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Common eye diseases in older adults of southern Germany: results from the KORA-Age study

Peter Reitmeir[1], Birgit Linkohr[2], Margit Heier[2], Sophie Molnos[2,3], Ralf Strobl[4,5], Holger Schulz[6], Michaela Breier[2,3], Theresa Faus[7], Dorothea M. Küster[2], Andrea Wulff[1], Harald Grallert[2,3], Eva Grill[4,5], Annette Peters[2], Jochen Graw[7]

[1]Helmholtz Zentrum München, Deutsches Forschungszentrum für Umwelt und Gesundheit, Institute of Health Economics and Health Care Management, Neuherberg, Germany
[2]Helmholtz Zentrum München, Deutsches Forschungszentrum für Umwelt und Gesundheit, Institute of Epidemiology II, Neuherberg, Germany
[3]Helmholtz Zentrum München, Deutsches Forschungszentrum für Umwelt und Gesundheit, Research Unit Molecular Epidemiology, Neuherberg, Germany
[4]Ludwig-Maximilians-Universität, Institute for Medical Information Processing, Biometry and Epidemiology, Munich, Germany
[5]Ludwig-Maximilians-Universität, German Center for Vertigo and Balance Disorders, Munich, Germany
[6]Helmholtz Zentrum München, Deutsches Forschungszentrum für Umwelt und Gesundheit, Institute of Epidemiology I, Neuherberg, Germany
[7]Helmholtz Zentrum München, Deutsches Forschungszentrum für Umwelt und Gesundheit, Institute of Developmental Genetics, Neuherberg, Germany

Address correspondence to: J. Graw, Tel: +49-89-3187-2610; Email: graw@helmholtz-muenchen.de

Abstract

Purpose: a population-based study in the region of Augsburg (Germany, KORA) was used to identify the prevalence of eye diseases and their risk factors in a sample of aged individuals.
Methods: data originated from the KORA-Age study collected in 2012 and 822 participants (49.6% women, 50.4% men, aged 68–96 years) were asked standardised questions about eye diseases. Positive answers were validated and specified by treating ophthalmologists. Additional information came from laboratory data. Polymorphic markers were tested for candidate genes.
Results: we received validations and specifications for 339 participants. The most frequent eye diseases were cataracts (299 cases, 36%), dry eyes (120 cases, 15%), glaucoma (72 cases, 9%) and age-related macular degeneration (AMD) (68 cases, 8%). Almost all participants suffering from glaucoma or from AMD also had cataracts. Cataract surgery was associated with diabetes (in men; OR = 2.24; 95% confidence interval [CI] 1.11–4.53; P = 0.025) and smoking (in women; OR = 6.77; CI 1.62–28.35; $P = 0.009$). In men, treatments in airway diseases was associated with cataracts (glucocorticoids: OR = 5.29, CI 1.20–23.37; $P = 0.028$; sympathomimetics: OR = 4.57, CI 1.39–15.00; $P = 0.012$). Polymorphisms in two genes were associated with AMD (*ARMS2*: OR = 2.28, CI 1.48–3.51; $P = 0.005$; *CFH*: OR = 2.03, CI 1.35–3.06; $P = 0.010$).
Conclusion: combinations of eye diseases were frequent at old age. The importance of classical risk factors like diabetes, hypertension and airway diseases decreased either due to a survivor bias leaving healthier survivors in the older age group, or due to an increased influence of other up to now unknown risk factors.

Keywords: *older people, population study, ageing, cataract, AMD, glaucoma*

Introduction

More than any other species, humans are dependent on their vision for social interactions. Therefore, correct vision is one of the most prominent factors of quality of life. However, visual impairment is one of the leading disorders in older adults affecting 246 million people worldwide and an additional 39 million people are blind. Globally, the

major causes of visual impairment are refractive errors (43%), unoperated cataract (33%) and glaucoma (2%). 65% of all people suffering from visual impairment are aged 50 and older [1]. The global causes of blindness are cataract (51%), glaucoma (8%), age-related macula degeneration (AMD) (5%), childhood blindness and corneal opacities (each 4%), uncorrected refractive errors and trachoma (each 3%), diabetic retinopathy (1%) and undetermined causes (21%) [1]. Visual impairment of the aged population is one of the main causes of diminished independence, mobility restriction, falls and fractures [2, 3].

Besides being the most frequent eye disease, cataracts show various degrees of prevalence in different ethnic groups as outlined by several population-based studies. Moreover, cataracts are also discussed as an independent marker of early mortality [4]. Obviously, this is particularly true for nuclear or mixed cataracts. More recently, a meta-analysis of 10 population-based studies was published [5] indicating that the presence of any cataract was significantly associated with a higher risk of death (hazard ratio 1.43; 95% confidence interval 1.21–2.02; $P < 0.001$). However, it remains an open question whether cataract formation is a consequence of co-morbidities (like diabetes), of environmental factors (like UV-light or nutrition) or of genetic influences.

Similar questions have been raised also for the age-related macular degeneration (AMD), however with a different outcome: African Americans and Caribbeans have a higher frequency of cataracts than people of European origin [4], but in contrast, AMD has a higher prevalence in people of European ancestry compared with Hispanics, Asians and people of African ancestry [6]. Besides these differences in ethnical association, association with diabetes is frequently being reported for (late) AMD, too [7].

For Europe, a recent literature review was published on the prevalence of major eye diseases [4] focusing on AMD, glaucoma and diabetic retinopathy in general populations. The prevalence data given for AMD in individuals aged 65–75 years are 9–25%. Diabetic retinopathy affects 3–4% of the overall European population, but for individuals over 60 years of age it varies between 11% in Germany and 17% in France. For glaucoma, it varies between 3% in France and 14% in Germany [8].

For Southern Germany, we recently evaluated the prevalence of major eye diseases and co-morbidities in the population-based KORA-F4 study (Cooperative Health Research in the Region of Augsburg [Germany]) [9]. In this study, almost 2600 participants 32–71 years of age were asked in a questionnaire for the presence of cataracts, glaucoma and retinal disorders. Positive answers were validated and specified by treating ophthalmologists. We revealed a similar profile of major risk factors for cataracts (age, female sex and diabetes) [9] as described in other international studies [10–12].

As the unique feature of this study, we present here data of a cross-sectional study on older participants (aged 68–96 years). The objective of our study was to examine prevalences, co-morbidities and risk factors of eye diseases in the aged. Specifically, we wanted to show that the prevalence of the most relevant eye diseases increases in the higher age groups even stronger than at younger age indicating specific risk profiles for co-morbidity patterns and associated medication. Along this line, we tested whether eye diseases in older participants are associated with lifestyle parameters (smoking and alcohol consumption) and protective and risk alleles for eye diseases.

Methods

The population-based KORA-Age study was conducted in the region of Augsburg, Southern Germany [13]. An age- and sex-stratified sample of participants of the previous four cross-sectional surveys S1–S4 (1984–2000) [14] born before 1944 was invited to participate in an examination in 2009 (KORA-Age1) and was re-invited 3 years later for a follow-up. In 2012, 822 participants between 68 and 96 years of age completed re-examination (named KORA Age2) [15]. Since the previously reported F4 analysis [9] contributed only partly to Age2, Age2 could not be designed as follow-up (see Supplementary Figure S1, available at *Age and Ageing* online).

KORA-Age2 was carried out in accordance with the Declaration of Helsinki, including written informed consent of all participants and to contact the treating ophthalmologists. All study methods were approved by the ethics committee of the Bavarian Medical Association.

For the detailed description of the methods [estimation of eye disorders, assessment of co-variables, statistics and analysis of single nucleotide polymorphisms (SNPs)], please see Appendix 1 in Supplementary data, available at *Age and Ageing* online.

Results

Among all 822 participants, 465 participants (56.6%) reported the presence of cataracts, glaucoma, corneal or retinal disorders; 420 questionnaires were sent to the respective ophthalmologists for further validation and specification. Finally, 339 participants were validated from their treating ophthalmologists resulting in a response rate of 80.7% and a validation rate between 64% and 87% (see Supplementary Table S2, available at *Age and Ageing* online). The most common validated eye disease in our cohort was cataracts, followed by dry eye, glaucoma and AMD (the numbers and some sub-classifications are shown in Table 1). The results of all co-variables (both continuous and binary) are given separately for each sex in Supplementary Table S3, available at *Age and Ageing* online.

Our overall cataract prevalence was 43%, but glaucoma and AMD co-occurred mainly with cataracts (Figure 1). In cases of the known age of onset of cataracts and glaucoma ($n = 35$), we did not observe a preferential sequence of the two events (cataract→glaucoma: $n = 18$; glaucoma→cataract: $n = 17$). In contrast, for the co-occurrence of cataracts and AMD ($n = 37$), the sequence cataract→retina diseases/

Table 1. Sub-classification of eye disorders by ophthalmologists.

Eye disease	Number of cases[a]
Cornea diseases	129 (16%)
Dry eye	120
Cornea opacification	38
Cataracts	299 (36%)
Nuclear cataract only	77
Cortical cataract only	76
Nuclear and cortical cataract	38
Posterior cataract only	20
Subcapsular cataract only	9
Posterior and subcapsular cataract	0
No detailed diagnosis given	76
Cataract extraction	190[b]
Glaucoma	72 (9%)
Open-angle glaucoma	53
Optic nerve excavation	35
Visual field anomalies	25
Closed-angle glaucoma	6
Retinal disorders	110 (14%)
AMD	68
Macula oedema	9
Thrombosis	9
Gliosis of the macula	6
Vessel anomaly	5
Diabetic retinopathy	5
Tumour	2
Retinitis pigmentosa	1
Retinoschisis	1

[a]Combined diagnoses are possible; percentage is given for the entire cohort (n = 822).

[b]Representing 63% of the overall cataracts. There is no sex effect (P = 0.155); in 59% of the cataractous males and in 67% of the cataractous women cataracts have been extracted.

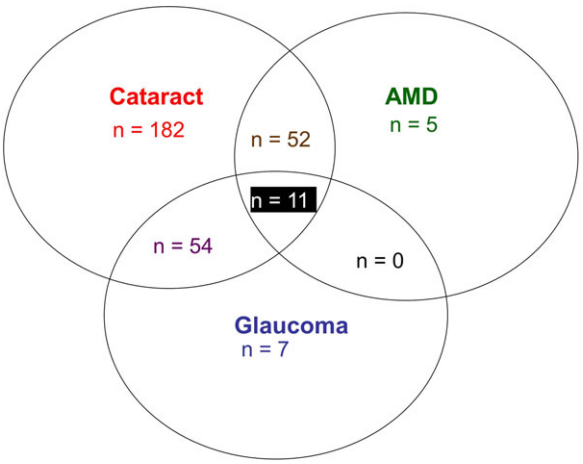

Figure 1. Overlapping prevalence of the three major eye diseases (validated cases only).

AMD was more frequent (n = 29) than the opposite direction (AMD/retinal diseases→cataract: n = 8) (P = 0.001, two-sided binomial test).

The age-dependent increase of the prevalence of major eye diseases, dry eyes, cataracts, glaucoma and AMD is given in Supplementary Figure S2, available at *Age and Ageing* online. The risk of dry eyes increased with age (P = 0.013), and women had a higher risk for dry eyes than men [odds ratio = 1.89 (1.28–2.79), P = 0.001]. For cataracts, we observed a highly significant association between increasing age and the frequency of cataracts (P < 0.001) with female sex as a relevant risk factor [odds ratio for women versus men = 1.76 (1.28–2.41), P < 0.001]. Among the 72 validated cases of glaucoma, most were open-angle glaucoma (74% of all glaucoma cases). With age, the risk of glaucoma increased (P = 0.004), but we did not observe any sex difference (P = 0.443). Among the 68 cases of AMD, we observed similarly an increasing risk with age (P < 0.001) and no sex effect (P = 0.610).

In analysing co-morbidity of eye diseases (Table 2) with diabetes, hypertension and airway diseases, we identified a significant association of diabetes with cataract surgery in men. Similarly, sympathomimetic drugs or inhaled glucocorticoids (used in the treatment of chronic airway diseases) were highly significant risk factors for cataracts in older men. Other eye disorders did not show co-morbidity with diabetes, hypertension and airway diseases, even if different subgroups of eye diseases (Table 1) were analysed.

Statistically significant findings among lifestyle and laboratory data are summarised also in Table 2. We identified alcohol and actual smoking only in older women as a risk factor for glaucoma or cataract surgery, respectively. Thyroid hormone replacement therapy in women was a risk factor for dry-eye syndrome, but was inversely associated with AMD. Males treated with thyroid hormones had a significantly higher risk for glaucoma. Among metabolites and enzyme activities, uric acid and alkaline phosphate activity appear to have protective effects in women only: alkaline phosphatase for dry eye syndrome and uric acid for cataracts in general.

We investigated a limited number of candidate genes (see Supplementary Table S1, available at *Age and Ageing* online) for their association with eye disorders. Due to low minor allele frequencies and the low sample size of KORA, we had limited power to detect significant associations for AMD and glaucoma. Nevertheless, two SNPs (*rs1049024* within the *ARMS2* gene [age-related maculopathy susceptibility gene 2], and *rs1061170* within the *CFH* gene encoding the complement factor H) showed a significant association with AMD (for all odds ratio and *P*-value, see Supplementary Table S4, available at *Age and Ageing* online).

Discussion

In this study, we could confirm diabetes (in men) and smoking (in women) as risk factors for cataract surgery and common SNPs in the genes *ARMS2* and *CFH* for AMD. Moreover, many of our other findings are also in agreement with previous studies, e.g. our overall cataract prevalence is comparable to a recent population-based study in Finland [17], and the risk of sympathomimetic drugs or inhaled glucocorticoids for cataractogenesis is

Table 2. Association of major eye diseases with common illnesses, medication, laboratory data or lifestyle factors.

Eye disease	Associated factor	OR	CI lower	CI upper	*P* value
(a) in women					
Dry eye	Alkaline phosphatase (μkat/l)	0.39	0.17	0.86	0.019
Dry eye	Thyroid therapy (yes)	1.77	1.05	2.98	0.033
AMD	Thyroid therapy (yes)	0.35	0.14	0.87	0.023
Glaucoma	Alcohol (no)	0.35	0.13	0.96	0.042
Cataract	Uric acid (mg/dl)	0.74	0.60	0.91	0.005
Cataract surgery	Alkaline phosphatase (μkat/l)	0.33	0.15	0.75	0.008
Cataract surgery	Actual smoker (yes)	6.77	1.62	28.35	0.009
(b) in men					
Glaucoma	Thyroid therapy (yes)	3.06	1.25	7.49	0.015
Cataract	Haemoglobin (g/l)	1.42	1.08	1.87	0.014
Cataract	Mean corpuscular haemoglobin (pg)	0.24	0.08	0.76	0.015
Cataract	Erythrocytes (100,000 cells/μl)	0.34	0.14	0.81	0.015
Cataracts	Sympathomimetics (yes)	4.57	1.39	15.00	0.012
Cataracts	Glucocorticoids (yes)	5.29	1.20	23.37	0.028
Cataract surgery	Diabetes (yes)	2.24	1.11	4.53	0.025

All models calculated are adjusted for age and gender.

well known (for a recent review see [18]). The preferred sequence of cataract formation followed by AMD is also in line with previous observations of an association of cataract surgery with late AMD [19]. On the other hand, the low frequency of diabetic retinopathy in our cohort of older people is surprising compared to previous studies [reviewed in 4]. It might be argued that most of the affected patients did not survive to become included into our cohort of older people, because these patients suffer from an increased burden of mortality due to complications of chronic hyperglycaemia, like renal failure and cardiovascular diseases [20].

Moreover, the significantly higher risk for glaucoma in males treated with thyroid hormones is consistent with the observation that hypothyroidism patients were found to have a greater risk of developing open-angle glaucoma than the control cohort [21]. Besides the different features of the various eye diseases, the sex-specific differences are also important to notice. These detailed aspects refine the previous knowledge of sex-dependent prevalence in age-related eye diseases that are discussed mainly in the context of hormonal changes in women over lifetime [22].

Concerning the association with genetic risk factors for age-related eye diseases, we observed only two SNPs (in the genes *ARMS2* and *CFH*) being significantly associated with AMD. Among others, both are frequently found to be associated with AMD [23–27]. However, we could not confirm the protective and risk alleles for cataracts, which we have found previously for the younger KORA cohort [9].

The SNP in the *ARMS2* gene leading to an A69S exchange is predicted to be probably damaging (PolyPhen-2, http://genetics.bwh.harvard.edu/pph2/, score of 0.994), since it introduces a Ser residue, which might be used as a new phosphorylation site (score of 0.905, NetPhos 2.0. http://www.cbs.dtu.dk/services/NetPhos/). The SNP in the *CFH* gene corresponds to the amino-acid exchange Tyr402His in the *CFH* gene, but the Tyr residue is most likely not used as a phosphorylation site (score 0.142, NetPhos 2.0).

Nevertheless, we are aware of the limits of our study design: in general, our findings of ocular disorders are restricted to clinically relevant cases, and less severe phenotypes may have remained in the controls. Since aged persons in Germany usually see an ophthalmologist routinely, such misclassification bias might be neglected in the higher age group. Moreover, the individual ophthalmologists might use slightly different diagnostic criteria leading to a kind of uncertainty in the designation of the diseases. However, all diagnostic criteria have to fulfil the requirements of the German health-care insurances resulting in an intrinsic standardisation of our study.

Since association of age-related eye disorders with common diseases or lifestyle factors could be found only for cataract surgery, one might argue it is due to a survivor bias wherein severe diabetes leads to early mortality leaving only healthier survivors in the older age group [28]. This argument might hold true also for all other risk estimates and for other eye diseases.

As in our previous study [9], the main strength of this study is that self-reported eye diseases were validated and specified by treating ophthalmologists that allows a more detailed analysis than non-validated studies [16]. Moreover, there are two important aspects raised by this study in older participants that are different to previous studies. First, in older participants combinations of eye diseases are more frequent than in the younger cohorts. This makes the isolated consideration of particular eye disorders unhelpful for the therapy of older patients. Therefore, an integrated point of view might be rather appropriate. Second, the impact of classical risk factors like diabetes, hypertension and airway diseases decreases either due to a survivor bias leaving healthier survivors in the older age group, or due to an increased influence of other, up to now unknown, risk

factors. If cataracts are the main entry point also for other eye diseases like AMD and glaucoma, the prevention of cataracts should get a very high priority.

Key points

- At older age, eye diseases affect ~50% of a population.
- At older age, combinations of eye diseases were more frequent than in younger people.
- At older age, the importance of classical risk factors for eye diseases (e.g. diabetes, hypertension, airway diseases) decreases.

Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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