FOUR-YEAR INCIDENCE OF DIABETIC RETINOPATHY IN THE LOS ANGELES LATINO EYE STUDY (LALES): EVALUATION OF HOW BIOLOGIC RISK INDICATORS AND BARRIERS TO TREATMENT CONTRIBUTE TO DISEASE DEVELOPMENT

DISSERTATION

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By

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Objective: To examine 4-year incidence of diabetic retinopathy (DR) and to assess relationships between both biologic indicators and barriers to care on the development of DR.

Methods: The Los Angeles Latino Eye Study (LALES) is a population-based study of primarily Mexican-Americans. Participants were considered at risk for DR if both diabetes was present and they were free of DR at baseline. Definite diabetes was defined as either having 1) a self-reported history and treatment of diabetes, or 2) levels of hemoglobin A1C (HbA1c), or 3) random blood glucose of at least 7.0% and 200 mg/100 mL. All participants underwent a standardized ophthalmic examination. DR was detected by grading of stereoscopic fundus photographs using the modified Airlie House classification scheme. Biologic risk factors, such as HbA1c, random blood glucose, systolic and diastolic blood pressure, were assessed to determine its relationship with incidence of DR. Measures impacting barriers to health care, such as insurance status, were also evaluated to determine its relationship to development of DR. Trend tests were done to assess differences in incidence when stratifying by age and duration of diabetes (defined at baseline). Risk variables were analyzed using logistic regression.

Results: Of the 893 participants with diabetes who were seen at follow-up, 745 had gradable photographs. Of those, only 412 were free of retinopathy at baseline and were
considered to be at-risk for DR at follow-up. The four-year cumulative incidence of DR was 27.9% (115/412). Significant increases in incidence were seen across both increasing age (p=0.04) and increasing duration of diabetes (p<0.001) strata. Biologic risk factors shown to increase risk of DR were smaller waist-hip ratio (OR: 1.4; 95% CI: 0.8, 2.6), longer duration of diabetes (OR: 2.5 to 8.3 for 1-4 years to 15+ years, respectively), higher HbA1c (OR: 1.5; 95% CI: 1.3, 1.7), and an increase in HbA1c level from baseline to follow-up (OR: 2.3; 95% CI: 1.2, 4.3). Being born in the US decreased risk for development of DR (OR: 0.4; 95% CI: 0.2, 0.8). Insulin use (OR: 1.1; 95% CI: 0.5, 2.3) confounded the relationship between waist-hip ratio and development of DR. Significant barriers to care that increased the risk of DR were known history of diabetes (OR: 5.2; 95% CI: 2.2, 11.9), lack of vision insurance (OR: 1.8; 95% CI: 1.0, 3.8), increasing age (OR: 0.96; 95% CI: 0.93, 0.99), and an increase in HbA1c by vision insurance interaction (OR: 1.3; 95% CI: 1.03, 1.5). Primary language spoken (English: OR: 0.9; 95% CI: 0.4, 1.9; Both English and Spanish: OR: 1.3; 95% CI: 0.6, 2.6) was a confounder in the model.

**Conclusion:** Four-year incidence of DR among Latinos is high. Results indicate that this may be due to a combination of both increasing biologic risks as well as increasing barriers to care. High incidence of DR among Latinos suggests the need for initiating screening programs within Latino communities. Biologic indicators and barriers to care found to be significant in this dissertation could be used to identify Latinos that are highly susceptible to developing DR.
Dedicated to my husband, Paul Allison, to my parents, Kim & Ding Bung Chung, and to my Macbook.
I could not have done this without your patience and support.
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CHAPTER 1

INTRODUCTION

Latinos\(^1\), the largest US minority and the fastest growing segment of the United States (US) population, are an ethnic subgroup with unique demographic, socioeconomic, mortality, morbidity, and ocular disease characteristics. The US Census estimates that as of 2000, 12.5% of residents in this country, or 35 million people, were Latino (1). This percentage is expected to double by the year 2025 (2). Additionally, during the next decade, Latinos will account for 2 out of every 3 people entering the United States (3). Compared to other ethnic groups, Latinos have a greater disease burden (4), and this burden is expected to increase over the next several decades.

Latinos living in the US exhibit high rates of diabetic retinopathy (DR). Retinopathy is the leading cause of new cases of visual impairment and blindness in the working age population in the United States (5) and is also the second leading cause of visual impairment and blindness among Latinos (6). It usually manifests itself in those with diabetes and is the most severe ocular outcome that results from diabetes. The prevalence of retinopathy in those with diabetes is approximately 33% (7).

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\(^1\) For purposes of simplicity, the terms “Latinos” and “Hispanics” are used interchangeably in this document and encompass all those who came to the United States from Latin America. In actuality, “Latinos” refer to those of Native American, Asian, or African ancestry who reside in Latin America, whereas “Hispanics” refer to those of European ancestry who may also live in Latin America.
Latinos are at high risk for retinopathy because they have a higher prevalence of diabetes compared to other racial and ethnic groups. According to the US Department of Health and Human Services, the prevalence rate of diabetes among Latinos was about twice that seen in non-Latinos (8). Moreover, diabetes remains as number five on the list of the top 10 leading causes of death among Latinos (9). Since prevalence of DR among diabetics is roughly 33%, Latinos likely have a larger number of DR cases compared to other ethnic groups.

The prevalence of diabetes increased about 100% over the last two decades (10) in the US, and is expected to continue to increase in the future. This burden is primarily seen in the elderly (over age of 65), which poses a concern when one considers the aging baby boomers in the United States. The rapid increase of diabetes rates emphasizes the public health importance of studying retinopathy.

Retinopathy can be prevented by controlling hemoglobin A1c levels in the blood, also known as having glycemic control (11). Furthermore, the visual impairment and blindness that results from retinopathy is preventable through early detection and surgery. For this reason, the American Diabetes Association (ADA) recommends a dilated eye examination for those diagnosed with Type 1 diabetes beginning at 5 years post-diagnosis and those diagnosed with Type 2 diabetes beginning at the time of onset. However, this recommendation is rarely followed, especially by Latinos who have previous knowledge of their diabetes condition (12, 13).

Barriers such as no medical insurance or lack of nearby ophthalmology clinics contribute to the low compliance among Latinos for yearly diabetes exams (12, 13). To date, no study has identified which barriers to care contribute to development of diabetic
retinopathy; studies have only examined which factors predict compliance with the recommended eye exam.

Studies on rates of retinopathy in Latinos are scarce. Most of the large-scale population-based studies have been done on Caucasians (14, 15). Only one large population-based study focusing on Latinos have collected cross-sectional information and obtained only prevalence data (16) and found that retinopathy occurs more often among Latinos compared to Caucasians. Moreover, the question of why retinopathy is more common among Latinos still remains unclear.

Examining the relationship between both biologic risk factors and barriers to care on risk of DR may explain some of the reason why Latinos have high rates of retinopathy compared to other ethnic groups. This can help predict 1) who is at higher risk for retinopathy and 2) what Latino-specific patterns of health care use increases risk of retinopathy and resulting blindness. The information gathered from this research can be used to effectively plan and implement culturally sensitive programs targeting individuals who are at greater risk for retinopathy and blindness.

This research proposes to answer three questions:

1) What is the four-year cumulative incidence of diabetic retinopathy among Latinos and how does it compare to other racial/ethnic subgroups?

2) What are the biologic and demographic risk factors that predict incidence of diabetic retinopathy in Latinos?

3) What is the association between barriers to health care use and development of diabetic retinopathy in Latinos?
These three questions will be addressed using data collected from the Los Angeles Latino Eye Study (LALES). LALES is a large-scale, population-based, follow-up study of Latinos residing in the Los Angeles area.

LALES has completed two waves of data collection (baseline, 4-year follow-up) on several thousand Latinos, and nearly all subjects who completed baseline examination have returned to participate in the 4-year follow-up exam. All analyses were conducted on patients who were newly diagnosed with diabetic retinopathy (incident cases) at the time of 4-year follow-up examination.
Overview on diabetes

Diabetes mellitus affects approximately 171 million people worldwide and is expected to double in the number of cases by the year 2030, according to the World Health Organization (17). This accounts for approximately 6% of the world’s population. There are three main types of diabetes recognized by the World Health Organization: Type 1, Type 2, and gestational diabetes (17). Gestational diabetes occurs during pregnancy and for purposes of research in diabetic retinopathy is not of major concern.

The difference between Type 1 and Type 2 diabetes is slight and depends on whether the beta cells in the pancreas are able or unable to produce sufficient insulin to prevent hyperglycemia (18). Type 1 diabetes is caused by an autoimmune destruction of the pancreatic cells and whereas Type 2 diabetes is caused by tissue-wide resistance to insulin leading to eventual destruction of pancreatic cells. Type 1 diabetes is usually referred to as child-onset diabetes (before age 30) and Type 2 diabetes is usually referred to adult-onset diabetes (after age 30).

Diabetes has many comorbid conditions that increase morbidity and mortality in the general population (19-21). Two of the most common problems that occur with diabetes are obesity and hypertension. These two conditions are important predisposing
factors that contribute to heart disease (21), the number one killer in the United States (22). Furthermore, since diabetic retinopathy occurs in about a third of diabetic patients, it can be deduced that the prevalence of cardiovascular problems among those with DR is high (7).

The majority of the diabetes burden falls on those who self-identify as being Latino or Hispanic. A study conducted by Haffner et al. revealed that Mexican-Americans have threefold greater prevalence of diabetes than Non-Hispanic whites (23). Researchers postulate that because Latinos have a relatively high prevalence of diabetes, the absolute number of cases of disease that co-occur with diabetes, such as DR, is also higher among Latinos.

**Overview on diabetic retinopathy**

**General statistics and information**

Diabetic retinopathy is the most severe ocular disease that can develop as a result of having diabetes (24).

Although diabetic retinopathy occurs almost exclusively in those already manifesting Type 1 or Type 2 diabetes, the prevalence of retinopathy in this population of diabetics is very high. A recent study done by Wong et al. showed that, among individuals in their multiethnic cohort with diabetes, 1/3 already had diabetic retinopathy (7). This proportion varied depending on the population under investigation. Another study published in 2004 reported that an estimated 4.1 million people age 40 and older have diabetic retinopathy in the United States, and approximately 1 in every 12 persons in this group have advanced, vision-threatening retinopathy (25). Moreover, the prevalence of retinopathy in this study for those with diabetes mellitus was approximately
40.3%. This number is projected to increase significantly in the future due to the aging population, emphasizing the public health importance of diabetic retinopathy.

Diabetic retinopathy has several stages of severity. Mild or early diabetic retinopathy can be defined as presence of microaneurysms, small outpouchings from retinal capillaries, and intraretinal hemorrhages (26). Severe retinopathy shows evidence of fibrous proliferation in the retina. Signs of early retinopathy are seen in nearly everyone who had Type 1 diabetes for twenty years (27) and in about 80% of those with Type 2 diabetes for twenty years (28).

Many comorbid systemic conditions that significantly impact a person’s morbidity and mortality are also associated with diabetic retinopathy. Previous studies have reported an association between systemic conditions and development of DR. Some of these comorbid conditions are congestive heart failure, cardiovascular disease, hypertension, hyperglycemia and obesity (19, 21, 29). For instance, Silva and colleagues showed that hypertension increased the risk of diabetic retinopathy (30). Therefore, aggressive treatment of systemic conditions can prevent or even reduce symptoms of retinopathy (31).

Since retinopathy occurs concurrently with many other comorbid conditions that associate itself with diabetes and impact mortality, studies on retinopathy are prone to survival bias. Survival, or prevalent case bias, is present in this population of diabetics since interference of comorbid conditions significantly impacts the individual’s mortality. As a result, persons with severe diabetes are less likely to survive and/or be healthy enough to participate in the study as compared to persons with less severe diabetes.
Survival bias can also be common among incidence studies, especially in those who are free of retinopathy but have had diabetes for an extended period of time. The chance of surviving and remaining retinopathy-free for more a couple of decades following diagnosis of diabetes mellitus is very low (32-35). For this reason, researchers often study retinopathy in terms of duration of diabetes (defined as the absolute difference of age at baseline exam and age of diabetes onset). Previous studies consistently show that duration of diabetes is significantly associated with incidence of diabetic retinopathy (11, 36-39).

Incidence of retinopathy increases with increasing duration, but decreases when duration reaches 15+ years. There are two things to consider when evaluating DR among unhealthy persons with severe diabetes for 15 or more years: 1) the small chance of survival (competing risks) and/or 2) the small chance that these individuals will remain free of DR for 15 years after being diagnosed with diabetes (36). On the other hand, healthier individuals have less severe forms of diabetes and are more likely to remain free of DR for 15+ years. Therefore, healthy persons are systematically different from unhealthy persons with more severe forms of diabetes.

Diabetic retinopathy is also the only adult ocular condition that has been shown to co-occur in individuals with many other systemic conditions. These conditions in turn significantly impact an individual’s morbidity and mortality. There have been some evidence of glaucoma and its relationship to cardiovascular disease, but these associations are not as strong as those seen with diabetic retinopathy and are inconsistent in the literature (40, 41). Understanding retinopathy in the population can provide insight
into other diabetes-related conditions that impact a person’s morbidity, mortality, and quality of life.

**Pathogenesis of DR**

Diabetic retinopathy impacts the back of the eye where the retina is located. This part of the eye is rich with blood vessels. When a patient is exposed to prolonged hyperglycemia, these vessels become blocked, creating an oxygen-deprived ischemic environment. As a result, these vessels proliferate and become more permeable (42).

Pericytes, a type of cell that provides vascular stability and controls endothelial proliferation, are reduced in number at the onset of diabetic retinopathy. With the loss of these cells comes loss of control over processes normally controlled by pericytes. As the capillary wall becomes more permeable, blood leaks out into the retina and the vitreous gel, creating a hemorrhage. This type of bleeding occurs in both the retina (known as retinal hemorrhage) and the vitreous gel surrounding the retina (vitreous hemorrhage), and can result in visual impairment or blindness.

Early changes in the retina because of diabetic retinopathy can be seen in the form of microaneurysms, hemorrhages, and hard/soft exudates. In later stages, both neovascularization (new blood vessels) and fibrous proliferation are evident. This results in vitreous hemorrhage and retinal detachment. Vitreous hemorrhage and retinal detachment renders the individual highly susceptible to blindness.

**Stages of DR**

Each stage and its description is given below (26):

1. Mild nonproliferative diabetic retinopathy: Microaneurysms (small areas of balloon-like swelling in the retina’s tiny blood vessels) occur
2. Moderate nonproliferative diabetic retinopathy: Vessels that nourish the retina are blocked.

3. Severe nonproliferative diabetic retinopathy: Many more blood vessels are blocked, depriving the retina of oxygen and blood. The retina sends signals to the rest of the body to create new blood vessels (known as neovascularization).

4. Proliferative diabetic retinopathy: The most severe stage, the new blood vessels created are abnormal and fragile. The vessels grow along the retina and within the vitreous gel. These vessels are fragile and even though they themselves do not cause vision loss, they are thin and fragile and if they break, the leakage of blood can create severe vision loss. This bleeding is known as vitreous hemorrhage.

Detection of DR

There are several methods commonly used to diagnose diabetic retinopathy. The first, known as the Doppler flowmeter, measures retinal blood flow by using laser beams that project into the retinal vessel (43). The second, known as the scanning laser ophthalmoscope, also measures retinal blood flow by producing a video fluorescein angiogram and measures the movement of blood in the retinal vessels (44). Third, known as functional magnetic resonance imaging (fMRI), measures oxygenation in the retina by comparing the change in the amount of oxygen in the retina when the subject is breathing 100% oxygen as opposed to 95% oxygen and 5% carbon dioxide (45). Finally, use of fundus photography taken during a dilated eye exam can diagnose diabetic retinopathy by looking for presence of microaneurysms, exudates, fibrous proliferation, and/or retinal hemorrhage (46).
Prevention of DR

Diabetic retinopathy is preventable through proper medical care and rigorous treatment of diabetes. Those with controlled diabetes are at lower risk for developing retinopathy than individuals who do not have controlled diabetes (38). Having controlled diabetes is another of saying maintaining glycemic control (i.e. low hemoglobin A1c levels).

Glycemic control can substantially reduce the rate of retinopathy in the population by inhibiting the onset of disease. Sometimes glycemic control can be attained by intensive insulin therapy with the goal of reducing hemoglobin A1c levels. Hemoglobin A1c, or glycosylated hemoglobin, measures the average plasma glucose concentration over prolonged periods of time. Glycosylation of the hemoglobin molecule occurs when glucose binds to hemoglobin, forming glycated hemoglobin. High levels of glycated hemoglobin in the blood are a sign of prediabetes or uncontrolled diabetes. Mean of hemoglobin A1c levels in a diabetic population is usually 9.9%\(^2\). The Diabetes Control and Complications Trial (DCCT) found that achieving a mean hemoglobin A1c level of 7.9% or lower reduced incidence of retinopathy as much as 76% (47).

The United Kingdom Prospective Diabetes Study found similar results when they used insulin therapy. This study reported a 37% reduction in risk of diabetic retinopathy when undergoing insulin therapy (48). Other studies have also supported the conclusion that aggressive insulin treatment to attain glycemic control decreases the risk of diabetic retinopathy (49, 50).

\(^2\) Percent of hemoglobin molecules in the red blood cells
Treatment of DR

Patients with diabetic retinopathy usually remain asymptomatic until the very late stages of disease. At that time, surgical intervention is needed in order to treat and slow the progression of retinopathy.

The treatment of diabetic retinopathy becomes invasive after its onset and progression to more severe stages of disease. Depending on the stage of disease, it can be treated by either focal photocoagulation or panretinal photocoagulation, surgical procedures that have been shown in a randomized trial to be effective in improving visual acuity and other symptoms associated with diabetic retinopathy. The first of these trials is known as the Early Treatment Diabetic Retinopathy Study (ETDRS) and examined cases of early diabetic retinopathy (51). The second of these is known as the Diabetic Retinopathy Study (DRS) and investigated treatment for more severe cases of diabetic retinopathy (52).

Focal photocoagulation is most effective when used in cases where the individual has macular edema along with mild forms of disease, such as nonproliferative diabetic retinopathy (53). Panretinal photocoagulation treatment is most beneficial in those who have severe forms of DR, such as proliferative diabetic retinopathy (PDR) (52).

In the two studies mentioned above (ETDRS and DRS), each eye was randomized into a treatment arm and a control arm. Therefore, the participant acted as his/her own control. In the eight months following the procedure, patients showed vast improvements in visual acuity over time and significant differences between the eye that received treatment and the contralateral eye with no treatment (51, 52).
Evidence of prior panretinal photocoagulation treatment suggests that the individual was previously diagnosed with severe proliferative retinopathy. This type of surgical treatment improves retinopathy in those with severe PDR. Therefore, panretinal photocoagulation can be used to control the progression of retinopathy only in the most severe stages.
CHAPTER 3

LITERATURE REVIEW

Introduction to other ocular epidemiologic studies

Three large-scale, longitudinal, population-based studies have been done thus far. These studies examine ocular diseases (such as diabetic retinopathy) common among adults. Their study samples are limited to adults and their samples are homogenous with respect to racial/ethnic breakdown.

The largest and most widely known study done on ocular diseases was conducted in a small town of Beaver Dam, Wisconsin. There are two separate yet well-known studies conducted in this town led by the same principal investigator. The more recent study, known as the Beaver Dam Eye Study (BDES) (54), primarily investigates all the major ocular conditions affecting Caucasian adults in the United States: visual impairment, diabetic retinopathy, age-related macular degeneration, glaucoma, and lens opacities. The other study, known as the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) (27), began data collection in the 1980s on only diabetic retinopathy. The investigators recruited a Caucasian population with diabetes from this small Wisconsin town and followed them forward, gathering prevalence, incidence, and risk factor data for over 15 years.
A second often-cited study is the Blue Mountain Eye Study (BMES) (15, 55), conducted in Sydney, Australia. Similar to the study in Beaver Dam, this study also gathered data on the primary ocular diseases affecting adults. This study recruited Caucasian individuals over the age of 40 and collected baseline and follow-up measures. Thus far, this study has been in progress for approximately 10 years. Cumulative five-year incidence estimates have already been published for diabetic retinopathy (56).

The third study, known as the Barbados Incidence Study for Eye Disease (BISED) (57, 58), was conducted in the Barbados islands. Again, adults over the age of 40 were recruited. Most participants in the study were Afro-Caribbean. The main foci of this study were glaucoma and lens opacities, since these conditions are more prevalent among those with African ancestry. However, rates of diabetic retinopathy have also been reported in their study (57-59).

The informativeness of having these three studies is that the Los Angeles Latino Eye Study (LALES), a large-scale, population-based epidemiological study of ocular diseases in Latinos, can make cross-study comparisons in rates of diabetic retinopathy. It also allows researchers to make inferences as to how racial and/or ethnic characteristics influence rates of retinopathy, since these other studies consist of participants of different ethnic backgrounds.

Studies on prevalence and incidence of DR

Rates among non-Latino populations

Studies done with non-Hispanics have primarily focused on prevalence of diabetic retinopathy. Only a select few have collected enough follow-up data to be able to calculate incidence rates. The rates of diabetic retinopathy seen in non-Hispanic
populations are high and vary dramatically depending on the population under study and the methods of defining disease.

The prevalence estimates of retinopathy reported in international studies vary considerably. The Australian Diabetes, Obesity and Lifestyle study (AusDiab), conducted in Australia, reported an overall prevalence of 15.3%. This percentage ranged from 6.2% to 21.9% for those newly diagnosed with diabetes to those with known Type 2 diabetes, respectively (60). Another Australian study reported a prevalence of 13.4% (61) and study done in Japan reported that 35.8% of their patients had diabetic retinopathy (62).

Reported prevalence of retinopathy in the United States also varies considerably. A pooled study done in the US reported an overall prevalence of retinopathy (25). This study was primarily composed of non-Hispanics, although Hispanics were also included if they were involved in any of the studies included in this pooled analysis. The crude prevalence of retinopathy and vision-threatening retinopathy was 40.3% and 8.2%, respectively.

Additional estimates of prevalence of retinopathy in the United States, calculated from the 1999 National Health Interview Survey and the 2000 US Census, were 3.4% and 0.75% for diabetic retinopathy and vision-threatening retinopathy, respectively (1, 63). Percentages from this study are much lower than percentages reported in population-based research studies. These results highlight the importance of conducting large-scale population-based studies, since using estimates derived from self-reported survey data underestimates the true prevalence of retinopathy in the United States.
Few population-based studies have collected sufficient data to obtain both prevalence and incidence estimates of diabetic retinopathy. The Melbourne Visual Impairment Project reported a 5-year cumulative incidence of 11% and a 5-year prevalence percentage of 35.7% (64). This study had a very small at-risk cohort (n=73) at five-year follow-up, suggesting that the incidence estimates had poor precision.

WESDR, conducted by Klein et al., reported a prevalence of 28.8% and a 4-year cumulative incidence of 47% (14, 28). This study consisted of Caucasians living in Beaver Dam, Wisconsin who were previously diagnosed with having diabetes.

Leske et al. reported that the prevalence of retinopathy in the Barbados sample was 19.4% in those who reported they were black, 15.4% in those of mixed black and white, and 7.5% of those who self-report white or other (65). Four-year cumulative incidence calculated in the same cohort were 30.1% (39). This percentage ranged from 39.1% with known diabetes at baseline to 20.9% in those newly diagnosed with diabetes.

Mitchell et al. found that the prevalence of retinopathy in Caucasians participating in Blue Mountain Eye Study was 32.4% (82/253) (15). The 5-year cumulative incidence of retinopathy in the same sample was 22.2% (56). The prevalence percentage for BMES was comparable to WESDR, but the incidence estimate for BMES was significantly lower than WESDR.

The prevalence varies among studies, but overall, it can be concluded that the prevalence of retinopathy among those with diabetes is high. More importantly, the incidence is also high. High cumulative incidence estimates in these studies underscore the need for collecting thorough follow-up data on these study populations to determine how rapidly retinopathy develops among individuals with diabetes.
Rates among Latino populations

Very few studies have estimated prevalence/incidence of diabetic retinopathy among Latino populations. Prior to LALES, the most well-known study on Hispanics was the Proyecto Ver study, where the investigator recruited a sample of Hispanics residing in Arizona (16). This study reported prevalence estimates and found that the prevalence of retinopathy in Hispanics is almost twice that seen in Caucasians. Out of a sample of 4,774, 1,044 were diagnosed with diabetes at baseline examination. Among those 1,044 patients with diabetes, 48% had retinopathy and 32% had moderate to severe non-proliferative retinopathy at baseline examination. However, as mentioned above, this is a prevalence study, which limits researchers from drawing conclusions regarding temporal relationships between exposure and disease.

The San Luis Study obtained four-year incidence estimates on their data collected from 1984 to 1992 (66). The four-year cumulative incidence of diabetic retinopathy reported in this study was 22.5%. However, this study was both small [at-risk cohort (n=169)] and young [ages 20-74]. A study population this small is not powered enough to obtain precise estimates of incidence and investigate exposure-disease relationships.

Varma et al. conducted a pooled study that combined data from BDES, LALES, and Proyecto Ver and examined the ethnic-specific impact on prevalence of diabetic retinopathy (67). The studies representing Latinos/Hispanics were LALES and Proyecto Ver and the study representing non-Hispanic whites was BDES. Results showed that those that have Latino or Hispanic ancestry are two times more likely to have DR and seven times more likely to have PDR. Interestingly, these associations for ethnicity on DR remained even after controlling for risk factors for DR.
Another study, the Multi-ethnic Study of Atherosclerosis (MESA) examined a multi-ethnic cohort (7), including Latino subjects. The overall prevalence of diabetic retinopathy was 33.2% (n=778). The Latino-specific prevalence percentage was 37.4%. Retinopathy was more common among blacks and Hispanics as compared to whites and Chinese. However, the overall number of Hispanic participants in the study is so small (n=235) that it is difficult to obtain accurate Latino-specific incidence estimates.

Therefore, the largest study to date that has examined retinopathy in a population-based sample of Latinos is LALES. In 2004, the prevalence estimates among Latinos was 46.9% among the 1217 patients diagnosed with definite diabetes (5). The advantage of conducting a large-scale study focusing only on one ethnic group is that it allows for comparability with respect to other large-scale, racially homogenous studies focusing on a different ethnic group, such as WESDR (14, 36, 38), BISED (39, 65, 68), or BMES (15, 56).

Studies on biologic risk factors for DR

Risk factors among non-Latino populations

Most studies examining risk relationships on non-Hispanic samples have enough data to examine risk factors for prevalent diabetic retinopathy. Studies that examined risk factors for “prevalent diabetic retinopathy” meant that only baseline exposure and disease information was collected and analyzed. Only WESDR and BISED have published results on risk factors for incident diabetic retinopathy (38, 39). Studies that investigated risk factors for “incident diabetic retinopathy” meant that the study collected both baseline and follow-up data on exposures and disease. The advantage of conducting
studies geared towards gathering risk factors for development (incident) retinopathy is that temporal trends of exposure-disease relationships could be better understood.

One such study, conducted in Sweden, considered risk factors for prevalent diabetic retinopathy (69). Results from this study showed that worse metabolic control, hypertension, elevated systolic and diastolic blood pressure, younger age of onset, and a longer duration of diabetes were associated with diabetic retinopathy. The sample was limited to only those with Type 1 (insulin dependent) diabetes mellitus, so these risk factors cannot be generalized to all those with diabetes.

Tapp et al. conducted a study in Australia, which collected information on risk factors for prevalent diabetic retinopathy. The Australian Diabetes, Obesity and Lifestyle study (AusDiab) reported that duration of diabetes, levels of glycosylated hemoglobin, and systolic blood pressure were all associated with risk of retinopathy (60).

Klein et al. also published results on risk factors for prevalence of retinopathy for the WESDR study. The results were published in two separate studies, one focused on those with Type 1 diabetes and the other focused on those with Type 2 diabetes. Risk factors for Type 1 diabetes were longer duration, older age, and higher levels of glycosylated hemoglobin (27). Risk factors for Type 2 diabetes included longer duration of diabetes, younger age of diagnosis, higher glycosylated hemoglobin levels, higher systolic blood pressure, use of insulin, presence of proteinuria, and small body mass (28).

Klein et al. also reported on risk factors for the 14-year incidence of diabetic retinopathy in the WESDR study. The risk factor found to be significantly predictive of incidence of proliferative diabetic retinopathy was blood pressure (70). Significant risk factors contributing to progression in this cohort included baseline retinopathy severity
level (discussed in detail below), glycosylated hemoglobin, ≥ 30 aspirin/month, and hypertension. Risk factors for incidence any diabetic retinopathy (inclusive of proliferative and non-proliferative) were not assessed since by the time participants had reached 14 years of follow-up, 96% of them already had signs of diabetic retinopathy.

Leske et al. published results on risk factors for the 4-year incidence of diabetic retinopathy in the Afro-Caribbeans participating in the BISED study (39). Risk factors reported for incidence of retinopathy were increased systolic blood pressure, use of oral hypoglycemics (medications prescribed by doctor to control diabetes), use of insulin, and elevated glycosylated hemoglobin levels.

Duration of diabetes has been consistently shown to be a significant predictor of whether someone will develop diabetic retinopathy. In both the Wisconsin Epidemiologic Study for Diabetic Retinopathy and Barbados Incidence Study for Eye Disease, when their results were stratified by duration of diabetes, the incidence of diabetic retinopathy increases significantly with increasing duration (14, 38, 39, 71). In incidence studies, this increase is present across all duration strata except for those who have been diagnosed with diabetes for 15 years or more, after which the percentages drop (14, 39). This is because there is a high chance that someone who has diabetes for 15 years or more already have retinopathy (thus, cannot be at-risk for incidence), or are susceptible to the competing risks that lead to death (32-35). Mortality rates among persons with diabetes still remain high, and increase significantly with increasing duration of diabetes. In addition, persons without DR after 15 years of having diabetes are different than persons that do develop DR in that they have some characteristic that protects them from retinopathy.
In fact, by the time WESDR conducted its 14-year incidence study of diabetic retinopathy, 96% of participants had retinopathy (38). By the time this research was completed, duration of diabetes (measured at baseline) was at least 14 years in all the subjects, since the same cohort was followed from baseline forward in time for fourteen years.

While these results may suggest patterns of risk factors seen in Caucasians, they cannot be generalized to a Latino population comprised of predominately Mexican-American immigrants.

Risk factors among Latino populations

Thus far, only two studies have attempted to identify risk factors for incidence of diabetic retinopathy in a Latino population. Both of these studies are multiethnic and include both Hispanics and non-Hispanics.

The first is San Luis study, which identified risk factors in a mixed sample of Hispanic and non-Hispanic persons in Colorado. The only significant risk factor for incidence of diabetic retinopathy was use of exogenous insulin, although systolic and diastolic blood pressures were also found to be marginally significant (66). However, due to the small cohort (n=169), it is difficult to draw conclusions about risk factors on a multivariable level.

The MESA study (n=778) described above also included a small sample of Hispanic participants (n=235) (72). This study examined risk factors associated with diabetic retinopathy and found that retinopathy occurs at high rates among middle-aged persons and among those with hypertension and hyperglycemia. Significant independent
predictors of retinopathy were longer duration of diabetes, higher fasting glucose, use of oral medication or insulin, and greater waist-hip ratio.

Several more studies have examined risk factors for prevalence of diabetic retinopathy. The San Luis study also assessed risk factors for prevalence of disease and found that use of exogenous insulin, increased duration of diabetes, younger age at diagnosis, increased glycosylated hemoglobin, and increased systolic blood pressure (73). The small cohort (n=279, 166 Hispanics and 85 non-Hispanic Whites) makes it difficult to ascertain exposure-disease relationships.

Another large study examining risk factors for prevalence of diabetic retinopathy in a Latino population is the Proyecto Ver study (n=1023) (74). They found that low socioeconomic status (SES), Native-American ancestry, higher acculturation, increasing body mass index (BMI), and lower education predicted diabetic retinopathy in a Latino population. Unlike other studies, this study examined sociodemographic markers, rather than only biological markers, that may explain why Latinos have relatively high rates of diabetic retinopathy.

Finally, LALES (n=1219) examined risk factors for prevalence of diabetic retinopathy in a population-based sample of Latinos from Southern California (11). Risk factors for diabetic retinopathy found to be significant in this sample included male gender, increased glycosylated hemoglobin level, higher systolic blood pressure, insulin treatment, and increased duration of diabetes. To date, this is the largest study on risk factors for the prevalence of diabetic retinopathy among Latinos.

Results of studies on Hispanics have been relatively consistent on which risk factors were found to be significant for incidence of retinopathy. However, these studies
have focused primarily on risk factors for prevalence. The two studies that have
examined risk factors for incidence, namely the San Luis study and the MESA study,
were highly underpowered.

**Studies on barriers to care for diabetic patients**

Risk factors discussed above for diabetic retinopathy primarily involve biologic
risk factors for disease. Contributing factors such as age, duration of diabetes, and
medical history information are all significant predictors but do not separate minority
populations from non-minority populations.

Wilson et al. conducted a study on ophthalmologic conditions among minority
populations, particularly among Hispanic populations. Their findings show that
Hispanics are disproportionately affected by ocular disease compared to whites (75).
Additionally, they pointed out that understanding what makes Hispanics different from
Caucasians is important in addressing these disparities. External risk factors, such as
access to care, lack of education, and low income make the risk factors for disease in
minority populations multifactorial. Hispanics not only have similar types of biological
triggers for disease as seen in a Caucasian population, but they also experience additional
barriers listed above, which may contribute to increased risk of ocular disease.

Many studies have investigated the relationship between access to care and
compliance with diabetes treatment, but none have investigated relationships between
barriers and developing retinopathy in a Latino population.

**Barriers among non-Latino populations**

Despite the recommendations by the American Diabetes Association to obtain a
dilated eye examination every 12 months, compliance is very low, even among non-
Latino populations. In the Melbourne Visual Impairment cohort, it was found that the majority of those with severe diabetic retinopathy were treated, however, those without severe retinopathy did not comply with regular dilated fundus examinations (64). This lack of preventive care seen in those with diabetes could account for some of the reason why the rates are high.

Moss et al. analyzed data collected from the WESDR study. They examined factors associated with having a dilated eye examination in persons with diabetes (76). Those with higher income, more education, vision insurance, more severe retinopathy, history of glaucoma or cataract, and longer onset of diabetes were more likely to comply with ADA guidelines.

One possible reason why compliance of ADA guidelines is low is because of barriers imposed by the medical system in this country. Factors such as doctors not advising their patients to get an eye exam or waiting too long for an appointment all likely contribute to low compliance rates. Chin et al. conducted a study on 279 physicians examined why diabetic patients do not comply with care guidelines recommended to them by medical professionals (77). The study found that physicians feel patients have a problem with both the affordability of eye care and communication (language barriers). Moreover, 25% of physicians admitted forgetting to order the eye exam. Additional barriers include the long wait for an appointment (sometimes up to 1 year), poor access to care, and poor patient education regarding care of diabetes (78).

In short, compliance with this recommended guideline is low. Those that do not comply are largely Hispanics. One research study showed that about 1/3 of those with diabetes had never had a dilated eye exam and about 50% of those individuals have
retinopathy (79). In addition, those who have lower compliance rates were mostly black or Hispanic, overweight, and have lower socioeconomic status.

**Barriers among Latino populations**

The frequency of which Latinos with diabetes have regular eye exams is very low. One reason may be because of the illegal status of some Latinos in the United States (80), resulting in reluctance by undocumented Latinos to see a medical professional for necessary treatment. Another reason for this is Latinos are often unaware they even have diabetes (13). However, even if they are aware of having diabetes, many do not receive eye treatment. Paz et al. found that out of 821 individuals previously diagnosed with diabetes, 535 (65%) had not complied with the ADA recommendations (12).

The language barrier is another one of the reasons why Latinos may have low rates of compliance with ADA guidelines. Some Latinos have limited English proficiency, and are therefore less likely than Caucasian patients to establish a relationship with their physician (81). This was seen in a study by Pippins et al., who found that English language proficiency was associated with better quality of primary care among Latinos (82).

Several studies have found that in addition to the language barrier and having no prior diagnosis of diabetes, factors such as high cost, lack of services, and lack of knowledge as to where to go for care often prevent Latinos from seeking appropriate services (13). Protective factors for Latinos seeking health services were insurance coverage, prior diagnosis of a systemic disease (such as hypertension), had a routine physical in the past 12 months, higher education level, and lower levels of glycosylated hemoglobin (12, 13).
Significance

Studying the biologic risks and barriers to healthcare that increase the incidence of diabetic retinopathy among Latinos with diabetes is important for several reasons:

1) The pattern of risk factors seen among Latinos are unique compared to those seen among Caucasian populations, especially since Latinos have barriers to care that are not as common in Caucasians with diabetes.

2) Diabetic retinopathy is the leading cause of blindness among working-age Latinos. However, very few studies have examined risk factors for incidence of diabetic retinopathy in a Latino population and those studies have not been sufficiently powered enough to report robust results.

3) Studying incidence removes the potential of prevalent case bias that may adversely affect the results found in studies on prevalence. Moreover, risk indicators for incidence allows researchers to draw conclusions regarding temporal exposure-disease relationships.

4) Those with diabetic retinopathy likely have comorbid systemic conditions caused by their diabetes that significantly increase risk of mortality.

Objective

The goal of this dissertation was to use data collected from the Los Angeles Latino Eye Study (LALES) to examine biologic risks and barriers to care that may predict overall incidence of diabetic retinopathy. Cross-study comparisons will be made to address differences among risk factors that may exist across various racial groups. Study participants consisted of Latinos residing in the southern California region.
CHAPTER 4

STUDY DESIGN AND STATISTICAL METHODS

Objective of LALES

Overall, Latinos have a greater burden of ocular disease as compared to non-Hispanic Whites (5, 83). The Los Angeles Latino Eye Study (LALES) intends to measure exactly how much of the burden of ocular disease is carried by those self-identifying themselves as Latinos.

There have been two waves of data collection in LALES (84). LALES 1 collected baseline data from 2000-2004 and looked at prevalence of ocular disease. LALES 2, the four-year follow-up study of LALES 1, collected follow-up data from 2004-2008 and focused on the estimating the 4-year cumulative incidence of ocular disease. Similar measures were collected at the baseline and follow-up examinations. Each participant completed a home questionnaire, a clinical exam, and a clinical questionnaire. A detailed description of LALES 1 study methods can be found elsewhere (84), but are summarized below.

The major goal of LALES was to measure prevalence, incidence, and disease progression among Latinos for five major ocular diseases: visual impairment, diabetic retinopathy, glaucoma, lens opacities, age-related macular degeneration. Among all these
diseases, with the exception of glaucoma and late (advanced) AMD, Latinos have higher prevalence rates than Non-Hispanic whites (5, 83, 85, 86).

**Study population**

The overall objective of LALES was to investigate ocular diseases among Latinos using a large-scale population-based epidemiologic approach.

Latinos were recruited from six Census tracts in La Puente, CA. La Puente is a community east of Los Angeles and is characterized as being a middle class suburban city in Los Angeles County. The sample size target was 80% of the 7789 participants eligible for LALES in La Puente.

La Puente was chosen for several reasons. One, the area is primarily residential, which made it easier for interviewers to collect data on participants. Two, it is comprised of 83% Latinos, which provided a large enough sample to recruit from in order to have enough participants to reliably estimate ocular disease rates. Three, there has been an immense amount of support from key stakeholders such as church leaders and local ophthalmologists and optometrists. Four, the area is in close proximity to the University of Southern California Medical Center and Los Angeles County Hospital. Five, the age distribution of Latinos in La Puente closely resembles the age distribution of Latinos in the United States.

**Eligibility criteria**

In order to be eligible for the study, each person had to be a permanent resident of the household, defined by whether the person considers the place of residence to be permanent, or whether he/she sleeps at the residence most of the time, or lives in the house at least six months per year. In addition to satisfying the residency requirement,
there were three additional criteria that participants had to meet in order to participate in LALES.

1. They need to be at least 40 years of age.
2. They had to reside in one of the six Census tracts in the La Puente area.
3. They had to self-identify themselves as being Latino or of Latino heritage.

Each subject was asked to sign a consent form before participating, which described his/her rights to dropout of the study at any time. This study was approved by the USC Institutional Review Board and meets the guidelines set by the Declaration of Helsinki.

Description of data collection

Each participant was asked to complete an interviewer-administered in-home interview and ophthalmologist-administered clinical exam. Home interviews consisted of a staff member going to the participant’s house and completing a detailed questionnaire. This questionnaire collected information on each patient regarding items such as income, medical history, acculturation, prescription use, education and self-reported health status. The interview lasted approximately three hours.

After completing the in-home questionnaire, the participant was asked to attend an eye clinic for a detailed eye examination.

The detailed eye exam was composed of six general areas:

1. Examining vital signs
2. Looking at visual acuity
3. Pupil Assessment/visual fields
4. IOP/Slit Lamp Exam/Dilation
5. **Fundus photos**/Optic Disc photo
6. Ophthalmologic exam

Data from fundus photos (area 5) was used to diagnose diabetic retinopathy. This is an in-depth exam and lasts approximately four hours.

Some participants chose to only complete the home questionnaire or the clinic exam. The LALES study group considered the data from a participant complete only if he/she completed the clinic exam. Rigorous data management measures, such as generating weekly/monthly analysis and quality control reports, were implemented during the entire period of data collection for LALES.

Disease definitions

Diagnosing diabetes mellitus

There are several criteria that LALES used for defining diabetes mellitus.

LALES considered only those who had a diagnosis of definite diabetes to be at-risk for developing diabetic retinopathy. LALES staff diagnosed all cases of diabetes using information collected from the in-home questionnaire and/or the clinical examination. To be diagnosed with diabetes, at least one of the following criteria must be true.

1. Self-reported history of diabetes mellitus and/or treatment of diabetes
2. Hemoglobin A1c levels greater than or equal to 7.0% and/or random blood glucose level greater than or equal to 200.0 mg/100 mL

Diabetes was defined in LALES as definite, probable, and none. Two methods were used to diagnose diabetes. The first relied history and treatment of disease (self-reported) and the second used hemoglobin A1c levels and random blood glucose levels (from laboratory examination). Treatment of diabetes consisted of using insulin only, diet modification only, or both insulin and diet modification regiments. History of
diabetes information was collected from the home questionnaire in the section inquiring about medical history. Lab tests were conducted during the clinical examination, normally given after completing the home questionnaire. The lab results from a participant’s clinical examination provided the levels of both hemoglobin A1c and random\(^3\) blood glucose.

The LALES definition of *definite* diabetes is: 1) History of diabetes mellitus and treatment of diabetes, or 2) Hemoglobin A1c levels \(\geq 7.0\%\) or random blood glucose levels \(\geq 200.0\, \text{mg/100 mL}\). The definition of *probable* diabetes is: 1) History of diabetes mellitus or treatment of diabetes, and 2) Hemoglobin A1c levels \(\geq 7.0\%\) or random blood glucose levels \(\geq 200.0\, \text{mg/100 mL}\).

Diabetic retinopathy, as mentioned above, usually occurs only in those with *definite* diabetes mellitus. Therefore, only participants with definite diabetes were included in the at-risk cohort. Moreover, only a select number of participants who were classified as definite diabetes had gradable photographs in at least one eye.

Persons with no reported history or treatment of diabetes (failed to meet criterion #1 above), but had a clinical definition of diabetes (met criterion #2 above) were assigned a duration of diabetes value of < 1 year (new case). Therefore, new cases (< 1 year) of diabetes were classified into two groups: 1) individuals with no history or treatment of diabetes but have clinical signs of diabetes, or 2) individuals that have history and treatment of diabetes but were diagnosed less than a year ago by a physician.

\(^3\) Random blood glucose refers to the glucose levels in the blood when measured at any time of the day. This is in contrast to the more desirable measure of fasting blood glucose, which is obtained when one fasts for at least 12 hours. Unfortunately, because of the logistics in study design, it was difficult to obtain fasting blood glucose.
Diagnosing diabetic retinopathy

Per-person definition

For analyses of data on diabetic retinopathy, DR was defined on a “per-person” basis as opposed to a “per-eye” basis. “Per-person” retinopathy occurs when the person has retinopathy in at least one eye. “Per-eye” retinopathy occurs when the person has retinopathy in the specific eye. Therefore, according to the “per-person” definition states of retinopathy, if at least one eye has DR, then the individual is classified as having DR. On the other hand, if both eyes are free of DR, the individual is considered free of DR.

Stages and classifying disease

The grading and classification scheme for diabetic retinopathy is complicated since there are many stages of disease severity. There are two main types of diabetic retinopathy: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). The first signs of diabetic retinopathy are microaneurysms, or small outpouchings from retinal capillaries, and intraretinal hemorrhages (26). These signs are present in nearly all individuals having diabetes more than 20 years (27, 28). As the disease progresses to more severe stages (proliferative diabetic retinopathy), more intraretinal hemorrhages are present.

Grading of photographs for diagnosing diabetic retinopathy

The method used in diagnosing diabetic retinopathy with fundus photography is the Airlie House Classification system (87). This system has been modified over the years.

The Airlie House system was first used by those involved with the Early Treatment Diabetic Retinopathy Study (ETDRS) (87). It has been modified several times
(88-90) and these modified standards were used for some of the early studies on diabetic retinopathy, such as the Diabetes Control and Complications Trial (DCCT) (47).

The staff for the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) developed an alternative method that was faster, relatively inexpensive, and standardized (46). This version was modified once again from the methods used earlier in the ETDRS study. Klein and colleagues examined fundus photographs and graded seven stereoscopic standard fields (46). A level of severity was assigned to each eye according to the largest degree of retinopathy present in the seven fields. Klein and colleagues compared their results to the results obtained using ETDRS modified Airlie House method and came up with similar results (91).

LALES investigators worked in collaboration with the investigators at WESDR and employed methods similar to that of WESDR for grading fundus photographs taken during the clinical examination. WESDR investigators were responsible for grading the fundus photographs and diagnosing retinopathy in all of the LALES subjects.

According to the standards developed by WESDR, a person can be classified as either having (in order of increasing severity):

1. No diabetic retinopathy
2. Mild non-proliferative diabetic retinopathy (Mild NPDR)
3. Moderate non-proliferative diabetic retinopathy (Moderate NPDR)
4. Severe non-proliferative diabetic retinopathy (Severe NPDR)
5. Proliferative diabetic retinopathy (PDR)
6. Proliferative diabetic retinopathy, with high risk characteristics (PDR, with HRC)
21-levels of diabetic retinopathy

There are 21 possible levels of diabetic retinopathy, and the levels range from 10-85. Graders of the fundus photographs examine both right eye and left eye and assign a diabetic retinopathy level to each eye. A participant's worse eye is determined by whichever eye (right or left) has a higher diabetic retinopathy level. A detailed description of the 21-levels of diabetic retinopathy can be in Table 4.1.

<table>
<thead>
<tr>
<th>Retinopathy level</th>
<th>Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Diabetic retinopathy absent</td>
</tr>
<tr>
<td>12</td>
<td>Non-diabetic retinopathy</td>
</tr>
<tr>
<td>13</td>
<td>Questionable retinopathy</td>
</tr>
<tr>
<td>14</td>
<td>Hard exudates, soft exudates, or intraretinal microvascular abnormalities (IRMA) without microaneurysms (MAs)</td>
</tr>
<tr>
<td>15</td>
<td>Retinal hemorrhages (H) only without MAs</td>
</tr>
<tr>
<td>20</td>
<td>MAs only</td>
</tr>
<tr>
<td>31</td>
<td>Mild non-proliferative diabetic retinopathy (NPDR)</td>
</tr>
<tr>
<td>37</td>
<td>Mild/moderate NPDR</td>
</tr>
<tr>
<td>43</td>
<td>Moderate NPDR</td>
</tr>
<tr>
<td>47</td>
<td>Moderately severe NPDR</td>
</tr>
<tr>
<td>53</td>
<td>Severe NPDR</td>
</tr>
<tr>
<td>60</td>
<td>Fibrous proliferations only</td>
</tr>
<tr>
<td>61</td>
<td>Same rules as level 10-15 with scatter photocoagulation treatment present</td>
</tr>
<tr>
<td>62</td>
<td>Same rules as level 20 with scatter Rx present</td>
</tr>
<tr>
<td>63</td>
<td>Same rules as level 31 or 37, with scatter photocoagulation treatment present</td>
</tr>
<tr>
<td>64</td>
<td>Same rules as level 43, 47 or 53 with scatter photocoagulation treatment present</td>
</tr>
<tr>
<td>65</td>
<td>Mild/Moderate proliferative diabetic retinopathy (PDR)</td>
</tr>
<tr>
<td>71</td>
<td>Diabetic Retinopathy Study high-risk characteristics (DRS-HRC)</td>
</tr>
<tr>
<td>75</td>
<td>Severe DRS-HRC</td>
</tr>
<tr>
<td>81</td>
<td>Advanced PDR</td>
</tr>
<tr>
<td>85</td>
<td>End-stage PDR</td>
</tr>
</tbody>
</table>

Table 4.1: 21-levels of DR and associated lesions classified by the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scheme
15-steps of diabetic retinopathy

When Klein et al. graded their own photographs for their study, they utilized a 15-step scoring system (36-38). The 15-step scale is broken down by diabetic retinopathy level, ranging from level 10 as having no diabetic retinopathy, to level 60, characterizing the most severe case, proliferative diabetic retinopathy (PDR).

The presence of retinopathy in an individual as well as the severity (mild, moderate, severe) of retinopathy is derived from the 15-step scale. This is a concatenated scale, meaning that the diabetic retinopathy level for the “worse eye” (defined above) is combined with the diabetic retinopathy level for the “better eye” to obtain a “per-person” diagnosis of retinopathy. When researchers in ocular epidemiology use the word “concatenate,” they mean that both the better eye and the worse eye are combined and a “per-person” diagnosis is made. A detailed description the concatenated 15-steps can be found in Table 4.2.
<table>
<thead>
<tr>
<th>Step</th>
<th>Concatenated scale</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10/10</td>
<td>No retinopathy</td>
</tr>
<tr>
<td>2</td>
<td>20/&lt;20</td>
<td>Minimal retinopathy</td>
</tr>
<tr>
<td>3</td>
<td>20/20</td>
<td>Minimal retinopathy</td>
</tr>
<tr>
<td>4</td>
<td>31/&lt;31</td>
<td>Mild NPDR</td>
</tr>
<tr>
<td>5</td>
<td>31/31</td>
<td>Mild NPDR</td>
</tr>
<tr>
<td>6</td>
<td>37/&lt;37</td>
<td>Mild NPDR</td>
</tr>
<tr>
<td>7</td>
<td>37/37</td>
<td>Mild NPDR</td>
</tr>
<tr>
<td>8</td>
<td>43/&lt;43</td>
<td>Moderate NPDR</td>
</tr>
<tr>
<td>9</td>
<td>43/43</td>
<td>Moderate NPDR</td>
</tr>
<tr>
<td>10</td>
<td>47/&lt;47</td>
<td>Severe NPDR</td>
</tr>
<tr>
<td>11</td>
<td>47/47</td>
<td>Severe NPDR</td>
</tr>
<tr>
<td>12</td>
<td>53/&lt;53</td>
<td>Severe NPDR</td>
</tr>
<tr>
<td>13</td>
<td>53/53</td>
<td>Severe NPDR</td>
</tr>
<tr>
<td>14</td>
<td>60+/&lt;60</td>
<td>Any PDR</td>
</tr>
<tr>
<td>15</td>
<td>60+/60+</td>
<td>Any PDR</td>
</tr>
</tbody>
</table>

Table 4.2: 15-step concatenated scale for assessing incidence of diabetic retinopathy in the Los Angeles Latino Eye Study

The “/” character above separates the level in worse eye from the level in better eye. For example, a person with a concatenated score of 47/<47 means that his worse eye is at level 47 and his better eye is less than level 47.

15-step classification and its relationship to the 21-levels

Crucial to the understanding of the two classification systems is that the 15-steps results in a “per-person” diagnosis whereas the 21-levels results in a “per-eye” diagnosis.

To make the grading of LALES comparable to WESDR, LALES collapsed those with diabetic retinopathy levels 10, 12, and 13 into level 10 and those with levels 14, 15, 16 into level 20. Additionally, any levels greater than 60 (61-65, 71, 75, 81, 85) were collapsed into 60. This was done so the 15-step grading system of LALES is the same as the one used in WESDR.
The reason why all those who were worse than level 60 (PDR) were collapsed into level 60 is because individuals with that level of severity are in an entirely different situation than those with no PDR. Many individuals who have PDR choose to have panretinal photocoagulation and so the disease rates in this group are largely influenced by surgical intervention (36). Therefore, those with PDR vary from those with NPDR because patients with PDR can improve through surgical intervention.

Table 4.3 describes how the 21-levels of DR and the 15-step concatenated scale interrelate to categorize an individual into one of six possible categories of retinopathy listed above (No DR, Mild NPDR, Moderate NPDR, Severe NPDR, PDR, and PDR with HRC).

<table>
<thead>
<tr>
<th>Disease classification</th>
<th>“Per-eye”</th>
<th>“Per-person”</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21-levels* (10-85)</td>
<td>15-steps (1-15)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respondent does not have retinopathy</th>
<th>10, 12, 13</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respondent has retinopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal Retinopathy</td>
<td>14, 15, 20</td>
<td>2-3</td>
</tr>
<tr>
<td>Mild NPDR</td>
<td>31, 37</td>
<td>4-7</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>43</td>
<td>8-9</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>47, 53</td>
<td>10-13</td>
</tr>
<tr>
<td>PDR</td>
<td>60, 61, 62, 63, 64, 65, 71, 75, 81, 85</td>
<td>14-15</td>
</tr>
</tbody>
</table>

*Level in the worse eye

Table 4.3: 21-levels of diabetic retinopathy translated into the concatenated 15-steps
Role of medical practitioners in diagnosing disease

There were two specialists within the WESDR study who were responsible for grading all the LALES fundus photographs. Two graders were used to minimize measurement error. Furthermore, to ensure inter-rater reliability, the two graders had to agree on a diagnosis, or else a third grader was required to adjudicate. A flow-chart describing what happens at each stage of the process to diagnose diabetic retinopathy can be found in Appendix A.

The graders made their diagnoses independently of other graders. This was to minimize bias that could result by reviewers being influenced by previous diagnoses. The results of fundus photo reviews were entered into a database and cleaned, and the data were sent from the University of Wisconsin to the University of Southern California, where the data were used for analyses on diabetic retinopathy.

Protocol for missing/ungradable data

Situations were encountered where a participant’s fundus photographs could not be graded for one or both eyes. In these cases, the photographs were entered as being ungradable. Ungradable photos meant that a decision of whether a person had diabetic retinopathy could not be made.

The individual cannot be considered at-risk for retinopathy if both eyes had missing data or ungradable photos. However, if data for the left eye was missing/ungradable and data for the right eye was present for both waves, then “per-person” retinopathy status can be assessed. Thus, data needed to be available for the same eye at both waves. Table 4.4 below shows the relationship between missing and available data for how “per-person” outcome was assessed for each scenario.
### Table 4.4: Treatment of missing and/or ungradable data

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Baseline Left</th>
<th>Baseline Right</th>
<th>Follow-up Left</th>
<th>Follow-up Right</th>
<th>Disease outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Missing</td>
<td>Disease</td>
<td>Disease</td>
<td>Missing</td>
<td>Unknown</td>
</tr>
<tr>
<td>2</td>
<td>No disease</td>
<td>Ungradable</td>
<td>Disease</td>
<td>Ungradable</td>
<td>Disease</td>
</tr>
<tr>
<td>3</td>
<td>Missing</td>
<td>Ungradable</td>
<td>Disease</td>
<td>Disease</td>
<td>Unknown</td>
</tr>
<tr>
<td>4</td>
<td>No Disease</td>
<td>No Disease</td>
<td>Missing</td>
<td>Missing</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**Defining incidence of diabetic retinopathy**

Both baseline and follow-up data were merged to calculate cumulative incidence and to model risk factors for incidence of diabetic retinopathy. As a result, only participants who completed both waves were included in the analytical cohort.

Those included in the at-risk cohort for incidence of retinopathy included those who 1) had no retinopathy disease at baseline, and 2) had definite diabetes at baseline. Therefore, the number at-risk, or the denominator of the incidence calculation, reflected the number of people in LALES without retinopathy at baseline. If data are available for only one eye for both waves, then two criteria had to be met in order for the person to be included in the at-risk cohort. One, data had to be available in the same eye (right or left) at both baseline and follow-up, and two, that eye must have been disease-free at baseline.

A participant was considered at-risk for *any* diabetic retinopathy if they had a concatenated score of 10/10 (step 1) at baseline. For incidence to occur, the respondent needed to move from 10/10 at baseline to 20/≤20 (step 2) or higher at follow-up.

Incidence of *any* diabetic retinopathy was inclusive of all NPDR and PDR incident cases. This is the classic definition of incidence used by WESDR (14).

**Development of diabetic retinopathy**
Diabetic retinopathy has a unique course of disease development. There are some exceptions (92), but in general, one must have diabetes in order to be at-risk for diabetic retinopathy. Therefore, the diabetes first needs to develop in order for the person to be at-risk for retinopathy.

Information on duration of Type 1 or Type 2 diabetes was collected during LALES baseline examination on each participant with definite diabetes mellitus. The amount of time the subject was considered at-risk was also known by when onset of diabetes occurred.

Four-year follow-up data provided information on those who developed disease within the four years. Although when exactly disease occurred in this four-year time span is unclear, strict and consistent grading protocols at both waves of data collection can conclude that disease occurred sometime between baseline and follow-up examination. A figure depicting the course of diabetes and subsequent development of retinopathy is shown in Appendix B.

**Statistical methods**

**Participants versus nonparticipants**

To ascertain the effect of loss to follow-up bias resulting from participants dropping out at follow-up, a comparison of participants versus nonparticipants was conducted. Participants included those who completed a clinical exam in both waves. Nonparticipants include those who:

1. Completed a clinical exam at baseline but no clinical exam at follow-up and
2. Refused exam or could not be located.
Persons classified as nonparticipants did not include those who have died in the time between both waves of data collection, since death is an event that cannot be controlled and thus its influence over whether the participant would have remained in the study cannot be assessed.

Student t-test for independent samples was used to determine differences between participants and nonparticipants for continuous variables and the chi-square test was used to detect differences for categorical variables.

**Incidence calculations**

Four-year cumulative incidence was calculated as a proportion of the total number of incident cases seen at follow-up divided by the number at-risk for disease. These proportions were reported as percentages. Percentages were stratified by age (40-49, 50-59, 60-69, 70-79, 80+) and duration of diabetes (<1 year, 1-4 years, 5-9 years, 10-14 years, 15+ years). Test for trend analysis was performed to detect differences in incidence across strata. Both age and duration were defined at baseline examination to make it consistent with other studies, who also stratified by baseline measures (14, 39, 56, 71). To be considered at-risk for disease at follow-up, patients needed to be 1) free of retinopathy at baseline and 2) classified as diabetic at baseline.

Incidence estimates were annualized to make them comparable with other studies. Since different studies had various follow-up times, taking the cumulative incidence percentage divided by the number of follow-up years annualized the incidence estimate, making comparisons with other studies valid and meaningful. This assumed that the incidence estimates remain constant each year, but because data from other studies were
not readily accessible, annualized incidence estimates were calculated in this simplified manner.

**Age of onset of diabetes**

Additional analyses were conducted to determine if age of onset of diabetes could be used to determine development of retinopathy. In other words, are those that were diagnosed with diabetes at a younger age at higher or lower risk to develop retinopathy than those diagnosed with diabetes at an older age, even after controlling for duration of diabetes?

For example, take person A, who was diagnosed at age 30 with diabetes and person B, who was diagnosed at age 70 with diabetes. Given that person A is now 40, person B is now 80, and they both have had diabetes for 10 years, is person A at higher or lower risk for developing retinopathy than person B?

Age at diagnosis of diabetes was calculated with the following formula:

Age at dx = Age at baseline exam (in years) – Duration of diabetes (in years)

**Analyses of risk factors and barriers to care**

**Change in exposure status**

Certain types of risk factors, such as glycosylated hemoglobin, have the potential to change over a four-year period. In these scenarios, taking the difference of the follow-up measure from the baseline measure created a change variable. For variables with a small range of values, ratios of the follow-up to the baseline measure were calculated. For variables with a wide range of values, taking the absolute difference of the follow-up measure from the baseline measure resulted in the change variable. Change variables, along with its baseline measure, were included in the regression models.
Descriptive statistics

Simple descriptive statistics were calculated to assess differences among the various exposure variables between cases of DR and controls. This was done to estimate the exposure percentages for categorical variables and to calculate the mean and standard error for continuous variables for both cases and controls.

Comparisons between cases and controls for each exposure variable were done using t-tests (continuous variables) and chi-square tests (categorical variables). Specific attention was placed on whether there was any sparse cell counts (less than 5) for any of the variables. Sparse cell counts could lead to an inflation of the regression coefficient and will threaten the validity of the results.

Crude risk ratio (RR) estimates were calculated for various categorical risk variables using the following formula:

\[
RR = \frac{a}{a + b} \times \frac{c}{c + d},
\]

where both \(a\) and \(c\) represent the number of cases in the exposed and unexposed group, respectively, and both \(b\) and \(d\) represent the number of controls in the exposed and unexposed group, respectively. Comparisons between risk ratios and odds ratios were done to determine the impact the rare disease assumption had on estimated odds ratios.

Predictive model

The interest for this analysis lies in investigating many different predictors of disease and seeing which ones significantly predict outcome. Therefore, the model building process was approached using a predictive, or hypothesis-generating method, where one does not have an \textit{a priori} hypothesis as to which variables are the best
predictors. In a predictive model, researchers are interested in all the predictors and do not place more or less weight on one particular variable.

**Regression analysis**

Logistic regression analysis was performed for both analysis of biologic risk factors and analysis of barriers. Its use in this study is appropriate since the outcome of interest is dichotomous (yes/no for disease) and there were only two waves of cross-sectional data collection. Use of longitudinal methods, such as Cox or Poisson regression, was considered and then discarded for a couple reasons: 1) at least three waves of data collection are usually required to use these longitudinal methods, and 2) time-to-event (Cox) or duration of exposure (Poisson) needs to be known (93). Time-to-event for everyone in this study was four years, since it was not known at which point within the four-year time span they developed DR, therefore Cox regression was not a logical choice. Information on duration of exposure was missing for many of the independent predictors, so Poisson regression was also not feasible.

Logistic regression uses the logit transformation to make the equation resemble the one used for linear regression. The logit-transformed equation has one main advantage. The transformation makes the equation linear, which in turn makes the coefficients more interpretable. The logit-transformed equation is shown below:

\[
g(x) = \ln \left( \frac{\pi(x)}{1 - \pi(x)} \right),
\]

where \(\pi(x)\) represents the probability of an individual that has the value of \(x\) to develop the outcome (94).
In logistic regression, one of the most important assumptions is whether the continuous variable is linear in the logit. Variables such as body mass index (BMI), age, blood pressure, etc. that were continuous in nature were individually examined to see if continuity in the logit existed. The most common method to determine linearity in the logit uses fractional polynomials. Fractional polynomials tests each exposure variable to determine what order the exposure variable should appear in the model. If the first order model (the linear model) proved to be the best, then the covariate was entered into the logistic model as continuous. Another method used LOWESS (linearly weighted scatterplot smoothing) plots of the continuous variable versus the logit to see if the relationship appeared linear. Linearity in the logit was assessed for all the continuous variables on the univariate level and then once again for the continuous variables that were included in the final model.

Another important step before conducting regression analysis is to see whether each categorical variable has enough observations across all its values. One needs to be mindful of small cell counts because including these variables in a regression equation can inflate the estimated beta coefficient.

After assessing each variable and deciding how each variable would appear in the model, it was then time to begin building many different univariate models. A variable qualified as being significant if the univariate model produces a p-value of less than 0.20. Normally, the convention is to consider significance at the 0.05 level. However, 0.20 was chosen to be conservative. It is not advisable to exclude a variable at the very first step of the model building process just because of a p-value, especially if in reality that variable is an important predictor of the outcome.
The variables that indicate change in exposure status (measuring change from baseline to follow-up) were analyzed at the univariate level by including both the baseline variable and the change variable in the model.

The next step of the model building process used a **backwards selection** approach. This involved taking all the variables that had p-values less than 0.20 and including them all in a multivariable model. All variables that were not significant at the 0.05 significance level in the multivariable models were excluded from the models.

Use of backwards selection in building the multivariable model involved several steps. Exclusion of the single variable with highest p-value was done at each step. Also at each step, after a variable was excluded from the model, the model was re-run using all remaining variables. This process was repeated until all variables in the model met the criteria for the 0.05 significance level.

After models were constructed and all covariates had p-values of less than 0.05, every variable that was excluded in the univariate step was once again added one by one into the model. This was done for couple of reasons. First, it verifies that no variables originally excluded would be significant in the multivariable model. Second, it checks for confounders.

Confounders were detected by examining their impact on the beta coefficients in the final regression model. In our approach, if removal of a confounder from the model changed the beta coefficient of the exposure variable by more than 15%, then this variable was considered a confounder.

Presence of effect modifiers was detected using logistic methods. A variable was usually considered an effect modifier if the main effects and its interaction variable were
significant in the model. Effect modifiers were centered to remove the possibility of collinearity between the interaction term and its main effects. Biologically plausible interaction variables were created. Also, an interaction term between barriers to care and biological predictors of disease was created and included in the final model. This additional analysis was done to examine how the combined effects of both biological predictors of disease and barriers to care increase risk of retinopathy.

The likelihood ratio test determines if inclusion or exclusion of variables significantly improves the model. The test statistic resulting from the likelihood ratio test is referred to as deviance. Deviance follows a chi-square distribution and is calculated by comparing the log-likelihood values of the reduced versus full model. The formula for deviance is shown below (94):

\[
\text{Deviance} = -2 \ln (\text{likelihood ratio})
\]

If inclusion of a variable did not result in a significant deviance statistic, the variable should not be included in the final model. Simpler models should always be used whenever possible.

The number of outcomes available in the dataset limited the creation of complex multivariable models using logistic regression. The “rule of ten” states that for every variable included in the multivariable model, there must be at least ten cases of retinopathy. Analyses of multiple exposures, therefore, cannot be conducted with rare diseases since the number of outcomes in the study will usually be too small.

Collinearity in the regression model was ascertained by using the \textit{vif} command in STATA. This command gives a value corresponding to the tolerance of the variables in the model. If the tolerance is greater than 100, it can be concluded that collinearity may
exist. Collinearity results in the inclusion of a variable into the model only because it was highly correlated with another significant predictor.

The goal of logistic regression is to produce valid odds ratios estimates so conclusions can be made on how each variable contributes to the odds of getting disease. Odds ratios obtained from a case control study provide a good estimate of the relative risk obtained from a cohort study if disease is rare. Odds ratios for categorical variables are easier to interpret than odds ratios for continuous variables. However, inclusion of categorical variables decreases the power since additional degrees of freedom are added to the model.

The odds ratio is calculated by taking the exponential of the logit difference. The formula is described below:

\[ OR = e^{g(x+1) - g(x)} = e^\beta, \]

where \( g(x+1) \) refers to the change in logit for a one unit change in \( x \) and \( \beta \) refers to the regression coefficient of that variable (94). Using the formula above calculated an adjusted odds ratio (adjusted for all other predictors). Simple calculation of adjusted odds ratios makes logistic regression a powerful tool in epidemiology.

Calculating odds ratios for dichotomous variables can be done using the formula below:

\[ \text{Odds Ratio} = e^\beta, \]

where \( \beta \) refers to the regression coefficient of that particular variable (94). For example, if the coefficient \( \beta \) is equal to 1.5 for someone who smokes versus someone who does not smoke, then the odds of disease for someone who smokes are \( e^{1.5} \approx 4.48 \) times higher than the odds of disease for someone who does not smoke. The referent categories were
the lowest numbered category and comparisons of odds ratios were made in relation to
the referent category.

On the other hand, interpreting odds ratios for continuous variables are slightly
more difficult. The odds ratio was calculated using this formula:

\[
\text{Odds Ratio} = e^{c\beta},
\]

where \( c \) corresponds to the amount of change in units in the variable of interest and \( \beta \)
corresponds to the regression parameter. For example, if \( \beta = 0.15 \) for someone who is 40
years of age (the youngest age for the entire sample), and assuming age is continuous,
then for someone who is 50 years of age, the odds ratio would be

\[
e^{(10*0.15)} = 1.16
\]

To determine how well the model predicts the actual data, the Hosmer-Lemeshow
goodness of fit statistic was performed (94). This test follows a chi-square distribution.
A p-value greater than 0.05 means one fails to reject the null hypothesis (\( H_0: \) The model
fits the data) and that the model has acceptable fit.

Accuracy of how well the model predicts retinopathy status was determined by
examining the area under the ROC curve. In general, a larger area under the curve means
better accuracy. The x-axis of the ROC plot represents 1-specificity (1 - proportion of
true negative) and the y-axis represents sensitivity (proportion of true positive). A large
area under the ROC curve (> 0.70) is preferred since it means the [1-specificity] value is
minimized across all values of sensitivity.

Sensitivity/specificity plots were created to visualize the relationship between
sensitivity and specificity. The sensitivity/specificity plots show, based on the final
logistic model, the optimal cut-point for sensitivity and specificity probabilities. This
was determined by determining where the two lines on the graph intersect. Sensitivity analysis was also conducted to determine how well the model performed if used for screening of diabetic retinopathy.

Diagnostic measures such as deviance, leverage, and residual values were calculated to detect outlying covariate patterns in the data. Of the three tests used in conducting diagnostics, residual and deviance are the most important. It is essential to locate covariate patterns that are outliers because covariate patterns are the unit of analysis in the log-likelihood calculation described in the equation above. Detection of outliers was done using the individual scatterplots of predicted probability by both deviance and residual values.

If deletion of an outlying covariate pattern changed the estimated regression coefficient by a significant percentage (> 25%), then deletion of that covariate pattern was considered. However, with sample size limitations, deletion of multiple observations could actually harm the analysis since it could potentially reduce the number of outcomes.

All statistical analysis were conducted using both STATA 9.0 (95) and SAS (Statistical Application Software) version 9 (96).

LOWESS plot

LOWESS plots were created to describe the relationship between specific continuous variables and predicted probabilities for incidence of retinopathy. Predicted probabilities of diabetic retinopathy were calculated from the regression model. The graph showed the relationship between a predictor and the probability of retinopathy, after adjusting for other influential covariates. Graphs were created using STATA (95).
**Conceptual model**

The conceptual model derived by LALES staff to explain the interrelationships of various risk factors in the development of diabetic retinopathy can be found in Appendix C. These risk factors include barriers/access to care variables, biologic variables, sociodemographic variables and psychosocial variables. This dissertation focused on the 1) biologic/sociodemographic variables and 2) access to care variables that were shown in this conceptual model.

**Description of variables**

**Variables for biologic risk factors**

Many biologic risk factors for diabetic retinopathy were measured during the clinic examination. Both hemoglobin A1c (a.k.a. glycosylated hemoglobin) and random blood glucose levels were measured from lab results. Table 4.5 describes the characteristics of each variable.
This measure was obtained from the clinical exam by a trained ophthalmologist. Information on the other variables is collected through self-report from the home questionnaire.

* The change variables were derived by calculating the ratio of the follow-up to the baseline measure (for hemoglobin A1c) or by calculating the difference between baseline and follow-up (for all other remaining variables)

*These cut points for waist-hip ratio were used in the LALES paper on biologic risk factors for prevalent diabetic retinopathy (11)

Table 4.5: Description of variables used in analyses of biologic risk factors for development of DR

<table>
<thead>
<tr>
<th>Variable name</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Referent group</th>
<th>Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>X</td>
<td></td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>Gender</td>
<td>X</td>
<td>Female</td>
<td></td>
<td>0 = Female 1 = Male</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>X</td>
<td></td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>X</td>
<td></td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>ΔBody mass index (BMI)*</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>Waist/Hip Ratio*</td>
<td>X</td>
<td>&gt; 0.95 (Male)</td>
<td></td>
<td>0 = No 1 = Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 0.8 (Female)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country of birth</td>
<td>X</td>
<td>Other country</td>
<td></td>
<td>0 = Other 1 = U.S.</td>
</tr>
<tr>
<td>Refractive error*</td>
<td>X</td>
<td></td>
<td></td>
<td>-0.5 - +0.5 1 = +0.5 - +3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = &gt; +3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin for diabetes</td>
<td>X</td>
<td>No insulin</td>
<td></td>
<td>0 = No 1 = Yes</td>
</tr>
<tr>
<td>Systolic blood pressure (SBP)*</td>
<td>X</td>
<td></td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>Δ SBP*</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>Diastolic Blood pressure (DBP)*</td>
<td>X</td>
<td></td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>Δ DBP*</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>Hemoglobin A1c (HbA1c)*</td>
<td>X</td>
<td></td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>Δ HbA1c*</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>Random blood glucose*</td>
<td>X</td>
<td></td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>Δ Random blood glucose*</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Continuous</td>
</tr>
</tbody>
</table>
The change variables, such as change in random blood glucose, were derived by taking the absolute difference between the follow-up measure and the baseline measure. Ratios were calculated for hemoglobin A1c since there were a small range of A1c values (4.7-14.0). Change values were not calculated for age and duration of diabetes variables since other studies used data collected at baseline for these two variables (38). Gender and country of birth are not time-varying covariates so no change scores were derived from these measures.
Barriers to care

Table 4.6: Description of variables used in analyses of barriers to care for development of DR

<table>
<thead>
<tr>
<th>Variable name</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Referent group</th>
<th>Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>X</td>
<td></td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>Gender</td>
<td>X</td>
<td>Female</td>
<td>0 = Female</td>
<td>1 = Male</td>
</tr>
<tr>
<td>Acculturation</td>
<td></td>
<td></td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>Known history of diabetes</td>
<td>X</td>
<td>No prior</td>
<td>0 = No</td>
<td>1 = Yes</td>
</tr>
<tr>
<td>Income</td>
<td>X</td>
<td>&lt; $20,000/yr</td>
<td>0 = &lt; $20,000/yr</td>
<td>1 = ≥ $20,000/yr</td>
</tr>
<tr>
<td>Country of birth</td>
<td>X</td>
<td>Other</td>
<td>0 = Other country</td>
<td>1 = United States</td>
</tr>
<tr>
<td>Education level</td>
<td>X</td>
<td>Spanish</td>
<td>1 = Spanish</td>
<td>2 = English</td>
</tr>
<tr>
<td>Time last seen a doctor</td>
<td>X</td>
<td>Continuous</td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>Medical Insurance status</td>
<td>X</td>
<td>No insurance</td>
<td>0 = No insurance</td>
<td>1 = Insurance</td>
</tr>
<tr>
<td>Vision insurance status</td>
<td>X</td>
<td>No insurance</td>
<td>0 = No insurance</td>
<td>1 = Insurance</td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td>X</td>
<td></td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>Δ Number of comorbidities</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>Has primary care physician or primary clinic</td>
<td>X</td>
<td>Has no doctor/clinic</td>
<td>0 = No</td>
<td>1 = Yes</td>
</tr>
<tr>
<td>Physical exam in past 12 months</td>
<td>X</td>
<td>No exam</td>
<td>0 = No exam</td>
<td>1 = Exam</td>
</tr>
<tr>
<td>Eye exam in past 12 months</td>
<td>X</td>
<td>No exam</td>
<td>0 = No exam</td>
<td>1 = Exam</td>
</tr>
</tbody>
</table>

*The change variables were derived by calculating the difference between the baseline and follow-up measures
CHAPTER 5

CALCULATION OF SAMPLE SIZE AND PRECISION ESTIMATES

Sample size calculation

The LALES incidence study is a 4-year follow-up study with a population-based sample of Latinos. This section describes the sample sizes required to perform risk factor analyses for incidence of retinopathy. The first step of the sample size analysis is to estimate the expected number of participants who are at-risk for incident eye disease. At baseline, the potential sample size (assuming 100% response rate) was n=7789. The actual sample size of LALES at baseline was n=6357, resulting in a 82% response out of an original possible cohort of 7789. A pilot study showed that over 80% of participants would be willing to return for their follow-up examination.

To estimate the number of incidence cases for diabetic retinopathy, the number of cases from baseline, 1217, along with the prevalence of DR at baseline, 46.9% (n=571) were considered.

A realistic expectation for total number of participants returning for follow-up is n=4768, which is a 75% response of the original 6357 cohort. Similarly, assuming a 75% response in the diabetic population, n=913 have diabetes at follow-up. Of these 913 participants, 484 are at-risk for DR (assuming 75% of the 571 DR cases from baseline return, n=429; 913 minus 429 is 484).
The number of expected incident cases of retinopathy at follow-up, using 4-year cumulative incidence estimates from Barbados Eye Study (30.1%) (39), is n=146. Table 5.1 shows the expected number of cases.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Type</th>
<th># at-risk</th>
<th>Incidence</th>
<th># of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Any DR (NPDR+PDR)</td>
<td>484</td>
<td>30.1%</td>
<td>146</td>
</tr>
</tbody>
</table>

Table 5.1: Expected number of incident cases of DR

**Precision estimates for age-specific calculations**

After calculating the expected number of cases for both incidence, precision estimates were made for various sample sizes to show that even with small incidence estimates, the sample will still be large enough to calculate precise estimates of incidence. Table 5.2 below shows the expected sample size of follow-up for the entire LALES cohort along with expected number of individuals for each age category.

The estimates, even for a cumulative incidence of 0.5%, are still quite precise given that the overall study sample is large. Table 5.2 confirms that age-specific incidence estimates can be calculated with good precision.
<table>
<thead>
<tr>
<th>4-year incidence (%)</th>
<th>N = 4,768 (total)</th>
<th>N = 1,838 (40-49)</th>
<th>N = 1,436 (50–59)</th>
<th>N = 921 (60-69)</th>
<th>N = 573 (70+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>(0.3, 0.7)</td>
<td>(0.2, 0.8)</td>
<td>(0.1, 0.9)</td>
<td>(0.0,1.0)</td>
<td>(0.0, 1.1)</td>
</tr>
<tr>
<td>1</td>
<td>(0.7, 1.3)</td>
<td>(0.5, 1.5)</td>
<td>(0.5, 1.5)</td>
<td>(0.4, 1.6)</td>
<td>(0.2, 1.8)</td>
</tr>
<tr>
<td>2</td>
<td>(1.6, 2.4)</td>
<td>(1.4, 2.6)</td>
<td>(1.3, 2.7)</td>
<td>(1.1, 2.9)</td>
<td>(0.9, 3.1)</td>
</tr>
<tr>
<td>4</td>
<td>(3.4, 4.6)</td>
<td>(3.1, 4.9)</td>
<td>(3.0, 5.0)</td>
<td>(2.7, 5.3)</td>
<td>(2.4, 5.6)</td>
</tr>
<tr>
<td>8</td>
<td>(7.2, 8.8)</td>
<td>(6.8, 9.2)</td>
<td>(6.6, 9.4)</td>
<td>(6.2, 9.8)</td>
<td>(5.8, 10.2)</td>
</tr>
<tr>
<td>16</td>
<td>(15.0, 17.0)</td>
<td>(14.3, 17.7)</td>
<td>(14.1, 17.9)</td>
<td>(13.6, 18.4)</td>
<td>(13.0, 19.0)</td>
</tr>
<tr>
<td>20</td>
<td>(18.9, 21.1)</td>
<td>(18.2, 21.8)</td>
<td>(17.9, 22.1)</td>
<td>(17.4, 22.6)</td>
<td>(16.7, 23.3)</td>
</tr>
<tr>
<td>30</td>
<td>(28.7, 31.3)</td>
<td>(27.9, 32.1)</td>
<td>(27.6, 32.4)</td>
<td>(27.0, 33.0)</td>
<td>(26.2, 33.8)</td>
</tr>
<tr>
<td>40</td>
<td>(38.6, 41.4)</td>
<td>(37.8, 42.2)</td>
<td>(37.5, 42.5)</td>
<td>(36.8, 43.2)</td>
<td>(36.0, 44.0)</td>
</tr>
</tbody>
</table>

Table 5.2: Precision estimates for various sample sizes in the Los Angeles Latino Eye Study

**Detectable relative risks**

Calculation of minimum detectable relative risks was performed using the number of expected incident cases calculated above. The significance level (alpha) was set at 0.05, and the power (1 - beta) was set at 0.80. For purposes of calculating these sample sizes, a case-control design was assumed where the cases were defined as those with diabetic retinopathy and controls were those who were free of retinopathy.

The information needed to calculate minimum detectable relative risk is alpha, beta, estimated prevalence of risk factor in the general population (can be gathered from previous literature), and a desirable detectable difference between cases and controls. For example, if one would like to detect a risk difference of 0.5, then the minimum detectable relative risk required be 1.5, assuming that controls have a risk of 1.0 and cases have a risk of 1.5.

The formula used to calculate minimum detectable relative risk is:
\[
\ln HR = \frac{(Z_{\alpha} + Z_{\beta})}{\sum_{i=1}^{n} p_i(1 - p_i)D_i},
\]

where HR standards for hazard ratio, \(Z_{\alpha}\) is 1.96 (corresponding to alpha=0.05), \(Z_{\beta}\) is 0.84 (corresponding to beta=0.20), \(p_i\) is the proportion of those in stratum \(i\) exposed to the risk factor, and \(D_i\) stands for the number of cases in stratum \(i\). The sample was divided into age strata, and the denominator was summed over all strata.

The table below shows detectable relative risks given the expected number of cases calculated in Table 5.1. The top row represents a general prevalence of the given risk factor in the general population. The left column represents the number of outcomes expected.

<table>
<thead>
<tr>
<th>Expected number of cases</th>
<th>0.05</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum detectable relative risk</td>
<td>146</td>
<td>2.83</td>
<td>2.10</td>
<td>1.70</td>
<td>1.55</td>
<td>1.47</td>
<td>1.42</td>
<td>1.39</td>
</tr>
</tbody>
</table>

Controls are defined here as full cohort excluding cases.

\(^1\)Prevalence of exposure in the general population

Table 5.3: Detectable relative risks for an expected number of cases of DR and prevalence of a given risk factor using the remaining cohort as controls

The number of controls in each group varies depending on the number of people at-risk for disease, as described above in Table 5.3. This table describes what the minimum detectable difference is for cases and controls, given a specific exposure prevalence.
For example, assume the risk factor of interest is obesity and the outcome of interest is diabetic retinopathy. Also assume obesity has a prevalence among controls of 0.4. There are 146 expected incident cases of retinopathy at follow-up. Using Table 5.3, one can expect to detect a relative risk of 1.47. Assuming that those who are obese are at an 80% increased risk of developing diabetic retinopathy, their expected odds ratio is 1.80. Since this is above the 1.47 threshold for detection, a sample size of 146 will be sufficient for detecting this association.

Sample size calculations vary depending on how many disease outcomes one expects to have and what particular risk factor is of interest. In general, for rare diseases such as proliferative diabetic retinopathy, it will be difficult to detect an accurate association with the given risk factor unless if the association is very pronounced. This was the reason why *any* diabetic retinopathy (inclusive of both non-proliferative and proliferative diabetic retinopathy) was used to maximize the number of disease outcomes.
CHAPTER 6

RESULTS

Response “rate”

Out of 7,789 eligible participants at baseline, 82% (n=6,357) completed the clinical examination and thus were considered “complete” participants. Of those, 240 died during the period between baseline and follow-up. Of the remaining 6,117 living eligibles, 75.5% (n=4,616) returned to complete the 4-year follow-up examination.

Figure 6.1 shows the participant flowchart for ascertaining the at-risk cohort for incidence of diabetic retinopathy. This figure focused on only those with diabetes, since only those with diabetes were at-risk for retinopathy. There were only 893 definite diabetes patients that returned for follow-up exam. The analytical cohort composed of 745 persons after calculating the number of participants who have gradable photos in the same eye (right and/or left) at both baseline and follow-up.
Figure 6.1. Participation flowchart for assessing 4-year incidence of DR in the Los Angeles Latino Eye Study.
Figure 6.1 continued

*Photographs were not taken due to participant refusal or poor dilation.

†Photographs were not gradable for DR due to media opacities, poor camera focus, or other conditions (e.g. diabetic macular edema).

Participants versus nonparticipants

893 participants with diabetes completed the clinical exam at both baseline and follow-up, and 186 participants with diabetes who completed baseline examination were unable to return for the follow-up exam for a reason other than death. The results of comparing participants to nonparticipants are summarized in Table 6.1.
Table 6.1: Comparison of participants to nonparticipants at the 4-year follow-up in the Los Angeles Latino Eye Study

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Participants* (N = 893)</th>
<th>Nonparticipants† (N = 186)</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female)</td>
<td>520 (58%)</td>
<td>105 (56%)</td>
<td>0.643</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (± SD)</td>
<td>57.4 (± 9.7)</td>
<td>56.0 (± 10.4)</td>
<td>0.514</td>
</tr>
<tr>
<td>40-49</td>
<td>193 (22%)</td>
<td>50 (27%)</td>
<td>0.349</td>
</tr>
<tr>
<td>50-59</td>
<td>319 (36%)</td>
<td>61 (33%)</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>253 (28%)</td>
<td>45 (24%)</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>112 (13%)</td>
<td>28 (15%)</td>
<td></td>
</tr>
<tr>
<td>80+</td>
<td>16 (2%)</td>
<td>2 (1%)</td>
<td></td>
</tr>
<tr>
<td>Country of birth (U.S.)</td>
<td>254 (28%)</td>
<td>54 (29%)</td>
<td>0.878</td>
</tr>
<tr>
<td>Acculturation (low</td>
<td>&lt;1.9</td>
<td>)</td>
<td>321 (36%)</td>
</tr>
<tr>
<td>Working status (employed)</td>
<td>337 (38%)</td>
<td>54 (29%)</td>
<td>0.024</td>
</tr>
<tr>
<td>Education level ≥ 12 years</td>
<td>277 (31%)</td>
<td>49 (26%)</td>
<td>0.203</td>
</tr>
<tr>
<td>Marital status (married)</td>
<td>615 (69%)</td>
<td>110 (59%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Income level &gt; $40,000</td>
<td>95 (11%)</td>
<td>16 (9%)</td>
<td>0.410</td>
</tr>
<tr>
<td>Health insurance</td>
<td>639 (72%)</td>
<td>107 (58%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 2 comorbidities§</td>
<td>661 (74%)</td>
<td>135 (73%)</td>
<td>0.667</td>
</tr>
<tr>
<td>Self-reported health</td>
<td>99 (11%)</td>
<td>17 (9%)</td>
<td>0.433</td>
</tr>
<tr>
<td>excellent/very good</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td>422 (47%)</td>
<td>82 (44%)</td>
<td>0.408</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>724 (82%)</td>
<td>148 (80%)</td>
<td>0.614</td>
</tr>
<tr>
<td>Self-reported vision</td>
<td>349 (39%)</td>
<td>50 (27%)</td>
<td>0.002</td>
</tr>
<tr>
<td>excellent/good</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-home binocular near vision better than 20/40</td>
<td>821 (92%)</td>
<td>159 (85%)</td>
<td>0.005</td>
</tr>
<tr>
<td>History of any ocular disease</td>
<td>225 (25%)</td>
<td>40 (22%)</td>
<td>0.284</td>
</tr>
<tr>
<td>History of cataract</td>
<td>144 (16%)</td>
<td>20 (11%)</td>
<td>0.063</td>
</tr>
<tr>
<td>History of glaucoma</td>
<td>40 (5%)</td>
<td>15 (8%)</td>
<td>0.044</td>
</tr>
<tr>
<td>History of macular degeneration</td>
<td>13 (1%)</td>
<td>5 (3%)</td>
<td>0.233</td>
</tr>
<tr>
<td>History of diabetic retinopathy</td>
<td>94 (11%)</td>
<td>18 (10%)</td>
<td>0.726</td>
</tr>
</tbody>
</table>
Table 6.1 continued

*All participants diagnosed with diabetes and completing the clinical examinations at follow-up.

†Nonparticipants of the follow-up examination who had participated in the baseline examination. Include persons who refused the follow-up examination.

‡P-value based on chi-square test for categorical variables, student’s t-test for continuous variables.

§Comorbidities refer to the summation of the following medical conditions: arthritis, diabetes, back pain, hypertension, deafness, asthma, angina, skin cancer, other cancers, heart disease, stroke, and heart failure.

Participants significantly differed from nonparticipants in employment status, marital status, health status, self-reported vision, in-home binocular vision better than 20/40, insurance status, and self-reported history of glaucoma. The largest difference was seen in health insurance status, where 72% of the participants reported having health insurance compared to 58% of the nonparticipants report having health insurance.

Number of incident cases

The 4-year cumulative incidence for diabetic retinopathy is shown in Table 6.2.
<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>4-year Cumulative Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N*</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>92</td>
</tr>
<tr>
<td>50-59</td>
<td>149</td>
</tr>
<tr>
<td>60-69</td>
<td>114</td>
</tr>
<tr>
<td>70-79</td>
<td>48</td>
</tr>
<tr>
<td>80+</td>
<td>9</td>
</tr>
<tr>
<td>Overall</td>
<td>412</td>
</tr>
</tbody>
</table>

| Duration of Diabetes (years) |    |    |            |
| New§                      | 143| 23 | 16.1 (10.2, 22.1) |
| 1-4                       | 125| 35 | 28.0 (20.1, 35.9) |
| 5-9                       | 67 | 21 | 31.3 (20.2, 42.5) |
| 10-14                     | 46 | 23 | 50.0 (35.6, 64.5) |
| ≥ 15                      | 31 | 13 | 41.9 (24.6, 59.3) |
| Overall                   | 412| 115| 27.9 (23.6, 32.2) |

N = number at-risk at baseline. n = number of DR cases. P = Test of trend. Incidence data presented as percent (95% confidence interval), estimated for persons with gradable fundus photographs at baseline and at follow-up, and having diagnosis of definite diabetes.

*At-risk cohort: Patient did not have evidence of any DR at baseline (severity level 10/10) and were at-risk of developing DR in one or both eyes at follow-up (severity level >20/≤ 20 or >20/>20). (Data presented include 66 persons with incidence in one eye and 49 persons with incidence in both eyes).

§Refers to persons who were newly diagnosed with diabetes at the time of baseline examination or who were diagnosed with diabetes less than one year prior to baseline examination.

Table 6.2: Estimated 4-year cumulative incidence of diabetic retinopathy stratified by age and duration of diabetes at baseline.
The overall 4-year cumulative incidence of diabetic retinopathy in the LALES population was found to be 27.9% (115/412). Incidence estimates ranged from 36.4% to 44.4% for those 40-49 years of age to those 80 or more years of age, respectively. Percentages ranged from to 16.1% for new cases of diabetes to 41.9% among those having diabetes 15 years or more. These numbers differ significantly across both age (test for trend, \( p = 0.036 \)) and diabetes duration strata (test for trend, \( p < 0.001 \)).

Despite the significant trend seen for both variables, they display different patterns across increasing age and duration groups. Cumulative incidence estimates are highest at the youngest and oldest age groups, suggesting a u-shaped curve. In contrast, duration of diabetes show increasing percentages across increasing duration subgroups, but dip slightly when duration is 15 years or more. These relationships are explained in more detail in the discussion section.

**Age of diabetes diagnosis and its relationship to development of retinopathy**

A comparison of what age subjects were diagnosed with diabetes and for how long they were diagnosed with diabetes before developing retinopathy is shown in Table 6.3.
As described in Table 6.3, the “age of onset”-specific incidence of retinopathy, while controlling for duration of diabetes, is higher in the younger age of onset group as compared to the older age of onset group. This suggests that those that are diagnosed with diabetes at a younger age are at higher risk than those that are diagnosed at an older age, even if these two groups have had diabetes for the same length of time.

### Biologic risk factors for incidence of DR

#### Assessing linearity in the logit

Continuous risk factors for diabetic retinopathy, such as age, duration of diabetes, diastolic and systolic blood pressure, hemoglobin A1c, and random blood glucose were checked for whether they appeared linear in the logit. Of those, *hemoglobin A1c, age, BMI, systolic blood pressure, diastolic blood pressure* and *random blood glucose* were all linear in the logit, so they remained as continuous variables in the regression analysis.
The variable that failed to satisfy the criterion for linearity was *duration of diabetes*. The values of this variable were collapsed into the following categories:

1 = New case (< 1 year)
2 = 1-4 years
3 = 5-9 years
4 = 10-14 years
5 = 15+ years

**Descriptive statistics**

Comparisons of cases of DR to controls across various biologic risk factors are found in Table 6.4.
## Categorical variables

<table>
<thead>
<tr>
<th>Variable name</th>
<th>Values</th>
<th>DR</th>
<th>Total§</th>
<th>CI</th>
<th>cRR</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist-Hip ratio</td>
<td>&gt; cut-off</td>
<td>74</td>
<td>289</td>
<td>24.6</td>
<td>1.0</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>≤ cut-off†</td>
<td>40</td>
<td>114</td>
<td>35.1</td>
<td>1.43</td>
<td></td>
</tr>
<tr>
<td>Birthplace</td>
<td>Other country</td>
<td>92</td>
<td>301</td>
<td>30.6</td>
<td>1.0</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>United States</td>
<td>23</td>
<td>110</td>
<td>20.9</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>66</td>
<td>254</td>
<td>26.0</td>
<td>1.0</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>49</td>
<td>158</td>
<td>31.0</td>
<td>1.19</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>No</td>
<td>79</td>
<td>241</td>
<td>32.8</td>
<td>1.0</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>15</td>
<td>40</td>
<td>37.5</td>
<td>1.14</td>
<td></td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>&lt;1 year</td>
<td>23</td>
<td>143</td>
<td>16.1</td>
<td>1.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>1-4 years</td>
<td>35</td>
<td>125</td>
<td>28.0</td>
<td>1.74</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-9 years</td>
<td>21</td>
<td>67</td>
<td>31.3</td>
<td>1.95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10-14 years</td>
<td>23</td>
<td>46</td>
<td>50.0</td>
<td>3.11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15+ years</td>
<td>13</td>
<td>31</td>
<td>41.9</td>
<td>2.61</td>
<td></td>
</tr>
<tr>
<td>Refractive error</td>
<td>-0.5 to +0.5</td>
<td>11</td>
<td>37</td>
<td>29.7</td>
<td>1.0</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>+0.5 to +3.0</td>
<td>59</td>
<td>231</td>
<td>25.5</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; +3.0</td>
<td>11</td>
<td>46</td>
<td>23.9</td>
<td>0.80</td>
<td></td>
</tr>
</tbody>
</table>

## Continuous variables

<table>
<thead>
<tr>
<th>Variable name</th>
<th>No DR Mean (SE)</th>
<th>DR Mean (SE)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58.4 (0.6)</td>
<td>55.8 (0.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>7.9 (0.1)</td>
<td>9.0 (0.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Random blood glucose</td>
<td>175.3 (5.0)</td>
<td>213.5 (8.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body mass index</td>
<td>33.1 (0.4)</td>
<td>32.5 (0.6)</td>
<td>0.38</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>76.3 (0.6)</td>
<td>76.4 (1.0)</td>
<td>0.44</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>128.0 (1.1)</td>
<td>126.5 (1.6)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

DR = Diabetic retinopathy. CI: Cumulative incidence estimate per 100 persons.  cRR = Crude risk ratio.

§Totals reported may be different for each variable because of missing data

*P-value based on chi-square test for categorical variables and student’s t-test for continuous variables

†Cut-off is 0.80 for females and 0.95 for males

Table 6.4: Descriptive statistics for biologic risk factors comparing cases of DR to controls
Table 6.4 shows that those who developed diabetic retinopathy differed significantly from those who did not develop retinopathy on levels of hemoglobin A1c, random blood glucose, waist-hip ratio, age, and duration of diabetes (p<0.05). There was a mild difference with country of birth (p=0.05). The numbers of cases of DR are sufficient across the different strata of each biologic risk factor.

Univariate results

Univariate results are presented in Table 6.5. Variables significant at the univariate level include duration of diabetes, Δ insulin, birthplace, waist-hip ratio, age, random blood glucose, Δ random blood glucose, hemoglobin A1c, and Δ hemoglobin A1c. The ratio measuring Δ hemoglobin A1c was collapsed into the following categories: 0 = ratio < 1, 1 = ratio ≥ 1, to make the odds ratio easily interpretable. Significance was assessed at the 0.20 significance level for inclusion of the variable into the multivariable analysis.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Values</th>
<th>Coefficient</th>
<th>P-value*</th>
<th>cOR (95% CI)</th>
<th>cRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diabetes</td>
<td>&lt; 1 year</td>
<td>-----</td>
<td>-----</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td></td>
<td>1-4 years</td>
<td>0.71</td>
<td>0.019</td>
<td>2.0 (1.2, 3.7)</td>
<td>1.74</td>
</tr>
<tr>
<td></td>
<td>5-9 years</td>
<td>0.87</td>
<td>0.013</td>
<td>2.4 (1.2, 4.7)</td>
<td>1.95</td>
</tr>
<tr>
<td></td>
<td>10-14 years</td>
<td>1.65</td>
<td>&lt;0.001</td>
<td>5.2 (2.5, 10.8)</td>
<td>3.11</td>
</tr>
<tr>
<td></td>
<td>15+ years</td>
<td>1.32</td>
<td>0.002</td>
<td>3.8 (1.6, 8.7)</td>
<td>2.61</td>
</tr>
<tr>
<td>Insulin</td>
<td>Yes</td>
<td>0.21</td>
<td>0.588</td>
<td>1.2 (0.6, 2.4)</td>
<td>1.14</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>0.24</td>
<td>0.269</td>
<td>1.3 (0.8, 2.0)</td>
<td>1.19</td>
</tr>
<tr>
<td>Birthplace</td>
<td>Other</td>
<td>-----</td>
<td>-----</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td></td>
<td>United States</td>
<td>-0.51</td>
<td>0.055</td>
<td>0.6 (0.4, 1.0)</td>
<td>0.68</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>≤ cut-off†</td>
<td>0.51</td>
<td>0.034</td>
<td>1.7 (1.0, 2.7)</td>
<td>1.43</td>
</tr>
<tr>
<td>Refractive error</td>
<td>&lt; +0.5</td>
<td>-----</td>
<td>-----</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td></td>
<td>+0.5 to +3.0</td>
<td>-0.21</td>
<td>0.591</td>
<td>0.8 (0.4, 1.7)</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>&gt; +3.0</td>
<td>-0.30</td>
<td>0.551</td>
<td>0.7 (0.3, 2.0)</td>
<td>0.80</td>
</tr>
<tr>
<td>Age</td>
<td>Continuous</td>
<td>-0.03</td>
<td>0.018</td>
<td>0.97*</td>
<td>-----</td>
</tr>
<tr>
<td>R. blood glucose</td>
<td>Continuous</td>
<td>0.005</td>
<td>&lt;0.001</td>
<td>1.00*</td>
<td>-----</td>
</tr>
<tr>
<td>Δ R. blood glucose++</td>
<td>Continuous</td>
<td>-0.004</td>
<td>0.003</td>
<td>1.00*</td>
<td>-----</td>
</tr>
<tr>
<td>Body mass index</td>
<td>Continuous</td>
<td>-0.02</td>
<td>0.375</td>
<td>0.98 (0.95, 1.02)</td>
<td>-----</td>
</tr>
<tr>
<td>Δ Body mass index++</td>
<td>Continuous</td>
<td>0.042</td>
<td>0.351</td>
<td>1.04 (0.95, 1.14)</td>
<td>-----</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>Continuous</td>
<td>-0.004</td>
<td>0.438</td>
<td>0.99 (0.98, 1.01)</td>
<td>-----</td>
</tr>
<tr>
<td>Δ Systolic BP++</td>
<td>Continuous</td>
<td>-0.004</td>
<td>0.619</td>
<td>0.99 (0.98, 1.01)</td>
<td>-----</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>Continuous</td>
<td>0.001</td>
<td>0.899</td>
<td>1.00 (0.98, 1.02)</td>
<td>-----</td>
</tr>
<tr>
<td>Δ Diastolic BP++</td>
<td>Continuous</td>
<td>0.005</td>
<td>0.629</td>
<td>1.00 (0.98, 1.03)</td>
<td>-----</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>Continuous</td>
<td>0.29</td>
<td>&lt;0.001</td>
<td>1.3 (1.2, 1.5)</td>
<td>-----</td>
</tr>
<tr>
<td>Δ Hemoglobin A1c++</td>
<td>Ratio &lt; 1</td>
<td>-----</td>
<td>-----</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td></td>
<td>Ratio ≥ 1</td>
<td>0.74</td>
<td>&lt;0.005</td>
<td>2.1 (1.2, 3.5)</td>
<td>-----</td>
</tr>
</tbody>
</table>

cOR = Crude odds ratio. cRR = Crude risk ratio. R. blood glucose = Random blood glucose.

*P-value of the Wald z-statistic

† Cut-off is 0.80 for females and 0.95 for males

§ Confidence intervals too narrow to report

++ Change variables were adjusted for baseline values

Table 6.5: Univariate logistic regression results for biologic risk factors on incidence of DR
Multivariable results

The variables that were significant at the multivariable level were duration of diabetes, birthplace, waist-hip ratio, hemoglobin A1c, and Δ hemoglobin A1c. All other variables significant at the univariate level dropped out of the multivariable model. The remaining variables that were excluded at the univariate level were then added to the preliminary multivariable model to check for possible confounding. The only variable that appeared to be a confounder was insulin use, so although it was dropped at the univariate level, it was included in the final model. By including insulin use into the model, the coefficient for many other variables, such as waist-hip ratio and duration of diabetes, changed significantly (more than 20%). For example, inclusion of insulin into the model altered the coefficient for waist-hip ratio from 0.64 to 0.33.

Assessment of effect modifiers was done to verify that no interaction terms were being left out of the model. The biologically plausible interaction terms were created from main effects that were significant in the multivariable model. The interaction terms that were assessed were:

1. Hemoglobin A1c * waist-hip ratio
2. Hemoglobin A1c * duration of diabetes

No significant effect modifiers were found.

The final multivariable model is shown in Table 6.6.
Table 6.6: Multivariable model for biologic risk factors on incidence of DR among Hispanic/Latino persons with diabetes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Coefficient</th>
<th>P-value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td></td>
<td>1.0 (referent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4 years</td>
<td>0.92</td>
<td>0.186</td>
<td>2.51</td>
<td>0.64, 9.85</td>
<td></td>
</tr>
<tr>
<td>5-9 years</td>
<td>1.41</td>
<td>0.052</td>
<td>4.09</td>
<td>0.99, 16.86</td>
<td></td>
</tr>
<tr>
<td>10-14 years</td>
<td>1.85</td>
<td>0.120</td>
<td>6.36</td>
<td>1.51, 26.75</td>
<td></td>
</tr>
<tr>
<td>15+ years</td>
<td>2.12</td>
<td>0.007</td>
<td>8.33</td>
<td>1.79, 38.77</td>
<td></td>
</tr>
<tr>
<td>Birthplace</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>1.0 (referent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>-1.01</td>
<td>0.007</td>
<td>0.36</td>
<td>0.18, 0.76</td>
<td></td>
</tr>
<tr>
<td>Waist-hip ratio ≤ cut-off</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>Continuous</td>
<td>0.38</td>
<td>&lt;0.001</td>
<td>1.47</td>
<td>1.26, 1.71</td>
</tr>
<tr>
<td>Δ Hemoglobin A1c*</td>
<td>Continuous</td>
<td>0.83</td>
<td>0.010</td>
<td>2.29</td>
<td>1.22, 4.31</td>
</tr>
<tr>
<td>Insulin use</td>
<td>Yes</td>
<td>0.05</td>
<td>0.891</td>
<td>1.06</td>
<td>0.49, 2.27</td>
</tr>
<tr>
<td>Constant</td>
<td>------</td>
<td>-5.44</td>
<td>&lt;0.001</td>
<td>------</td>
<td>------</td>
</tr>
</tbody>
</table>

Cut-off is 0.80 for females and 0.95 for males

*1 (Ratio of follow-up to baseline ≥ 1) versus 0 (Ratio of follow-up to baseline < 1)

No multicollinearity was present in the final model. Linearity in the logit was once again assessed for the continuous variables in the final model, namely, hemoglobin A1c, and once again, this variable satisfied the assumption.

Goodness-of-Fit and Discrimination

The Hosmer-Lemeshow goodness-of-fit test produced a p-value of 0.2473, indicating the model’s fit was acceptable. The area under the ROC curve, which measures discrimination, was also acceptable (0.755).

The sensitivity/specificity curve is found in Figure 6.2.
One needs a probability cut-off of approximately 0.25 in order to maximize sensitivity and specificity.

Sensitivity analysis was conducted assuming a 0.50 probability cut-off for retinopathy. The results are listed below:

- Sensitivity- \( \text{Pr}( +|D) \): 41.76%
- Specificity- \( \text{Pr}( -|\neg D) \): 88.70%
- Positive predictive value- \( \text{Pr}( D|+) \): 65.52%
- Negative predictive value- \( \text{Pr}(\neg D|-) \): 74.76%

This model can be used to correctly detect those without disease (true negatives), as shown by its high specificity value. On the other hand, the model should not be used to detect those with disease, since sensitivity value is quite low. Overall, this model
correctly classified 72.76% of all cases, providing evidence that the biologic risk indicators listed in Table 6.6 could be used for screening for retinopathy.

**Diagnostics**

Graphs of the residual and deviance with predicted probability of retinopathy were created to check for outlying covariate patterns. The graphs are shown in Figure 6.3.
Figure 6.3: Diagnostic plots of a) residual and b) deviance for multivariable model of biologic risk factors on incidence of DR.
There are five outlying covariate observations, which are represented by the circled points on the plots. However, because these five are all incident cases of diabetic retinopathy and removal of the observation do not substantially alter the regression coefficients, the decision was made to keep these observations in the final model.

Relationship of A1c with risk of retinopathy

A lowess plot was created to depict the relationship between A1c and risk of diabetic retinopathy. The lowess plot controlled for the variables that were significant in the multivariable model shown in Table 6.6. The plot reveals that the risk of retinopathy increases with increasing A1c level.

The lowess plot is presented in Figure 6.4.

Figure 6.4: Lowess plot of predicted probability of DR versus hemoglobin A1c, adjusting for biologic risk factors significant in the multivariable model
Barriers to care on development of DR

Assessing linearity in the logit

The continuous variables of age, number of comorbidities, acculturation, education, and time last seen a physician were assessed for linearity in the logit using the fracpoly method in STATA. All were linear with the exception of time last seen a physician, which was categorized into:

1 = 0 years
2 = 1 year
3 = 2 years
4 = 3 or more years

Descriptive statistics

Comparisons between those with diabetic retinopathy and those no diabetic retinopathy across different barriers to care variables can be shown in Table 6.7. These two groups differed in terms of known history of diabetes and age (p < 0.05) and showed a mild difference with birthplace (p=0.054) and vision insurance (p=0.055). There are no sparse cells.

Crude risk ratio estimates were calculated for various categorical variables.

---

4 “Barriers to care” in Latino populations refer to health-seeking patterns among Latinos which often differ from health-seeking patterns among Caucasians. Differences in health-seeking behaviors in Latinos compared to Caucasians may be significantly associated with the development of retinopathy, especially since maintaining controlled diabetes (by medical intervention) is an important method of prevention for retinopathy.
### Table 6.7: Descriptive statistics for barriers to healthcare comparing cases of DR to controls

<table>
<thead>
<tr>
<th>Variable name</th>
<th>Values</th>
<th>DR</th>
<th>Total§</th>
<th>CI</th>
<th>cRR</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Categorical variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hx of diabetes</td>
<td>No</td>
<td>19</td>
<td>118</td>
<td>16.1</td>
<td>1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>96</td>
<td>293</td>
<td>32.8</td>
<td>2.03</td>
<td></td>
</tr>
<tr>
<td>Last time saw doctor</td>
<td>&lt; 1 year</td>
<td>17</td>
<td>54</td>
<td>31.5</td>
<td>1.0</td>
<td>0.202</td>
</tr>
<tr>
<td></td>
<td>1 year</td>
<td>43</td>
<td>151</td>
<td>28.5</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>12</td>
<td>66</td>
<td>18.2</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 or more years</td>
<td>42</td>
<td>130</td>
<td>32.3</td>
<td>1.03</td>
<td></td>
</tr>
<tr>
<td>Primary language</td>
<td>Spanish</td>
<td>37</td>
<td>136</td>
<td>27.2</td>
<td>1.0</td>
<td>0.558</td>
</tr>
<tr>
<td></td>
<td>English</td>
<td>14</td>
<td>64</td>
<td>21.9</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>19</td>
<td>63</td>
<td>30.2</td>
<td>1.11</td>
<td></td>
</tr>
<tr>
<td>Birthplace</td>
<td>Other country</td>
<td>92</td>
<td>301</td>
<td>30.6</td>
<td>1.0</td>
<td>0.054</td>
</tr>
<tr>
<td></td>
<td>United States</td>
<td>23</td>
<td>110</td>
<td>20.9</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Income</td>
<td>&lt; $20,000</td>
<td>48</td>
<td>176</td>
<td>27.3</td>
<td>1.0</td>
<td>0.460</td>
</tr>
<tr>
<td></td>
<td>≥ $20,000</td>
<td>54</td>
<td>175</td>
<td>30.9</td>
<td>1.13</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>66</td>
<td>254</td>
<td>26.0</td>
<td>1.0</td>
<td>0.269</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>49</td>
<td>158</td>
<td>31.0</td>
<td>1.19</td>
<td></td>
</tr>
<tr>
<td>Health insurance</td>
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<td>39</td>
<td>122</td>
<td>32.0</td>
<td>1.0</td>
<td>0.242</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>76</td>
<td>289</td>
<td>26.3</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Vision insurance</td>
<td>No</td>
<td>55</td>
<td>167</td>
<td>32.9</td>
<td>1.0</td>
<td>0.055</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>59</td>
<td>243</td>
<td>24.3</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Particular clinic or doctor</td>
<td>No</td>
<td>10</td>
<td>33</td>
<td>30.3</td>
<td>1.0</td>
<td>0.803</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>104</td>
<td>368</td>
<td>28.3</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Physical exam in last year</td>
<td>No</td>
<td>58</td>
<td>191</td>
<td>30.4</td>
<td>1.0</td>
<td>0.385</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>55</td>
<td>208</td>
<td>26.4</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>Eye exam in last year</td>
<td>No</td>
<td>82</td>
<td>271</td>
<td>30.3</td>
<td>1.0</td>
<td>0.278</td>
</tr>
<tr>
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<td>Yes</td>
<td>32</td>
<td>128</td>
<td>25.0</td>
<td>0.83</td>
<td></td>
</tr>
</tbody>
</table>

| Continuous variables            |        |          |        |        |     |         |
| Variable name                   | No DR  | DR       | Mean (SE) | Mean (SE) | P-value* |
| Age                            | 58.4 (0.6) | 55.8 (0.9) | 0.02    |
| Acculturation                  | 1.9 (0.1)  | 1.8 (0.1)  | 0.21    |
| No. of comorbidities           | 2.7 (0.1)  | 2.7 (0.2)  | 0.88    |
| Education                      | 8.2 (0.3)  | 7.8 (0.5)  | 0.42    |

DR = Diabetic retinopathy. CI = Cumulative incidence estimates per 100 persons. cRR = Crude risk ratio. Hx of diabetes = Known history of diabetes.
Table 6.7 continued

§Totals represented in this column are not all equal because of missing values

*P-value based on chi-square test for categorical variables, student’s t-test for continuous variables

Univariate results

The univariate logistic regression results are shown in Table 6.8. Results of the analyses indicated the significant variables are known history of diabetes, birthplace, Δ income, Δ health insurance, vision insurance and age. All other variables were not significant at the univariate level.
The multivariable model was constructed from the variables that were significant at the univariate level. Variables that remained in the model after backwards selection were known history of diabetes, vision insurance, and age. The variable that measured
primary language spoken was found to be a possible confounder, so it was included in the model even though it was not significant at the univariate level.

Interaction terms that were evaluated in the multivariable model were:

1. Vision insurance * known history of diabetes
2. Age * known history of diabetes
3. Hemoglobin A1c level * vision insurance

The third interaction term was created to validate the conceptual model shown in Appendix C. Specifically, it was done to examine whether the combined effects of barriers to care with biological precursors to disease significantly impact retinopathy. A1c was used because it was shown in Table 6.6 to be significantly associated with retinopathy.

The first two interaction terms were not significant, however, the third one (A1c * insurance) was significant and therefore included in the final multivariable model, shown in Table 6.9.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Coefficient</th>
<th>P-value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx of diabetes</td>
<td>Yes</td>
<td>1.64</td>
<td>&lt;0.001</td>
<td>5.18</td>
<td>2.24, 11.94</td>
</tr>
<tr>
<td>Vision insurance</td>
<td>No</td>
<td>0.60</td>
<td>0.045</td>
<td>1.82</td>
<td>1.01, 3.38</td>
</tr>
<tr>
<td>Age</td>
<td>Continuous</td>
<td>-0.04</td>
<td>0.016</td>
<td>0.96</td>
<td>0.93, 0.99</td>
</tr>
<tr>
<td>Primary language</td>
<td>Spanish</td>
<td>1.0 (referent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>English</td>
<td>-0.12</td>
<td>0.744</td>
<td>0.89</td>
<td>0.42, 1.87</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>0.26</td>
<td>0.481</td>
<td>1.29</td>
<td>0.63, 2.64</td>
</tr>
<tr>
<td>A1c x vision insurance</td>
<td>Continuous</td>
<td>0.23</td>
<td>0.021</td>
<td>1.25</td>
<td>1.03, 1.52</td>
</tr>
<tr>
<td>Constant</td>
<td>------</td>
<td>0.31</td>
<td>0.742</td>
<td>-----</td>
<td>-----</td>
</tr>
</tbody>
</table>

# Vision insurance for this interaction term was recoded as (0=Insurance; 1=No insurance). Interaction term was centered on the mean to remove the possibility of collinearity. The main effect of A1c was not included in final multivariable model because A1c could be an intervening variable and adjusting for it in the model is not advised (97).

Table 6.9: Multivariable model for barriers to healthcare on incidence of DR among Hispanic/Latino persons with diabetes

No evidence of collinearity was present in this final model. Linearity in the logit was once again assessed for age, which remained linear in the final model.

Goodness-of-Fit and Discrimination

The Hosmer-Lemeshow goodness-of-fit test produced a p-value of 0.490, showing that the model has acceptable fit. The area under the ROC curve was 0.7287, which indicates the model has acceptable discrimination.

Sensitivity analysis was calculated assuming a probability cut-off of 0.50. These values can be estimated from Figure 6.5. The sensitivity and specificity values at the probability cut-off of 0.50 are as follows:

Sensitivity- Pr( +| D): 15.94%
Specificity- Pr( -|~D): 94.30%
Positive predictive value- Pr( D| +): 50.00%

Negative predictive value- Pr(~D| -): 75.83%

The model on barriers to care correctly classified 73.66% of all diabetic retinopathy cases. The majority (73.66%) of those that have predicted probabilities greater than 0.50 were correctly classified as having retinopathy, providing evidence that the barriers to care model shown in Table 6.9 could be used as a screening tool for retinopathy.

Figure 6.5: Sensitivity/specificity curve for final multivariable model of barriers to care on incidence of DR among Latino/Hispanic persons with diabetes

This model is efficient in detecting those without disease (true negatives), as shown by its high specificity. A graph of sensitivity, specificity, and probability is shown
in Figure 6.5. This figure indicates that the probability cut-off needed to maximize sensitivity and specificity is somewhere between 0.25-0.30.

Diagnostics

Graphs of residual and deviance were created to check for possible outlying covariate patterns. The graphs of residual and deviance are shown in Figure 6.6.
Figure 6.6: Diagnostic plots of a) residual and b) deviance values for multivariable model of barriers to care on incidence of DR

As shown in Figure 6.6, there were five outlying covariate observations. However, these observations were not deleted since they all were cases of retinopathy and removal of these participants did not significantly change the regression coefficients.
Lowess plot

A lowess plot of age versus predicted probability of diabetic retinopathy, while controlling for significant barriers shown in Table 6.9, is shown in Figure 6.7. This plot shows an inverse relationship between probability of retinopathy and age. The predicted probability of DR levels off after 70 years of age.

Figure 6.7: Lowess plot of predicted probability of DR versus age, adjusting for barriers significant in the multivariable model
CHAPTER 7

DISCUSSION

4-year cumulative incidence of DR

The incidence of diabetic retinopathy in this representative sample of Latinos is relatively high compared to other racial groups.

Duration of diabetes showed a strong association with incidence. Incidence estimates increase until the duration reaches 15+ years, at which time incidence decreases. One explanation for this is that those with most severe cases of retinopathy were already diagnosed with retinopathy at baseline. In fact, 79.6% of those with diabetes for 15 or more years were found to have retinopathy at baseline (5) and were excluded from the at-risk cohort for incidence. The remaining 20.4% not diagnosed at baseline may be biologically protected from retinopathy or may have discovered means to control their diabetes and prevent development of retinopathy.

Cumulative incidence estimates are highest in the youngest and oldest age groups. This seems counterintuitive at first. However, two things must be considered when interpreting the relationship between age and diabetic retinopathy:

1) Diabetes can manifest itself at any age (from childhood to old age)
2) Incidence increases with increasing duration of diabetes
Those who fall in the 40-49 year old age group were not at high risk for retinopathy at baseline because they were recently diagnosed with diabetes. In fact, 72% of those who were in the youngest age category had duration of diabetes for 0-5 years at the time of baseline examination. At 4-year follow-up examination, those same individuals were at high risk for retinopathy since 4-9 years have passed since the onset of diabetes.

Results from Table 6.2 reveal that those who are at highest risk of developing retinopathy are 1) in the younger and oldest age groups, and 2) have had diabetes for a lengthy amount of time. Therefore, appropriate screening measures should be implemented for such individuals so that disease can be detected and treated properly, before it progresses to the severe stage of proliferative diabetic retinopathy.

**Incidence estimates of DR, stratified by age of diabetes diagnosis**

Results from Table 6.3 reveal that higher incidence of DR were found in those who were diagnosed with diabetes at a younger age. These patterns were shown to be consistent across all duration of diabetes strata. A schematic showing development of diabetes and subsequent development of retinopathy between two persons is shown below:
DM = Diabetes Mellitus onset. DR = Diabetic retinopathy onset

*Risk of DR in Person B > Risk of DR in Person A

Figure 7.1: Representation of two individuals (Person A and Person B) with duration of diabetes of 10 years

Interestingly, the patterns shown in Table 6.3 were consistent with findings reported in a previous study by Cotter et al., which listed DR as the leading cause of visual impairment and blindness in the working age population (6). Klein et al. found a similar relationship between young age of onset and progression of retinopathy and suggest this may be due to younger persons being more likely to have severe diabetes (38).

Comparison with other studies

Appendix D shows the comparison of annualized incidence estimates between LALES and other studies. Latinos in LALES report higher incidence of retinopathy compared to non-Hispanic whites in other studies (56, 64, 66, 98). The exception for non-Hispanic whites would be the WESDR 4-year incidence study, which reported high incidence estimates because the study cohort consisted of only those with diabetes (14). By targeting their recruitment efforts to only those with diabetes, participants in the WESDR study were different than participants from population-based studies, which
focused on recruiting any adult over the age of 40 that met the residency requirement and wanted to participate. In fact, compared to LALES, the WESDR study had a large number of Type 1 diabetics (71). Therefore, the study design in LALES differed significantly from WESDR. LALES recruited a sample representative of the general population regardless of their diabetes status. This difference in study design makes it difficult to compare percentages between WESDR and LALES.

Latinos in LALES report similar incidence of retinopathy compared to Afro-Caribbeans participating in BISED (39). These results indicate that retinopathy occurs more frequently among those classified as an ethnic and/or racial minority, further emphasizing the need to target screening and intervention programs to those identifying themselves as an ethnic and/or racial minority.

All other studies that reported incidence estimates stratified by duration of diabetes showed a similar trend with duration and incidence as reported in LALES; the annualized cumulative incidence estimates increase as the duration of diabetes increases.

**Biologic risk factors of DR**

Significant risk factors for diagnosis of diabetic retinopathy were hemoglobin A1c, Δ hemoglobin A1c, duration of diabetes, waist-hip ratio, birthplace, and insulin use. Certain risk factors, such as duration of diabetes and birthplace, cannot be modified. However, others such as hemoglobin A1c and waist-hip ratio can theoretically be modified through proper medical intervention. Each variable and its contribution to retinopathy is discussed below:

**Duration of diabetes.** Duration of diabetes was a significant predictor of retinopathy risk in LALES, a finding consistent with studies on both non-Hispanic and
Hispanic populations (5, 11, 14, 39). Also consistent with other studies, the odds ratios for diabetic retinopathy generally increased across increasing strata of duration. These results suggest that duration of diabetes is a reliable predictor of DR risk, independent of race or ethnicity. Both univariate odds ratios and risk ratios reported in Table 6.3 increase across all strata of diabetes duration, although the estimates decrease for those with the longest duration (15+ years). One possible explanation for this is that those that remained free of DR for 15+ years post-diagnosis of diabetes may be systemically different than those who were previously diagnosed with retinopathy (and therefore cannot be considered for incidence) or died. In brief, individuals who have no retinopathy after 15 years of having diabetes may differ from those who already developed retinopathy in that they possess some biological characteristic that protects them from DR.

Birthplace. Birthplace has not been considered in studies other than LALES as a potential risk factor for DR (14, 39). It was included in the prevalence study of diabetic retinopathy in LALES and was not found to be significant (11). A variation of this measure, however, was used in the Proyecto VER study in the form of acculturation, which is associated with birthplace (74). Those that were born outside of the United States have a significantly increased odds of DR compared to those who were native-born. Birthplace is a crude measure of how cultural differences between Hispanics and non-Hispanics impact DR risk. This relationship is unique to Latinos and may suggest why DR among Hispanics is higher than in non-Hispanic whites.

Hemoglobin A1c. A measure of glycemic control, high hemoglobin A1c levels is perhaps the strongest predictor of diabetic retinopathy. Studies spanning different racial
and ethnic groups have cited A1c levels to be a reliable predictor of DR (11, 38, 39, 74, 99). Moreover, having an A1c level ≥ 7.0% is one of the requirements in LALES that classifies a person as having definite diabetes mellitus, as described above on page 32. The LOWESS plot in Figure 6.4 indicates that probability for developing retinopathy after four-year follow-up period increases linearly with increasing A1c levels. The relationship seen in Figure 6.4 is supported by the results in the multivariable model shown in Table 6.6.

**Change in Hemoglobin A1c.** The results in Table 6.6 showed that an increase of A1c from baseline to follow-up increases a person’s odds of developing DR. This variable, consisting of two categories (0=ratio < 1, 1=ratio ≥ 1), showed that those who have higher A1c levels at follow-up exam compared to baseline exam (ratio ≥ 1) have a 2.29 higher odds of retinopathy compared to those who actually lowered their A1c levels from baseline to follow-up (ratio < 1). Other studies have considered hemoglobin A1c measured at baseline in their models (39), but Klein et al. reported in their 14-year incidence study that change in A1c levels from baseline to four-year follow-up contributes significantly to increased risk for proliferative diabetic retinopathy (38). Increasing A1c levels from baseline to four-year follow-up indicates a loss of glycemic control, thereby making the individual susceptible to developing DR. Previous studies in Latinos did not examine how change in A1c levels correspond to development of DR (23, 73, 74, 84, 100).

**Insulin.** Insulin use confounded the relationship between waist-hip ratio and development of diabetes by modifying the regression coefficient for waist-hip ratio. Insulin use is restricted to all people with Type 1 diabetes and some people with Type 2
diabetes. Additionally, patients with Type 2 diabetes and insulin dependence generally have a more severe form of disease (insulin use is usually a surrogate measure of glycemic control). Insulin use has been found in previous observational studies to be a significant predictor for prevalence of retinopathy, including the LALES study on risk factors for prevalence of retinopathy (11, 39). This finding contradicts results reported in DCCT study, a clinical trial investigating how insulin treatment can reduce DR risk. DCCT study found that aggressive insulin treatment substantially reduces the development and progression of diabetic retinopathy anywhere from 34% to 76% (47).

The contradicting results between observational studies and clinical trials can be explained by differences in methodology between the two study designs. Clinical trials are able to monitor insulin use whereas observational studies rely on self-reported information about insulin use. The Hawthorne effect may have influenced the results from the DCCT trial since participants were aware their behaviors were being closely observed.

**Waist-hip ratio.** The results suggest that a smaller waist-hip ratio increases risk of DR. This variable remained significant at the multivariable level until the addition of insulin, a confounder. However, because it was confounded by insulin use, it was left in the final multivariable model. Waist-hip ratio is a measure of whether someone is overweight by examining central adiposity, and could be a sign of insulin resistance (101). Waist-hip ratio as a predictor for diabetic retinopathy is a unique finding reported previously in studies with small sample sizes (7, 102), however, results from these studies show that larger waist-hip ratio increases risk of DR. It is also suggested that Hispanics have larger waist-hip ratios as compared to non-Hispanics (103). In fact, the mean waist-
hip ratio among 412 participants in LALES at-risk for DR was 0.88 and 0.94 for females and males, respectively. However, its Latino-specific impact on retinopathy is unclear since large studies on other ethnic samples did not include waist-hip ratio as a predictor of DR development.

Comparison with other studies

The significant risk factors identified in LALES were similar to those seen in various other studies, providing evidence for the consistency of these risk factors towards development of DR. Moreover, since the incidence estimates were higher among Hispanics than non-Hispanics, there possibly are other characteristics among Hispanics (e.g. barriers to care), aside from biological factors, that differentiate them from non-Hispanics on risk of developing DR.

Barriers to care on development of DR

Factors such as insurance status, primary language, age, and known history of diabetes all contribute to risk of DR. Those that are younger, have a known history of diabetes, speak Spanish, and do not have insurance are at higher risk for diabetic retinopathy than those who do not have these characteristics. Certain barriers to care, such as insurance status, are also modifiable. Some of these barriers (e.g. language spoken) are specific to minority populations and have been previously shown to prevent Latinos from receiving proper care for their diabetes (76-79, 104, 105).

Vision insurance status. Insurance has been shown in previous studies to impact health-seeking behavior in Latinos with diabetes (12, 13). Those with no vision insurance are not as likely to comply with the ADA recommendation of yearly eye examinations. Having no insurance does not directly lead to development of DR, but
lack of proper diabetes treatment (not complying with the ADA recommended dilated eye exam every year) may eventually cause the patient to develop retinopathy.

**Vision insurance status with hemoglobin A1c.** Perhaps the most interesting finding from this study is the significant interaction term of insurance with A1c. As the conceptual model in Appendix C suggests, these barriers to care do not contribute directly to DR. Rather, they act as precursors to the development of biological factors that directly lead to disease. Interaction between high levels of hemoglobin A1c (a strong biological predictor) and lack of vision insurance (a strong sociodemographic predictor) is evidence of this relationship. Those that have high levels of A1c and do not have vision insurance have a 1.25 times higher odds of developing DR. The relationship can be explained as such: Those that have insurance are more likely visit their medical practitioners; these medical practitioners advise them to keep their diabetes under control (i.e. maintain low hemoglobin A1c levels); the combined effect of having insurance and controlled diabetes significantly reduces their risk for retinopathy (26).

**Known history of diabetes.** Not surprisingly, known history of diabetes increases a person’s risk for retinopathy, especially when considering that individuals with known history have longer duration of diabetes. Nonetheless, Unzueta et al. previously controlled for known history of diabetes in their model because of its potential role towards seeking medical treatment for diabetes (13). Intuitively, individuals who knew their diabetes status should have been more likely to obtain yearly eye exams for diabetes. However, those with history versus those with no history did not differ in the frequency of getting a yearly eye exam (43% versus 48%, respectively). Therefore,
having a history of diabetes does not increase a person’s chance to seek proper diabetes care.

**Primary language spoken.** Primary language spoken was a confounder and significantly altered several exposure-disease relationships, such as having vision insurance, with its inclusion in the model. Those that spoke only Spanish or both English and Spanish were at a slightly increased odds of developing retinopathy as compared to those who primarily spoke English only. Language is associated with retinopathy by acting as a potential barrier for patients to receive proper care for their diabetes, thereby increasing their risk for retinopathy (77, 104).

**Age.** Increasing age decreases the risk for developing retinopathy, even after controlling for other independent risk factors. The relationship with age has been reported to be significant in the LALES prevalence study of diabetic retinopathy (11). This relationship was depicted graphically in figure 6.7, as increasing age resulted in decreased probability of DR. Retinopathy could potentially impact all adult-aged diabetics since it usually occurs 10-15 years post-onset of diabetes (Table 6.2). Individuals that were at highest risk for DR were: 1) those diagnosed with diabetes at a young age (Table 6.3) and 2) those in the younger age category at the time of baseline examination (Table 6.2). In fact, those that were diagnosed with diabetes between 0-40 years of age had a mean duration of 15.2 years prior to entering the study, which put them at high risk for DR.

The majority barriers that influence access to care among Latinos for diabetes were also associated with increased risk of retinopathy (12). Results in Tables 6.6 and 6.9 show relationships of both barriers to care and biologic characteristics increasing risk
of DR. As emphasized earlier, barriers to care are believed to have a higher impact on DR incidence among Latinos as compared to Caucasians (75). The fundamental pathway by which retinopathy occurs is that those who have barriers to care are less likely to receive treatment for diabetes, leading to uncontrolled diabetes (high A1c levels) and subsequent development of retinopathy. Figure 7.2 below illustrates the possible mechanism by which retinopathy develops in Latinos.

Figure 7.2: Diagram illustrating the steps to development of DR as summarized from the results of this dissertation.

In short, these barriers not only contribute to lower compliance with diabetes care among Latinos (12, 13), but also contribute to increasing the biologic risks that increases risk of retinopathy among Latinos.

No previous study has examined which Latino-specific barriers increase the risk of retinopathy. Understanding how these barriers contribute to development of DR helps to separate Latinos from Caucasians and may explain part of why Latinos have excess risk of retinopathy as compared to Caucasians.
Study limitations

The number of retinopathy outcomes in this study is small (n=115). Four-year follow-up data may not be enough to accurately assess risk factors for retinopathy. Despite the relatively small numbers, the cohort still has over 100 outcomes of disease; this is enough to generate a simple multivariable model using logistic regression. The final multivariable models also do not violate the “rule of 10,” which states that the inclusion of each variable into the model requires at least 10 outcomes of disease. Moreover, the minimum detectable relative risk (formula on page 59), revealed that given a 30-40% prevalence of exposure, the minimum detectable relative risk ranged from 1.52-1.61, providing evidence that the analyses was powered enough to detect relatively small risks.

The results of LALES cannot be generalized to all Latinos residing in the United States. However, since LALES is composed primarily of those who have Mexican ancestry (94.7%), it is safe to conclude that the results can be generalized to those in the United States with Mexican heritage. Moreover, the age breakdown of LALES closely matches the age breakdown of Mexican-Americans, according to the US Census (84).

Third, LALES did not include persons who were institutionalized. In an article published by Klein et al., it was shown that those individuals who are institutionalized in nursing homes or group homes have a much higher rate of ocular disease than those who reside at home (106). Although LALES does not address this population, previous studies reveal that due to cultural reasons, Latinos are less likely to institutionalize their elderly than Caucasians (107). For this reason, exclusion of the institutionalized Latino population probably had a negligible impact on the overall results.
Fourth, because LALES recruited all eligible adults living in a household, there may be some family clustering effect that biases the results of the study. Family clustering effect is a type of design effect that is undesirable because it can potentially violate the assumption of independent observations. Family members are not completely independent of each other across areas of sociodemographic and even biologic characteristics. However, LALES has previously shown that the family clustering effect does not appear to operate in this study cohort (83).

There is a possibility of bias in the results due to loss to follow-up. Despite the high participation “rate”, participants and nonparticipants differed significantly with regard to several factors that may have led to an underestimation of the true incidence of diabetic retinopathy. For example, at baseline, nonparticipants were significantly less likely to have excellent or good self-reported vision or to have in-home binocular near vision better than 20/40. Nonparticipants also were less likely to have health insurance, a potential barrier to on-going ophthalmic care.

However, further analyses revealed that the difference between participants and nonparticipants was minimal with respect to its impact on cumulative incidence estimates. A cumulative incidence of diabetic retinopathy for nonparticipants was predicted using the multivariable model developed in Table 6.6 and the overall percentage was 30.5% (95% CI: 21.8%, 39.2%), whereas the actual observed incidence for participants was 27.9% (95% CI: 23.6%, 32.2%). These results suggest that although the expected incidence of DR among nonparticipants is higher than the observed incidence among participants, the difference is slight, indicating that the two groups may not differ as much as the results from Table 6.1 may suggest.
Odds ratios estimated from logistic regression may be inflated, since DR is not considered a rare disease. Comparison of the risk ratios to the odds ratios in Tables 6.5 and 6.8 reveal that the odds ratio occasionally under/overestimates the risk ratio. Zhang et al. suggests that estimating odds ratios in situations where the rare disease assumption does not hold results in an overestimation of the risk ratio, especially when the magnitude of the effect is large (108). However, alternative methods would be to use Poisson regression or Cox regression. Although Poisson or Cox regression would be the preferred method (109), especially for nonrare disease such as DR, both methods would not be appropriate. Poisson regression would not be appropriate in this case since information on duration of exposure was not known. Cox regression, normally reserved for longitudinal datasets, would also not be appropriate for two reasons: 1) there are only two waves of data and therefore one should not use longitudinal methods such as Cox regression (93), and 2) time-to-event was not known. Therefore, after considering the study limitations and the alternative methods that were available, the decision was made to use logistic regression.

Inaccurate reporting of when biological onset of diabetes occurred could result in misclassification that may bias the results in either direction (nondifferential misclassification), since duration of diabetes is derived from this information. It is difficult to obtain an accurate date of onset for diabetes for two reasons. One, participants may be unaware they had diabetes and were told of their disease status for the first time during their LALES baseline examination. 119 out of 412 (39%) of participants met this criterion. Two, even if previously told by a medical professional they had diabetes, it is impossible to identify the exact moment in time the biological
onset of diabetes occurred. Misclassification bias is common in all epidemiology studies. However, LALES investigators made a concerted effort to gather as accurate of information as possible and even used lab results from the examination to verify the information gathered from each participant.

Individuals with either Type 1 or Type 2 diabetes were included in this study. Because the LALES sample had a small percentage of participants classified as Type 1, estimates of risks and incidence of DR may be biased due to the inclusion of Type 1 diabetics. Klein et al. separated those with Type 1 from those with Type 2 in the WESDR study (14, 27, 28, 71). They reported higher cumulative incidence among Type 1 diabetics (57%) as compared to Type 2 diabetics (34% and 57% for non-insulin and insulin participants, respectively). However, given that only 9 out of the 412 participants at-risk for DR at 4-year follow-up were diagnosed with Type 1 diabetes, the distinction between Type 1 and Type 2 diabetes would be difficult due to small sample sizes.

Finally, using baseline adjustment and change scores in a regression model has its shortcomings. In brief, it does not fully account for the intrapersonal correlation between the baseline variable and the follow-up variable, since they are measured in the same person. However, since more waves of data are needed in order to use complex methods such as longitudinal data analysis, using baseline adjustment and change scores in regression is a better alternative when only two waves of data are available.

Study strengths

LALES is the largest incidence study of eye diseases in the world. Other studies, such as BDES, BMES, and BISED, reported that approximately 3,000 participants returned for a follow-up exam. In contrast, LALES has reported 4,616 (4,616/6,117;
75.5% response), which is a relatively high participation “rate.” LALES has also collected prevalence and incidence estimates on more Latinos than in any other study. Compared to other studies on incidence of diabetic retinopathy, LALES has the highest number at-risk (n=412) (Appendix D). Moreover, its results arguably have substantial external validity since they can be generalized to Mexican-Americans.

LALES recruiting methods also contribute to its strength. The first wave of data collection had an 82% response (6,357/7,789). Recruiting 6,357 participants from a community predominately comprised of Mexican-Americans requires cultural understanding, involvement of trusted community members, and discussions with potential participant’s family members. LALES investigators recognized these barriers and have implemented specific approaches to help increase participation in an otherwise hard-to-reach population.

The first of these approaches involved forming strong bonds with key stakeholders in the La Puente community to help with the promotion of the study. On top of this, LALES received public endorsement by medical practitioners and ophthalmologists in the area. Two, LALES investigators opened a clinic in La Puente for the study so participants had a convenient commute to both baseline and follow-up examinations. Three, interviewers were recruited who were fluent in Spanish so they could go door-to-door to recruit participants and encourage participation. Four, LALES representatives went into the community to give talks and answer questions about the study. And finally, participants who were not able to make it into the La Puente clinic were asked to participate in an in-home examination for both baseline and follow-up.
As mentioned earlier, minority groups in the United States have higher rates of ocular disease, much of it attributed to their lack of healthcare access (74, 75, 110). For instance, 68% of those who were at-risk for DR reported they had not received an eye exam in the past year. An additional strength of LALES is that it provides complete eye examinations to Latinos and resources for them to receive further treatment, if needed. In fact, 10% of those diagnosed with cataracts at the baseline exam went on to receive cataract surgery, resulting in a disappearance of their condition. Although LALES is not designed to be an intervention program, the medical attention these participants receive improve their eye health.

Involvement of outside consultants who are experts in their field helped to strengthen the integrity of the study. Dr. Ron Klein (the principal investigator for the BDES and WESDR studies) is considered an expert in epidemiology of diabetic retinopathy and is a collaborator on the project. He was also responsible for grading all the fundus photographs and advised the LALES group on questions regarding diabetic retinopathy. Also, collaboration with the Battelle Survey Research Center strengthened the quality of the interviews by having people on staff who had have experience conducting interviewer-administered questionnaires.

Finally, rigorous data checks and management contribute to the strength of LALES. Weekly reports describing number of participants examined, along with monthly quality control and analysis reports, were run consistently throughout the data collection phase. Built-in error checks in the databases were created to reduce the possibility of recording incorrect data. Weekly comparisons of numbers between Battelle (responsible for the home questionnaire) and LALES clinic staff (responsible for the
clinic examination) were done to ensure that there were no discrepancies in overall cohort.

Ideas for future research

Pooled analysis

The prevalence of severe ocular diseases, such as proliferative diabetic retinopathy (PDR), is low in the population. In LALES, the 4-year cumulative incidence of PDR was 7.2%. Obtaining precise incidence estimates of PDR is difficult because the disease is rare.

Small sample sizes also make it hard to conduct certain statistical analyses such as using regression techniques to examine biologic or sociodemographic risk factors that predict the rare outcomes. Many studies have employed methods such as pooling data from multiple studies to create an adequate sample size to conduct meaningful analyses (111, 112). These studies have shown that using a meta-analytical approach can lead to both robust and meaningful conclusions about rare diseases.

Future studies should use this meta-analytic approach to analyze risk factors for rare ocular disease outcomes, such as PDR. There are enough studies worldwide on diabetic retinopathy, such as WESDR, BMES, and BISED, which have incidence data that can be pooled together. To date, no one has done a pooled analysis of the incidence of diabetic retinopathy.

A pooled analysis could also assess the effect of ethnicity on DR. Varma et al. conducted a pooled study comparing results of Latino-only studies to results of non-Latino studies and found that those who are Latino are at an increased risk of retinopathy compared to non-Latinos (67).
Assessment of barriers to care among Latinos

Although Table 6.9 describes results that are related to health-seeking behaviors among Latinos in LALES, it is not clear whether these barriers will also increase the risk of disease in studies on other ethnic groups. One way to address this question is to conduct a study recruiting both Latinos and Caucasians and measure patterns of accessing health care. It could be hypothesized that Latinos have a lower prevalence of complying with diabetes treatment, contributing to increased DR risk. By conducting a study comparing Latinos and Caucasians, one could isolate the effect of ethnicity and calculate how much excess risk Latinos experience because of noncompliance towards diabetes treatment.

Case-base approach

Appendix E shows that the odds ratio under/overestimates the relative risk if the disease is not rare. One way to circumvent the rare disease assumption if one has a nonrare outcome is to use a case-base approach, as suggested by Greenland (113), Wang (114) and Kupper (115). A traditional case-control study, such as LALES, chooses its control group after all the cases have been ascertained. This type of case-control study reduces both the number of exposed controls \(b\) and the number of unexposed controls \(d\), since both \(b\) and \(d\) represent the absolute difference of the total number at-risk from the number of cases of disease (Appendix E). The case-base approach, in contrast, selects a random sample of controls at the outset of the study, regardless of whether or not these controls develop disease in the future. Therefore, the \(b\) and \(d\) terms are maximized and are large relative to \(a\) and \(c\). The rare disease assumption does not need
to hold true in a case-base study and the odds ratio will be an unbiased estimator of the risk ratio.

**Analysis of DR using a multifactorial approach**

Results from this dissertation revealed that modeling risk factors for diabetic retinopathy among Latinos should include at least two components: barriers to healthcare and biological indicators. The significant interaction term created with vision insurance by hemoglobin A1c shown in Table 6.9 supports the inclusion of variables measuring biologic characteristics and variables measuring barriers to care into a model predicting DR among Latinos. Suggestions for this approach could be to use the biologic risk factors (Table 6.6) and barriers to care (Table 6.9) that were significant and generating another multivariable model combining results from both tables.

**Additional waves of data collection**

Future studies should focus on collecting additional waves of follow-up data on a sample of Latinos two reasons:

1) More outcomes of disease, resulting in a larger sample size, can be identified, thereby permitting researchers to examine more complicated risk factor models

2) It allows use of more complex statistical methods if there are three or more waves of data collections

Logistic regression was used for this study because there were only two waves of data collection. Although utilizing logistic methods to analyze baseline variables and change scores was the best that could be done given the limited number of waves of data collection, it still had its shortcomings. Collecting additional waves of data would reduce these problems by allowing researchers to use completely different methods of analysis.
such as Cox regression. Three or more waves of data collection would also permit researchers to also use methods such as generalized estimating equations (GEE) and structural equation modeling (SEM).

**Analyses of risk factors using GEE**

When three of more waves of data are collected, longitudinal data analysis can be used. Prior use of longitudinal methods to analyze exposure-disease relationships was not possible since LALES did not have three or more waves of data collection.

Longitudinal data analysis uses a multilevel model of change (93). The first level involves considering individual trajectories of change and determining a model to predict individual changes. The second model looks at inter-individual differences in these trajectories, assuming that the overall sample as a fixed average change trajectory. Since LALES outcome data has a binomial distribution, generalized estimating equations (GEE) should be used.

GEE is a specific type of longitudinal data analysis used to analyze how risk of disease changes over time (93). It can effectively analyze correlated data arising from repeated measurements when the response is not normally distributed. This type of analyses allows researchers to examine change in an individual’s risk over time and the overall change in the sample’s risk over time. Since the study would have repeated measurements and its outcome would be binomially distributed (disease/no disease), GEE would be an appropriate method to use.

**Analyses of risk factors using SEM**

An alternative method for analyzing risk factors associated with disease is by using structural equation models (SEM). SEM is becoming more widely used in studying
health outcomes. Previous literature has published results using SEM when investigating exercise (116) and substance use/abuse among adults (117) and adolescents (118). SEM analysis is commonly used when exploring the validity of causal models.

LALES staff devised a conceptual model, as shown in Appendix C, which represents a true theoretical model of risk of DR. This model is based on *a priori* assumptions, which are gathered from previous knowledge usually obtained from the published literature. Structural equation modeling confirms whether these theoretical models are statistically valid.

SEM examines the various pathways represented in the conceptual models and helps in understanding the relationship patterns among the different risk factors. The goal of using SEM in analyzing risk factors for retinopathy is two-fold: 1) to understand patterns of covariance among the set of risk factors for DR, and 2) to explain as much of the variance as possible with the conceptual model specified *a priori* by the LALES researchers (119). The results of SEM often can be used to support or refute previous assumptions made in the literature about exposure-disease relationships.

In short, analysis of the conceptual model using SEM should be a future area of research. Results from this analyses can help researchers visualize the complex web of causation (120), as proposed by Krieger, or generate causal pies (121), as proposed by Rothman, in order to explain how multiple exposures interplay to result in an outcome of disease.
CHAPTER 8

PUBLIC HEALTH IMPLICATIONS AND INTERVENTION

Impact of DR on quality of life

Individuals suffering from DR tend to have a lower health-related quality of life (HRQOL). According to Mahzar et al. those with diabetic retinopathy in LALES have a significantly decreased HRQOL compared to those without diabetic retinopathy (122). These deficits usually manifest themselves in a person’s driving ability, however, overall decreases in quality of life measurements were seen across all instruments used to measure HRQOL.

Impact of DR on mortality

Previous research has shown that DR and resulting visual impairment can contribute significantly to mortality. The Blue Mountain Eye Study, conducted in Sydney, Australia, found that those with visual impairment coupled with a specific eye condition such as diabetic retinopathy were at an increased risk for mortality than those without those eye conditions (123). This study examined all-cause mortality rates and found that those with any ocular disease had as much as a 50% increased risk of dying (hazard ratio = 1.5).

Researchers in Beaver Dam Eye Study investigated the impact of visual impairment and found that those who were visually impaired, and had a specific ocular
condition such as diabetic retinopathy or age-related macular degeneration, had a higher risk of mortality (124, 125). They found that, after controlling for various risk factors, both retinopathy severity and visual impairment were associated with increased risk of ischemic heart disease mortality. This increased mortality was not explained by traditional risk factors for mortality. Researchers associated with the Beaver Dam study suggest that these eye diseases may serve as markers for mortality in the general population (125).

**Impact of DR on morbidity**

Aside from retinopathy, diabetes has many other comorbid systemic conditions such as hypertension, kidney failure, and obesity (126). Like retinopathy, these problems can be controlled and/or prevented by maintaining proper glycemic control (127). Moreover, aggressive treatment of these comorbid systemic conditions can preserve a person’s sight (31), highlighting the importance prompt diagnosis and treatment of diabetes.

**Screening of DR**

Results from the sensitivity/specificity analyses reveal that using the measures listed in Tables 6.6 and 6.9 is an efficient way to screen for DR among Latinos. These models are extremely robust for detecting false positives, as indicated by the high sensitivity values shown in the sensitivity/specificity curves (Figures 6.2 and 6.5). From a public health perspective, this finding is crucial, since Latinos have a larger burden of DR compared to non-Hispanic whites. Moreover, screening for DR is recommended since maintaining proper diabetes treatment can prevent onset of DR.
Screening for DR among Latinos with diabetes could prove to be an effective intervention strategy. In fact, 27.7% (114/412) of participants in this LALES incidence study on DR were never diagnosed and treated for diabetes. Therefore, screening programs should not only target Latinos with known diabetes, but also target entire Latino communities to screen for both diabetes and retinopathy. Education on how to maintain diabetes control as well as resources on where to receive diabetes care should be provided at these programs.

**Cultural considerations for Latinos**

Creating culturally appropriate interventions for Latinos is important in order to significantly impact DR in this ethnic group.

Barriers to healthcare must be addressed in order to significantly impact retinopathy. As shown earlier, one of the reasons why the incidence of retinopathy is relatively is because Latinos may not have adequate diabetes care. High rates of DR may be highly influenced by the fact that Hispanics are more likely than whites to have uncontrolled diabetes and worse glycemic control (104). Poor glycemic control is one of the risk factors that has been consistently shown to be significant both in the LALES diabetic retinopathy prevalence study (11) and the incidence study discussed above.

Some barriers that prevent Hispanics from complying with the recommended guideline of a yearly eye exam are socioeconomic status, acculturation, gender, and education (12, 13). Understanding these barriers to seeking health care is important when developing community-based health care programs directed toward the Latino population. Aside from barriers to care that predict utilization of services, one must also be aware of possible differences in cultural norms.
One such difference may be that Latinos feel less comfortable with medical practitioners (105). The staff at LALES has implemented methods, such as hiring interviewers and clinicians who were bilingual, so that participants feel comfortable communicating in their native language. The staff at LALES also worked to gain the support of key stakeholders in La Puente, California.

Also, Hispanics generally consider the opinion of other family members to be of key importance, even when it involves decisions about personal health (128). Therefore, it is usually recommended to allow family members to get involved when one is trying to improve the health of Latino communities. For example, LALES staff interviewed all eligible individuals living in a household to get the whole family involved in the study. Although there may be some problems with non-independent observations while using this approach, involvement of family members is beneficial in a Latino population.

Summary

Retinopathy has a host of public health implications that range from reduced health-related quality of life, increased mortality, and comorbid systemic conditions such as heart disease and hypertension. The issues associated with retinopathy emphasize the public health importance of DR. Culturally sensitive interventions should be implemented in Latinos to help reduce the impact of retinopathy. Screening programs for retinopathy should be initiated to detect DR among Latinos. Considerations of the barriers that prevent Latinos from complying with diabetes treatment are important when planning these interventions.
CHAPTER 9

SUMMARY

Cumulative incidence of diabetic retinopathy among Latinos is relatively high and varies significantly among strata of both age and duration of diabetes (Table 6.2). Biological factors that increase risk of DR are generally the same ones that have been consistently shown in previous studies, namely, insulin use, diabetes duration, hemoglobin A1c, and age (11, 38). Although these results focus on what is occurring at the biological level to make the individual more susceptible to DR, it does not address what separates Latinos from other ethnic groups with respect to access to healthcare.

Additional investigation of possible barriers to health care that separate Latinos from other ethnic groups is needed. It was revealed in this study that certain barriers to care experienced by Latinos contribute to an increased risk of DR by influencing whether Latinos receive proper care for their diabetes and thereby maintain glycemic control. These barriers are not as prevalent among Caucasians (75).

Many barriers to care, such as lack of insurance, along with biological risk factors, such as high hemoglobin A1c levels, are modifiable. Moreover, these modifiable risk factors also significantly impact DR in the population. Therefore, successful reduction of these barriers or biological factors from the population could theoretically decrease incidence of DR among Latinos.
The results reported in this dissertation provide evidence that DR in Latinos is a public health concern. DR among Latinos is understudied compared to non-Latinos. Medical practitioners and researchers should be aware of the impact of DR and place more emphasis on ways to prevent or screen for retinopathy in this fast-growing minority population. Programs need to focus primarily on those who have the risk factors found to contribute to DR.
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96. SAS Institute. SAS. Cary, NC.


APPENDIX A

PROCEDURE FOR DIAGNOSING DIABETIC RETINOPATHY
DM = Diabetes Mellitus. OERC = Ocular Epidemiology Recording Center

Figure A.1: Flow-chart for diagnosing diabetic retinopathy with fundus photography
APPENDIX B

DIABETES AND SUBSEQUENT DEVELOPMENT OF RETINOPATHY
Figure B.1: Onset of diabetes and subsequent development of retinopathy in five patients diagnosed with diabetes at or before baseline examination.
APPENDIX C

CONCEPTUAL MODEL FOR DIABETIC RETINOPATHY
Figure C.1: Conceptual model illustrating relationships between various risk factors for incidence of diabetic retinopathy

- Baseline Diabetic Retinopathy Status
  - ↑Age, ↑male gender, ↓acculturation, ↓income, ↓education.

- Psychosocial Attributes
  - ↓social support, +internal locus of control, ↑depression.

- Socio demographic Factors
  - Personal Health Practice Factors
    - ↓Physical activity, -knowledge of eye disease, ↓intake of antioxidant
  - Biological Risk
    - Diabetes
    - Complications: ↑duration of diabetes, ↑number of co-morbidities, ↑Blood pressure, ↑BMI.
    - Diabetes severity/ control
      - ↑hemoglobin A1c, ↑blood glucose, ↑Insulin
  - ↑Incidence of Diabetic Retinopathy

- Health Care Access and Utilization Factors
  - ↓insurance status, -attitudes towards health care, ↓utilization of eye care, health care, and ↑preventive care, and ↑barriers to care.
Figure C.1 continued

* This model will validate previously known associations and explore possible new associations.

↑ indicates increase in the level of the variable. For example ↑ on age means older age, ↑ in use of steroids means greater use of steroids.
↓ indicates decrease in the level of the variable. + indicates presence of a factor. – indicates absence of a factor.

‡ Data on these variables were not collected
APPENDIX D

CROSS-STUDY COMPARISONS OF INCIDENCE OF DIABETIC RETINOPATHY
<table>
<thead>
<tr>
<th>Study population and location</th>
<th>Year of study</th>
<th>Age range (years)</th>
<th>Crude Annual Incidence of DR*</th>
<th>Crude Annual Incidence of DR by duration of diabetes (years) % (95% CI)</th>
<th>Follow-up n</th>
<th>5-9 % (95% CI)</th>
<th>10-14</th>
<th>≥ 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latinos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Los Angeles, USA</td>
<td>2000-2003</td>
<td>≥ 40</td>
<td>412</td>
<td>7.0 (4.5, 9.5)</td>
<td>5.4</td>
<td>7.8</td>
<td>12.5</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>2004-2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1.7, 9.1)</td>
<td>(2.9, 22.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1.4, 14.3)</td>
<td>(0.0, 21.3)</td>
<td></td>
</tr>
<tr>
<td>San Luis Valley, USA</td>
<td>1984-1988</td>
<td>20-74</td>
<td>116</td>
<td>5.2 (1.2, 9.2)</td>
<td>Did not stratify results by duration of diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-descent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbados</td>
<td>1988-1992</td>
<td>40-84</td>
<td>306</td>
<td>7.5 (5.0, 10.0)</td>
<td>5.7</td>
<td>12.7</td>
<td>10.0</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>1992-1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2.5, 8.9)</td>
<td>(0.0, 21.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(4.3, 21.1)</td>
<td>(0.0, 18.2)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wisconsin, USA</td>
<td>1980-1982</td>
<td>≥ 30</td>
<td>320</td>
<td>8.6 (5.5, 11.7)</td>
<td>7.8</td>
<td>8.1</td>
<td>9.5</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td>1984-1986</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(3.5, 12.0)</td>
<td>(0.0, 20.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1982</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2.7, 13.4)</td>
<td>(2.1, 23.6)</td>
<td></td>
</tr>
<tr>
<td>San Luis Valley, USA</td>
<td>1984-1988</td>
<td>20-74</td>
<td>53</td>
<td>6.6 (0.0, 13.2)</td>
<td>Did not stratify results by duration of diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blue Mountains, Australia</td>
<td>1992-1994</td>
<td>≥ 49</td>
<td>90</td>
<td>4.4 (0.2, 8.7)</td>
<td>Did not stratify results by duration of diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1997-1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melbourne, Australia</td>
<td>1992-1994</td>
<td>≥ 40</td>
<td>73</td>
<td>2.2 (0.0, 5.6)</td>
<td>Did not stratify results by duration of diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1997-1999</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Table D.1: Estimated annual incidence of diabetic retinopathy in population-based studies
n = number at risk for DR with definite diabetes at baseline. DR = diabetic retinopathy. CI = confidence interval.

*Incidence of DR defined as absence of retinopathy in both eyes for persons with definite diabetes at baseline, and presence of any retinopathy in either eye at follow-up. Crude annual incidence estimated from 4-year incidence for studies in Los Angeles, San Luis Valley, Barbados and Wisconsin, and 5-year incidence for studies in Melbourne and Blue Mountains.

†Include persons who were newly diagnosed with diabetes at the time of baseline examination.
APPENDIX E

ODDS RATIO VERSUS RISK RATIO FOR NONRARE DISEASE
Objective: Compare the formulas of OR and RR to determine when these two formulas will be equivalent

Step 1
Create 2 x 2 table

<table>
<thead>
<tr>
<th></th>
<th>Disease</th>
<th>No Disease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>A</td>
<td>b</td>
<td>a + b</td>
</tr>
<tr>
<td>Not exposed</td>
<td>C</td>
<td>d</td>
<td>c + d</td>
</tr>
</tbody>
</table>

Step 2
Write down formulas for OR and RR

\[
OR = \frac{a}{b} = \frac{a}{c} = \frac{ad}{bc}
\]

\[
RR = \frac{a/(a + b)}{c/(c + d)}
\]

Step 3
How do you make OR = RR?
YOU MINIMIZE THE A & C TERMS or YOU MAXIMIZE THE B & D TERMS
The A & C terms then become negligible for the:
  1) \( a + b \)
  2) \( c + d \)
terms in the equation for RR. Therefore:
  1) \( a + b \approx b \)
  2) \( c + d \approx d \)

Step 4
The A & C terms of the 2 x 2 table represent # with disease in the exposed group and the unexposed group. Therefore, in order to minimize these terms, the # with disease needs to be small, and

DISEASE NEEDS TO BE RARE

Step 5
Application of these formulas to DR:
DR is not rare in the population. The percentage of diabetic with DR is about 30%. Therefore, OR will under/overestimate RR.
Alternative solutions

Rodrigues mentions three different types of case-control designs (1). The first and most common type is when controls are defined as those who are free of disease after the study period is over. This type of study design requires that disease be rare in order OR to be an unbiased estimate of RR.

The second type, originally suggested Kupper, is called a hybrid epidemiological study in which cases include all cases of disease and controls are sampled from the population at-risk at the beginning of the study (2). Another way to say this type of study is a case-cohort (or case-base) study. The control group is selected independent of whether they even develop disease in the future. The relative risks can be calculated using maximum likelihood estimation, as suggested by Sato (3). Cummings and Koepsell also agree that using this method will lead to unbiased estimate of the risk ratio, even under conditions where the outcome is not rare (4).

The third type, suggested by Greenland, is to use incidence density sampling method, in which controls are randomly selected at each time point in which a case develops disease (5, 6). The control group is selected independent of whether or not they develop disease in the future. Cox regression is the appropriate method to use in this scenario (7).

How this applies to the formulae for OR and RR

These two scenarios, as suggested by Greenland and Kupper, maximizes the $b$ and $d$ terms since a random sample of controls are selected from the TOTAL PAR (population at-risk), regardless of whether or not they develop disease in the future. Normally, those that develop disease ($a$ and $c$ terms) are SUBTRACTED from the $b$ and
terms, and if disease is common, the subtraction of $a$ and $c$ from $b$ and $d$ can decrease the value of $b$ and $d$. Under case-cohort or incidence density sampling, the $a$ and $c$ terms will not be subtracted from the $b$ and $d$ terms. As a result, the $b$ and $d$ terms will be maximized.

Therefore, the rare disease assumption for incident cases is not needed if the case-control studies are designed using either the case-cohort or the incidence density sampling methods.

**Application for this dissertation**

Un fortunately, LALES was designed to be a traditional case-control study in which controls are defined as those who do not have disease at the end of case ascertainment. Therefore, the rare disease assumption should be upheld. Methods suggested by Zhang could be employed so as to get a relatively unbiased estimate of the relative risk (8).

Could incidence density sampling and/or case-cohort design be applied to the LALES data? The answer is no. Both the case-cohort and the incidence density sampling design would not be appropriate since time-to-event (time to DR) is not known.

However, for purposes of this dissertation, a **CASE-BASE** approach could be used in which controls are sampled from the entire PAR and cases are taken from ALL the cases that develop DR (9). A case-base study is the same as a case-cohort study except that there is no time-to-event component in case-base studies. Logistic regression could be used in this case (7). **In a case-base approach, the rare disease assumption does not need to be met.** The OR will be an unbiased estimate of the RR.


