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The association between family history of diabetes and vision impairment in the US population

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Abstract

The association between family history of diabetes and vision impairment in the US population

By Weiqing Gao

Objective: To study the association between familial risk of diabetes and the prevalence of uncorrectable vision impairment among adults living in the US.

Research design and Methods: The sample analyzed is from a cross sectional, nationally representative survey of the US population (1999-2004 National Health and Nutrition Examination Survey, NHANES, n=12,742). Diabetes was defined as diagnosed (the participant acknowledged receiving a diagnosis of diabetes from a health professional) and previously undiagnosed (a fasting glucose ≥ 126 mg/dl detected during the survey). Familial risks were classified as average, moderate and high. Uncorrectable vision impairment was defined as visual acuity worse than 20/40 in the better seeing eye after an objective autorefraction test. Prevalence and odds ratio of uncorrectable vision impairment were estimated for each familial risk class after controlling for key covariates.

Results: The crude prevalence of uncorrectable vision impairment for each familial risk class was 1.1%, 1.1% and 1.3% respectively. There was a statistically significant association between familial risks of diabetes and uncorrectable vision impairment even after controlling for sex, age, race/ethnicity, education, smoking, BMI, hypertension, hypercholesterolemia and duration of diabetes. The odds of having uncorrectable vision impairment for people at moderate or high family risk, compared with people at average familial risk, was 2.29 (95%CI, 1.02-5.14), independently of all other covariates.

Conclusions: In a nationally representative sample of the US adult population with diabetes, family history of diabetes was significantly and independently associated with the prevalence of uncorrectable vision impairment.

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INTROUDUCTION

Diabetes is a leading cause of morbidity and mortality in the United States. In 2007, there were 17.9. million Americans with diagnosed diabetes mellitus, and an additional 5.7 million had undiagnosed diabetes (1). That means 7.8% of the US population had diabetes. Although an epidemic of diabetes has been recognized over the past decade in the US, the incidence of diabetes is still expected to increase continuously as the population ages, obesity increases, and high-risk minority groups grow (2). By 2050 the number of individuals with diagnosed diabetes in the United States is estimated to triple (3). Nevertheless, recent studies have found that lifestyle interventions through physical exercise and diet can prevent and delay diabetes (3).

Characterized by chronically elevated blood glucose (hyperglycemia), diabetes mellitus is a group of metabolic abnormalities resulting from inadequate secretion of insulin from the pancreas or by body resistance to the effects of insulin, or both. Chronic hyperglycemia can affect multiple organ and systems which ultimately lead to serious complications and even death. There are two major types of diabetes complications: 1) microvascular complications, which affect the nervous system, the renal system and the vision system; 2) macrovascular complications, such as cardiovascular disease, stroke, and peripheral vascular disease. Of the four major types of diabetes, Type 2 diabetes accounts for about 90-95% of all cases of diabetes. About 5-10% diabetes are type 1. Gestational diabetes and other genetic or drug related cases of diabetes are relatively rare (4).

Although the pathogenesis of type 2 diabetes is complex, strong risk factors include age, sex, obesity, physical inactivity and family history (5). The prevalence of diabetes is also elevated among individuals with hypertension or dyslipidemias and among women with a prior history of gestational diabetes (5). Several studies (6-10) show evidence of genetic susceptibility for type 2 diabetes. Recent genome-wide association studies (GWAS) have found multiple common genetic variants associated with type 2 diabetes (11-12). However, the utility of genetic profiles alone for predicting the risk of diabetes is limited (13). Family history, which encompasses not only genetic predisposition but also environmental and behavioral factors shared by close relatives, is still a good indicator of the risk of diabetes. As a risk factor for diabetes, family history has been well established across different studies including a variety of ethnic groups. Typically, a positive family history of diabetes increases the risk of the disease from two to six times over the risk in the absence of such history (14-23). Further, the risk associated with family history is graded (the more relatives with the disease the higher the risk) and the association is independent of other known risk factors such as age, BMI, hypertension, education and smoking (24). In addition, as a screening tool for early detection and prevention of diabetes, family history is easy and practical to deploy. Family history of diabetes is a promising tool for health programs aimed at reducing the growing epidemic of diabetes in the US.

According to the 2000 US census, poor vision or blindness affects approximately 1 in 28 Americans older than 40 years (25). The number of blindness in the US is projected to increase by 70% to 1.6 million by 2020 (25). It is not only about the burden

related to healthcare cost; vision impairment affects profoundly the quality of life and significantly decreases mobility (27-28). Diabetic retinopathy, the most common micro vascular complication of diabetes, is considered to be a major cause of vision impairment in the U.S (25). The number of American over 40 years old with diabetic retinopathy will triple in 2050 from 6.7 million to 19.4 million (26). Diabetic macular edema and proliferative diabetic retinopathy are two major causes of vision loss (25). Retinopathy can begin to develop as early as 7 years before the clinical diagnosis of type 2 diabetes (29). In addition, diabetes increases the risk of visual impairment through other ocular conditions such as cataract, glaucoma and refractive errors (30-35). Even age-related macular degeneration, the leading cause of uncorrectable visual impairment in Americans over the age of 50 years, has been shown to have an independent association with diabetes (36-38). The risk of diabetic related vision loss can be greatly reduced by the early detection and effective treatment of diabetes.

A recent national study has shown that uncorrectable vision impairment has an independent association with diabetes even after controlling for other covariates (39). Previous studies on this subject came mainly from selected populations or small regions and did not include undiagnosed diabetes (40-42). Very few studies have explored the association between visual impairment or diabetic retinopathy and family history of diabetes (43), and there is no national study on this matter. Using NHANES data from 1999 to 2004, this study analyzed the prevalence of vision impairment among cases of diagnosed, undiagnosed diabetes and how this impairment relates to family history of diabetes. The aim of this study was to contribute to expand the role of family history

from a tool that helps in the detection and prevention of diabetes to a tool that also helps in the detection and prevention of complications of this disease.

LITERATURE REVIEW

Diabetes is a leading cause of morbidity and mortality in the United States. In the last 15 years, the number of Americans with diagnosed diabetes has more than doubled (3). The incidence of diabetes is still expected to increase continuously as members of the US population age, become more obese, and the numbers of high-risk people from racial and ethnic minorities increase (2). By 2050, the number of individuals with diagnosed diabetes in the United States is estimated to reach 48.3 million (3). Diabetes mellitus is a group of chronic metabolic abnormalities resulting from inadequate secretion of insulin by the pancreas or body resistance to the effects of insulin, or both. There are mainly four clinically distinct types of diabetes: type 1, type2, gestational and other types. Type 2 diabetes also called "adult onset diabetes" accounts for 90-95% of all cases of diabetes (4). This type of diabetes is mainly due to insulin resistance. As the disease progresses, the beta cells in the pancreas could not produce enough insulin to overcome the resistance and eventually stop producing insulin. Prediabetes is when the concentration of glucose in blood is higher than normal but it is not high enough to meet the criteria for a diagnosis of diabetes (2).

Characterized by chronic hyperglycemia, diabetes affects multiple organs in the body. In the long term, uncontrolled diabetes can lead to serious complications and ultimately cause death. There are two major types of complications. Microvascular complications include damage to the nervous system (neuropathy), the renal system (nephropathy) and the eyes (retinopathy). Macrovascular complications include cardiovascular disease, stroke, and peripheral vascular disease (28). Data from

NHANES of 1999-2004 indicate that the prevalence of microvascular complications including chronic kidney disease, foot problems and retinopathy are much higher than the prevalence of macrovascular complications (2).

Although the pathogenesis of type 2 diabetes is complex, a number of risk factors have been recognized. Nonmodifiable risk factors for type 2 diabetes include age, race/ethnicity, low birth weight, family history and history of gestational diabetes. African Americans are more likely to have diabetes than whites (2). Modifiable risk factors include physical inactivity, increased body mass index (BMI), hypertension, dyslipidemia, smoking and alcohol use (56-57). In addition, psychosocial factor such as depression, stress, lower education and lower social support have been found to increase the risk for diabetes (58-60). Among the above risk factors age, sex, obesity, physical inactivity and family history are identified as strong risk factors (5).

Several studies (6-10) show evidence of genetic susceptibility for type 2 diabetes. Recent genome-wide association studies (GWAS) have found multiple common genetic variants associated with type 2 diabetes (11-12). However, the utility of genetic profiles alone for predicting the risk of diabetes is limited (13). Family history, which encompasses not only genetic predisposition but also environmental and behavioral factors shared by close relatives, is still a good indicator of the risk of diabetes. As a risk factor for diabetes, family history has been well established across different studies including a variety of ethnic groups. Typically, a positive family history of diabetes increases the risk of the disease from two to six times over the risk in the absence of such history (14-23). Further, the risk associated with family history is graded (the more

relatives with the disease the higher the risk) and the association is independent of other known risk factors such as age, BMI, hypertension, education and smoking (24). In addition, as a screening tool for early detection and prevention of diabetes, family history is easy and practical to deploy. Family history of diabetes is a promising tool for health programs aimed at reducing the growing epidemic of diabetes in the US.

Vision impairment is a major public health issue as well (25, 51). According to the 1997-2005 National Health Interview Survey, the annual rate of any vision impairment ranged from 8.6% to 10% (51). The prevalence and related causes of vision impairment varied according to ethnicity, age, or residential status (25, 27, 40-42). Based on the 2000 US Census, 2.8% of US residents have impaired vision. The leading cause of blindness among whites is age-related macular degeneration, while among blacks cataract and glaucoma are the leading causes of blindness. Cataract is the leading cause of poor vision among whites, blacks and Hispanics (25). The Baltimore Eye Survey found that the prevalence of visual impairment for people over 40 years old was 2.7% in whites and 3.3% in blacks. The leading causes of visual impairment were cataract (35.8%), age-related macular degeneration (14.2%), diabetic retinopathy (6.6%), glaucoma (4.7%), and other retinal disorders (7.3%). Among black people cataract, diabetic retinopathy and glaucoma were more common as a causes of visual impairment, while age-related macular degeneration was the leading cause of visual impairment among white people (40). Findings from the Salisbury Eye Evaluation study, focused on older Americans, 65 to 84 years, were consistent with the findings of Baltimore Eye Survey (42).

Several studies have found that diabetes contributes to vision impairment through multiple ocular conditions. The Blue Mountains Eye study confirmed that diabetes is a risk factor for age-related cataract and impaired fasting glucose is a possible risk factor for cortical cataract. BMI and hypertension are also associated with incident cataracts. Cardiovascular disease or associated risk factors from the metabolic syndrome probably contribute more to cataracts than cardiovascular disease alone. Besides secondary glaucoma, diabetes (especially long term diabetes) also contributes to open angle glaucoma (33-34). Though there is some controversy about the association between diabetes and age related macular degeneration (AMD), recent studies support the conclusion that diabetes contributes to the late stages of AMD (37-38).

Diabetes retinopathy is the leading cause of new cases of blindness in adults Americans. Each year more than 10,000 new cases of blindness in the United States are attributed to diabetic retinopathy (1). About 3.4% of US adults 40 years old have diabetic retinopathy and 0.75% develop vision-threatening diabetic retinopathy (48). A recent NHANES study (2005 to 2008) found that the prevalence of diabetic retinopathy and vision threatening diabetic retinopathy were 28.5% and 4.4% among people with diabetes in the US population (39). According to the Early Treatment Diabetic Retinopathy Study (ETDRS) the grading scale for diabetic retinopathy is defined by the presence of retinal mircoaneurysms or retinal blot hemorrhages. Severe lesions, which include hard or soft exudates, intra-retinal microvascular abnormalities, new vessels and hemorrhage of pre-retinal or vitreous and fibroproliferants, could accompany these conditions (43). Vision threatening diabetic retinopathy is the level of retinopathy at

which damage to the vision system and even blindness could result. The mechanisms by which diabetic retinopathy causes vision loss include severe nonproliferative diabetic retinopathy, proliferative diabetic retinopathy and macular edema. Proliferative diabetic retinopathy is assessed by the presence of retinal neovascularization or the formation of abnormal new blood vessels (44).

Studies show that diabetic retinopathy can develop earlier in the prediabetes phase and maybe an earlier indicator of dysfunctions in the microcirculation of other organs (28). However many cases of diabetic retinopathy are asymptomatic in their earlier stages. Higher hemoglobin A1c level, longer duration of diabetes, insulin use, and higher systolic blood pressure were found independently associated with diabetic retinopathy (39, 48-50). Early detection and treatment of diabetes retinopathy and effective manage of hyperglycemia can reduce the risk of vision loss (45-47).

METHODS

Study Hypothesis

This study used a cross-sectional design to test the hypothesis that family history of diabetes is positively associated with vision impairment in the adult US population.

Sample and Study Population

The data used in this study came from the National Health and Nutrition Examination Survey (NHANES, 1999-2004). NHANES is an annual survey conducted by the Centers for Disease Control and Prevention and is designed to be nationally representative of the non-institutionalized US population. The survey uses a complex multistage sampling design and includes a household interview followed by series of detailed physical and laboratory examinations conducted at a mobile clinic. After the first interview, participants were randomly assigned to a morning or afternoon visit to the clinic. Fasting glucose was measured in the morning after an overnight fast, which is required for assessment of diabetes (4). NHANES 1999-2004 also included a vision examination.

This study included a 6-year sample of adults (aged ≥ 20 years, n= 15,332). Most of them (92.8%) received a physical examination and 6,943 were examined in the morning. Sample weights were used to obtain national estimates from each of the subsamples (interview, medical exam, morning medical exam). These estimates obtained were those of a typical year within the 6-year period.

Main variables

A participant was considered to have diagnosed diabetes if he or she reported a previous diagnosis of diabetes from a health care professional or undiagnosed diabetes if the participant reported no previous diagnosis of diabetes but his or her fasting glucose was ≥126 mg/dl at the time of the exam (4). Fasting glucose was also used to determine the diabetes status of women who reported a previous diagnosis of just gestational diabetes. There was no attempt to distinguish between type 1 and type 2 diabetes but the sample was restricted to adults (≥20 years old); therefore, the results apply mostly to type 2 diabetes.

Family history of diabetes was determined according to the participant's answers to the following questions: "Including living and deceased, were any of your biological relatives, that is, blood relatives, including grandparents, parents, brothers, and sisters, ever told by a health professional that they had diabetes? " If the answer was "yes," then they were asked, which family member? The options to choose from included first degree relatives (mother, father, brother, sister) and second degree relatives (grandparents from paternal and/or maternal side), refused, or don't know (51). Familial risk of diabetes was categorized into three levels as follows: *1*) high: at least two first-degree relatives or one first-degree and at least two second-degree relatives with diabetes from the same lineage; *2*) moderate: one first-degree and one second-degree relative with diabetes, or only one first degree relative with diabetes, or at least two second-degree relatives from the same lineage; or *3*) average: no close relative with diabetes or, at most, one second-degree relative with diabetes (51).

Distance visual acuity (VA) was measured as presenting distance visual acuity for participants twelve years old with usual correction (glasses, contact lenses or none). Only for participants whose presenting visual acuity worse than 20/30, objective refraction test was administered and distance visual acuity was measured again after the test. The ARK-760 (Nidek Co Ltd, Tokyo, Japan) auto refractor was used for objective refraction test.

This study adopted the most used classification of Vision impairment (VI), which includes three classes: presenting VI, uncorrectable VI, and correctable VI. Presenting VI was defined as presenting visual acuity worse than 20/40 in the better-seeing eye before an objective auto refraction test. Uncorrectable VI was defined as visual acuity worse than 20/40 in the better-seeing eye after an objective auto refraction test. Correctable VI was defined as visual acuity worse than 20/40 in the better seeing eye before an objective auto refraction test that could be improved to normal (VA≥20/40) after an objective auto refraction test.

Covariates

Age was categorized in four groups: 20 -39 years, 40 -59 years, 60 - 79 years, and ≥ 80 years; Four Ethnic/racial groups were included: non-Hispanic white, non-Hispanic black, Mexican American, and other (none Mexican American Hispanic and self elected multiple races); BMI was calculated as weight in kilograms divided by height in meters squared. Four BMI categories were considered: ≤18.5, 18.5 -24.9, 25–29.9, and ≥30 kg/m2. Systolic or diastolic blood pressure was measured three to four times, after a 5-min rest. The first reading was ignored and the average of the last two or three

determinations was recorded as the blood pressure (52). Hypertension was defined as a diastolic blood pressure ≥90 mmHg or a systolic blood pressure ≥140 mmHg or the acknowledgment of treatment for high blood pressure (52). Smoking status was defined as current smoker (≥100 cigarettes lifetime and currently smoking), former smoker (≥100 cigarettes lifetime and currently not smoking) and never smoked. Education was categorized into three classes: <high school, high school and >high school. Duration of diabetes was self-reported as the number of years after the first diagnosis diabetes. Hypercholesterolemia is considered when total cholesterol was ≥240 mg/dL.

Exclusions

In addition to excluding participants younger than 20 years, participants with the following characteristics were also excluded: pregnant (n=13), unknown diabetes status (n=9), family history of diabetes missing (n=260) or vision acuity missing (n=2306). The final sample size for this study was of 12,742, with complete data from both the interview and the vision exam; there were 5,556 people with valid glucose data from the morning physical examination sample.

Statistic Analyses

The data were analyzed using SAS version 9.2 (SAS Institute, Cary, North Carolina) (53), and SUDAAN version 10.1 (54). According to the complex multistage sample design, NHANES selected participants randomly but the probability of selection was not the same for all participants (i.e., varied by stage). A statistical weight was assigned to each participant to account for the differences in the probability of selection and to make the survey representative of the US population. For example, data for

undiagnosed diabetes were analyzed using the weights for the morning sample. Adjusted odd ratios were obtained by multiple logistic regression models.

RESULTS

The characteristics of the participants stratified by three levels of familial risk of diabetes are shown in Table 1. In all variables, except for smokers, there were well detectable trends across the three familial risk levels. The crude prevalence of both presenting and uncorrectable vision impairment (VI) increased as the familial risk levels increased from average to high. The trend was stronger for uncorrectable VI than for presenting VI. As expected, the prevalence of both diagnosed and undiagnosed diabetes increased as the familial risk levels increased.

The average age among people at high familial risk for diabetes was 52 years. The average ages among people at moderate and average familial risk level were 48 and 45 years respectively (Table 1). The average duration of diabetes for US adults was 11.7 year; it increased according to the level of family risks. The average duration of diabetes for high, moderate, and average familial risk of diabetes was 13.8.0, 11.3 and 10.0 years, respectively. The prevalence of uncorrectable VI and presenting VI at ages 40 - 79 years are higher among those participants at moderate or high familial risk than among participants at average familial risk. Participants at high familial risk were more likely to have high blood pressure and hypercholesterolemia than participants at moderate and average familial risk. Participants with less than a high school education were more likely to be in the high and moderate familial risk categories.

Among participants with diagnosed diabetes, the overall prevalence of uncorrectable VI among people at above average (moderate or high) familial risk is higher than those at average family risk ($P=0.015 <.05$). Table 2 displays the estimated

prevalence of uncorrectable VI according to diabetes status and several variables commonly associated with the risk of diabetes. The number of participants with undiagnosed diabetes was too small for the analyses; so, they were pooled with the total cases of diabetes (not shown in the table). Among participants with diagnosed diabetes, the prevalence of uncorrectable VI increased in virtually every variable as the familial risk increased from average to above average. The exceptions were in the age category over 80 years. There were no data available in several categories. Among participants with diabetes (diagnosed or previously undiagnosed), those between 40 and 80 years of age at moderate or high familial risk were more likely to have uncorrectable VI than those with average familial risk. Males with less than high school education, hypercholesterolemia and hypertension and at above average familial risk had a higher prevalence of uncorrectable VI than those at average risk. The overall estimated prevalence of uncorrectable VI among US adults with diagnosed diabetes at above and at average familial risk were 3.1% (95% CI, 2.0-4.8) and 1.4% (95% CI, 0.7-2.8) respectively. This difference is statistically significant ($P=0.015<0.05$).

Among total diabetes population the overall prevalence of uncorrectable VI of people with above average family risk is higher than that among those at average familial risk, but the difference is not statistically significant ($P=0.09$)(not shown in table). The prevalence of uncorrectable VI for participants at above average and average familial risk were 1.8% (95%CI, 1.0-2.5) and 0.7% (95%CI, 0.3-1.0) respectively. In contrast, among the population without diabetes, the prevalence of uncorrectable VI among people above average familial risk was lower than that among people at average

risk people (P=0.07) (see table 2). Compared to people without diabetes at average family risk, the odds of having uncorrectable VI for people with diabetes at above average familial risk are 14.54 (95% CI, 7.35-28.74) times as likely.

The prevalence of uncorrectable VI increases with age until reaching the age(≥80 years) among people with diabetes (diagnosed or total). In contrast, this trend is not observable among people without diabetes (Table 2). In both diabetes groups, participants at above average family history had the highest prevalence of uncorrectable VI among those aged 60 to 80 years. The second highest prevalence of uncorrectable VI was among those aged 40 to 60 years

The prevalence of presenting VI and correctable VI among people with diabetes (diagnosed or total) were not statistically significant different (p>0.05) across the two familial risk levels. The overall estimated prevalence of presenting VI and uncorrectable VI in US adults was 6.3% and 1.1%, respectively. Approximately 2.5% of the adult people with diagnosed diabetes in the US have uncorrectable VI and 10.2% have presenting VI. Among adults without diabetes, the prevalence of uncorrectable VI and presenting VI were 1.0% and 5.9%, respectively.

The associations of various risk factors with uncorrectable VI among individuals with diagnosed diabetes are shown in Table 3. In multivariate analysis, the independent and significant risk factors for uncorrectable vision impairment include age (OR, 1.10 per year; 95% CI, 1.06-1.14), family history of diabetes (OR, 2.29; 95% CI, 1.02-5.14), duration of diabetes (OR, 1.02 per year; 95% CI, 1.00-1.04) and educational level (OR, 3.11; 95% CI 1.14-8.54 less than high school vs. more than high school). People with

above average familial risk are 2 to 4 times as likely to have uncorrectable VI than people at average familial risk after adjusting for age, sex, race/ethnicity, education, duration of diabetes, smoking, hypertension and hypercholesterolemia.

DISCUSSION

This study has shown that family history of diabetes is significantly associated with the prevalence of uncorrectable vision impairment among people with diabetes (self-reported), independently of age, duration of diabetes, sex, race or ethnicity, educational attainment, high blood pressure, hyperlipidemia, smoking and BMI. In contrast, there is no association between uncorrectable visual impairment and family history of diabetes among adults without diabetes. The prevalence of uncorrectable vision impairment is higher among cases of undiagnosed diabetes with moderate or high familial risk of diabetes than among those with average family risk, but the difference is not statistically significant. Although this study found that a family history of diabetes has a graded association with the prevalence of vision impairment and uncorrectable vision impairment among US adults in general, the association is not statistically significant.

The results from this study indicate that the association between uncorrectable vision impairment and family history of diabetes could be mediated through the increased risk of diabetes. This result is consistent with the well-established findings that family history of diabetes is significantly and independently associated with diagnosed diabetes in US adults. The risk of diabetes among people with a positive family history of the disease is about 2 to 6 fold than the risk among those without such family history (14-23). Meantime, this study is consistent with a recent NHANES study that used the same dataset and reported that uncorrectable visual impairment has an independent association with diagnosed diabetes (39).

Prior findings also support the association between uncorrectable vision impairment and family history of diabetes. For example, several studies have found that diabetes contributes to vision impairment through multiple ocular conditions (33-34). It's been long recognized diabetes could cause secondary glaucoma and might contribute to open angle glaucoma. Diabetes is also a risk factor for age-related cataract. The relation between diabetes and age related macular degeneration is not well established but recent studies tend to support a positive association (37-38). From a pathogenic point of view, diabetic retinopathy, diabetes related glaucoma, cataract, refractive errors and even age-related macular degeneration could all be counted as complications of diabetes (3, 33-34). The independent association found here between family history of diabetes and visual impairment was significant only among people with diabetes but not in the general population. This finding indicates that family history of diabetes is not only a strong risk factor for the disease but also for its complications. People with diabetes and a high or moderate familial risk of the disease were 2.29 to 3.6 times more likely to show uncorrectable visual impairment as were adults with diabetes but with only average familial risk, independently of other covariates.

A cohort study reported that signs of retinopathy predict diabetes for participants with family history of diabetes, while among individuals without such family history the retinopathy was not associated with diabetes (61). Our study is consistent with this finding and indicates that people with diabetes and a positive family history of the disease are more likely to have uncorrectable visual impairment.

An earlier study showed that family history, especially parental diabetes, leads to an earlier onset of diabetes. Other studies have shown that the duration of diabetes is independently associated with diabetic retinopathy (63). Together, these findings may help explain why family history of diabetes is a risk factor for uncorrectable visual impairment.

Diabetes-associated retinopathy could start early, at the pre-diabetes stage, and it is indicative of microcirculation changes in other systems (29). However, diabetic retinopathy could be asymptomatic, people with normal but elevated levels of glucose in blood can develop retinopathy without further developing diabetes (65-65). People whose diabetes go undiagnosed for a long period might already show signs of complications at (or shortly after) the time of diagnosis. This may help explain why this study found no association between family history of diabetes and uncorrectable visual impairment among people with undiagnosed diabetes.

Recent studies confirmed that a tight control of glucose in blood is the most effective measure to prevent diabetes complications (65). More than half of the cases of uncorrectable visual impairment could be treated with surgery. Diabetic retinopathy, if detected and treated early, could cause no further vision damage. This study showed that family history of diabetes may help identify people at high risk of uncorrectable visual impairment, which can lead to early detection and treatment of diabetic retinopathy and other diabetes-related eye diseases. Comprehensive eye examinations could be performed more frequently among this high-risk group. This examination includes medical and ocular history, visual acuity or refraction test, intraocular pressure

measurement and dilated eye examinations including vitreous, retinal and optic nerve head examinations (39).

This is the first national study that reports an association between family history of diabetes and uncorrectable vision impairment. The inclusion of cases of undiagnosed diabetes and the use of a graded familial risk made a strong case for the association between visual impairment and family history of diabetes among people whose diabetes was diagnosed previously.

This study has limitations. First, NHANES data comes from the noninstitutionlized US population, the results do not apply to the institutionalized population where diabetes and visual problems could be common. This way, the results of this study could underestimate the prevalence of vision impairments, including the uncorrectable ones. Second, this study excluded participants who did not have information on family history of diabetes (n=260) or participants who could not see due to temporary infections or were completely blind (n=8). Some participants did not attend the visual acuity tests, which decreased the sample size and might have introduced bias in the sample. Third, there could be a recall bias for family history of diabetes. Those with the disease could be more likely to remember their family history (24). NHANES data do not disclose whether participants knew about their family history of diabetes first before being diagnosed with the disease. However, previous studies indicate that family history of diabetes is also a risk factor among people with previously undiagnosed diabetes, among whom recall bias is less likely (24).

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Table 1. Characteristics of participants by family risk of diabetes, National Health And Nutrition Exam Survey 1999-2004

Variables	Sample N (%)	Weighted N (%)	Weighted distribution (95% CI) by familial risk of diabetes			
			Average (n=8518)	Moderate (n=3053)	High (n=1171)	P-value
Age (yrs)						
20 - 39	4612 (36.2)	72958710 (39.7)	43.4(41.4-45.3)	34.1(31.6-36.7)	23.7(21.0-26.6)	
40 - 59	3785 (29.7)	70424766 (38.3)	35.8(34.0-37.7)	43.0(40.7-45.4)	47.0(44.0-50.1)	
60 - 79	3396 (26.7)	33531170 (18.3)	16.9(15.7-18.0)	19.8(18.3-21.4)	26.1(22.6-29.9)	
≥ 80	949 (7.4)	6783924 (3.7)	4.0(3.5-4.5)	3.1(2.6-3.6)	3.2(2.3-4.4)	<0.0001*
Age (yrs) **	46(0.28)		44.8 (0.3)	47.5 (0.4)	51.6 (0.6)	<0.0001*
Diabetes duration (yrs)**	11.7(0.57)		10.0 (0.8)	11.3 (0.7)	13.8 (0.9)	0.0006*
Sex						
Male	6064 (47.6)	88252999 (48.0)	49.5(48.4-50.5)	46.2(44.1-48.3)	40.9(37.3-44.7)	
Female	6678 (52.4)	95445570 (52.0)	50.5(49.5-51.6)	53.8(51.7-55.9)	59.1(55.3-62.7)	<0.0001*
Race/Ethnicity						
Non-Hispanic White	6551 (51.4)	133596496 (72.7)	74.7(71.3-77.8)	70.8(66.6-74.6)	60.7(53.7-67.4)	
Non-Hispanic Black	2438 (19.1)	19578279 (10.7)	9.5(7.9-11.5)	11.9(9.6-14.7)	17.0(13.7-21.0)	
Mexican American	2813 (22.1)	12963674 (7.1)	6.4(5.2-8.0)	8.0(6.1-10.5)	9.8(6.4-14.6)	
Other race	940 (7.4)	17560121 (9.6)	9.3(7.0-12.3)	9.3(6.9-12.4)	12.4(8.5-17.8)	<0.0001*
BMI						
< 18.5	201 (1.6)	3525475 (2.0)	2.3(2.0-2.8)	1.2(0.8-1.8)	0.7(0.3-1.7)	
18.5 to 24.9	3743 (30.0)	58375885 (32.4)	35.7(34.2-37.2)	26.3(24.2-28.4)	21.0(17.8-24.5)	
25 to 29.9	4493 (36.0)	62113896 (34.4)	34.2(32.6-35.9)	35.7(33.3-38.1)	32.7(28.6-37.1)	
≥ 30	4031 (32.3)	56386085 (31.3)	27.8(26.2-29.5)	36.9(34.7-39.2)	45.6(41.2-50.1)	<0.0001*
Education						
Less than high school	3967 (31.2)	36364206 (19.8)	18.1(16.9-19.4)	21.7(19.4-24.2)	29.5(25.4-34.0)	
High school	3050 (24.0)	47886837 (26.1)	26.0(24.2-27.8)	25.6(23.1-28.3)	29.0(25.4-32.8)	
More than high school	5706 (44.8)	99228261 (54.1)	55.9(53.8-58.0)	52.7(49.1-56.3)	41.5(37.3-45.9)	<0.0001*

Table 1. Characteristics of participants by family risk of diabetes, National Health And Nutrition Exam Survey 1999-2004

Variables	Sample N (%)	Weighted N (%)	Weighted distribution (95% CI) by familial risk of diabetes			
			Average (n=8518)	Moderate (n=3053)	High (n=1171)	P-value
Hypercholesterolemia						
No	9871 (81.9)	145025065 (82.8)	83.5(82.3-84.6)	81.8(80.1-83.4)	80.0(76.4-83.2)	
Yes	2182 (18.1)	30083493 (17.2)	16.5(15.4-17.7)	18.2(16.6-19.9)	20.0(16.8-23.6)	0.0454*
Smoking status						
Current smoker	2782 (21.9)	45295914 (24.7)	24.5(23.1-25.9)	25.2(22.8-27.7)	25.2(21.9-28.8)	
Former smoker	3409 (26.8)	46658277 (25.4)	25.5(23.8-27.2)	25.0(22.8-27.4)	26.5(23.5-29.7)	
None smoker	6537 (51.4)	91571755 (49.9)	50.1(48.2-52.0)	49.8(47.1-52.5)	48.4(44.1-52.6)	0.9006
Hypertension						
Yes	5167 (40.6)	64139088 (34.9)	31.9(30.2-33.8)	39.6(37.4-41.8)	47.9(43.9-51.9)	
No	7568 (59.4)	119484966 (65.1)	68.1(66.2-69.8)	60.4(58.2-62.6)	52.1(48.1-56.1)	<0.0001*
Vision Status						
Presenting VI	1113(8.7)	11494504(6.3)	4.3(3.9-4.7)	1.5(1.2-1.7)	0.5(0.7-8.2)	
Normal vision	11629 (91.3)	172204066 (93.7)	93.8(93.3-94.4)	93.7(92.4-94.8)	93.2(91.2-94.8)	0.80401
Vision impairment (Presenting VI)						
Uncorrectable	244 (1.9)	2075294 (1.1)	1.1(1.0-1.4)	1.1(0.7-1.5)	1.3(0.8-2.1)	
Correctable	762 (6.0)	8629336 (4.7)	4.6(4.2-5.2)	4.9(4.0-5.9)	4.6(3.3-6.3)	
Correction unknown	107 (0.8)	789874 (0.4)	0.4(0.3-0.6)	0.4(0.3-0.6)	0.9(0.5-1.6)	0.5592
Diabetes status						
Diagnosed	1209 (9.6)	12493897 (6.8)	3.5(3.1-4.0)	11.1(9.7-12.8)	24.9(22.0-28.1)	
Undiagnosed	190(1.5)	4988404(2.7)	2.0(1.5-2.4)	3.4(2.5-4.4)	6.4(3.8-9.0)	
Without diabetes	11343 (89.0)	169905408 (90.6)	94.2(93.4-95.0)	86.4(83.8-88.9)	70.0(65.1-74.9)	<0.0001*
Overall	12742	183698569	69.1(67.7-70.4)	23.4(22.2-24.5)	7.6(6.9-8.3)	

Table 2. Estimated prevalence of uncorrectable vision impairment among US adults with and without diagnosed diabetes

	With Diagnosed Diabetes			Without Diagnosed Diabetes		
Risk factors	**Overall (95% CI)**	**Average (n=426)**	**Moderate or high (n=783)**	**Overall (95% CI)**	**Average (n=8021)**	**Moderate or high (n=3335)**
Age (yrs)						
20 - 39	NA	NA	NA	0.7 (0.4-1.0)	0.7 (0.4-1.2)	0.4 (0.2-1.1)
40 - 59	0.7 (0.2-2.4)	NA	0.9 (0.3-3.5)	0.2 (0.1-0.5)	0.3 (0.1-0.7)	0.1 (0.0-0.4)
60 - 79	3.7 (2.3-5.9)	1.3 (0.6-2.7)	5.2 (3.2-8.5)	1.8 (1.4-2.4)	2.0 (1.4-2.9)	1.3 (0.7-2.5)
≥ 80	10.4 (6.3-16.7)	9.1 (3.5-21.5)	11.7 (5.8-22.1)	10.3 (7.9-13.2)	10.4 (8.0-13.5)	9.6 (5.4-16.6)
Sex						
Male	1.7 (0.9-3.1)	1.1 (0.4-3.1)	2.1 (1.0-4.4)	0.9 (0.7-1.1)	1.1 (0.9-1.3)	0.4 (0.2-0.8)
Female	3.3 (2.1-5.2)	1.8 (0.8-3.9)	4.0 (2.3-6.6)	1.1 (0.8-1.4)	1.2 (0.8-1.6)	0.9 (0.5-1.5)
Race/Ethnicity						
Non-Hispanic White	2.3 (1.4-3.8)	1.1 (0.4-2.7)	3.1 (1.8-5.5)	1.0 (0.8-1.2)	1.1 (0.9-1.4)	0.6 (0.3-1.1)
Non-Hispanic Black	2.8 (1.4-5.7)	3.2 (1.1-8.7)	2.6 (1.1-6.4)	1.0 (0.7-1.6)	1.2 (0.7-1.8)	0.8 (0.3-1.8)
Mexican American	2.7 (1.5-4.8)	4.0 (2.1-7.7)	2.1 (0.9-4.8)	1.1 (0.7-1.7)	1.4 (0.9-2.2)	0.6 (0.3-1.4)
Other race	3.4 (1.2-9.6)	NA	4.5 (1.5-12.5)	1.2 (0.7-2.1)	1.1 (0.6-2.2)	1.5 (0.6-3.5)
BMI Category						
< 18.5	NA	NA	NA	0.9 (0.2-4.1)	1.1 (0.3-5.0)	NA
18.5 to 24.9	1.4 (0.6-3.6)	0.4 (0.1-1.3)	2.0 (0.7-5.7)	1.0 (0.8-1.3)	1.2 (0.8-1.6)	0.5 (0.2-1.0)
25 to 29.9	4.1 (2.3-7.3)	2.6 (1.1-5.7)	5.0 (2.6-9.5)	1.2 (0.9-1.6)	1.4 (1.0-2.0)	0.7 (0.4-1.2)
≥ 30	2.1 (1.1-3.8)	1.2 (0.5-2.9)	2.6 (1.3-5.1)	0.7 (0.5-1.0)	0.6 (0.3-1.0)	0.9 (0.5-1.5)
Education						
Less than high school	5.0 (3.1-8.2)	4.2 (2.2-7.8)	5.5 (3.1-9.5)	2.0 (1.5-2.6)	2.5 (1.9-3.2)	1.0 (0.5-1.9)
High school	2.2 (0.9-5.3)	0.1 (0.0-0.5)	3.3 (1.3-8.0)	1.3 (1.0-1.6)	1.5 (1.1-1.9)	0.7 (0.4-1.2)
More than high school	0.8 (0.4-1.7)	0.2 (0.0-1.5)	1.1 (0.5-2.4)	0.5 (0.4-0.8)	0.6 (0.4-0.8)	0.5 (0.3-1.0)
Hypercholesterolemia						
No	2.3 (1.4-3.8)	1.4 (0.7-3.0)	2.8 (1.6-4.9)	1.0 (0.8-1.2)	1.1 (0.9-1.3)	0.7 (0.4-1.2)
Yes	3.4 (1.6-7.3)	1.3 (0.3-6.8)	4.6 (2.0-10.4)	1.1 (0.8-1.6)	1.4 (0.9-2.1)	0.5 (0.2-1.3)
Smoking status						
Current smoker	1.7 (0.6-4.7)	2.0 (0.6-7.0)	1.5 (0.3-7.5)	0.6 (0.4-1.0)	0.7 (0.4-1.2)	0.4 (0.1-1.2)
Former smoker	3.8 (2.1-6.7)	1.2 (0.3-4.2)	5.4 (3.1-9.3)	1.1 (0.7-1.6)	1.2 (0.8-1.8)	0.8 (0.4-1.6)
No smoker	2.0 (1.1-3.5)	1.3 (0.6-3.1)	2.3 (1.2-4.5)	1.2 (0.9-1.5)	1.3 (1.0-1.7)	0.8 (0.4-1.3)
Hypertension						
Yes	3.0 (1.9-4.7)	1.4 (0.6-3.1)	4.0 (2.5-6.3)	1.6 (1.3-2.0)	2.0 (1.6-2.4)	1.0 (0.5-1.7)
No	1.5 (0.6-3.5)	1.6 (0.5-5.1)	1.4 (0.4-4.8)	0.7 (0.5-0.9)	0.8 (0.6-1.0)	0.5 (0.3-0.8)
Overall	2.5 (1.7-3.8)	1.4 (0.7-2.8)	3.1 (2.0-4.8)	1.0 (0.8-1.2)	1.1 (0.9-1.4)	0.7 (0.4-1.0)

Table 3. Adjusted odds ratios from multiple logistic regression model for uncorrectable vision impairment among people with diagnosed diabetes

Variable in the model	Odds ratio	95% CI	*P*-Value
Age per year	1.10	(1.06-1.14)	*<0.0001
Duration of diabetes per year	1.02	1.00-1.04	0.01
Sex			
Male	0.66	(0.28-1.59)	0.41
Female	1	(Reference)	
Race/Ethnicity			
Non-Hispanic White	1	(Reference)	
Non-Hispanic Black	1.05	(0.38-2.91)	0.45
Mexican American	1.59	(0.59-4.29)	0.65
Other (including other Hisp)	1.85	(0.37-9.18)	0.44
BMI (kg/m^2) per unit	0.99	0.93-1.06	0.68
Education			
Less than high school	3.11	1.14-8.54	0.005
High school	2.07	0.59-7.28	0.03
More than high school	1	(Reference)	
Total Cholesterol (mg/dL) per unit	1.00	1.00-1.01	0.04
Smoker			
Current smoker	2.44	(0.59-10.10)	0.12
Former smoker	2.67	(0.91-7.81)	0.08
No smoker	1	(Reference)	
Hypertension			
No	1	(Reference)	
Yes	0.96	(0.34-2.69)	0.81
Familial risk of diabetes			
Above average	2.29	(1.02-5.14)	0.01
Average	1	(Reference)	