	40	17	0.071	0.449	0.8 (0.5–1.4)
CRYBA1	rs1047790	C→T	Gly→Gly	62	35	3	70	29	1	79	19	2	0.620	0.374	0.6 (0.3–1.2)
CRYBA4	rs5761637	T→C	Phe→Phe	86	14	—	71	25	2	70	27	3	0.817	0.741	1.1 (0.6–2.0)
CRYBB2	rs16986560	G→T	Ala→Ser	93	7	—	94	4	—	99	1	—	1.00	0.449	0.4 (0.0–1.9)
CRYBB2§	rs8140949	G→A	Gly→Gly	63	33	4	54	41	5	62	33	5	0.621	0.419	0.7 (0.4–1.2)
CRYBB3	rs17670506	G→A	Arg→Gln	81	17	2	90	9	1	87	12	1	0.190	0.309	2.1 (0.9–4.5)
CRYBB3	rs9608378	C→G	His→Asp	47	45	8	35	50	15	43	34	23	0.592	0.226	**0.6 (0.3–0.9)**
CRYGB	rs796287	A→C	Ile→Leu	52	42	6	55	36	8	50	40	10	0.444	0.449	1.3 (0.8–2.2)
CRYGD§	rs2242074	C→T	Tyr→Tyr	30	42	28	39	42	19	31	47	22	0.103	0.400	1.4 (0.8–2.4)
CRYGD	rs2305430	A→G	Arg→Arg	92	4	4	83	15	2	83	17	—	0.445	0.342	1.7 (0.9–3.3)
CRYGN	rs2075001	C→T	Asp→Asp	92	8	—	85	15	—	80	17	3	0.701	0.365	1.7 (0.9–3.4)
EPHA2	rs35903225	G→A	Arg→His	97	3	—	94	6	—	97	3	—	1.00	0.504	0.5 (0.1–2.1)
GJA3	rs11617415	G→A	Ala→Ala	65	32	3	68	29	3	65	33	2	0.830	0.365	1.5 (0.9–2.7)
GJA8	rs3766503	C→T	Leu→Leu	88	12	—	92	8	—	84	16	—	1.00	**0.002**	**4.0 (1.8–8.9)**
LIM2	rs8111243	C→T	Ser→Ser		nd		98	1	—	100	—	—	1.00	0.449	3.0 (0.3–37.0)
PITX3	rs2281983	C→T	Ile→Ile		nd		34	50	14	32	51	17	0.422	0.419	0.7 (0.4–1.2)
SIX5§	rs2014377	C→G	Leu→Val		nd		66	29	5	68	32	—	1.00	1.000	1.0 (0.5–1.7)
SIX5	rs2341097	G→A	Val→Met	40	52	8	42	48	10	31	53	16	0.283	0.741	1.1 (0.7–2.0)

OR is given for association of the minor allele with cataracts; results with violation of the HWE are not presented. nd, not determined.

* HapMap CEU, HapMap-YRI, AGI_ASP or the AFD EUR Panel.

† Calculated for the entire population.

‡ All variables were adjusted for age and sex, controlling for false discovery rate and calculated for a dominant model; *P* values were calculated using Fisher's exact test and were adjusted controlling for false discovery rate of <0.05; missing values were imported using k-nearest neighbors (R program).

§ ARMS method.

response rate of the treating ophthalmologist, it provides authentic information. This approach, however, does not allow estimating the number of undetected cases; they are most likely less severe and do not yet force patients to seek medical support. The broad variation of false responses by the participants in the questionnaire demonstrates that "cataracts" are not only the most frequent eye disease,[3] but also best known in the population with only 12% false answers compared with the other eye disorders tested here. Particularly, the high false-positive responses in cornea and retina disorders are remarkable; in general, the validation rates demonstrate clearly that a questionnaire should not be used without validation from treating ophthalmologists.

One limitation of the present study was its restriction to people up to 71 years of age, which generally led to low prevalence data for the age-related eye diseases. For cataracts, a clear age- and sex-dependent increase was demonstrated, as expected from earlier studies.[2,6,7] The prevalence of any cataract in the different population-based studies varies between 31.5% and 82.9% in the age group of 70 to 74 years[41]; this is higher than that in our study and might be due to our restriction to clinically relevant cases. Another explanation might be that people suffering from chronic diseases such as diabetes or hypertension should undergo regular screening for side effects on the eye; they are, thus, more likely to be examined by ophthalmologists and diagnosed with ocular disorders. Furthermore, misclassification bias might be considered, particularly for the controls; it is greater in the younger ages where eye examination is less common.

Besides these considerations, our results did not support previous findings regarding risk factors like smoking[42–44] or a high body mass index.[45,46] As mentioned previously, our study picked up rather severe cases, which might be a difference from studies with standardized ophthalmic examinations, where also less severe phenotypes can be detected (a marginal effect of smoking disappears when age is controlled). Moreover, in the last years, the smoking behavior has changed as well as the doses used in inhaled corticosteroids. This may also explain why we cannot find an association between smoking behavior and cataracts in our study. Similar arguments might be discussed for finding no association between cataracts and alcohol consumption; however, previous findings on the association between cataract and alcohol consumption are also inconsistent (for a recent review, see Hiratsuka et al.[47]).

Eye Diseases and Comorbidity

In this basic report, we studied associations of glaucoma and cataract to diabetes, hypertension, airway diseases, and their respective medical treatments. Even if the participants were asked for drugs used within the last 7 days, for chronic disorders as discussed here, we can also assume a chronic treatment. Moreover, we also included corticosteroids because of their wide use[48] and previous reports on their role in cataract formation.[34] We support previous research studies showing that diabetes is associated with an increased risk of cataracts[49] and glaucoma.[50] It is noteworthy that we also found a strong effect for the female sex in the diabetes-associated risk of cataracts; this is also true for the treatment of diabetes. There is no explanation for the missing association in males. However, it should be mentioned that in the well-established EMORY mouse model for senile cataracts female mice also develop cataracts earlier than males.[51]

Our study is in agreement with previous reports demonstrating hypertension being a risk factor for cataracts[52]; however, the Bejing Eye Study did not find such an association.[53] As in diabetes, treatment of hypertension by various types of drugs does not decrease the risk for cataracts, which is in line with previous findings in the Blue Mountain Eye Study.[54] Again, we observed an association almost only in females; there

is no explanation, so far, why the risk for cataracts in males is associated only with ACE inhibitors or angiotensin antagonists.

Inhaled corticosteroid therapy with or without combination with long-acting β-adrenergic agonists represents the most important treatment for asthma; they are also prescribed for patients suffering from COPDs.[55] Therefore, airway diseases are of particular interest for the development of cataracts because corticosteroids have been discussed in the past to be involved in cataract formation.[34,56,57] Interestingly, our study showed that drugs used in airway diseases are not associated with cataracts, but with glaucoma. This might be due to frequently prescribed compounds applied by metered-dose inhalers, β-adrenergic agonists, or anticholinergics, which are regularly used in the therapy of (chronic) airway diseases.[58,59]

In contrast to our results on the treatment in airway diseases, we identified a very strong and highly significant association of cataracts with ophthalmological corticosteroids in women. Even if the total numbers are small and the confidence intervals fairly broad, the odds ratio for cataracts is very high. Because of the small numbers, these data must be judged with concern and, theoretically, these drugs might be prescribed because of an ocular disorder; however, it is not very likely that they are used for cataract treatment. Therefore, these results warrant further detailed biochemical studies.

Genetic Aspects of Age-Related Cataracts

Another aspect of the present study concerns the genetic component of age-related ocular disorders. For congenital and juvenile ocular disorders, a broad variety of genes have been identified, which (if affected by a mutation) lead to cataract or glaucoma.[60] However, for age-related diseases, this relationship is not yet established in a similar manner. Only a few previous studies discussed various genetic components for age-related cataracts.[61–67] Therefore, we also tested the possibility that those genes involved in congenital or childhood cataracts would also be involved in the development of age-related cataracts. Despite the limited numbers of cataracts and their morphologic diversity, one SNP within the *GJA8* gene revealed an association with age-related cataracts. Similarly, Zhou et al.[36] also reported in a Chinese case-control study with 301 individuals variations in the *GJA8* gene being significantly associated with age-related cataracts. Another susceptibility gene for age-related cataracts is the *EPHA2* gene.[35] However, it should be mentioned that the minor allele of *CRYBB3* had a statistically significant protective effect on cataract formation. Association studies in our cohort did not reveal an additional risk for cataracts. However, to identify further genetic polymorphisms associated with age-related cataracts, this part of the study has to be repeated in an unbiased, genomewide manner with a larger cohort of cataract cases.

In conclusion, the actual study also demonstrates the feasibility of a questionnaire-based study for ocular epidemiology, if the responses of the participants are validated. We confirmed a high association of diabetes and hypertension with cataract formation and demonstrated that common treatment strategies are also frequently associated with comorbidity of the eye. Ophthalmological corticosteroids in particular were strongly associated with cataracts and may be a significant risk factor in early-onset cataracts.

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