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Factors Associated with Prevalent Diabetic Retinopathy in Chinese Americans: The Chinese American Eye Study

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Abstract

Objective—To identify factors associated with prevalent diabetic retinopathy (DR) among Chinese American adults with type 2 diabetes mellitus (T2DM), and to compare these factors to ones previously described for a population-based sample of Latinos with a higher DR prevalence.

Design—Population-based cross-sectional study.

Participants—4582 Chinese Americans aged 50 or older residing in Monterey Park, California.

Methods—Participants completed an in-home questionnaire on socio-demographic status and medical history, and a comprehensive clinical eye examination, using the same protocol implemented in the Los Angeles Latino Eye Study. Fundus photographs from 7 Early Treatment Diabetic Retinopathy fields were graded in a masked manner using a modified Airlie House grading system to assess presence and severity of DR. Logistic regression analyses based on a conceptual model of DR risk identified factors associated with prevalent DR.

Main Outcome Measures—Odds ratios (ORs) and 95% confidence intervals (CIs) for factors associated with DR and vision-threatening DR (VTDR).

Results—In total, 238 participants were diagnosed with any DR; 27 of these were classified as having VTDR. Both, any DR and VTDR showed statistically significant positive associations with

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T2DM duration ($OR_{5-9 \text{ years}} = 1.24$, $OR_{10-14 \text{ years}} = 2.07$, $OR_{15+\text{years}} = 3.99$), glycosylated hemoglobin (HbA1c) ($OR_{6.5-6.9\%} = 1.33$, $OR_{7-7.9\%} = 1.86$, $OR_{8\%+} = 3.22$), systolic blood pressure (SBP) ($OR_{\text{per } 10\text{mmHg}+} = 1.19$), and insulin treatment ($OR_{\text{insulin}+} = 2.44$). For VTDR, we also found novel associations with antihypertensive drugs ($OR: 0.18$; 95% CI: 0.06–0.61) and statins ($OR: 4.96$; 95% CI: 1.60–16.41). Chinese Americans and Latinos had a nearly identical DR probability based on HbA1c and SBP. However, Latinos had a higher DR probability at every year of duration of T2DM (< 5 years).

Conclusions—While we observed an overall lower DR prevalence in Chinese Americans than in Latinos (35.8% of individuals with T2DM in Chinese Americans versus 42.0% in Latinos), our data indicate that the impact of increasing HbA1c and SBP on DR probability is incrementally the same in both populations. However, increasing T2DM duration is associated with higher DR probability in Latinos than Chinese Americans, even after controlling for other known predictors. Novel factors associated with VTDR include antihypertensive drugs and statins. However, to determine if these drugs impact VTDR susceptibility, we need longitudinal data and more cases.

Type 2 diabetes mellitus (T2DM) is a fast-growing public health challenge in the United States, with 1.7 million new cases each year and a prevalence of 9.3%.¹ T2DM causes numerous complications, which may result in cardiovascular and kidney disease, neuropathy, and eye damage.² Diabetic retinopathy (DR), a common ocular manifestation of T2DM, accounts for 12% of all new cases of blindness per year in the United States, and is the leading cause of blindness for people aged 20 to 64.³ The number of people impacted by DR in the US is expected to increase by more than 80% by 2050,⁴ having a strong negative impact on vision loss, blindness, health-related quality of life⁵, and the economy.⁶ To prevent DR and to identify contributors to disparities in DR burden, we must characterize factors associated with this disease in multiethnic population-based samples. In the United States, studies have assessed factors associated with prevalent and incident DR primarily in non-Hispanic whites^{7–14} and Hispanics.^{15,16} There are data gaps for other racial/ethnic groups, including Chinese Americans.

As one of the fastest growing populations in the United States,¹⁷ Chinese Americans increased in number by nearly 40% between 2000 and 2010, from 2.9 million to 4.0 million.¹⁸ Among participants in the National Health and Nutrition Examination Survey (NHANES), Asian Americans (not distinguished by country of origin) were found to be particularly susceptible to T2DM, and to develop the disease at much lower body mass indexes than non-Hispanic whites, blacks, or Hispanics.¹⁹ A similar pattern of early and high susceptibility to T2DM has been described specifically among ethnic Chinese in Hong Kong, Taiwan, and mainland China.²⁰ These patterns of T2DM, a precursor to DR, suggest that adequate inclusion of Chinese Americans in ophthalmic research may reveal important information on susceptibility to T2DM and DR.

As the first large, population-based study of eye health in Chinese Americans, the Chinese American Eye Study (CHES) offers the first opportunity to identify factors associated with prevalent DR and to explore factors driving disparities between DR prevalence in CHES and in a study of urban Latinos.¹⁶ Both CHES and the Los Angeles Latino Eye Study (LALES)¹⁶ were conducted among urban populations in Los Angeles County, California,

using similar methodology. We previously reported that Chinese Americans have DR prevalence that is higher than non-Hispanic whites but lower than Hispanics.²¹ In the present study, we developed a conceptual model of factors known or hypothesized to be associated with DR or vision-threatening DR (VTDR) based on four categories: socio-demographic, personal health practice, health care access and utilization, and biological measures. The statistical models for DR were developed in CHES and were then applied to LALES to evaluate the relative importance of the included predictors for the two racial/ethnic groups. This enabled us to evaluate potential variation in risk factors influencing DR prevalence between these two groups.

METHODS

CHES

CHES is a population-based cross-sectional study designed to assess the prevalence of visual impairment, eye disease, and visual function in Chinese Americans. Participants included 4582 adults aged 50 years and older, of self-identified Chinese ancestry, residing in 10 census tracts in Monterey Park, California. Data was collected from February 2010 to October 2013. The study adhered to the guidelines of the Declaration of Helsinki, and was approved by the Institutional Review Board/Ethics Committee of the University of Southern California.

Interview and Examination Procedures

Canvassers invited eligible individuals to participate in the study, and then administered an in-home questionnaire covering demographics, medical and ocular histories, insurance status, access to care, and acculturation on the Suinn-Lew Asian Self-Identity Acculturation (SL-ASIA) scale.²² After completing the in-home questionnaire, participants were scheduled for a visit to the study's Local Eye Examination Center, where they received a comprehensive eye exam performed by trained ophthalmologists and a clinical interview that collected information on quality of life and visual function. The eye exam included visual acuity assessment on presenting and best-corrected vision, slit lamp examination of anterior and posterior segment structures, and OCT imaging of the retina. Total cholesterol, high- and low-density lipoprotein, and triglycerides were measured using the Cholestech LDX system (Alere, Waltham, MA, USA). Random blood glucose and glycosylated hemoglobin (HbA1c) were measured using the Hemocue B-Glucose Analyzer (Hemocue Inc., Lake Forest, CA, USA) and the DCA Vantage Analyzer (Siemens Healthcare, Norwood, MA, USA), respectively. For diabetic participants, fundus photographs from the 7 standard Early Treatment Diabetic Retinopathy Study²³ stereoscopic fields were taken in each eye using the Topcon TRC digital 50EX retinal camera (Topcon Corporation, Paramus, NJ, USA).

Risk Factor Assessment

Variables contributing to the conceptual model were obtained from the in-home and clinical questionnaires along with the eye examination. Socio-demographic factors included: age; gender; country of birth (China, Taiwan, Vietnam, other); income; years of education (fewer than 12 years, 12 years or more); marital status (married/living with partner, divorced/

separated/widowed, never married); and acculturation on the SL-ASIA scale. Personal health practice factors included: smoking (never smoked, former smoker, current smoker); alcohol consumption (never drank, former drinker, current drinker); treatment used for diabetes mellitus (DM) (oral medication, insulin, diet); use of anti-inflammatory drugs, statins, and antihypertensive drugs (never used, ever used); and for women, use of oral contraceptives and female hormones (never used, ever used). Health care access and utilization factors included having health and vision insurance coverage, having a particular doctor or clinic, and ever being unable to access care. Biological risk factors included cataracts, the number of comorbidities, refractive error, axial length, body mass index, waist-to-hip ratio, self-reported duration of diabetes, random serum blood glucose, HbA1c levels, systolic blood pressure (SBP), diastolic blood pressure, pulse pressure, mean ocular perfusion pressure, total cholesterol, low- and high-density lipoprotein, and triglycerides.

Determination of T2DM

Participants were classified as having diabetes mellitus (DM) if they reported a prior diagnosis and were currently on a treatment regimen (oral hypoglycemic medications, insulin, or diet), or if their HbA1c levels were 6.5% or above. DM duration was calculated as the difference between the self-reported year of diagnosis and the time of examination. In the case of participants newly diagnosed during the exam, duration was classified as 0. All definite cases of DM were considered to be T2DM if they were not being treated with insulin or they were diagnosed at age 30 or older.

Definition and Grading of DR

In the study, diabetic retinopathy (DR) was defined as retinopathy in participants who were determined to have DM. The fundus photographs from 7 standard fields for each eye underwent masked grading for DR at the ocular reading center at Madison, Wisconsin, using a grading protocol that was a modified version of the Early Treatment Diabetic Retinopathy Study (ETDRS) adaption of the Airlie House classification of DR. Eyes were graded as having no DR (levels 10–13), non-proliferative DR (mild: levels 14–20; moderate: levels 31–43; severe: levels 47–53), or proliferative DR (levels 60–85). Proliferative DR and severe non-proliferative DR were classified as **vision-threatening (VTDR)**, while mild and moderate non-proliferative DR were classified as **non-vision-threatening (NVTDR)**.

LALES

LALES is an existing population-based cross-sectional study that measures DR prevalence and risk factors among Latinos, primarily Mexican Americans, living in La Puente, California. Because its methodology²⁴ so closely matches CHES, it is possible to evaluate risk factors for DR prevalence in both studies. This enables the evaluation of differences in variables that drive DR prevalence by race/ethnicity.

Data and Statistical Analyses

Each potential predictor of DR prevalence was evaluated for its univariate association with any DR using exact logistic regression, with diabetics without DR used as the reference group. Additionally, to determine whether there was heterogeneity in the associations

between VTDR and NVTDR, we used exact logistic regression to evaluate the univariate association between each predictor and DR type (VTDR vs. NVTDR), solely among DR cases. From these analyses, exact p values were generated that indicated the significance of the association between each predictor and any DR, and the significance of any heterogeneity in the associations between VTDR and NVTDR cases. For continuous predictor variables, we assessed the assumption of a linear association with DR through visual inspection, and those deemed to have a non-linear association were modeled as categorical variables, with cut points chosen based on the shape of their association with DR as well as clinical significance.

Logistic regression was used to separately evaluate the multivariate associations between DR prevalence (defined as any DR case) and the potential socio-demographic, personal health practice, health care access/utilization, and biological predictors included in the conceptual model. Each category of predictors in the conceptual model was modeled separately, with all of the predictors in each category modeled together in a logistic regression model using stepwise selection. Predictors were kept in the category-specific models if they were significant at a p value of .10 or smaller. Oral contraceptive and female hormone use were modeled in women only in a stepwise logistic regression, with health practice factors that were significant among all participants forced into the model. For the final model, the significant predictors from each category-specific model were combined into one logistic regression model, and predictors with a p value of .05 or greater were removed from the model through backward selection. Odds ratios (ORs) and 95% confidence intervals (CIs) were generated for the predictors that remained in the model.

In order to determine whether additional predictors are associated with VTDR or NVTDR, we performed a similar category-specific analysis of the predictors in each conceptual model category, modeling VTDR and NVTDR cases separately. For VTDR and NVTDR separately, all additional predictors that were significant at a p value of .10 or smaller in the category-specific models were combined into a final model, forcing in all predictors that were significant in the final model for any DR. Predictors with a p value of .05 or greater were removed from each final model through backward selection. ORs and 95% CIs were generated for the predictors remaining in the VTDR and NVTDR models.

There were only 30 diabetic macular edema (DME) cases in our sample therefore the sample size was too small to derive an independent risk factor model for DME. To explore the potential risk factors for DME, we used the same approach used for VTDR and NVTDR. We fit a risk factor model for DME using the factors identified for DR and evaluated whether any additional variables from a DME category-specific analysis additionally contributed to the model. We produced locally weighted regression (LOESS) plots of predicted DR prevalence across the significant predictors using the predicted values of disease risk from our any DR and subtype-specific DR risk factor models using Stata/SE 11.2 (StataCorp LP, College Station, TX, USA). Further, we applied our risk factor model for any DR to the LALES population, with the addition of gender, a risk factor for DR in LALES. We then produced LOESS plots of the predicted DR prevalence across the same predictors for LALES, in order to provide an interethnic comparison. Because LALES did

not collect comparable information on use of antihypertensive drugs, we do not report an interethnic comparison for the CHES VTDR risk factor model.

RESULTS

Table 1a and 1b shows the frequencies and descriptive statistics of the potential predictors along with p values summarizing the univariate associations of each predictor with DR (defined as any DR case). Also shown are the frequencies and descriptive statistics for the DR cases stratified by DR type (VTDR vs. NVTDR), with p values summarizing the univariate associations of each predictor with DR type. Briefly, participants with DR had higher random blood glucose, HbA1c, SBP, pulse pressure, and mean ocular perfusion pressure, and lower total cholesterol than participants without DR. Participants with DR also had longer DM duration and were more likely to be treated with oral antidiabetic medications and insulin. Patients with VTDR were more likely to be treated with insulin than patients with NVTDR. Risk factors were included in Table 1a and Table 1b if they had significant univariate association (for any DR or by DR type) or if they were included in the final multivariate risk factor models for any DR and VTDR. Frequencies and descriptive statistics for all of the considered risk factors are reported in Supplementary Table 1.

Table 2 shows the associations for the predictors in the final multivariate model for any DR. Treatment with insulin, DM duration, HbA1c, and SBP maintained significant DR associations when modeled together in the multivariate model. Age, which did not have a significant univariate association with DR ($p = .124$), had an inverse association with DR ($p = .012$) when forced in the multivariate model, with older age associated with lower DR risk. The most significant predictor for prevalent DR in the final model was DM duration ($p = 1 \times 10^{-5}$), with participants with a DM duration of 10 to 14 years having an adjusted OR of 2.07 (95% CI: 1.23–3.50), and participants with a DM duration of 15 years or more having an adjusted OR of 3.99 (95% CI: 2.26–7.05). SBP was strongly associated with prevalent DR, with each 10 mmHg increase having an adjusted OR of 1.91 (95% CI: 1.08–1.31). HbA1c level was also highly associated with DR ($p = .001$), particularly among participants with an HbA1c level of 8.0% or more (OR: 3.32, 95% CI: 1.77–5.86). Patients taking insulin have an elevated prevalence of DR, with an adjusted OR of 2.44 (95% CI: 1.14–5.20).

Table 2 also shows the associations for the predictors in the final multivariate models for VTDR and NVTDR. For both of these final multivariate models, we forced in the predictors that were associated with any DR. With the exception of age, all of the predictors that were significantly associated with any DR were also associated with VTDR. Additionally, antihypertensive drugs and statins, which were not associated with any DR, were associated with VTDR. Antihypertensive drugs were inversely associated with VTDR, with an OR of 0.18 (95% CI: 0.06–0.61), while statins were positively associated with prevalent VTDR, with an OR of 4.96 (95% CI: 1.50–16.41). With the exception of insulin treatment, all predictors that were significantly associated with any DR were associated with NVTDR. There were no additional predictors associated with NVTDR beyond those identified for any DR.

There were no additional risk factors that were significant for DME beyond the risk factors included in the any DR risk factor model. Of the significant DR risk factors, SBP ($p = 0.0001$) DM duration ($p = 0.004$), and HbA1c ($p = 0.043$) were also associated with DME. Just as for DR, increasing SBP and DM duration were associated with increasing risk of DME. Each 10mmHg increase in SBP had an adjusted OR of 1.47 (95% CI: 1.21–1.79). Compared to participants with a DM duration of less than 5 years, those with a duration of 5 to 9 years had an adjusted OR of 2.45 (95% CI: 0.72–8.35), those with a duration of 10 to 14 years had an adjusted OR of 4.49 (95% CI: 1.33–15.18), and those with a duration of 15 or more years had an adjusted OR of 8.63 (95% CI: 2.64–28.23). The association of HbA1c with DME appeared to be non-linear, with lower DME risk among participants with levels between 6.5% and 7.9% compared to those with levels below 6.5%, and higher DME risk among participants with levels above 8%. However, the HbA1c level-specific adjusted ORs ($OR_{6.5-6.9\%} = 0.25$, $OR_{7-7.9\%} = 0.83$, $OR_{8\%+} = 1.74$) were not significant ($p_{6.5-6.9\%} = 0.065$, $p_{7-7.9\%} = 0.745$, $p_{8\%+} = 0.331$).

The LOESS plots of predicted DR controlling for all model covariates, including HbA1c (Figure 1a) and holding HbA1c fixed at the lowest category level (Figure 1b), are shown by SBP in mmHg for CHES and LALES. SBP appears to have a nearly linear association with DR (Figure 1a) and VTDR (Figure 4a) through 160 mmHg, with a pattern of accelerating prevalence of DR with SBP thereafter. The interethnic comparison with LALES shows that Latinos have a similar pattern of linearly increasing prevalence of any DR as described for CHES. Compared to CHES participants, LALES participants had higher predicted probability of DR at every level of SBP through 160 mmHG.

Similar LOESS plots of predicted DR, controlling for HbA1c (Figure 2a) and holding HbA1c fixed at the lowest category level (Figure 2b), are shown by DM duration for CHES and LALES. DM duration was linearly associated with DR (Figures 2a and 2b) and VTDR (Figure 4b), with a possible plateau at durations above 20 years observed for DR, but not VTDR. The predicted probability of DR was higher for Latinos than Chinese Americans at every DM duration (> 5 years), and this remained true after adjusting for HbA1c in the prediction model (Figure 2a) or while holding HbA1c constant (Figure 2b). HbA1c appears to be associated with increasing prevalence of DR (Figure 3) and VTDR (Figure 4c) for HbA1c levels between 6.5% and 9%, with predicted probability reaching a plateau thereafter. The predicted probability of DR was nearly identical for Latinos and Chinese Americans at every HbA1c level (Figure 3).

DISCUSSION

Using CHES data, we found increasing DM duration, increasing SBP, higher HbA1c, and insulin use to be independently associated with DR prevalence. In addition to these relatively well-known risk factors, use of statins and antihypertensive drugs were associated with VTDR, with statins associated with increased prevalence and antihypertensive drugs associated with decreased prevalence. While we observed an overall lower prevalence of DR in CHES than in LALES, the impact of increasing levels of HbA1c and SBP on DR probability is incrementally the same in both populations. However, increasing DM duration

is associated with higher DR probability in Latinos than in Chinese Americans, even after controlling for other known predictors.

The seemingly protective association of age with any DR probability is largely weighted by the effect in the oldest participants, with those 80 years or older having an adjusted OR of 0.25 (95% CI: 0.11–0.58) compared to those in their 50s. Participants 80 years and older have a very long DM duration: 38% of 80 year olds had DM duration of 15 years or more, compared to 5% of participants in their 50s. This is true despite the DR prevalence of 24% in those 80 years and older, compared to 39% in participants in their 50s. The low DM duration-adjusted odds of DR in those 80 years and older potentially reflect a survivorship bias, wherein the oldest individuals have a low tendency to develop complications, and thus have low DR prevalence in spite of their long DM durations.

Results from our any DR model were consistent with the adjusted multivariate results from previous population-based studies of ethnic Chinese populations and US-based studies of non-Hispanic whites. DM duration^{7,8,11–14,25–30} and HbA1c^{7,8,14,26,29,31} in particular were consistently found to be significant independent predictors of DR incidence and prevalence in previous studies. SBP^{7,8,11,26,28,30} and insulin treatment^{7,11,25,27,30} were other frequently reported predictors. Our finding of statins and antihypertensive drugs as potential predictors for VTDR prevalence is novel. Few previous population-based studies considered these drugs in their models.

DM duration was a strong risk factor for any DR ($OR_{5-9 \text{ years}} = 1.24$, $OR_{10-14 \text{ years}} = 2.07$, $OR_{15+\text{years}} = 3.99$), even after controlling for all other significant predictive variables in the model, including HbA1c. DM duration, considered a surrogate for the length of exposure to hyperglycemia, has consistently been a predictor for DR incidence^{13,14,26} and prevalence^{7,8,11,12,27–30} in studies of non-Hispanic whites in the US and Chinese, with the exception of the Hong Kong study³¹ of incidence among Chinese. HbA1c, a measure of glycemic control, also was associated with any DR in our model, particularly at levels above 8.0%, reflecting uncontrolled DM. This is expected, given that HbA1c approximates a roughly three-month average of blood glucose levels,³² and that hyperglycemia is a well-established cause of DR.³³ Further, HbA1c has been consistently found to be a predictor for DR incidence^{14,26,31} and prevalence^{7,8,29} in studies where it was considered. In studies where HbA1c was not considered, blood glucose, a correlated measure of glycemic control, was found to be associated with DR incidence¹³ and prevalence^{11,27,28}, with the exception of the Taiwan study²⁵ of prevalence among Chinese and the Cardiovascular Health Study (CHS) study¹² of prevalence among US non-Hispanic whites.

SBP was a strong predictor in both the any DR ($OR_{\text{per } 10\text{mmHg}+} = 1.19$) and VTDR ($OR_{\text{per } 10\text{mmHg}+} = 1.17$) models. There is a strong biological basis for this association: systemic hypertension leads to capillary damage in the eyes of hyperglycemic patients, who have impaired auto regulation of retinal perfusion, causing the development and progression of DR.³⁴ However, there is conflicting evidence from previous studies as to whether SBP is itself a causal factor for DR. Among Chinese, SBP was found to be statistically significantly associated with DR prevalence in the Handan Eye Study,²⁸ but not in the Taiwan study²⁵ or the Beijing Eye Study.²⁷ SBP was associated with DR progression in the Kinmen study²⁶

but not in the Hong Kong study.³¹ For US non-Hispanic whites, SBP was associated with DR prevalence in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)⁷ and the Atherosclerosis Risk in Communities Study (ARIC),¹¹ but not in CHS.¹² The Rochester study¹³ and the Pittsburgh Epidemiology of Diabetes Complications Study (EDC)¹⁴ did not find any association of SBP with DR incidence or progression.

Insulin treatment was associated with any DR ($OR_{\text{insulin}+} = 2.44$; 95% CI: 1.1, 5.2) and VTDR ($OR_{\text{insulin}+} = 16.5$; 95% CI: 3.9, 68.9) in our model, but not with NVTDR. This may be due to the fact that individuals with more severe or poorly controlled DM may be more likely to be prescribed insulin. The association of insulin treatment with DR has been inconsistent across studies. Among Chinese, insulin treatment was significantly associated with DR prevalence in the Beijing study²⁷ and with proliferative DR prevalence in the Taiwan²⁵ study, but had no significant association with DR incidence in Kinmen²⁶ and Hong Kong,³¹ and no association with DR prevalence in Handan.²⁸ Among US non-Hispanic whites, insulin treatment was associated with DR incidence in Rochester¹³ and with DR prevalence in WESDR⁷ and ARIC,¹¹ but was not associated with DR prevalence in CHS.¹²

Our two most novel findings in CHES were the associations of statins and antihypertensive drugs with VTDR. Statin use had a strong positive association (OR: 4.96; 95% CI: 1.60–16.41) with VTDR, a result that has not been reported in previous studies, which rarely considered this drug. A recent analysis of type 1 diabetes patients in WESDR found no association of statin use with incidence of proliferative DR and macular edema.³⁵ There is some biological plausibility to the association between statins and VTDR. It is well established that statin use increases the risk of developing T2DM,³⁶ and is associated with poor glycemic control³⁷ and comorbidities in diabetic patients.³⁸ However, because our model controls for DM duration and glycemic control, the biological mechanism by which statin use impacts VTDR risk could involve glycemic control or some other unrecognized pathway. The Shanghai and Hong Kong studies of DR of any type considered statin use as a predictor and found no significant association with DR prevalence, although they did not report results for VTDR in particular. We found that antihypertensive drugs had a protective association with VTDR (OR: 0.18; 95% CI: 0.06–0.61) after controlling for SBP, indicating a mechanism beyond their blood pressure-lowering effect. Antihypertensive drugs have been found to have a protective effect against other DM complications, such as diabetic nephropathy, due to their blocking effect on the renin-angiotensin system (RAS), an effect that is independent of the drugs' effect on blood pressure.³⁹ Clinical studies have indicated that RAS blockade in the eye is associated with less severe DR.⁴⁰ Antihypertensive drugs were only examined independently as a potential predictor in the Shanghai study,³⁰ in which they had a negative association with DR prevalence among pre-diabetic patients with hypertension.

Our results are similar to those previously reported in LALES.¹⁶ We found the same predictors for any DR prevalence that were previously reported in LALES, with the exception of male gender. The lack of association of gender is consistent with previous studies conducted in ethnic Chinese populations. Although DM duration was the most important predictor for DR in both LALES and CHES, we see a pattern of a slower increase in DR prevalence over DM duration in CHES compared to LALES. SBP was another

important predictor for DR in both LALES and CHES; we found similar or slightly lower DR prevalence across increasing values of SBP for CHES compared to LALES. In contrast, HbA1c appears to predict nearly identical DR prevalence in both LALES and CHES. When we held HbA1c levels constant, the difference in DR prevalence by DM duration did not diminish between the two studies, suggesting that the effect is distinct between the Chinese American and Hispanic populations.

A primary strength of CHES is that it is the first population-based study of a Chinese American population to examine risk factors for DR. The CHES sample is demographically representative of Chinese Americans aged 50 and older, and thus the study results can be generalized to this rapidly growing population. Another strength is the study's standardized protocols for procuring fundus photographs from 7 stereoscopic fields and grading the photographs. A major limitation of the study is its cross-sectional design, which precludes us from examining the temporal relationship between the examined predictors and DR. Another limitation is the possibility of survivorship bias, in which participants with DR and higher levels of predictors for the disease are less likely to survive and be included in our sample. Such a bias would reduce the strength of association that we find between DR and the predictors, meaning that our study may underestimate those associations. Another limitation is the small number of participants with VTDR, which raises the possibility that the novel associations we found for VTDR are driven by peculiarities of our sample.

In conclusion, our population-based study of Chinese Americans with T2DM characterizes factors associated with DR prevalence. Knowledge of these factors is important for recognizing high-risk populations. Our study suggests that antihypertensive drugs may decrease prevalence of DR among T2DM patients, while statins may increase the risk of VTDR. However, both of these novel findings were based on a relatively small sample of participants with VTDR, and thus further research is warranted before reaching definitive conclusions about these drugs. Our interethnic comparison with LALES indicates the similar impact of increasing SBP and HbA1c in Chinese Americans and Latinos. However, Chinese Americans appear to be less susceptible to DR over longer DM duration, even after controlling for HbA1c levels. This suggests that factors specific to the Chinese American population reduce their susceptibility to DR over longer periods of DM duration, compared to the Hispanic population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations and Acronyms

ARIC	(Atherosclerosis Risk in Communities Study)
CHES	(Chinese American Eye Study)
CHS	(Cardiovascular Health Study)
CI	(confidence interval)
DM	(diabetes mellitus)
DME	(diabetic macular edema)
DR	(diabetic retinopathy)
EDC	(Pittsburgh Epidemiology of Diabetes Complications Study)
ETDRS	(Early Treatment Diabetic Retinopathy Study)
LALES	(Los Angeles Latino Eye Study)
LOESS	(locally weighted regression)
NHANES	(National Health and Nutrition Examination Survey)
NVTDR	(non-vision-threatening diabetic retinopathy)
OR	(odds ratio)
SBP	(systolic blood pressure)
T2DM	(type 2 diabetes mellitus)
VTDR	(vision-threatening diabetic retinopathy)
WESDR	(Wisconsin Epidemiologic Study of Diabetic Retinopathy)

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Figure 1a.
Allowing A1C to vary

Figure 1b.
Holding A1C fixed at baseline category

Figure 2a.
Allowing A1C to vary

Figure 2b.
Holding A1C fixed at baseline category

Figure 3.

Figure 4a.

Figure 4b.

Figure 4c.

Table 1a
Univariate Associations of Sociodemographic and Personal Health Practice Factors with Any Diabetic Retinopathy and Between DR Subtypes

Risk Factors	Any DR vs No DR				DR Cases by Subtype			
	Any DR (n=238)		None (n=427)		NVTDR (n=211)		VTDR (n=27)	
	n	(%)	n	(%)	n	(%)	n	(%)
<u>Sociodemographic factors</u>								
Age								
50 to 59 years	88	37.0	137	32.1	79	37.4	9	33.3
60 to 69 years	93	39.1	179	41.9	80	37.9	13	48.1
70 to 79 years	42	17.6	64	15.0	39	18.5	3	11.1
80 years and above	15	6.3	47	11.0	13	6.2	2	7.4
Sex								
Female	117	49.2	242	56.7	106	50.2	11	40.7
Male	121	50.8	185	43.3	105	49.8	16	59.3
<u>Personal health practice factors</u>								
Anti-hypertensive drugs [*]								
Never used	120	50.4	212	49.8	104	49.3	16	59.3
Ever used	118	49.6	214	50.2	107	50.7	11	40.7
Treated for diabetes with insulin [*]								
No	209	87.8	409	96.2	191	90.5	18	66.7
Yes	29	12.2	16	3.8	20	9.5	9	33.3
Treated for diabetes with pills [*]								
No	82	34.5	182	42.8	68	32.2	14	51.9
Yes	156	65.5	243	57.2	143	67.8	13	48.1
Statins [*]								
Never used	182	76.8	319	74.7	165	78.6	17	63.0
Ever used	55	23.2	108	25.3	45	21.4	10	37.0

DR = diabetic retinopathy; NVTDR = non-vision-threatening diabetic retinopathy; VTDR = vision-threatening diabetic retinopathy

^{*} Personal health practice factors: 1 subject did not report anti-hypertensive drugs, 2 did not report treatments for diabetes, 1 did not report statins; biologic risk factors: 9 subjects have missing diabetes duration, 45 have missing glycosylated hemoglobin, 6 have missing BMI.

Table 1b
Univariate Associations of Biologic Risk Factors with Any Diabetic Retinopathy and Between DR Subtypes

Risk Factors	Any DR vs No DR				DR Cases by Subtype			
	Any DR (n=238)		None (n=427)		NVTDR (n=211)		VTDR (n=27)	
	n	(%)	n	(%)	n	(%)	n	(%)
<u>Biologic risk factors</u>								
Known duration of diabetes *								
Less than 5 years	96	40.9	246	58.4	89	42.8	7	25.9
5 to 9 years	40	17.0	74	17.6	36	17.3	4	14.8
10 to 14 years	44	18.7	58	13.8	40	19.2	4	14.8
15 years and above	55	23.4	43	10.2	43	20.7	12	44.4
Random serum blood glucose *								
Less than 100 mg/dL	44	20.2	113	28.4	42	21.6	2	8.3
100 to 139 mg/dL	66	30.3	147	36.9	60	30.9	6	25.0
140 to 199 mg/dL	63	28.9	97	24.4	57	29.4	6	25.0
200 mg/dL and above	45	20.6	41	10.3	35	18.0	10	41.7
Glycosylated hemoglobin *								
Less than 6.5%	34	15.4	99	24.8	31	15.8	3	12.0
6.5 to 6.99%	63	28.5	155	38.8	60	30.6	3	12.0
7 to 7.99%	70	31.7	104	26.1	62	31.6	8	32.0
8% and above	54	24.4	41	10.3	43	21.9	11	44.0
Body mass index *								
Less than 25 kg/m ²	97	41.6	185	43.4	85	41.3	12	44.4
25 to 29.9 kg/m ²	104	44.6	186	43.7	92	44.7	12	44.4
30 kg/m ² and above	32	13.7	55	12.9	29	14.1	3	11.1
Total cholesterol *								
Less than 150 mg/dL	59	27.4	84	21.0	51	26.8	8	32.0
150 to 199 mg/dL	103	47.9	178	44.5	93	48.9	10	40.0
200 mg/dL and above	53	24.7	138	34.5	46	24.2	7	28.0
	Mean	SD	Mean	SD	Mean	SD	Mean	SD

Risk Factors	Any DR vs No DR				DR Cases by Subtype				P value	
	Any DR (n=238)		None (n=427)		NVTDR (n=211)		VTDR (n=27)			
	n	(%)	n	(%)	n	(%)	n	(%)		
Systolic blood pressure (mm Hg)	133.5	19.2	128.4	18.1	0.001	132.9	18.6	138.4	23.1	0.155

DR = diabetic retinopathy; NVTDR = non-vision-threatening diabetic retinopathy; VTDR = vision-threatening diabetic retinopathy

* Personal health practice factors: 1 subject did not report anti-hypertensive drugs, 2 did not report treatments for diabetes, 1 did not report statins; biologic risk factors: 9 subjects have missing diabetes duration, 45 have missing glycosylated hemoglobin, 6 have missing BMI.

Table 2

Multivariate Risk Factor Models of Diabetic Retinopathy

Risk Factor	Any DR			VTDR			NVTDR		
	OR (95% CI)	P value		OR (95% CI)	P value		OR (95% CI)	P value	
SBP (per 10 mm Hg)	1.19 (1.08–1.31)	.0003		1.81 (1.37–2.38)	2×10^{-5}		1.17 (1.06–1.29)	.002	
Age									
50 to 59 years (index)	1.00	.012		1.00	.167		1.00	.023	
60 to 69 years	0.73 (0.48–1.10)			0.61 (0.19–1.97)			0.72 (0.47–1.10)		
70 to 79 years	0.76 (0.44–1.32)			0.17 (0.03–1.14)			0.82 (0.47–1.43)		
80 years and above	0.25 (0.11–0.58)			0.13 (0.01–1.39)			0.27 (0.12–0.64)		
Treated for diabetes with insulin									
No (index)	1.00	.021		1.00	.0001		1.00	.118	
Yes	2.44 (1.14–5.20)			16.48 (3.94–68.90)			1.90 (0.85–4.25)		
Known duration of diabetes									
Less than 5 years (index)	1.00	1×10^{-5}		1.00	.006		1.00	7×10^{-5}	
5 to 9 years	1.24 (0.74–2.06)			4.09 (0.81–20.77)			1.20 (0.71–2.03)		
10 to 14 years	2.07 (1.23–3.50)			2.90 (0.50–16.78)			2.08 (1.22–3.54)		
15 years and above	3.99 (2.26–7.05)			14.51 (3.17–66.49)			3.66 (2.04–6.57)		
HbA1c									
Less than 6.5% (index)	1.00	.001		1.00	.008		1.00	.005	
6.5 to 6.99%	1.33 (0.79–2.25)			0.41 (0.06–2.98)			1.39 (0.82–2.37)		
7 to 7.99%	1.86 (1.10–3.13)			2.38 (0.50–11.25)			1.86 (1.09–3.19)		
8% and above	3.22 (1.77–5.86)			5.75 (1.17–28.26)			2.94 (1.58–5.46)		
Antihypertensive drugs									
Never used (index)	*	*		1.00	.006		*	*	
Ever used				0.18 (0.06–0.61)					
Statins									
Never used (index)	*	*		1.00	.009		*	*	
Ever used				4.96 (1.50–16.41)					

CI = confidence interval; DR = diabetic retinopathy; HbA1c = glycosylated hemoglobin; OR = odds ratio; NVTDR = non-vision-threatening diabetic retinopathy; SBP = systolic blood pressure; VTDR = vision-threatening diabetic retinopathy

* Not included in the risk factor model

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