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Risk Factors for Four-Year Incidence and Progression of Age-Related Macular Degeneration: The Los Angeles Latino Eye Study

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Abstract

PURPOSE—To identify risk factors for 4-year incidence and progression of age-related macular degeneration (AMD) in adult Latinos.

DESIGN—Population-based prospective cohort study.

METHODS—Participants, aged 40 or older, from The Los Angeles Latino Eye Study (LALES) underwent standardized comprehensive ophthalmologic examinations at baseline and at 4 years of follow-up. Age-related macular degeneration was detected by grading 30-degree stereoscopic fundus photographs using the modified Wisconsin Age-Related Maculopathy Grading System. Multivariate stepwise logistic regression was used to examine the independent association of incidence and progression of AMD and baseline sociodemographic, behavioral, clinical, and ocular characteristics.

RESULTS—Multivariate analyses revealed that older age (OR per decade of age: 1.52; 95% CI: 1.29, 1.85) and higher pulse pressure (OR per 10 mm Hg: 2.54; 95% CI: 1.36, 4.76) were independently associated with the incidence of any AMD. The same factors were associated with early AMD, soft indistinct drusen, and retinal pigmentary abnormalities. Additionally, presence of clinically diagnosed diabetes mellitus was independently associated with increased retinal pigment

(OR: 1.66; 95% CI: 1.01, 2.85), and male gender was associated with retinal pigment epithelial depigmentation (OR 2.50; 95% CI: 1.48, 4.23). Older age (OR per decade of age: 2.20; 95% CI: 1.82, 2.67) and current smoking (OR: 2.85; 95% CI: 1.66, 4.90) were independently associated with progression of AMD.

CONCLUSIONS—Several modifiable risk factors were associated with 4-year incidence and progression of AMD in Latinos. The results suggest that interventions aimed at reducing pulse pressure and promoting smoking cessation may reduce incidence and progression of AMD, respectively.

AGE-RELATED MACULAR DEGENERATION (AMD) IS A progressive disorder of the macular area that becomes clinically apparent usually after 50 years of age. When it progresses to advanced stages it can result in severe loss of central vision with significant impact on quality of life.^{1–3} Age-related macular degeneration is the leading cause of irreversible blindness in the western world.^{4,5} With the shifting of population distribution to older age groups, the prevalence, effect, and healthcare cost of AMD is expected to increase substantially in these countries. In the United States alone, expenditure associated with AMD treatment in 2004 was \$525 million.⁶ Prevalence of AMD in the United States is expected to increase from about 10 million in 2010 to about 20 million in 2050⁶ and, hence, will continue to be an increasing public health problem,³ resulting in significant increase in healthcare expenses attributable to AMD.^{7–9}

Latinos constitute the largest and fastest-growing minority segment of the US population.^{10,11} If recent trends continue, the US Latino population is estimated to increase to 102.6 million in 2050, or 24.4% of the total population.¹⁰ But there is a relative lack of population-based data regarding ocular health in Latinos, and the factors associated with AMD incidence and progression among Latinos remain largely unexplored. Data from the Los Angeles Latino Eye Study (LALES) demonstrate a lower prevalence and incidence of early and late AMD compared to other populations.^{12,13} Therefore, it is important to understand whether different and modifiable factors are operative in Latinos that influence disease risk and progression and may explain the differences in rates.

In the LALES, examination of baseline data revealed several demographic (age, male gender, Native American ancestry, family history), behavioral (smoking, alcohol consumption), clinical (higher diastolic blood pressure [DBP], uncontrolled diastolic hypertension, pulse pressure), and ocular (presence of cataract, cataract surgery, and myopic refractive error) factors to be associated cross-sectionally with the prevalence of different AMD lesions in Latinos.^{14–17}

In the current analysis, we examine the relationships between these factors and the 4-year incidence and progression of AMD in the cohort to tease out factors that are associated with disease development vs those associated with disease duration. While cross-sectional studies can identify associations between risk factors and existing AMD, longitudinal incidence studies are required to determine the indicators that may be associated with the development of future AMD.

We believe that for the overall improvement of the public health status of the country it is imperative to reduce the incapacitating and costly burden of AMD in the fastest-growing segment of US population. Hence, it is crucial to identify the unique risk factors that are associated with and possibly contribute to the development of AMD in Latinos, which can aid in developing evidence-based public health programs to prevent vision loss in this population.

METHODS

LATINOS (HISPANICS, HISPANIC AMERICANS, AND LATINO Americans) are individuals who are born into or have descended from a Spanish-speaking community, regardless of race. In the United States, Latinos are a heterogeneous group, with the majority being of Mexican ancestry (66%). The Los Angeles Latino Eye Study is a population-based longitudinal study of eye disease in self-identified Latinos, aged 40 years and older, living in 6 census tracts in the city of La Puente, Los Angeles County, California. Baseline examination was performed from 2000 to 2003, with 4-year follow-up examination from 2004 to 2008. Details of the study design, methods, and baseline data have been reported elsewhere.¹¹

All eligible participants in the baseline LALES examination were invited to return for a home interview and a clinical examination. Similar questionnaire and examination procedures were used for both baseline and follow-up studies. In-home interviews were conducted after obtaining informed consent. Trained ophthalmologists and technicians performed a comprehensive ocular examination using standardized protocols, which included 30-degree stereoscopic color fundus photographs of Diabetic Retinopathy Study field 1 (centered on the optic disc), field 2 (centered on the macula), and a modified field 3 (nonstereoscopic, temporal to and including the fovea) on all participants.

RISK FACTOR ASSESSMENT

For this analysis, factors examined as possible risk factors included a number of sociodemographic, behavioral, clinical, and ocular characteristics selected in light of literature review and expert opinion. Among these, age, gender, country of birth, acculturation, working status, years of education, marital status, income, insurance coverage, smoking, alcohol in-take, history of high blood pressure, history of heart attack, and history of stroke were self reported (obtained from home questionnaire). Diabetes, systolic blood pressure (SBP), DBP, pulse pressure, height, and weight were clinically assessed. Ocular factors such as cataract, lens opacities, refractive error, iris color, and axial length were assessed by comprehensive ophthalmologic examination. Age was defined as age at the baseline examination. Systolic and diastolic blood pressures were the average of 3 baseline measurements. Body mass index was calculated as body weight/height².

AMD GRADING

In LALES, strict, uniform grading methods were adopted and used by experienced, masked graders at the Wisconsin Ocular Epidemiology Reading Center to grade individual AMD lesions following a modification of the Wisconsin Age-Related Maculopathy Grading System (WARMGS).¹⁸ Detailed descriptions of all grading procedures and definitions were previously reported.^{12,19} In brief, a lesion-by-lesion evaluation was performed at each examination to determine maximum drusen size, type, area, and retinal pigmentary abnormalities. Each eye was graded independent of the contralateral eye. Any clinically meaningful differences between 2 initial graders were adjudicated by a senior grader using standardized edit rules. Graders were masked to the year the photographs were taken. A side-by-side longitudinal grading of all eyes with meaningful (eg, defining incidence or progression of AMD and its lesions) clinical changes over the 4-year period was done before a final AMD grade was assigned. Strict quality control measures were also applied.

DEFINITIONS OF INCIDENT AMD

Definitions of AMD component lesions, including specific drusen size, drusen types, and retinal pigmentary abnormalities and incidence and progression of AMD, are the same as used in the Beaver Dam Eye Study (BDES) and have been described in detail elsewhere.¹²

Incident early AMD was defined as the absence of signs of advanced AMD and the presence of 1) soft indistinct or reticular drusen or 2) hard distinct or soft distinct drusen with pigmentary abnormalities (retinal pigment epithelial [RPE] depigmentation or increased retinal pigment) at 4-year follow-up in participants who did not have any evidence of AMD at baseline. *Incident advanced AMD* was defined as the presence of either 1) geographic atrophy or 2) exudative AMD at follow-up in people who had no evidence of AMD at baseline.

The 6-step modified Beaver Dam Eye Study severity scale was used to estimate the 4-year *progression of AMD*. Person-specific progression was reported by concatenating the score given for each eye, thus defining overall severity using the score from the more affected eye. Progression of AMD was defined as 2 steps or more increase in severity at 4-year follow-up in subjects with a severity level of 1 through 3 at baseline.¹⁸ We also restricted the definition of progression to a 2-step progression in those with definitive evidence of AMD at baseline. Per-eye progression was also defined and examined for risk factors in this restricted group.

STATISTICAL ANALYSES

The baseline characteristics of the cohort of this analysis and nonparticipants were analyzed using *t* tests for comparison of means and χ^2 tests for comparison of proportions. Sociodemographic, clinical, and ocular characteristics of participants with and without AMD were analyzed using *t* tests for comparison of means and χ^2 tests for comparison of proportions. Each AMD endpoint (any AMD, early AMD, soft indistinct drusen, increased retinal pigmentation, and decreased RPE) was modeled separately to investigate its association with different risk indicators.

The continuous variables of age, SBP, DBP and pulse pressure were initially modeled as both continuous and categorical variables. Due to departure from log-linearity assumption for the SBP, DBP, and pulse pressure, we modeled these in different ways and eventually dichotomized them into clinically meaningful categories. Age was modeled as a continuous variable (per decade of age). Other than employment status (employed, unemployed, retired) and smoking status (never, past, current), all other variables were dichotomous.

The unadjusted associations between the risk indicators and different endpoints were assessed by univariate logistic regression and odds ratios (OR) for each of the significant variables were calculated. The independent associations of significant predictors were evaluated by multiple logistic regression analyses with forward stepwise selection using a $P \leq .20$ criterion for entry into the model. The final multivariate predictive model comprised those factors that were significant at an alpha level of 0.05 after mutual adjustment. Generalized estimating equation was used to examine the risk factors for progression per eye.

To further assess the nature of the relationship between these risk factors and the endpoints, we used local regression methods adjusting for other covariates from the final logistic regression model and generated LOWESS (locally weighted smoothing regression) plots. The LOWESS plot uses an iterative, locally weighted, least-squares method to plot the best-fit line that sheds light on the qualitative nature of the relationship.²⁰

Possible effect modification of the association between AMD and the predictors was tested by incorporating the proper interaction term in the logistic regressions models. The analyses were performed using SAS software 9.2 (Sas, Inc, Cary, North Carolina, USA) and Stata version 11 (StataCorp, College Station, Texas, USA). All tests for significance were at *P* value .05 level.

RESULTS

STUDY COHORT

Of the 6100 living eligible participants identified, 4658 (76%) participated in the 4-year follow-up study. Mean follow-up period was 4.3 ($\pm$ 0.03) years. Mean age of participants was 54.7 $\pm$ 10.5 years, 60% were female, and 76% were born outside of the United States. At baseline, the demographic and socioeconomic characteristics of the participants were determined to be representative of the overall Latino population in Los Angeles County.¹¹

Living eligible subjects not included in the analysis sample comprised nonparticipants of the follow-up study, as well as participants with either missing or nongradable fundus photographs at baseline or follow-up examinations (Figure 1). Of those who completed the ophthalmologic examination (n = 4658), fundus photographs gradable for AMD lesions in at least 1 eye were available for 4029 participants. A total of 629 participants did not complete fundus photography for a variety of reasons. Of the 3931 follow-up participants with gradable fundus photographs, 3908 had gradable fundus photographs in at least 1 eye from their baseline examination, thus making this the analysis cohort.

The comparison of different demographic and clinical characteristics between participants included in the analysis cohort and the excluded subjects are summarized in Table 1. The major differences were that those in the final analysis cohort were more educated, more likely to be married, more likely to have comorbidities, and less likely to report worse visual health status. In addition, a lower proportion of the final analysis cohort had cataract or diabetic retinopathy compared to those who were not included. While the differences were statistically significant, the differences in frequencies between the participants and the nonparticipants tended to be small.

Table 2 compares the sociodemographic and clinical risk indicators of participants with any AMD to those without any AMD. The major differences between these 2 groups were age and age-related characteristics. Participants with AMD were statistically significantly older ($P < .001$), had more comorbidities ($P = .004$), and were more likely to be unemployed or retired ($P = .006$) than those without AMD. The AMD incident cases were also more likely to have a history of hypertension, higher mean SBP, higher mean pulse pressure, and a history of any lens opacity or cataract surgery.

INCIDENCE OF AMD AND RISK FACTORS

The incidences of late AMD (n = 8), incident geographic atrophy (n = 3), and incident exudative AMD (n = 5) were too small to allow robust risk factor analysis.

At 4-year follow-up, 100 of the 3908 participants (2.5%) were found to have any AMD (92 early and 8 late AMD). Of these, 35 participants were at level 10, 25 at level 20, 31 at level 40, 5 at level 50, and 4 at level 60 of the BDES severity scale.

In univariate analysis, age was the strongest risk factor. After age adjustment, the sociodemographic and clinical factors associated with the incidence of any AMD included older age, retirement, higher SBP, higher pulse pressure, presence of any cataract, cortical opacity, history of cataract surgery, and refractive error (myopia). Using stepwise logistic regression we found only older age (OR per decade of age: 1.52; 95% CI: 1.29, 1.85) and higher pulse pressure (OR 2.54; 95% CI: 1.36, 4.76 for >40 compared to ≤ 40 mm Hg) to be independently associated with incidence of any AMD (Table 3). To further evaluate whether the effect of pulse pressure was independent of hypertension, we restricted the analysis to normotensive participants with a baseline SBP of 140 mm Hg or less and baseline DBP of

90 mm Hg or less. The analysis revealed similar age-adjusted independent relationship between pulse pressure and any AMD (OR for AMD: 2.60; 95% CI: 1.38, 4.87).

Increasing age (OR per decade of age: 1.61; 95% CI: 1.32, 1.96) and higher pulse pressure (OR 2.79; 95% CI: 1.45, 5.35 for >40 mm Hg compared to ≤40 mm Hg) were statistically significant independent predictors of the incidence of early AMD, similar to any AMD (Table 3). The LOWESS plot revealed a relatively insidious increase in predicted probability of early AMD incidence up to 40 mm Hg of pulse pressure and a steep increase when pulse pressure reached more than 40 mm Hg (Figure 2). LOWESS analysis was suggestive of a nominal increase of predicted incidence of early AMD with increasing age from 40 to 65 years. The increasing trend was pronounced after age 65 years, with a very steep rise in people aged 80 year or older (Figure 3).

A total of 77 of the 3908 participants (2.03%) developed soft indistinct drusen in 1 or both eyes. Similar to the previous analyses, multivariate analyses revealed increasing age (OR per decade of age: 1.69; 95% CI: 1.37, 2.10) and increased pulse pressure (OR 2.69; 95% CI: 1.31, 5.52 for >40 mm Hg compared to ≤40 mm Hg) to be the statistically significant independent predictors of soft indistinct drusen. Using a LOWESS plot we found a steep increase in predicted probability of soft drusen incidence, similar to early AMD, when pulse pressure is 40 mm Hg or more (Figure 4). Also, similar to early AMD, the predicted incidence of soft drusen increased gradually with increasing age, with a pronounced increase after 65 years and highest incidence in the oldest age group (Figure 5).

At the end of LALES II there were 80 cases (80/3908; 2.3%) of increased retinal pigment. Multivariate analyses revealed increasing age (OR per decade of age: 1.20; 95% CI: 1.01, 1.50), high pulse pressure (OR 3.18; 95% CI: 1.56, 6.52 for >40 mm Hg compared to ≤40 mm Hg), and presence of clinically diagnosed diabetes mellitus at baseline (OR 1.66; 95% CI: 1.01, 2.85) as independent risk factors. There were 66 persons (66/ 3908; 1.9%) with incident RPE depigmentation. In univariate analysis, age was the strongest risk factor. After age adjustment, male gender, low income (<20 000 USD/year), high pulse pressure, and history of cataract surgery were significant risk factors with age (OR per decade of age: 1.30; 95% CI: 1.02, 1.65), male gender (OR 2.50; 95% CI: 1.48, 4.23), and pulse pressure (OR 1.91; 95% CI: 1.01, 3.77 for >40 mm Hg compared to ≤40 mm Hg) remaining independent predictors after multivariable stepwise logistic analyses.

PROGRESSION OF AMD AND RISK FACTORS

At 4-year follow-up, 87 of the 3908 participants (2.2%) had progression of AMD. Age-adjusted analysis revealed that the sociodemographic, behavioral, and clinical factors that increased the risk of progression of AMD included increased age; being widowed, unmarried, or divorced; being retired; being a current or former smoker; having a high pulse pressure; and the presence of any cataract or history of cataract surgery, cortical opacity, or refractive error (myopia). Stepwise logistic regression was suggestive of an independent association of age and smoking status in that older people (OR per decade of age: 1.30; 95% CI: 1.02, 1.65) and current smokers (OR 2.85; 95% CI: 1.66, 4.90 compared to nonsmokers) were at a higher risk of progressing to late maculopathies. Ex-smokers, however, were not significantly at a higher risk than nonsmokers (OR 1.25; 95% CI: 0.75, 2.07 compared to nonsmokers).

When multivariate analysis was restricted to the 42 participants (excluding anyone with any evidence of AMD at baseline) who had progressed from step 2 or more at baseline, the results were similar, with increasing age (2.03; 95% CI: 1.52, 2.71) and current smoking (OR 2.69; 95% CI: 1.19, 6.07, compared to nonsmokers) revealed as independent risk factors.

Progression was further defined and examined for each eye and similar independent association of age and smoking status was found in that older people (OR per decade of age: 2.15; 95% CI: 1.61, 2.89) and current smokers (OR 2.44; 95% CI: 1.09, 5.44 compared to nonsmokers) were at a higher risk of progressing to late maculopathies.

Figure 6 illustrates the qualitative nature of the relationship between age and AMD progression. The predicted probability of progression increased gradually with increasing age, with a pronounced increase after 65 years and the highest incidence in the oldest age group.

DISCUSSION

IN THIS LONGITUDINAL STUDY, OVER A 4-YEAR PERIOD we found older age, increased pulse pressure, diabetes mellitus, and male gender to be associated with incident early AMD in Latinos. Older age and current smoking were associated with increased risk of progression of AMD. Some of these findings are consistent with data from other population-based longitudinal studies, including the Beaver Dam Eye Study and the Blue Mountains Eye Study, which have used similar methodologies to detect and define AMD.^{9,18,19,21–25} However, we have found several novel associations, especially when the outcomes were defined as early AMD and soft drusen, that were not reported in earlier studies.

SOCIODEMOGRAPHIC RISK FACTORS

Numerous studies have demonstrated older age as the strongest risk factor of AMD prevalence, incidence, and progression. The relationship between age and prevalence of AMD was demonstrated previously with the LALES prevalence data.¹⁵ The present analyses demonstrated the increased risk of AMD incidence and progression with increasing age. It has been suggested that the ongoing subclinical pathogenetic processes, such as deposition of lipofuscin and thickening and loss of elasticity of the Bruch membrane, begin earlier in life. These changes are likely to manifest as clinical signs of early AMD as people age, due in part to the inability of the RPE in some individuals to process these degenerative products.^{1,15}

Gender difference in incident or prevalent AMD has been an inconsistent finding in most population-based studies.¹ The previous report from LALES prevalence data was suggestive of an increased risk of all and early AMD prevalence.¹⁵ In the present report we found an increased risk in male participants for RPE depigmentation only. The Blue Mountains Eye Study found a similar association, with higher prevalence of pigmentary changes in male subjects.²⁶ However, other studies failed to find similar association.¹⁹

The reasons for increased risk of RPE depigmentation in Latino men are not known, although several other known risk factors of AMD (eg, smoking, alcohol use, and cardiovascular disease) are found to be more prevalent in male subjects.^{1,8,27} Indeed, in LALES we noted that Latino men were more likely to smoke (19% vs 9%, $P < .001$) and drink alcohol regularly compared to Latino women (22% vs 3%). But even after adjusting for these variables, men were more likely than women to develop RPE depigmentation (OR 2.73; 95% CI: 1.52, 4.94).

BEHAVIORAL RISK FACTORS

The results of this study suggest an almost 3-fold increased risk of progression of AMD in current smokers ($P = .0004$). There was no such significant association in former smokers.

Smoking has been the most consistent modifiable behavioral risk factor in most population-based ocular epidemiologic studies.^{1,9,25,28} It has been found to be associated with all stages

of AMD. In particular, the risk has been found strongest in those who are current smokers.^{1,28} Reports from pooled studies including the BDES, Blue Mountains Eye Study, and Rotterdam Eye Study confirm the strength of this association in both prevalent²⁹ and incident AMD.²⁸ Some investigators have suggested the effect of cigarette smoking on AMD may be attributable to its negative effect on antioxidants.³⁰ In an experimental study, exposure to cigarette smoke resulted in the formation of sub-RPE deposits, thickening of the Bruch membrane, and accumulation of deposits in the Bruch membrane.³¹ In this report we found smoking to be associated with progression but not with incidence of AMD in Latinos.

CLINICAL RISK FACTORS

The association of blood pressure and AMD has been inconsistent in epidemiologic population-based studies. Our results suggest increased risks of all measures of AMD incidence with increased pulse pressure. The BDES found a positive association of pulse pressure with prevalence of RPE depigmentation and increased retinal pigmentation in male subjects only.²¹ However, in the 5-year cumulative incidence in BDES, higher pulse pressure was significantly associated with increased incidence of RPE depigmentation (OR per 10 mm Hg: 1.27; 95% CI: 1.14, 1.42) and exudative macular degeneration (OR per 10 mm Hg: 1.29; 95% CI: 1.02, 1.65), irrespective of gender.²² These findings were further confirmed by BDES 10-year incidence data.³² However, a number of other studies did not report this association.^{33,34} Also, the association of pulse pressure with soft drusen was not reported in other ethnicities. Pulse pressure emerged as the most important modifiable risk factor in this cohort.

To further evaluate whether the effect of pulse pressure was independent of hypertension, we restricted the analysis to normotensive participants and found a similar age-adjusted independent relationship (OR for AMD: 2.6; 95% CI: 1.4, 4.9). The steep increase in predicted probabilities of incidence of both early AMD and soft drusen at 40 mm Hg of pulse pressure is consistent with the frequently used clinical cut point to distinguish low and high pulse pressure.^{35–37} The underlying mechanism of increased pulse pressure on AMD risk may be attributable to age-related degenerative changes in collagen and elastin, resulting in a decrease in distensibility of blood vessels. This in turn results in higher systolic and lower diastolic blood pressure and widening of pulse pressure. Klein and associates³² postulated that a wide pulse pressure may be a marker of such degenerative changes occurring in the Bruch membrane in eyes at risk of incidence and progression of AMD. Other studies suggest that as one ages there is a gradual shift in the strength of prediction of cardiovascular disease risk from diastolic to systolic to pulse pressure, with pulse pressure being more predictive of cardiovascular disease risk than systolic or diastolic blood pressure in people 65 or older.^{35–40}

Diabetes is a disparate finding as a risk factor for AMD. In this study, presence of clinically diagnosed diabetes mellitus was independently associated with incidence of increased retinal pigmentation. The Blue Mountains Eye Study found an association of diabetes with geographic atrophy but not with increased retinal pigment or any other measure of early AMD.⁴¹ In BDES, diabetes was not associated with early AMD but was associated with neovascular AMD in persons 75 or older.⁴² A large number of studies found no association. The paucity of literature suggests caution in drawing any inference. However, diabetes as a risk factor of any disease in Latinos requires more attention, as diagnosed diabetes is 1.7 times more likely in Latinos than in non-Hispanic whites. Results from the most recent National Health and Nutrition Examination Survey demonstrate that diabetes is 1.7 times more prevalent in Mexican Americans than in non-Hispanic whites.⁴³ Results from different population-based studies have demonstrated that persons with diabetes are predisposed to developing different ocular conditions.^{44–49} Therefore, timely prevention, diagnosis, and

proper control of diabetes will likely have a positive impact on the burden of ocular disease in Latinos.

In LALES, there was a relative low rate of AMD progression. In this analysis we could not identify any protective factors that may affect AMD progression in Latinos. However, a previous analysis from LALES was suggestive of a low prevalence of the genetic risk factor of CFH Tyr402 polymorphism in Latinos.⁵⁰ Further analysis of distributions of genetic risk factors, both protective and deleterious, and their relationship to AMD may shed more light on factors that are likely to play a role in progression, or relative lack of it, in this population.

The suggested associations or lack thereof in this study should be interpreted with caution because of some limitations. The most important of these limitations is the relative infrequency of AMD cases in our cohort, which may have limited our ability to confirm some expected associations. Also, a very low incidence for late AMD, geographic atrophy, and neovascular AMD precluded robust risk factor analyses for these lesions. A longer follow-up study in the future may help us address this limitation.

Second, one potential limitation of the study is measurement error of the presence and severity of AMD. In LALES, strict, uniform grading methods were employed and adhered to as described in the methods. Moreover, since graders were masked to baseline disease status, any measurement error is unlikely to be differential. Any impact of such an error would attenuate the results and would not change any association.

Third, participants and nonparticipants for these analyses differed in several demographic and clinical indicators. But, as demonstrated in Table 1, even when the differences are statistically significant, the magnitudes of these differences are small and unlikely to have a significant effect on the results or unlikely to change the direction of association. Further, there were no significant differences in risk factors that were associated with different measures of AMD (like age, gender, or diabetes). Moreover, the factors that did differ between the participants and nonparticipants cannot explain the observed association. As for example, the participants were more likely to be hypertensive. But as discussed previously, pulse pressure was associated independent of hypertension. Then again, the participants were more likely to report better visual health, so it is unlikely that we would have more cases of AMD in our cohort of participants. If anything, we would have had fewer AMD cases, which is more likely to attenuate the effect estimates and thus unlikely to explain the associations.

Fourth, LALES lacked person time data and hence logistic regression was used for this analysis, which can potentially overestimate some associations. Also, these results may not be generalizable to all Latinos globally. However, the similarity of Latinos in LALES and in the United States suggests that these results can be generalized to all US Latinos.¹¹

In conclusion, in Latinos, increasing age, increased pulse pressure, and diabetes mellitus were associated with higher risks of incidence of early AMD, and increasing age and current smoking were associated with the progression of AMD. Some of the findings are similar to those reported by studies in non-Hispanic whites, suggesting some similarities in the pathogenesis of the disease between the 2 ethnic groups. Studies of genetic risk factors may explain the differences in risk factors for incidence of some early maculopathies like soft drusen. Because Latinos represent the largest minority group in the United States and exhibit different patterns of AMD incidence and progression than other ethnic groups, it is empirical to address the unique risk factors of AMD in Latinos. The fact that easily modifiable factors like pulse pressure were associated with Latinos may provide clinicians with important guidelines for preventive interventions. Further longitudinal studies of AMD progression in

Latinos are needed for conclusive inferences. It remains to be seen whether interventions aimed at reducing pulse pressure or stopping smoking would affect the incidence and progression of AMD in Latinos.

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Flow-chart of analysis cohort **FIGURE 1.**

Participant flow chart highlighting participants from Los Angeles Latino Eye Study (LALES) who were included and excluded from the analysis due to nonparticipation at 4-year follow-up or missing/nongradable fundus photograph at baseline or 4-year follow-up.

FIGURE 2.

Locally weighted scatterplot smoothing (LOWESS) plot illustrating the independent relationship between predicted 4-year incidence of early age-related macular degeneration (AMD) and pulse pressure (in mm Hg) in the Los Angeles Latino Eye Study (LALES). The predicted 4-year incidence of early AMD was obtained using locally weighted regression after adjusting for other covariates from the final logistic regression model.

FIGURE 3.

Locally weighted scatterplot smoothing (LOWESS) plot illustrating the independent relationship between predicted 4-year incidence of early age-related macular degeneration (AMD) and age (in years) in the Los Angeles Latino Eye Study (LALES). The predicted 4-year incidence of soft indistinct drusen was obtained using locally weighted regression after adjusting for other covariates from the final logistic regression model.

FIGURE 4.

Locally weighted scatterplot smoothing (LOWESS) plot illustrating the independent relationship between predicted 4-year incidence of soft indistinct drusen and pulse pressure (in mm Hg) in the Los Angeles Latino Eye Study (LALES). The predicted 4-year incidence of early AMD was obtained using locally weighted regression after adjusting for other covariates from the final logistic regression model.

FIGURE 5.

Locally weighted scatterplot smoothing (LOWESS) plot illustrating the independent relationship between predicted 4-year incidence of soft indistinct drusen and age (in years) in the Los Angeles Latino Eye Study (LALES). The predicted 4-year incidence of soft indistinct drusen was obtained using locally weighted regression after adjusting for other covariates from the final logistic regression model.

FIGURE 6.

Locally weighted scatterplot smoothing (LOWESS) plot illustrating the independent relationship between predicted 4-year progression of age-related macular degeneration (AMD) and age (in years) in the Los Angeles Latino Eye Study (LALES). The predicted 4-year progression of AMD was obtained using locally weighted regression after adjusting for other covariates from the final logistic regression model.

TABLE 1
Comparison of Participants and Nonparticipants in the 4-Year Follow-up: The Los Angeles Latino Eye Study

Characteristics	Analysis Cohort N = 3908		Nonparticipants or Excluded N = 2192		P
	N	%	N	%	
Gender (female)	2346	60.09	1257	57.53	.05
Age					
Mean (SD)	54.29 (10.1)		54.37 (11.35)		.77
Acculturation (low <1.9) ^a	1281	32.81	703	32.17	.61
Working status (employed)	2001	51.26	1068	48.88	.08
Education level <12 years	1348	34.53	695	31.81	.031
Marital status (married)	2791	71.49	1447	66.22	<.0001
Income level >\$40,000	499	12.90	266	12.26	.48
Health insurance	1292	33.09	905	41.42	<.0001
≥2 comorbidities	1594	40.83	801	36.66	.0014
Self-reported health excellent/very good	742	19.01	430	19.68	.52
History of hypertension	1162	29.84	598	27.41	.05
History of diabetes	689	17.65	414	18.95	.21
Self-reported vision excellent/good	1643	42.09	846	38.72	.01
Status of ocular disease at baseline					
Any ocular disease	1310	33.52	735	33.53	.99
Cataract	597	15.55	371	19.49	.002
Glaucoma	149	3.81	106	4.84	.06
AMD	361	9.24	183	10.37	.18
Diabetic retinopathy	521	13.34	289	15.55	.02

AMD = age-related macular degeneration.

P values were calculated using *t* test for continuous variables and χ^2 for categorical variables.

Data are presented as mean (SD) for age; frequency (%) for all other variables.

^a Acculturation was measured using the short-form Cuellar Acculturation Scale.

TABLE 2

Distribution of Baseline Sociodemographic, Clinical, and Ocular Characteristics by Age-Related Macular Degeneration Incidence Status: The Los Angeles Latino Eye Study

Variables	No AMD ^a (N =3800)	Incident AMD ^a (N = 100)	P Value ^b
Sociodemographic characteristics			
Age	54.3 (10.1)	60.8 (12.2)	<.001
Gender: female	2276 (59.9)	56 (58.0)	.57
Unemployed/retired	1860 (49.1)	65 (65)	.006
Income <\$20,000	1637 (43.1)	47 (47.0)	.65
Education <12 years	2493 (65.6)	64 (64.0)	.77
Health insurance: Yes	2542 (66.9)	74 (74.0)	.11
Vision insurance: Yes	2007 (52.8)	51 (51.0)	.74
Acculturation score ^c	1.8 (0.8)	1.8 (0.9)	.93
Country of birth (USA)	903 (23.8)	22 (22.0)	.77
Marital status (married/partner)	2706 (71.2)	35 (35.0)	<.001
Smoker	496 (13.1)	17 (17)	.24
Clinical characteristics			
Comorbidities	1.5 (1.5)	1.9 (1.6)	.004
History of hypertension	1137 (29.9)	44 (44)	.001
SBP	122.9 (18.5)	129.5 (17.4)	.006
DBP	75.8 (10.8)	76.0 (10.7)	.92
PP	47.1 (14.4)	53.4 (13.5)	<.001
Ocular characteristics			
Any lens opacity	616 (16.5)	21 (21.0)	.08
Cataract surgery	118 (3.1)	8 (8.0)	.005
Iris color (black/brown)	3409 (89.6)	89 (89.0)	.70
OPP	46.5 (8.1)	47.2 (8.2)	.37

AMD = age-related macular degeneration; DBP = diastolic blood pressure; OPP = ocular perfusion pressure; PP = pulse pressure; SBP = systolic blood pressure.

^aData are presented as mean (SD) for age, acculturation, SBP, DBP, PP, OPP, and comorbidities; frequency (%) for all other variables.

^bP values were calculated using *t* test for continuous variables and χ^2 for categorical variables.

^cAcculturation was measured using the short-form Cuellar Acculturation Scale.

TABLE 3
Independent Risk Factors for Incidence and Progression of Age-Related Macular Degeneration: The Los Angeles Latino Eye Study

Risk Factor	Incidence of Any AMD OR (95% CI) ^a	Incidence of Early AMD OR (95% CI) ^a	Incidence of Soft Indistinct Drusen OR (95% CI) ^a	Incidence of Increased Retinal Pigment OR (95% CI) ^a	Incidence of Decreased Retinal Pigment OR (95% CI) ^a	Progression of Any AMD OR (95% CI) ^a
Age (per decade)	1.52 (1.29, 1.85)	1.61 (1.32, 1.96)	1.69 (1.37, 2.10)	1.20 (1.01, 1.50)	1.30 (1.02, 1.65)	2.20 (1.82, 2.67)
Pulse pressure						
≤40 mm Hg	1	1	1	1	1	~
>40 mm Hg	2.54 (1.36, 4.76)	2.79 (1.45, 5.35)	2.69 (1.31, 5.52)	3.18 (1.56, 6.52)	1.91 (1.00, 3.77)	
Diabetes	~	~	~		~	~
No				1		
Yes				1.66 (1.01, 2.85)		
Smoking status	~	~	~	~	~	
Nonsmoker						1
Ever/past smoker						1.25 (0.75, 2.07)
Current smoker						2.85 (1.66, 4.90)
Gender	~	~	~	~		~
Female					1	
Male					2.50 (1.48, 4.23)	

~ = included in the final model but not statistically significant; AMD = age-related macular degeneration; CI = confidence interval; OR = odds ratio.

^a Odds ratios and confidence intervals adjusted for other variables in the model.