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Prevalence of and Risk Factors for Diabetic Macular Edema in the United States

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Abstract

Objective—Diabetic macular edema (DME) is a leading cause of vision loss in persons with diabetes mellitus. Although national estimates exist for the prevalence and risk factors of diabetic retinopathy among people with diabetes, to our knowledge no national estimates exist regarding the prevalence and factors associated with DME specifically. Therefore, the objective of this study was to estimate the prevalence of DME in the US population and identify risk factors associated with DME.

Design, Setting, and Participants—A cross-sectional analysis of 1038 participants aged 40 or older with diabetes and valid fundus photographs in the 2005 to 2008 National Health and Nutrition Examination Survey (NHANES).

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Study concept and design: Varma, Bressler, Doan, Danese, Dolan, Colman, Turpcu
Acquisition of data: Doan, Gleeson, Danese, Bower, Selvin, Turpcu
Analysis and interpretation of data: Varma, Bressler, Doan, Gleeson, Danese, Bower, Selvin, Dolan, Fine, Colman, Turpcu
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Main Outcome Measures—Overall prevalence of DME, as well as prevalence of DME according to age, race/ethnicity, and gender.

Results—Of the 1038 persons aged ≥40 years with diabetes mellitus analyzed for this study, 55 had DME, for an overall weighted prevalence of 3.8% (95% CI, 2.7%–4.9%) or approximately 746,000 persons in the US 2010 population aged 40 or older. There were no differences identified in the prevalence of DME by age or gender. Using multivariable logistic regression, non-Hispanic blacks had a greater odds of having DME compared with non-Hispanic whites (OR 2.64; 95% CI, 1.19–5.84; *P*=.02). Elevated levels of hemoglobin A_{1c} (OR 1.47; 95% CI, 1.26–1.71 for each 1%; *P*<.0001] and longer duration of diabetes (OR 8.51; 95% CI, 3.70–19.54 for ≥10 vs <10 years; *P*<. 0001) were also associated with DME prevalence.

Conclusion—These results suggest a greater burden of DME among non-Hispanic blacks, individuals with high levels of hemoglobin A_{1c}, and those with longer duration of diabetes. Given recent treatment advances in reducing vision loss and preserving vision in persons with DME, it is imperative that all persons with diabetes receive early screening; this recommendation is of even greater importance for those individuals at higher risk for DME.

Approximately 347 million persons worldwide have diabetes mellitus.[1,2] The Centers for Disease Control and Prevention estimates that, in 2010, 25.8 million persons (8.3% of the US population) had diabetes mellitus.[3] Substantial racial/ethnic differences in the prevalence of diabetes in the United States have also been noted. National estimates report that, in persons aged 20 years and older in the Unites States, 14.2% of American Indians and Alaskan natives, 12.6% of non-Hispanic blacks, 11.8% of Hispanics, 8.4% of Asian Americans, and 7.1% of non-Hispanic whites have been diagnosed with diabetes.[3]

Diabetic eye disease is a leading cause of vision loss in persons aged 20 to 74 years.[4] Of the visually disabling conditions in persons with diabetic eye disease, diabetic macular edema (DME), left untreated, is a common cause of vision loss.[5] DME affects central vision and can lead to decline in vision ranging from slight visual blurring to blindness, substantially affecting independence and quality of life.[6,7] At least since the 1980s and until 2010, focal/grid laser photocoagulation was the standard of care to treat macular edema, reduce the risk of vision loss, and increase the possibility of vision gain compared with no treatment.[8] More recently, in phase II and III trials with ranibizumab and aflibercept and phase II trials with bevacizumab, intravitreal injections of anti-vascular endothelial growth factor agents have been shown to be superior to focal/grid laser with respect to decreasing the risk of vision loss and increasing the possibility of vision gain.[9–14] In planning the needs and estimating the costs associated with these additional resources, it is important to ascertain an accurate estimate of the magnitude of and risk factors for DME in the United States.

Although the prevalence of diabetic retinopathy (DR) is well characterized,[15–19] by comparison, very little is known about the burden of DME in the United States. A few studies have provided prevalence estimates for individual race/ethnic groups from selected communities;[20,21] however, overall national prevalence of DME is unknown. Similarly, although numerous studies have assessed risk factors associated with DR,[22–25] few studies have assessed risk factors associated with a higher prevalence of DME.

The objectives of this study were to estimate the prevalence of DME in the US and to identify factors associated with the presence of DME in the general adult population in the United States.

METHODS

Data Source

The National Health and Nutrition Examination Study (NHANES) is a series of cross-sectional surveys conducted by the National Center for Health Statistics, a division of the Centers for Disease Control and Prevention.[26] Participants were selected using a stratified multistage probability sampling design of the non-institutionalized civilian population in the United States. For the current study, we combined data from NHANES 2005–2006 with that from the 2007–2008 cycle during which retinal photographs were obtained from participants 40 years or older. Subjects were excluded from the retinal imaging examination for blindness, eye infections, or eye patches on both eyes.[27] The NHANES protocol was approved by human subjects review board and written informed consent was obtained from all subjects.[28,29]

Study Population

This study included persons who completed the mobile examination visit (N=6797) with complete retinal imaging data (n=5351) and had diabetes mellitus (n=1038). Self-reported diabetes mellitus (n=798) was classified based on answering “yes” to the question, “Have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?” We included an additional 240 persons with diabetes based on either glycosylated hemoglobin A_{1c} (HbA_{1c}) ≥6.5%,[30] anti-diabetic medication use from the medication inventory file, or responding “yes” to the questions, “Are you now taking insulin?” or “Are you now taking diabetic pills to lower your blood sugar?” Diagnoses of DR and DME were based on grading of fundus photographs by masked graders at the University of Wisconsin Ocular Epidemiologic Reading Center (Madison, Wisconsin), using a single non-mydriatic image of the optic nerve and macula in each eye from a Canon CR6-45NM ophthalmic digital imaging system and Canon EOS 10D digital camera. For individuals with DME in both eyes, the worse-seeing eye based on visual acuity was used in this analysis.

Definition of Macular Edema

Macular edema was defined according to the NHANES Digital Grading Protocol,[31] which included thickening of the retina. If macular edema could not be graded in one of the eyes, the individual was assigned the score of the gradable eye. Photographs underwent a preliminary and detailed grading for the presence and degree of DR. Discrepancies between these gradings for presence and severity of DR were resolved by a senior grader.[27] If there were still discrepancies after 3 gradings, the case was adjudicated by a senior ophthalmologist.

Statistical Analysis

The prevalence of DME was calculated overall and by age group (40–49, 50–59, 60–69, and ≥70), gender, and race/ethnicity. Among those with diabetes, we also compared the

characteristics of persons with and without DME. The total number of cases of diabetes, DR without DME, and DME were estimated for the United States population by multiplying the prevalence estimates from NHANES with the total number of individuals aged 40 years or older in the 2010 US Census.[32–34]

Key variables of interest included: gender, race/ethnicity (non-Hispanic white/non-Hispanic black/Hispanic/Other), education level (less than/any college), health insurance (yes/no), smoking status (never/ever/current), age at screening, self-reported history of cardiovascular disease (CVD) (yes/no), HbA_{1c} (%), hypertension (yes/no), diabetes duration (<10/≥10 years), and current insulin use (yes/no). The Hispanic racial/ethnic category combined both Mexican American and non–Mexican American Hispanics. At the time of clinical visit, the following measurements were recorded: body mass index calculated from measured height and weight, HbA_{1c} (%) level, and blood pressure. The presence of hypertension was defined as the mean systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg recorded from 3 or 4 measurements, or use of prescription medication for hypertension. CVD was based on self-reported history of congestive heart failure, coronary heart disease, angina pectoris, or heart attack.

Factors associated with DME prevalence were evaluated using multivariable logistic regression models that included the following variables: age, gender, education level, race/ethnicity, health insurance status, body mass index, hypertension, history of CVD, insulin use, HbA_{1c} value, diabetes duration, and smoking status. Different model specifications were explored to evaluate whether the relationship between HbA_{1c} and DME prevalence was nonlinear. One model included HbA_{1c} along with other covariates; however, an alternative model also included quadratic and cubic terms for HbA_{1c}, both of which were statistically significant (*P* value <.01 for both). The adjusted relationship between HbA_{1c} level, diabetes duration, and the predicted probability of DME prevalence were shown using margin plots. Other covariates were plotted based on their mean values, but individual values of HbA_{1c} were used to show the marginal contribution of HbA_{1c}.

All analyses were performed incorporating the survey weights to account for the complex NHANES sampling design, oversampling, and survey nonresponse. The standard errors for all estimates were obtained using the Taylor series (linearization) method following recommended procedures.[35] *P* values <.05 were considered statistically significant. All analyses were conducted in SAS version 9.2 (SAS Institute, Cary, North Carolina) or Stata 12 (StataCorp LP, College Station, Texas).

RESULTS

Of the 1038 persons aged ≥40 years with diabetes mellitus in our study sample in NHANES, 55 had DME. The overall weighted prevalence of DME among persons with diabetes mellitus aged ≥40 years was 3.8% (95% confidence interval [CI], 2.7%–4.9%) (TABLE 1). This corresponds to approximately 746 000 individuals aged 40 or older in the US population in 2010. The prevalence of DME in this analysis was highest among non-Hispanic blacks and was approximately 3-fold higher than in the non-Hispanic white population [Figure 1; eTABLE 1]. There were no clear differences in DME prevalence by

age group or gender among this sample population [eTABLE 1]. Persons with DME had higher mean HbA_{1c} levels, longer duration of diabetes, were more likely to be insulin users, and were less likely to be current smokers compared with persons with diabetes but without DME [TABLE 2].

In the multivariable logistic regression model, non-Hispanic blacks were more likely to have DME compared with non-Hispanic whites (odds ratio [OR] 2.64; 95% CI, 1.19–5.84; *P*=0.02) [TABLE 3]. While the prevalence of DME was higher in Hispanic individuals compared with non-Hispanic whites, this result was not statistically significant (OR 1.96; 95% CI, 0.70–5.48; *P*=.20). Having diabetes for 10 years or more was associated with a higher prevalence of DME (OR 8.51; 95% CI, 3.70–19.54; *P*<0.0001). Higher HbA_{1c} value (per 1% point) was also associated with a higher prevalence of DME (OR 1.47; 95% CI, 1.26–1.71; *P*<.0001). However, when additional non-linear models were explored, HbA_{1c}^2, and HbA_{1c}^3 terms were a better fit than a model with a single HbA_{1c} term (*P*<.005, based likelihood ratio test). Figure 2 shows the relationship between HbA_{1c} levels and the predicted probability of DME prevalence stratified by diabetes duration. Individuals who were current smokers were less likely to have DME (OR 0.33; 95% CI, 0.15–0.74) compared with persons who never smoked.

COMMENT

This study provided a national estimate of the burden of DME in the United States. Additionally, it provided insight into potential risk factors for DME. Our study estimate of 3.8% as the prevalence of DME in the United States among individual with diabetes mellitus aged ≥40 years is much lower than the 9% reported by investigators in a cross-sectional study of 778 individuals with diabetes between 45 and 85 years of age (64.0 ± SD 9.2) in the Multi-Ethnic Study of Atherosclerosis (MESA).[21] The difference may be due to differences in the racial/ethnic composition of the subjects included in MESA, in which non-Hispanic blacks and Hispanics comprised 37% and 30% of the study sample, respectively. In the overall US population aged 45 to 85 years, the racial distribution is as follows: non-Hispanic whites, 74.0%; non-Hispanic blacks, 10.5%; and Hispanics, 9.6%.[36] When examined within each race/ethnic group, the DME prevalence reported in MESA among whites (2.7%) was comparable to our study but higher in non-Hispanic blacks and Hispanics (11.1% and 10.7%, respectively).

Although the prevalence of DME from this study is lower than the previously reported global estimates of 6.8% reported by Yau et al,[37] several factors make it difficult to compare the two estimates. Our study estimated prevalence for persons 40 years or older while the estimate by Yau et al. was age-standardized to the 2010 world diabetes population for persons aged 20–79 years. Additionally, the racial/ethnic group compositions differed between the global prevalence estimate by Yau et al and that in our study. For example, in Yau et al, 44% of the population was Caucasian while, as previously mentioned, the population of this US-only study included 74.0% non-Hispanic whites.

There are few population-based studies of DME prevalence in the US. The Beaver Dam Eye Study, a population based study in Wisconsin, reported that the prevalence of macular

edema among new and previously diagnosed diabetes patients (n=435) was 3%.[38] This study included a similar age group compared with our study; however, the patient population is not nationally representative of the US population and was conducted between 1988 and 1990. Recently, in their study of diabetic retinopathy also based on NHANES data from 2005–2008, Zhang et al estimated the US prevalence of clinically significant macula edema was 2.7%. Both of these studies provide estimates consistent with data from our report.

Variation exists in the identification of individuals with diabetes. In the 2011 National Diabetes Fact Sheet, the Centers for Disease Control and Prevention used fasting plasma glucose to identify persons with diabetes.[3] In our analysis, irrespective of definition of diabetes used, the overall prevalence of DME remained unchanged. For example, if the criterion regarding a history of medication use for diabetes were not used in our analysis, the overall prevalence of DME appeared to be the same (3.8%; 95% CI, 2.7%–4.9%).

In this study, non-Hispanic blacks were more likely to have DME compared with non-Hispanic whites. Although non-Hispanic blacks represented 16% of prevalent diabetes cases, they comprised 38% of the prevalent DME cases [TABLE 3]. By comparison, non-Hispanic whites represented 66% of prevalent diabetes cases but only 45% of prevalent DME cases [TABLE 3]. Our results corroborate reports from other studies. MESA also reported higher prevalence of DME among non-Hispanic blacks (4.2-fold) compared with non-Hispanic whites.[21] In another study, Emanuele and colleagues reported the odds of having clinically significant macular edema was 2.30 (95% CI, 1.33–4.00) for African Americans versus non-Hispanic whites.[39]

In the current study, we did not observe a higher prevalence of DME in Hispanics compared with non-Hispanic whites in either crude (5.1% [95% CI, 1.8%–8.3%] vs 2.6% [95% CI, 1.1%–4.0%]) or adjusted analyses (OR: 1.96 [95% CI: 0.70–5.48]; P=.20). The Veterans Affairs Diabetes Trial (VADT) reported an OR of 2.30 (95% CI, 1.35–3.92) for CSME comparing Hispanic versus non-Hispanic white patients.[39] Although our point estimate of 5.1% suggests the prevalence of DME may be higher among Hispanics compared with non-Hispanic whites (2.6%), the small sample size resulted in a large standard error, which precludes us from stating with confidence whether the prevalence of DME is indeed higher among Hispanics in our study.

In this study, age was not identified as an independent risk factor in multivariable analyses when controlling for duration of diabetes. It is possible that duration of diabetes is a more important risk factor for DME than age. However, another possible explanation for the lack of association between age and DME prevalence is a survival bias in the NHANES cohort.[40] If younger persons with more severe diabetes and DME died before entry into the cohort, the survey could be biased towards older persons with less severe disease.

Two risk factors identified in our study, elevated HbA_{1c} levels and longer diabetes duration, were also reported by Klein et al in a non-Hispanic white sample of persons with diabetes (whose age at diagnosis was 30 years or older) from Wisconsin.[20] Our results suggest that the relationship between HbA_{1c} and DME prevalence is not linear. The odds for DME

prevalence rose sharply beyond an HbA_{1c} level of 7% (particularly in persons with longer history of diabetes), whereas beyond 9% the relationship declines. This decline may reflect a survival disadvantage among individuals who have longer diabetes duration and elevated HbA_{1c} levels. Individuals with those characteristics may have died and therefore cannot be fully represented in cross-sectional data.[41,42] Further, few individuals in this group may not have robust statistics for this upper range of elevated HbA_{1c}.

Although in this study current smokers were less likely to have DME, the relationship between smoking and DME is not well understood. Some studies have reported an association between cigarette smoking and DR,[43–45] while other studies have found no significant relationship.[46–48] An analysis of data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) reported that smoking status was not related to incidence and progression of DR over 4 years. Pack-years smoked while diabetic was a risk factor for progression to proliferative retinopathy in older-onset insulin-taking persons in univariate analyses, but this relationship was not significant in multivariate analyses.[47] Similarly, a more recent analysis of 25-year data from WESDR found a univariate relation of higher incidence of macular edema in diabetic persons who smoked >15 pack-years after diabetes diagnosis; however, this relationship was not found to be significant in multivariate analyses.[49]

Our current study has several limitations, some of which are inherent to the NHANES dataset such as the exclusion of institutionalized individuals and lack of distinction between type 1 and type 2 diabetes.[18] These limitations may result in an underestimation of DME prevalence. Additionally, there was a relatively small number of subjects with DME (n=55), resulting in high imprecision for some of our estimates. This also limited further subgroup analyses. Further, the prevalence of DME by race/ethnic groups should be interpreted with caution. The retinal images were based only on non-mydriatic fundus photography, which may have underestimated the cases of DME when compared with a diagnosis made with optical coherence tomography or stereoscopic photography. Finally, the cross-sectional nature of NHANES precludes us from drawing firm conclusions regarding the temporality of the observed risk factor associations.

In the Unites States, approximately 1 out of every 25 people with diabetes who are aged 40 years or older has DME in at least 1 eye, corresponding to approximately 746 000 persons in this age group in 2010. These results highlight the high burden of DME among non-Hispanic blacks and robust associations with higher HbA_{1c} and longer duration of diabetes. Given recent treatment advances in reducing vision loss and preserving vision in DME, it is imperative that all persons with diabetes receive early screening; this recommendation is of even greater importance for those individuals at higher risk for DME.

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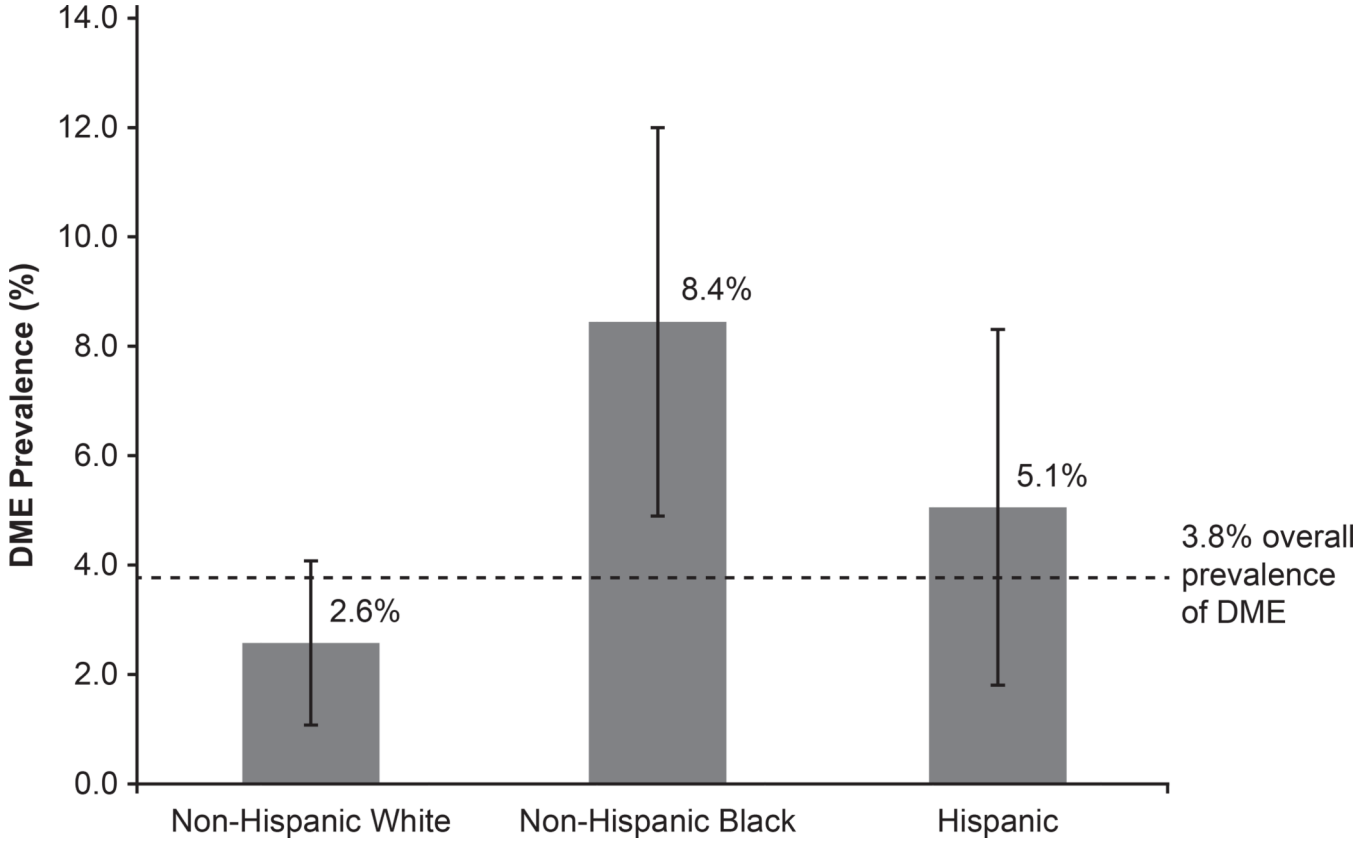

Figure 1. Prevalence of diabetic macular edema stratified by race/ethnicity in the US population aged 40 and over in NHANES

Error bars represent the 95% confidence intervals. Hispanic group combined both Mexican American and non–Mexican American Hispanics. DME, diabetic macular edema.

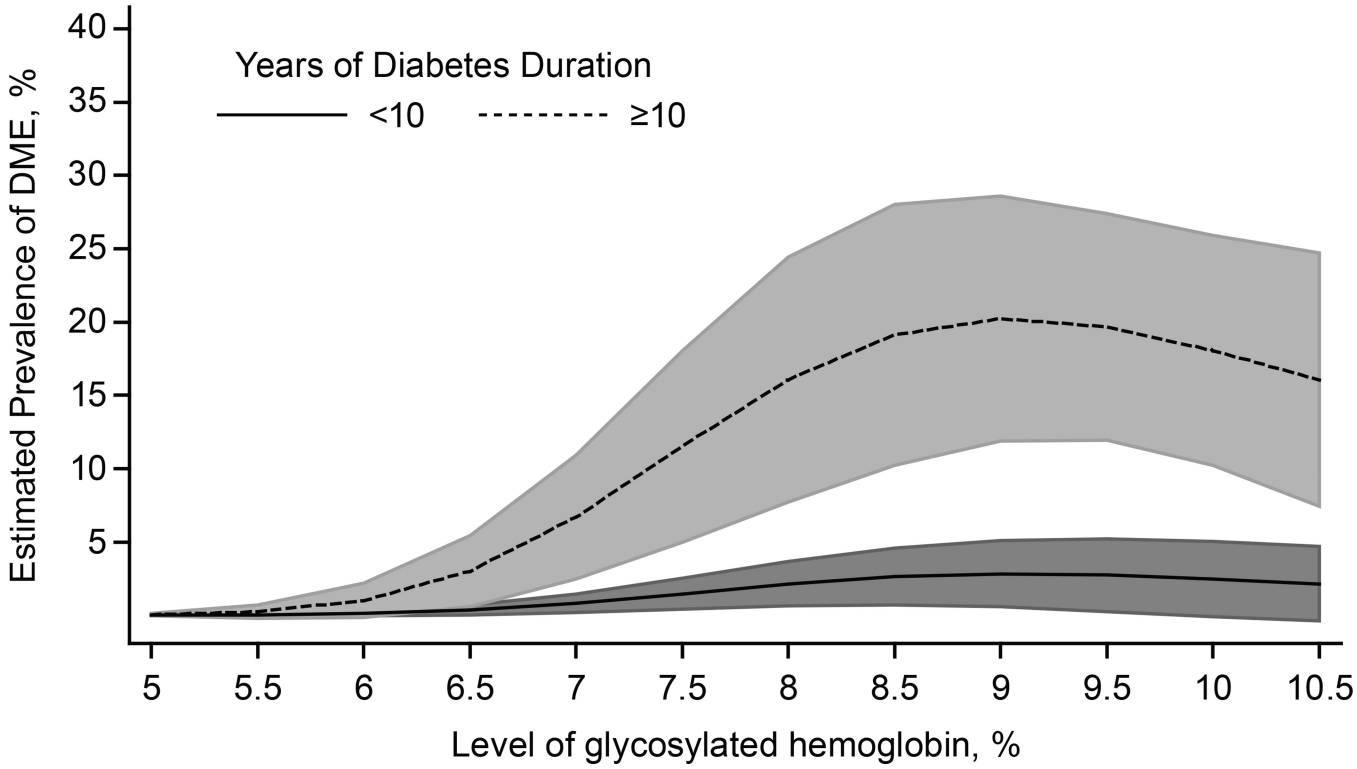

Figure 2. Estimated prevalence of diabetic macular edema by glycosylated hemoglobin levels (HbA_{1c}), stratified by diabetes duration, for all persons with diabetes mellitus in NHANES

The glycemia-specific prevalence data for all persons by each 0.5% difference were plotted to show the independent relationship of glycemia with prevalence of diabetic macular edema. Margin plot from a logistic regression model that included HbA_{1c}, HbA_{1c}^2, HbA_{1c}^3 terms (P<.01) and adjusted for all other covariates. Probabilities of DME prevalence were estimated at the mean of all other covariates but individual value HbA_{1c} from each subject was used. Shading indicates the 95% confidence intervals of the predicted probabilities. DME, diabetic macular edema.

Table 1

Prevalence Estimates Among US Adults With Diabetes Aged 40 Years or Older, Based on NHANES 2005–2008

Cohort	Cases in NHANES*, n	% of US Population With Diabetes Aged ≥40 y†, % (95% CI)	Estimated No. of Adults Aged ≥40 y in the US Population‡
Diabetes	1038	100	19.8 million
DME	55	3.8 (2.7%–4.9%)	746 000
DR without DME	270	24.0 (20.8%–27.3%)	4.7 million
Diabetes without DR or DME	713	72.2 (68.7%–75.7%)	14.3 million

Abbreviations: CI, confidence interval; DME, diabetic macular edema; DR, diabetic retinopathy; NHANES, National Health and Nutrition Examination Study

*Unweighted cases in NHANES.

†Derived from weighted frequencies in NHANES.

‡Based on 2010 US Census data.

Table 2

Baseline and Clinical Characteristics of Persons With and Without DME in the US Population Aged ≥40 Years With Diabetes, in NHANES 2005–2008

	Diabetes Without DME (Unweighted n=983)	Diabetes With DME (Unweighted n=55)
Characteristics	**Weighted Mean (95% CI)**	**Weighted Mean (95% CI)**
Age at screening, y	60.3 (59.4–61.2)	62.4 (59.0–65.8)
BMI, kg/m^2	33.0 (32.4–33.6)	33.8 (31.0–36.7)
HbA_{1C}, %	7.1 (7.0–7.3)	8.4 (7.8–8.9)
	Weighted % (95% CI)	**Weighted % (95% CI)**
Duration of diabetes, y		
<10 y	49.3 (45.4–53.3)	15.9 (5.3–26.6)†
≥10 y	26.6 (22.5–30.6)	70.1 (57.1–83.2)
Unknown duration	24.1 (19.4–28.8)	13.9 (2.3–25.5)†
Hypertension (yes), %	69.7 (66.2–73.2)	84.2 (71.9–96.5)
History of CVD* (yes), %	24.7 (21.0–28.4)	19.9 (10.0–29.9)
Women, %	50.9 (46.3–55.6)	55.9 (39.0–72.7)
Race/ethnicity, %		
Non-Hispanic white	66.0 (57.8–74.2)	44.6 (26.3–62.9)
Hispanic	12.6 (8.6–16.5)	17.1 (5.3–28.9)
Non-Hispanic black	16.3 (11.7–20.9)	38.3 (21.8–54.8)
Other	5.1 (2.4–7.9)	0
Smoking status, %		
Never	46.5 (41.4–51.5)	64.4 (50.0–78.0)
Ever	35.8 (31.6–39.9)	26.0 (11.0–41.0)
Current	17.7 (14.0–21.5)	9.5 (3.5–15.5)
Education level, %		
Less than college education	56.9 (51.7–62.0)	67.1 (51.8–82.4)
Any college	43.1 (38.0–48.3)	32.9 (17.6–48.2)

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DME, diabetic macular edema; HbA_{1C}, glycosylated hemoglobin A_{1C}; NHANES, National Health and Nutrition Examination Study.

*Based on self-report of congestive heart failure, coronary heart disease, angina pectoris, or heart attack.

†Standard error is >30% of estimate.

Table 3

Independent Factors Associated With Prevalence of Diabetic Macular Edema in the US Population Aged ≥40 Years With Diabetes, in NHANES 2005–2008*

Characteristics	Odds Ratio (95% CI)	*P* Value†
Non-Hispanic blacks (vs Non-Hispanic whites)	2.64 (1.19–5.84)	.02
Current smokers (vs never)	0.33 (0.15–0.74)	.01
HbA_{1C} (%)	1.47 (1.26–1.71)	<.0001
Diabetes duration ≥10 y (vs <10 y)	8.51 (3.70–19.54)	<.0001

Abbreviations: CI, confidence interval; DME, diabetic macular edema; HbA_{1C}, glycosylated hemoglobin A_{1c}; NHANES, National Health and Nutrition Examination Study.

*The likelihood of DME diagnosis was evaluated using a multivariable logistic regression model.

†*P* values for all other covariates in the model, including age at screening, gender, education level (any college vs no college), health insurance (yes vs no), body mass index, hypertension (yes vs no), history of CVD (yes vs no), and current insulin use (yes vs no), ever smoked (vs never) were >. 05. The odds ratio for the 'Other' race category was not reported because this group has a small sample size without any DME cases.