Published in final edited form as:

Ophthalmology. 2012 March ; 119(3): 547–554. doi:10.1016/j.opthta.2011.09.005.

Risk Factors for Cortical, Nuclear, Posterior Subcapsular, and Mixed Lens Opacities: The Los Angeles Latino Eye Study

Grace M. Richter, MD, MPH¹, Mina Torres, MS^{1,2}, Farzana Choudhury, MBBS, MPH², Stanley P. Azen, PhD^{1,2}, Rohit Varma, MD, MPH^{1,2}, and for the Los Angeles Latino Eye Study Group³

¹Doheny Eye Institute and Department of Ophthalmology, Keck School of Medicine, University of Southern California, 1450 San Pablo Street, Los Angeles, CA 90033

²Department of Preventive Medicine, Keck School of Medicine, University of Southern California, 1540 Alcazar Street, Los Angeles, CA 90089

Abstract

Purpose—To identify socio-demographic and biological risk factors associated with having cortical, nuclear, posterior sub-capsular (PSC), and mixed lens opacities.

Design—Population-based, cross-sectional study

Participants—Five thousand nine hundred forty-five Latinos 40 years and older from 6 census tracts in Los Angeles, California.

Methods—Participants underwent an interview and detailed eye examination, including best-corrected visual acuity and slit-lamp assessment of lens opacities using the Lens Opacities Classification System II. Univariate and stepwise logistic regression analyses were used to identify independent risk factors associated with each type of lens opacity.

Main Outcome Measures—Odds ratios for socio-demographic and biological risk factors associated with cortical only, nuclear only, PSC only, and mixed lens opacities.

Results—Of the 5945 participants with gradable lenses, 468 had cortical only lens opacities, 217 had nuclear only lens opacities, 27 had PSC only opacities, and 364 had mixed lens opacities. Older age, higher hemoglobin A1c, and history of diabetes mellitus were independent risk factors for cortical only lens opacities. Older age, smoking, and myopic refractive error were independent risk factors for nuclear only lens opacities. Higher systolic blood pressure and history of diabetes were independent risk factors for posterior sub-capsular lens opacities. Older age, myopic refractive error, history of diabetes, higher systolic blood pressure, female gender, and presence of large drusen were independent risk factors for mixed lens opacities.

Conclusions—The modifiable and non-modifiable risk factors identified in this study provide insight into the mechanisms related to the development of lens opacification. Improved glycemic

³A list of members of the Los Angeles Latino Eye Study Group is available at <http://aaojournal.org>.

© 2011 American Academy of Ophthalmology, Inc. Published by Elsevier Inc. All rights reserved.

Correspondence and reprint requests to: Rohit Varma, MD, MPH, Doheny Eye Institute, Suite 4900, 1450 San Pablo Street, Los Angeles, CA 90033. Phone: (323) 442-6411; FAX: (323) 446-6412; rvarma@usc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Financial Disclosure: The authors have no proprietary or commercial interest in any materials discussed in the manuscript.

control, smoking cessation and prevention, and blood pressure control may help to reduce the risk of having lens opacities and their associated vision loss.

Introduction

Age-related lens opacities (cataract) is the leading cause of blindness worldwide.¹ In the United States, over half of those aged 65 and over have lens opacities, and this costs Medicare alone approximately 3 billion dollars per year.² Furthermore, un-operated visually significant lens opacities significantly lower health-related quality of life by causing substantial visual and functional disability.³ For these reasons, understanding risk factors for developing lens opacities is a priority in public health.

Several past epidemiological studies have explored modifiable risk factors associated with lens opacities. In general, different risk factors have been associated with specific types of lens opacities.⁴ Past studies have largely involved non-Hispanic White, Asian, or African origin populations, but there is limited data exploring risk factors for lens opacities in Latinos. Latinos are a rapidly growing ethnic group in the United States (U.S.), with 25% of the U.S. population estimated to be Latino by the year 2050.⁵ Lens opacities have been identified as a leading cause of visual impairment and blindness in Latinos.⁶ Thus, the identification of risk factors associated with lens opacities among Latinos is important especially if modifiable risk factors can be identified and then targeted in public health prevention strategies.

The Los Angeles Latino Eye Study (LALES) is a population-based, cross-sectional study that has examined the prevalence of visual impairment, eye disease, and associated risk factors in Latinos 40 years of age and older living in Los Angeles County, California. The objective of the current study was to examine the relationship between socio-demographic and biological risk factors and the prevalence of cortical, nuclear, posterior sub-capsular (PSC) and mixed lens opacities in adult Latinos 40 years or older participating in LALES.

Methods

Study Cohort

The LALES study population consisted of self-identified Latinos ages 40 years and older living in the city of La Puente, California. This city was chosen because the socioeconomic and demographic characteristics of Latinos in the 6 census tracts of La Puente were alike to those of Latinos of Mexican origin in Los Angeles County, California, and the United States. Details of the study design, sampling strategy, and baseline data have been reported previously.⁷ Briefly, after all dwelling units were identified in La Puente, eligible residents (40 years or older and self-identified Latinos) were invited to participate in the study. Participants were invited to complete an in-home interview and a clinical examination at the Local Eye Examination Center (LEEC). Institutional review board and ethics committee approval were obtained by the Los Angeles County/University of Southern California Medical Center Institutional Review Board.

Interview and Clinical Examination Data

Details about the in-home interview and clinical examination have been previously described, but relevant details will be reported here briefly.⁷ After informed consent was obtained, participants were interviewed to collect socio-demographic information and medical and ocular history. Eligible participants underwent comprehensive eye examinations performed by an ophthalmologist and ophthalmic technician at the LALES local eye examination center (LEEC). Clinic examination data included presenting visual

acuity and best corrected visual acuity, both of which were recorded based on the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol. Participants who did not come to the LEEC were invited to undergo an in-home clinical examination by an ophthalmologist and ophthalmic technician. This also included presenting and best-corrected distance visual acuity measurements, using the ETDRS examination protocol, and an anterior segment examination with lens grading, using a portable slit lamp.

Lens Examination Protocol

Following dilation with tropicamide 1% and phenylephrine 2.5%, the lens was examined at the slit lamp. The Lens Opacities Classification System II (LOCS II) was used to classify opacities into 7 cortical (C0, Ctr, C1, CII, CIII, CIV, CV), 5 nuclear (N0, NI, NII, NIII, NIV), and 5 posterior sub-capsular (PSC; P0, P1, PII, PIII, PIV) grades of increasing severity, according to photographic standards.⁸ If assessment of the lens was not done, the reason for not doing so was documented (pseudophakia, aphakia, etc.). The reproducibility of lens grading using LOCS II was evaluated in the study between 2 examiners. The assessment consisted of grading of 50 participants and was measured by weighted kappa statistics, and the results showed moderate to good inter-grader agreement.

Definition of Lens Opacities

The definitions of lens opacities used in this study are the same as those used in the Barbados Eye Study.⁹

Cortical only, nuclear only, or PSC only lens opacity was defined in individuals with only a single type of opacity (with a LOCS II grading of ≥ 2) present between both eyes. If a participant had unilateral lens extraction, the LOCS II gradings from the contralateral phakic eye defined the lens opacity types in that individual.

Mixed type lens opacity was defined in individuals with 2 or more lens opacity types (each type with LOCS II grading of ≥ 2) present between both eyes. For example, a patient with a cortical opacity (with LOCS II grading of ≥ 2) in one eye and a nuclear opacity (with LOCS II grading of ≥ 2) in the other eye would be considered to have mixed type lens opacity.

Any cortical, any nuclear, or any posterior sub-capsular (PSC) lens opacity was defined by a LOCS II grading of ≥ 2 in either eye. Each participant was classified as having one or more types of lens opacities, and any participant having more than one type of lens opacity (each with LOCS II grading of ≥ 2) was included in *each* category that applied to them—any cortical, any nuclear, or any PSC. Therefore, participants with bilateral lens extraction were excluded, and participants with unilateral lens extraction were included if the other eye had that lens opacity with LOCS II grading of ≥ 2 .

Risk Factor Assessment

Candidate socio-demographic risk factors elicited from the interview included age, sex, acculturation, income, and education. Candidate biological risk factors for cortical, nuclear, and posterior sub-capsular lens opacities included medical and family history from the in-home interview, as well as clinical and ocular parameters measured during the clinical examination. Candidate biological risk factors elicited from the interview included: current smoking history, self-reported history of diabetes mellitus, self-reported history of hypertension, and family history of lens opacities. Candidate biological risk factors elicited from the clinical evaluation included: hemoglobin A1c level, body mass index, diagnosis of glaucoma, intraocular pressure, spherical equivalent refractive error, and presence of large drusen or any age-related macular degeneration (AMD) on grading of fundus photographs. Body mass index was defined as weight in kilograms divided by the square of the height in

meters (kg/m²). Body mass index categories were grouped as underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), and obese (≥ 30.0 kg/m²). Axial length was not used to assess the risk association with lens opacities because the instrumentation was limited in its ability to measure axial lengths in advanced opacities (only 3 percent of those with advanced opacities had axial length measurements).

Statistical Analyses

Chi-square analyses were conducted to assess the univariate association of each age-adjusted socio-demographic or biological risk factor with lens opacities (any, all, mixed, or only vs. no opacities). Socio-demographic or biological risk factors with a p-value ≤ 0.1 were considered as candidate risk factors for the multivariable logistic regression model. Stepwise logistic regression procedures were conducted to evaluate the independent associations and order of importance for each risk indicator. Different multivariate analyses were performed to evaluate independent socio-demographic and biological risk factors for the outcome of (a) cortical only lens opacities and (b) any cortical lens opacities, that is, any lens opacity with a cortical component (of LOCS II score of ≥2). While the former represents a cleaner analysis of direct associations with the specific lens opacity type, the latter may give additional insight into the natural history of developing any lens opacity with a cortical component. Similar pairs of multivariate analyses were performed for the other lens opacity types. Thus, multivariate analyses were performed for the following outcomes: cortical only, any cortical, nuclear only, any nuclear, posterior sub-capsular only, any posterior sub-capsular, and mixed opacities. The outcome of mixed opacities was comprised of people that had more than one type of opacity present between both eyes.

In addition, local regression methods adjusting for other covariates in the multivariate logistic model were used to generate LOWESS (locally weighted scatterplot smoothing regression) plots to characterize further the nature of the independent relationships between various risk factors and the various lens opacity types. All analyses were performed using the Statistical Analysis System (version 9.0, SAS Institute Inc, Cary, NC, and STATA Corp, College Station TX).

Results

Of the 5945 participants with gradable, LOCS II-graded lenses, 4832 had no lens opacities, 468 had cortical only lens opacities, 217 had nuclear only lens opacities, 27 had posterior sub-capsular (PSC) only lens opacities, and 364 had mixed type lens opacities. The mean ages were: 66.5 years for study participants with all lens changes, 62.4 years for those with cortical only lens opacities, 69.4 years for those with nuclear only lens opacities, 59.1 years for those with PSC only lens opacities, and 70.9 years for those with mixed type lens opacities (table 1). Frequency distribution of socio-demographic and biological characteristics among specific types of lens opacities, along with their univariate p-values are reported in tables 1 and 2.

In the case of cortical lens opacities, the same 3 risk factors were identified for both multivariate models. The independent socio-demographic and biological risk factors with odds ratios (OR) for cortical *only* lens opacities were: older age, higher hemoglobin A1c, and history of diabetes (table 3). Multivariate analysis for lens opacities with *any* cortical component revealed identical independent risk factors: older age (per year; OR 1.12; P-value <0.0001), higher hemoglobin A1c (per % increase; OR 1.09; P-value 0.008), and history of diabetes (OR 1.69; P-value <0.001).

In contrast to that for cortical opacities, the multivariate logistic models of independent socio-demographic and biological risk factors for (a) nuclear only lens opacities, and (b) any

nuclear lens opacities in our study population had some differences. The independent risk factors with odds ratios for nuclear only lens opacities were: older age, myopic spherical equivalent, and current smoking (table 4). However, the independent risk factors with odds ratios for any lens opacities with a nuclear component were: older age (per year; OR 1.21; P-value <0.0001), more myopic spherical equivalent (OR 0.82; P-value <0.0001), history of diabetes (OR 1.78; P-value <0.0001), and female gender (OR 1.45; P-value 0.003). Only older age and myopia were common between the two multivariate analyses. Current smoking was important in predicting nuclear only lens opacities, while history of diabetes and female gender became important in predicting lens opacities with any nuclear component.

The multivariate analyses for independent socio-demographic and biological risk factors of PSC only and any PSC lens opacities also had some differences, with the list of significant risk factors for any PSC lens opacities being more extensive. The independent biological risk factors for PSC only lens opacities were: higher systolic blood pressure and history of diabetes (table 5). The model for any lens opacities with a PSC component included two additional independent socio-demographic and biological risk factors: older age (per year; OR 1.11; P-value <0.0001), higher systolic blood pressure (per 1 mmHg increase; OR 1.01; P-value 0.01), history of diabetes (OR 1.72; P-value 0.01), and higher hemoglobin A1c (per % increase; OR 1.12; P-value 0.03).

Independent socio-demographic and biological risk factors for mixed type lens opacities included: myopic spherical equivalent, history of diabetes, female gender, presence of large drusen, older age, and systolic blood pressure (table 6). It is interesting to note that when we had persons with both large drusen and any AMD in the model, the latter was no longer significant in the model, indicating that presence of large drusen may be the more important contributor for this association. When large drusen was not included in the model (data not shown here), presence of any AMD remained significant independent of myopic refractive error, diabetes mellitus, female gender, older age, and systolic blood pressure. Most of these independent risk factors were present in the logistic regression models for specific lens opacity types, with the exception of the presence of large drusen, which was not significant in the other logistic regression models.

A LOWESS plot was used to predict prevalence of nuclear and cortical lens opacities with older age, adjusting for covariates (figure 1). It demonstrates a gradual increase in the prevalence of cortical lens opacities in people with older age from as early as age 40. In contrast, the increase in prevalence of nuclear lens opacities resembles an exponential curve with a relatively sharp increase in prevalence around age 60.

A LOWESS plot was also used to predict prevalence of cortical and PSC lens opacities with higher hemoglobin A1c, adjusting for covariates (figure 2). The predicted prevalence of each lens opacity type appears to increase within the low range of hemoglobin A1c values. Interestingly, there is a stabilization in the predicted prevalence of each lens opacity type with hemoglobin A1c between approximately 8–11%, but the predicted prevalence rises again in those with higher hemoglobin A1c at the highest range of A1c values.

Discussion

The Los Angeles Latino Eye Study (LALES) provides comprehensive data on risk factors for lens opacities in a U.S. Latino population. This cross-sectional investigation, using baseline data from LALES, revealed that: (1) older age, higher hemoglobin A1c, and history of diabetes mellitus were independent risk factors for having cortical lens opacities; (2) older age, current smoking, and myopic refractive error were independent risk factors for having

nuclear lens opacities; (3) higher systolic blood pressure and history of diabetes mellitus were independent risk factors for having posterior sub-capsular (PSC) lens opacities; and (4) independent socio-demographic and biological risk factors for having mixed type lens opacities were older age, myopic refractive error, history of diabetes mellitus, higher systolic blood pressure, female gender, and presence of large drusen on dilated fundus exam.

AGE

Cortical, nuclear, and mixed lens opacities were more likely to be present in individuals of older age. The development of lens opacities are often considered a normal part of the aging process, and have even been found to be an independent risk factor for early mortality.^{10–11} However, the link between age and lens opacification is likely not entirely causal, and it may be that increasing age represents increased cumulative exposure to numerous risk factors, including environmental factors such as ultraviolet B light radiation or oxidative damage.¹²

DIABETES MELLITUS AND GLYCATED HEMOGLOBIN

In our LALES population, a self-reported history of diabetes mellitus was an independent risk factor for cortical lens opacities, PSC lens opacities, and mixed type lens opacities. Elevated hemoglobin A1c levels, or glycated hemoglobin levels, which is a biological marker for chronic hyperglycemia and uncontrolled diabetes, was an independent risk factor for cortical lens opacities. This supports a direct relationship for poor glycemic control with cortical, and possibly PSC, lens opacities. The Barbados Eye study and the Beaver Dam Eye Study also reported significant associations between diabetes and prevalent or incident cortical, nuclear, and PSC lens opacities.^{13,14} Similarly, the Pathologies Oculaires Liées à l'Age (POLA) study reported significant associations between diabetes and cortical, PSC, and mixed lens opacities.¹⁵ In both the Barbados Eye Study and the Beaver Dam Eye Study, higher glycated hemoglobin levels were associated with cortical and nuclear opacities.^{13,14,16,17}

Studied mechanisms underlying the relationship between diabetic hyperglycemia and lens opacification include direct glycation of lens proteins, and sugar alcohols formed via the aldose reductase pathway having a direct toxic effect on lens fibers.¹⁸ Another proposed mechanism is the activation of calpains by elevated levels of calcium present in persons with diabetes mellitus, leading to insolubilization of lens crystallins and the subsequent opacification of the lens.¹⁹ Our findings reinforce this relationship and suggest that better diabetes control and diabetes education may be important in the prevention of lens opacification.

SMOKING

In our LALES investigation, current smoking status was an independent risk factor for nuclear lens opacities. The Blue Mountains Eye Study, the Beaver Dam Eye study, the Age-Related Eye Disease Study, and the Longitudinal Study of Cataract have all also reported a specific association between smoking and nuclear lens opacities.^{20–23} Mechanisms underlying the causal relationship between smoking and lens opacification likely involve oxidative lens damage, and have been explained by reduced antioxidant levels in smokers, increased reactive advanced glycation end products, direct toxicity from heavy metals found in cigarette smoke, and reduced antioxidant defense from tobacco use.^{24–27} It is interesting that *former* smoking was not significantly associated with nuclear lens opacities in our study (data not shown). A dose-response relationship between amount of smoking and risk for nuclear lens opacification has also been well-described in past studies^{20,28–30}, and suggests that both smoking prevention and cessation is likely to reduce the risk of having nuclear lens opacities.

MYOPIC REFRACTIVE ERROR

It is interesting that myopic refractive error as a continuous variable was associated with prevalent nuclear and mixed lens opacities. Large epidemiologic studies have previously focused on myopia defined by an arbitrarily set negative spherical equivalent cut-off rather than refractive error as a continuous variable.^{13,31–33} However, since a specific clinically significant level of myopia in this relationship is unknown, we analyzed refractive error as a continuous variable. While part of the association between more myopic refractive error and nuclear lens opacities may be explained by the myopic shift that is induced by nuclear sclerosis of the lens, it is possible that myopia also serves a causal role in the development of nuclear sclerosis. Potential mechanisms of myopia leading to nuclear sclerosis are largely undetermined, but some have hypothesized that axial myopia is the causal factor with a longer vitreous cavity causing decreased diffusion of nutrients to the posterior lens and thus inhibiting oxidative defense mechanisms.^{34,35,38,49} This theory is supported by the observations that hyperbaric oxygen treatment results in rapid nuclear lens opacification and that nuclear lens opacification frequently occurs after pars plana vitrectomy, whereby intraocular oxygen exposes the lens to high levels of oxygen.^{36–38} Longitudinal data from our study population, where refractive error is assessed prior to the onset of cataract, may help to elucidate a more direct role for myopia in the development of nuclear sclerosis.

SYSTOLIC BLOOD PRESSURE

Systolic blood pressure was found to be an independent risk factor for both PSC and mixed type lens opacities in our LALES investigation. The Blue Mountain Study (BMS) recently reported a relationship between blood pressure and having had cataract surgery from its 10-year incidence data.³⁹ Since those who undergo cataract surgery are usually those with visually significant lens opacities, it could be extrapolated that many of the BMS participants who underwent cataract surgery actually had PSC lens opacities, since PSC opacities are most likely to cause visual impairment.⁴⁰ This idea would support our LALES findings which link PSC opacities and systolic blood pressure. However, overall, reports of the relationship between hypertension and lens opacities have been largely inconsistent and nonspecific to lens opacity type.^{4,17,41} Some studies have suggested hypertension as a risk factor for specific types of lens opacities, while others report hypertension as a protective factor for specific types of lens opacities. The varying effects of different anti-hypertensive medications may be a confounding factor in all of these observational investigations, and an experimental study would likely further elucidate the relationship of hypertension and anti-hypertensive medications with lens opacification.

FEMALE GENDER

Female gender was an independent risk factor for mixed type lens opacities in this LALES investigation. Similar observations have been occasionally reported. In the Barbados Eye Study, female gender was an independent risk factor for incident nuclear and incident cortical lens opacities.^{13,16} In the POLA study, female gender was associated with prevalent cortical lens opacities and with having obtained cataract surgery.¹⁵ Reasons for increased lens opacification in females may be related to differing genetic or environmental factors in the studied populations.

LARGE DRUSEN

Our LALES investigation found the presence of large drusen to be independently associated with prevalent mixed lens opacities. Drusen, which are metabolic byproducts of retinal pigment epithelial cell metabolism, typically represent a clinical finding in AMD. In our analysis, large drusen seemed to be more of a driving force for the relationship between AMD and mixed lens opacities. We believe that large drusen are a more specific sign for

clinically significant age-related macular degeneration, and our results suggest that there may be etiologic pathways common to the development of lens opacification and large drusen in particular. There are several risk factors that have been identified for both AMD in general and lens opacities; these include female gender, smoking, sun exposure, and hypertension.^{13,16, 17,20, 28–30,41} Oxidative damage as measured by lipid peroxidation byproducts has been postulated in the pathogenesis of both lens opacification and AMD^{43,44}, and this common relationship with oxidative damage may explain the relationship of large drusen and mixed lens opacities. Further research on the pathogenesis of both eye diseases may clarify this relationship.

A limitation to the current investigation is its cross-sectional design, which limits our ability to understand temporal trends and relationships. Additionally, a lack of information regarding the onset of biological risk factors such as myopic refractive error limits our understanding of the entity as a causal risk factor for lens opacities.

Overall, our population-based, cross-sectional study of Los Angeles Latinos provides a rich source of data for the identification of biological risk factors for cortical, nuclear, posterior sub-capsular, and mixed lens opacities. Identifying these risk factors can inform public health efforts that seek to reduce the burden of modifiable risk factors such as diabetic glycemic control, smoking, and hypertension, and will provide valuable data for risk stratification based on both non-modifiable and modifiable risk factors. Finally, epidemiologic data reporting relationships between biological risk factors and specific lens opacity types can provide future directions for elucidating the mechanisms associated with the development of specific lens opacities.

Acknowledgments

Financial Support: National Institutes of Health Grants NEI U10-EY-11753 and EY-03040 and an unrestricted grant from the Research to Prevent Blindness, New York, NY, and Pfizer Inc. Rohit Varma is a Research to Prevent Blindness Sybil B. Harrington Scholar. The sponsors or funding organizations had no role in the design or conduct of this research.

References

1. Pascolini D, Mariotti SP, Pokharel GP, et al. 2002 global update of available data on visual impairment: a compilation of population-based prevalence studies. *Ophthalmic Epidemiol.* 2004; 11:67–115. [PubMed: 15255026]
2. Salm M, Belsky D, Sloan FA. Trends in cost of major eye disease to Medicare, 1991 to 2000. *Am J Ophthalmol.* 2006; 142:976–982. [PubMed: 17157582]
3. Brenner MH, Curbow B, Javitt JC, et al. Vision change and quality of life in the elderly: response to cataract surgery and treatment of other chronic ocular conditions. *Arch Ophthalmol.* 1993; 111:680–685. [PubMed: 8489453]
4. West S. Epidemiology of cataract: accomplishments over 25 years and future directions. *Ophthalmic Epidemiol.* 2007; 14:173–178. [PubMed: 17896293]
5. U.S. Census Bureau. Vol. 13. Washington, D.C.: U.S. Government Printing Office; 1996. Current Population Reports. Population Projections of the United States by Age, Sex, Race, and Hispanic origin: 1995 to 2050; p. P25-P1130. Available at: <http://www.census.gov/prod/1/pop/p25-1130/p251130.pdf>
6. Cotter SA, Varma R, Ying-Lai M, et al. Los Angeles Latino Eye Study Group. Causes of low vision and blindness in adult Latinos: the Los Angeles Latino Eye Study. *Ophthalmology.* 2006; 113:1574–1582. [PubMed: 16949442]
7. Varma R, Paz SH, Azen SP, et al. Los Angeles Latino Eye Study Group. The Los Angeles Latino Eye Study: design, methods, and baseline data. *Ophthalmology.* 2004; 111:1121–1131. [PubMed: 15177962]

8. Chylack LT Jr, Leske MC, McCarthy D, et al. Lens Opacities Classification System II (LOCS II). *Arch Ophthalmol*. 1989; 107:991–997. [PubMed: 2751471]
9. Leske MC, Connell AM, Wu SY, et al. Barbados Eye Study Group. Prevalence of lens opacities in the Barbados Eye Study. *Arch Ophthalmol*. 1997; 115:105–111. [PubMed: 9006434]
10. AREDS Research Group. Associations of mortality with ocular disorders and an intervention of high-dose antioxidants and zinc in the Age-Related Eye Disease Study: AREDS report no. 13. *Arch Ophthalmol*. 2004; 122:716–726. [PubMed: 15136320]
11. McGwin G Jr, Owsley C, Gauthreaux S. The association between cataract and mortality among older adults. *Ophthalmic Epidemiol*. 2003; 10:107–119. [PubMed: 12660859]
12. McCarty CA, Taylor HR. A review of the epidemiologic evidence linking ultraviolet radiation and cataracts. *Dev Ophthalmol*. 2002; 35:21–31. [PubMed: 12061276]
13. Leske MC, Wu SY, Nemesure B, Hennis A. Barbados Eye Studies Group. Risk factors for incident nuclear opacities. *Ophthalmology*. 2002; 109:1303–1308. [PubMed: 12093655]
14. Klein BE, Klein R, Wang Q, Moss SE. Older-onset diabetes and lens opacities: the Beaver Dam Eye Study. *Ophthalmic Epidemiol*. 1995; 2:49–55. [PubMed: 7585233]
15. Delcourt C, Cristol JP, Tessier F, et al. POLA Study Group. Risk factors for cortical, nuclear, and posterior sub-capsular cataracts: the POLA study. *Am J Epidemiol*. 2000; 151:497–504. [PubMed: 10707918]
16. Hennis A, Wu SY, Nemesure B, Leske MC. Barbados Eye Studies Group. Risk factors for incident cortical and posterior subcapsular lens opacities in the Barbados Eye Studies. *Arch Ophthalmol*. 2004; 122:525–530. [PubMed: 15078670]
17. Leske MC, Wu SY, Hennis A, et al. Barbados Eye Study Group. Diabetes, hypertension, and central obesity as cataract risk factors in a black population: the Barbados Eye Study. *Ophthalmology*. 1999; 106:35–41. [PubMed: 9917778]
18. Varma SD. Aldose reductase and the etiology of diabetic cataracts. *Curr Top Eye Res*. 1980; 3:91–155. [PubMed: 6807610]
19. Biswas S, Harris F, Singh J, Phoenix D. Role of calpains in diabetes mellitus-induced cataractogenesis: a mini review. *Mol Cell Biochem*. 2004; 261:151–159. [PubMed: 15362498]
20. Tan JS, Wang JJ, Younan C, et al. Smoking and the long-term incidence of cataract: the Blue Mountains Eye Study. *Ophthalmic Epidemiol*. 2008; 15:155–161. [PubMed: 18569810]
21. Klein BK, Klein R, Lee KE, Meuer SM. Socioeconomic and lifestyle factors and the 10-year incidence of age-related cataracts. *Am J Ophthalmol*. 2003; 136:506–512. [PubMed: 12967805]
22. Age-Related Eye Disease Study Research Group. Risk factors associated with age-related nuclear and cortical cataract: a case-control study in the Age-Related Eye Disease Study, AREDS report no. 5. *Ophthalmology*. 2001; 108:1400–1408. [PubMed: 11470690]
23. Leske MC, Chylack LT Jr, He Q, et al. LSC Group. Risk factors for nuclear opalescence in a longitudinal study. *Am J Epidemiol*. 1998; 147:36–41. [PubMed: 9440396]
24. Boscia F, Grattagliano I, Vendemiale G, et al. Protein oxidation and lens opacity in humans. *Invest Ophthalmol Vis Sci*. 2000; 41:2461–2465. [PubMed: 10937554]
25. Banerjee KK, Marimuthu P, Sarkar A, Chaudhuri RN. Influence of cigarette smoking on vitamin C, glutathione and lipid peroxidation status. *Indian J Pub Health*. 1998; 42:20–23. [PubMed: 10389502]
26. Nicholl ID, Stitt AW, Moore JE, et al. Increased levels of advanced glycation endproducts in the lenses and blood vessels of cigarette smokers. *Mol Med*. 1998; 4:594–601. [PubMed: 9848076]
27. Cekic O. Effect of cigarette smoking on copper, lead, and cadmium accumulation in human lens. *Br J Ophthalmol*. 1998; 82:186–188. [PubMed: 9613387]
28. Hiller R, Sperduto RD, Podgor MJ, et al. Cigarette smoking and the risk of development of lens opacities: the Framingham studies. *Arch Ophthalmol*. 1997; 115:1113–1118. [PubMed: 9298050]
29. Klein BE, Klein RE, Lee KE. Incident cataract after a five-year interval and lifestyle factors: the Beaver Dam Eye Study. *Ophthalmic Epidemiol*. 1999; 6:247–255. [PubMed: 10544339]
30. West S, Munoz B, Emmet EA, Taylor HR. Cigarette smoking and risk of nuclear cataracts. *Arch Ophthalmol*. 1989; 107:1166–1169. [PubMed: 2757547]

31. Chang MA, Congdon NG, Bykhovskaya I, et al. The association between myopia and various subtypes of lens opacity: SEE (Salisbury Eye Evaluation) project. *Ophthalmology*. 2005; 112:1395–1401. [PubMed: 15953641]
32. Younan C, Mitchell P, Cumming RG, et al. Myopia and incident cataract and cataract surgery: the Blue Mountains Eye Study. *Invest Ophthalmol Vis Sci*. 2002; 43:3625–3632. [PubMed: 12454028]
33. Kubo E, Kumamoto Y, Tsuzuki S, Akagi Y. Axial length, myopia, and the severity of lens opacity at the time of cataract surgery. *Arch Ophthalmol*. 2006; 124:1586–1590. [PubMed: 17102006]
34. Micelli-Ferrari T, Vendemiale G, Grattagliano I, et al. Role of lipid peroxidation in the pathogenesis of myopic and senile cataract. *Br J Ophthalmol*. 1996; 80:840–843. [PubMed: 8942384]
35. Simonelli F, Nesti A, Pensa M, et al. Lipid peroxidation and human cataractogenesis in diabetes and severe myopia. *Exp Eye Res*. 1989; 49:181–187. [PubMed: 2767166]
36. Holekamp NM, Shui YB, Beebe DC. Vitrectomy surgery increases oxygen exposure to the lens: a possible mechanism for nuclear cataract formation. *Am J Ophthalmol*. 2005; 139:302–310. [PubMed: 15733992]
37. Palmquist BM, Philipson B, Barr PO. Nuclear cataract and myopia during hyperbaric oxygen therapy. *Br J Ophthalmol*. 1984; 68:113–117. [PubMed: 6691953]
38. Thompson JT. The role of patient age and intraocular gas use in cataract progression after vitrectomy for macular holes and epiretinal membranes. *Am J Ophthalmol*. 2004; 137:250–257. [PubMed: 14962413]
39. Tan JS, Wang JJ, Mitchell P. Influence of diabetes and cardiovascular disease on the long-term incidence of cataract: the Blue Mountain Eye Study. *Ophthalmic Epidemiol*. 2008; 15:317–327. [PubMed: 18850468]
40. Varma R, Richter GM, Torres M, et al. Los Angeles Latino Eye Study Group. Four-year incidence and progression of lens opacities: the Los Angeles Latino Eye Study. *Am J Ophthalmol*. 2010; 149:728–734. [PubMed: 20181327]
41. Klein BE, Klein R, Jensen SC, Linton KL. Hypertension and lens opacities from the Beaver Dam Eye Study. *Am J Ophthalmol*. 1996; 119:640–646. [PubMed: 7733190]
42. West SK, Duncan DD, Munoz B, et al. Sunlight exposure and risk of lens opacities in a population-based study: the Salisbury Eye Evaluation project. *JAMA*. 1998; 280:714–718. [PubMed: 9728643]
43. Yamada Y, Tian J, Yang Y, et al. Oxidized low density lipoproteins induce a pathologic response by retinal pigmented epithelial cells. *J Neurochem*. 2008; 105:1187–1197. [PubMed: 18182060]
44. Beatty S, Koh H, Phil M, et al. The role of oxidative stress in the pathogenesis of age-related macular degeneration. *Surv Ophthalmol*. 2000; 45:115–134. [PubMed: 11033038]

Figure 1. LOWESS (Locally Weighted Scatterplot Smoothing) plots demonstrate higher predicted prevalences of nuclear and cortical lens opacities, adjusting for covariates, in those with older age. The increase is more gradual in the case of cortical lens opacities, and is more apparently exponential with nuclear lens opacities, particularly beginning around age 60.

Figure 2. LOWESS (Locally Weighted Scatterplot Smoothing) plots demonstrate that the predicted prevalences of cortical and posterior subcapsular (PSC) lens opacities, adjusted for covariates, is higher within the low range of hemoglobin A1c values, stabilize from approximately 8–11%, then rise again at the highest values of hemoglobin A1c.

Table 1
Distribution of Socio-demographic Risk Factors Stratified by Lens Opacity Type in Los Angeles Latino Eye Study Participants

Risk factors	No Opacity n=4832	All Lens Changes n=1095	Mixed Type n=364	Cortical Only n =468	Nuclear Only n=217	Posterior Subcapsular Only n=27
Mean Age ($\pm$ SD)	51.6 ($\pm$ 8.5) [†]	66.5 ($\pm$ 9.9) ^{**}	70.9 ($\pm$ 9.7) ^{**}	62.4 ($\pm$ 8.6) ^{**}	69.4 ($\pm$ 8.8) ^{**}	59.1 ($\pm$ 11.4) ^{**}
Female Gender	3222 (57.9%) [†]	643 (58.7%)	230 (63.2%) [*]	271 (57.9%)	129 (59.5%)	14 (51.8%)
Income <20,000	2008 (47.5%)	611 (66.5%) ^{**}	202 (67.5%) [*]	259 (64.7%) ^{**}	125 (69.4%) [*]	14 (66.7%) [*]
Low Acculturation Score <1.9 +	3251 (67.4%)	703 (64.3%) [*]	231 (63.6%) [*]	311 (66.4%)	131 (60.7%) [*]	17 (62.9%)
Less than High School Graduate	3083 (63.9%)	830 (75.9%) ^{**}	292 (80.4%) ^{**}	345 (73.6%) [*]	165 (76.6%) [*]	15 (55.6%)

[†] Data is shown in column frequencies and percents (%) or mean and standard deviation (SD).

⁺ Low acculturation score was defined as <1.9, using the Cuellar 9-item, 5-point scale developed for Mexican Americans and based on preferred language and which language the person can speak, read, or write.

Each opacity type is compared to the no opacity group using a t-test for continuous variables and a chi-square test for categorical variables.

Differences that are statistically significant at $p \leq 0.1$ are denoted with one asterisk(*), and at ≤ 0.05 are denoted with two asterisks(**).

For example the mean age 66.5 ($\pm$ 9.9) for all lens change is significantly higher compared to the mean age (51.6 $\pm$ 8.5) of the no opacity group, with p -value < 0.05. Risk factors with p -value ≤ 0.1 were considered as candidate risk factors for the multivariable logistic regression model.

Table 2
Distribution of clinical and biological risk factors stratified by Lens Opacity Type in Los Angeles Latino Eye Study participants

Risk factors	No Opacity n=4832	All Lens Changes n=1095	Mixed Type n=364	Nuclear Only n=217	Cortical Only n=468	Posterior Subcapsular Only n=27
Current Smoker	688 (14.3%) [†]	134 (12.4%) ^{**}	32 (9.1%) ^{**}	35 (16.3%)	60 (12.9%)	3 (11.1%)
History of Diabetes	651 (13.5%)	330 (30.2%) ^{**}	123 (33.9%) ^{**}	54 (25%) ^{**}	139 (29.7%) ^{**}	11 (40.7%) ^{**}
Hb A1C [‡] (mean ±SD)	6.1 (±0.98) [†]	6.5 (±1.8) ^{**}	6.5 (±1.7) ^{**}	6.2 (±1.5)	6.5 (±1.9) ^{**}	7.0 (±2.2) ^{**}
Hb A1C (>8%)	433 (9.1%)	169 (15.6%) ^{**}	58 (16.0%) ^{**}	21 (9.7%)	82 (17.7%) ^{**}	7 (25.9%) ^{**}
Hb A1C (>10%)	198 (4.1%)	68 (6.3%) ^{**}	20 (5.5%)	9 (4.2%)	36 (7.8%) ^{**}	3 (11.1%) [*]
Hypertension	1245 (26.1%)	492 (45.2%) ^{**}	190 (53.0%) ^{**}	92 (42.3%) ^{**}	189 (41.0%) ^{**}	11 (40.7%)
Body Mass Index ⁺						
Normal (reference)	490 (10.3%)	159 (14.9%)	55 (15.7%)	34 (16.7%)	64 (14.1%)	2 (7.4%)
Overweight	1863 (39.1%)	400 (37.6%)	136 (38.8%)	83 (40.7%)	165 (36.3%)	11 (40.7%)
Obese	2407 (50.1%)	499 (46.9%)	160 (45.6%) ^{**}	87 (42.7%) ^{**}	226 (49.7%)	14 (50.9%)
Glaucoma	67 (1.4%)	61 (5.6%) ^{**}	25 (6.9%) [*]	19 (8.8%) ^{**}	13 (2.8%)	2 (7.4%)
Intraocular Pressure	14.4 (±3.1)	15.1 (±4.3) ^{**}	15.4 (±5.6) ^{**}	15.6 (±3.9) ^{**}	14.8 (±3.2) [*]	15.6 (±3.0) [*]
Spherical Equivalent (Mean ±SD)	0.1 (±1.9)	0.2 (±2.9) ^{**}	-0.2 (±3.5) ^{**}	-0.03 (±3.2) [*]	0.6 (±1.8) ^{**}	-0.3 (±2.9)
Family History Cataract	1423 (30.4%)	285 (27.2%) ^{**}	97 (28.7%)	55 (27.2%)	123 (26.9%)	5 (20.8%)
Large Drusen	578 (12.1%)	228 (21.1%) ^{**}	80 (22.7%) ^{**}	50 (23.4%) ^{**}	89 (19.1%) ^{**}	5 (18.5%)
Any AMD [‡]	404 (8.5%)	134 (13.3%) ^{**}	54 (17.6%) ^{**}	29 (14.4%) ^{**}	43 (9.6%)	4 (15.4%)

[†] Data is shown in column frequencies and percents (%) or mean and standard deviation (SD).

[‡] Hemoglobin A1C level

⁺ Body Mass Index groups were divided into Normal (18.5–24.9 kg/m²), Overweight (25.0–29.9 kg/m²), and Obese (≥ 30.0 kg/m²).

[‡] AMD: Age-related macular degeneration.

The normal group comprised the reference group. Each opacity type is compared to the no opacity group using a t-test for continuous variables and a chi-square test for categorical variables. Differences that are statistically significant at p ≤ 0.1 are denoted with one asterisk(*), and at ≤ 0.05 are denoted with two asterisks(**).

For example, history of diabetes (30.2%) was significantly associated with lens changes compare to those with no opacity (13.5%), with p-value ≤ 0.1 were considered as candidate risk factors for the multivariable logistic regression model.

Table 3

Independent Socio-demographic and Biological Risk Factors Associated with **Cortical Only Opacities** in the Los Angeles Latino Eye Study

Risk Factors	OR (95%)*	P-Value
Age (per year)	1.07 (1.06, 1.08)	<0.0001
HbA1c [†] (per %)	1.09 (1.01, 1.17)	0.02
History of Diabetes	1.45 (1.07, 1.94)	0.01

* Odds ratio (95% confidence interval)

[†] Hemoglobin A1c

Table 4

Independent Socio-demographic and Biological Risk Factors Associated with **Nuclear Only Opacities** in the Los Angeles Latino Eye Study

Risk Factors	OR (95%)*	P-Value
Age (per year)	1.14 (1.12,1.16)	<0.0001
Spherical equivalent	0.91 (0.86, 0.96)	0.001
Current Smoking	1.73 (1.14, 2.65)	0.01

* Odds ratio (95% confidence interval)

Table 5

Independent Socio-demographic and Biological Risk Factors Associated with **Posterior Sub-capsular Only Opacities** in the Los Angeles Latino Eye Study

Risk Factors	OR (95%)*	P-Value
Systolic blood pressure (per 1mmHg)	1.02 (1.01, 1.04)	0.01
History of diabetes	2.96 (1.35, 6.48)	0.01

* Odds Ratio (95% confidence interval)

Table 6

Independent Biological Risk Factors Associated with **Mixed Lens Opacities** in the Los Angeles Latino Eye Study

RiskFactors	OR (95%)*	P-Value
Spherical Equivalent	0.85 (0.82, 0.89)	<0.0001
History of Diabetes	1.93 (1.45, 2.58)	<0.0001
Female Gender	1.49 (1.13, 1.95)	0.005
Large Drusen	1.19 (1.11, 1.27)	<0.0001
Age (per year)	1.17 (1.15, 1.19)	<0.0001
Systolic Blood Pressure (per 5mmHg)	1.01 (1.00,1.02)	0.008

* Odds Ratio (95% confidence interval)