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

Rohit Varma, MD, MPH; Neil M. Bressler, MD; Quan V. Doan, PharmD; Michelle Gleeson, PhD; Mark Danese, PhD; Julie K. Bower, PhD; Elizabeth Selvin, PhD; Chantal Dolan, PhD; Jennifer Fine, PhD; Shoshana Colman, PhD; Adam Turpcu, PhD

A

pproximately 347 million persons worldwide have diabetes mellitus.1,2 The Centers for Disease Control and Prevention estimates that 25.8 million persons (8.3% of the US population) had diabetes in 2010.3 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 or older in the United 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 received a diagnosis of 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 It 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 for treating macular edema, reducing the risk of vision loss, and increasing the possibility of vision gain compared with no treatment.8 More recently, in phase II and III trials of ranibizumab and aflibercept and phase II trials of bevancizumab, intravitreal injections of antivascular endothelial growth factor agents have been shown to be superior to focal/grid laser photocoagulation in decreasing the risk of vision loss and increasing the possibility of vision gain.9-13 In planning the

IMPORTANCE Diabetic macular edema (DME) is a leading cause of vision loss in persons with diabetes mellitus. Although there are national estimates for the prevalence of diabetic retinopathy and its risk factors among persons with diabetes, to our knowledge, no comparable estimates are available for DME specifically.

OBJECTIVES To estimate the prevalence of DME in the US population and to identify associated risk factors.

DESIGN, SETTING, AND PARTICIPANTS A cross-sectional analysis of 1038 participants aged 40 years or older with diabetes and valid fundus photographs in the 2005 to 2008 National Health and Nutrition Examination Survey.

MAIN OUTCOMES AND MEASURES The overall prevalence of DME and its prevalence according to age, race/ethnicity, and sex.

RESULTS Of the 1038 persons with diabetes 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 years or older. We identified no differences in the prevalence of DME by age or sex. Multivariable logistic regression analysis showed that the odds of having DME were higher for non-Hispanic blacks than for non-Hispanic whites (odds ratio [OR], 2.64; 95% CI, 1.19-5.84; P = .02). Elevated levels of glycosylated hemoglobin A1c (OR, 1.47; 95% CI, 1.26-1.71 for each 1%; P < .001) and longer duration of diabetes (OR, 8.51; 95% CI, 3.70-19.54 for ≥10 vs <10 years; P < .001) were also associated with DME prevalence.

CONCLUSIONS AND RELEVANCE These results suggest a greater burden of DME among non-Hispanic blacks, individuals with high levels of hemoglobin A1c, 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 even more important for those at higher risk for DME.


Published online August 14, 2014.

Author Affiliations: USC Eye Institute, Keck School of Medicine, University of Southern California, Los Angeles (Varma); Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland (Bressler, Selvin); Editor, JAMA Ophthalmology (Bressler); Outcomes Insights, Inc, Westlake Village, California (Doan, Gleeson, Danese); Division of Epidemiology, The Ohio State University College of Public Health, Columbus (Bower); Genentech, Inc, South San Francisco, California (Dolan, Fine, Colman, Turpcu).

Corresponding Author: Rohit Varma, MD, MPH, USC Eye Institute, Keck School of Medicine, University of Southern California, 1450 San Pablo St, Ste 4900, Los Angeles, CA 90033 (rvarma@usc.edu).
Diabetic Macular Edema in the United States

Methods

Data Source
The National Health and Nutrition Examination Survey (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. Participants were selected using a stratified, multistage probability sampling design of the noninstitutionalized civilian population in the United States. For the current study, we combined 2005-2006 NHANES data with that from the 2007-2008 cycle, during which retinal photographs were obtained from participants aged 40 years or older. Subjects were excluded from the retinal imaging examination if they had blindness, eye infections, or eye patches on both eyes. The NHANES protocol was approved by the human subjects review board, and written informed consent was obtained from all participants.

Study Population
This study included persons who completed the mobile examination visit \( N = 6797 \) with complete retinal imaging data \( (n = 5351) \) and had diabetes \( (n = 1038) \). Self-reported diabetes \( (n = 798) \) was classified based on a positive response to the question “Have you ever been told by a doctor or other professional that you have diabetes or sugar diabetes?” We included another 240 persons with a glycosylated hemoglobin \( A_h \) (Hba\(_h\)) value of at least 6.5%, antidiabetic medication use according to the medication inventory file, or a positive response to the question “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, using a single nonmydriatic 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 eye with worse visual acuity was used in this analysis.

Definition of Macular Edema
Macular edema was defined according to the NHANES Digital Grading Protocol, 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 were resolved by a senior grader. 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, or ≥70 years), sex, 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 US population by multiplying the prevalence estimates from the NHANES with the total number of individuals aged 40 years or older in the 2010 US Census.

Key variables of interest included sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), educational level (less than college or any college), health insurance (yes or no), smoking status (never, ever, or current), age at screening, self-reported history of cardiovascular disease (yes or no), Hba\(_h\) level (percentage), hypertension (yes or no), diabetes duration (<10 or ≥10 years), and current insulin use (yes or no). The Hispanic racial/ethnic category combined both Mexican American and non-Mexican American Hispanics. The following measurements were recorded at the clinic visit: body mass index calculated from measured height and weight, Hba\(_h\) level (as a percentage), and blood pressure. The presence of hypertension was defined as a mean systolic blood pressure of at least 140 mm Hg or a mean diastolic blood pressure of at least 90 mm Hg, recorded from 3 or 4 measurements, or the use of prescription medication for hypertension. A history of cardiovascular disease was based on a self-reported history of congestive heart failure, coronary heart disease, angina pectoris, or myocardial infarction.

Factors associated with DME prevalence were evaluated using multivariable logistic regression models that included the following variables: age, sex, educational level, race/ethnicity, health insurance status, body mass index, hypertension, history of cardiovascular disease, insulin use, Hba\(_h\) value, diabetes duration, and smoking status. Different model specifications were explored to evaluate whether the relationship between Hba\(_h\) and DME prevalence was nonlinear. One model included Hba\(_h\) along with other covariates, but an alternative model also included quadratic and cubic terms for Hba\(_h\), both of which were statistically significant \( (P<.01) \). The adjusted relationship between Hba\(_h\), 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 Hba\(_h\) values were used to show the marginal contribution of Hba\(_h\).

All analyses were performed incorporating the survey weights to account for the complex NHANES sampling design, oversampling, and survey nonresponse. The SEs for all estimates were obtained by using the Taylor series (linearization) method according to recommended procedures. Differences were considered statistically significant at \( P < .05 \). All
analyses were conducted with SAS (version 9.2; SAS Institute) or Stata12 (StataCorp LP) software.

Results

Of the 1038 persons aged 40 years or older with diabetes in our study sample in the NHANES, 55 had DME, for an overall weighted prevalence of 3.8% (95% CI, 2.7%-4.9%) (Table 1).

These data correspond to approximately 746 000 individuals aged 40 years 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 and eTable in the Supplement). There were no clear differences in DME prevalence by age group or sex among this sample population (eTable in the Supplement). Among persons with diabetes, those with DME had higher mean HbA1c levels than those without DME, a longer duration of diabetes, were more likely to use insulin, and were less likely to be current smokers (Table 2).

In the multivariable logistic regression model, non-Hispanic blacks were more likely to have DME than non-Hispanic whites (odds ratio [OR], 2.64; 95% CI, 1.19-5.84; P = .02) (Table 3). Although the prevalence of DME was higher in Hispanic individuals than in non-Hispanic whites, this difference was not statistically significant (OR, 1.96; 95% CI, 0.70-5.48; P = .20).

Having had diabetes for at least 10 years was associated with a higher prevalence of DME (OR, 8.51; 95% CI, 3.70-19.54; P < .001). Higher HbA1c value (per 1% point) was also associated with a higher prevalence of DME (OR, 1.47; 95% CI, 1.26-1.71; P < .001). However, when additional nonlinear models were explored, the quadratic and cubic terms for HbA1c were a better fit than a model with the linear HbA1c term (P < .005; based on likelihood ratio test). Figure 2 shows the relationship between HbA1c levels and the predicted probability of DME prevalence stratified by duration of diabetes. Individuals who were current smokers were less likely to have DME (OR, 0.33; 95% CI, 0.15-0.74) than those who had never smoked.

Discussion

This study provided a national estimate of the burden of DME in the United States. It also provided insight into potential risk factors for DME. Our study estimate of 3.8% as the prevalence of DME in the United States among individuals with diabetes mellitus aged 40 years or older is much lower than the 9% reported by investigators in a cross-sectional study of 778 individuals with diabetes aged 45 to 85 years (mean [SD] age, 64.0 [9.2] years) in the Multi-Ethnic Study of Atherosclerosis (MESA).21 The difference may be due to the racial/ethnic composition of the participants included in the 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 DME prevalence in the MESA was considered by race/ethnic group, the prevalence was comparable to our findings for whites (2.7%) but higher in non-Hispanic blacks and Hispanics (11.1% and 10.7%, respectively).

Although the prevalence of DME in this study is lower than the previously reported global estimates of 6.8% reported by Yau et al,27 several factors make it difficult to compare the estimates. Our study estimated prevalence for persons aged 40 years or older, whereas the estimate by Yau et al was age-standardized to the 2010 world diabetes population for persons aged 20 to 79 years. Moreover, the racial/ethnic compositions for the global prevalence estimate differed between that study and ours. For example, in the study by Yau et al, 44% of
Diabetic Macular Edema in the United States

Table 2. Baseline and Clinical Characteristics of Persons With or Without DME in the US Population Aged 40 Years or Older With Diabetes a

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diabetes Without DME (Unweighted n = 983)</th>
<th>Diabetes With DME (Unweighted n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at screening, mean, y</td>
<td>60.3 (59.4-61.2)</td>
<td>62.4 (59.0-65.8)</td>
</tr>
<tr>
<td>Body mass index, meanb</td>
<td>33.0 (32.4-33.6)</td>
<td>33.8 (31.0-36.7)</td>
</tr>
<tr>
<td>HbA1c, mean, %</td>
<td>7.1 (7.0-7.3)</td>
<td>8.4 (7.8-8.9)</td>
</tr>
<tr>
<td>Duration of diabetes, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 y</td>
<td>49.3 (45.4-53.3)</td>
<td>15.9 (5.3-26.6)</td>
</tr>
<tr>
<td>≥10 y</td>
<td>26.6 (22.5-30.6)</td>
<td>70.1 (51.7-83.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>24.1 (19.4-28.8)</td>
<td>13.9 (2.3-25.5)</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>69.7 (66.2-73.2)</td>
<td>84.2 (71.9-96.5)</td>
</tr>
<tr>
<td>History of CVD, %d</td>
<td>24.7 (21.0-28.4)</td>
<td>19.0 (10.0-29.9)</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>50.9 (46.3-55.6)</td>
<td>55.9 (39.0-72.7)</td>
</tr>
<tr>
<td>Race/ethnicity, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>66.0 (57.8-74.2)</td>
<td>44.6 (26.3-62.9)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>12.6 (8.6-16.5)</td>
<td>17.1 (3.5-38.9)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>16.3 (11.7-20.9)</td>
<td>38.3 (21.8-54.8)</td>
</tr>
<tr>
<td>Other</td>
<td>5.1 (2.4-7.9)</td>
<td>0</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>46.5 (41.4-51.5)</td>
<td>64.4 (50.0-78.0)</td>
</tr>
<tr>
<td>Ever</td>
<td>35.8 (31.6-39.9)</td>
<td>26.0 (11.0-41.0)</td>
</tr>
<tr>
<td>Current</td>
<td>17.7 (14.0-21.5)</td>
<td>9.5 (3.5-15.5)</td>
</tr>
<tr>
<td>Educational level, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than college education</td>
<td>56.9 (51.7-62.0)</td>
<td>67.1 (51.8-82.4)</td>
</tr>
<tr>
<td>Any college</td>
<td>43.1 (38.0-48.3)</td>
<td>32.9 (17.6-48.2)</td>
</tr>
</tbody>
</table>

Abbreviations: CVD, cardiovascular disease; DME, diabetic macular edema; HbA1c, glycosylated hemoglobin A1c.

a Data from the National Health and Nutrition Examination Survey (NHANES), 2005-2008. All means and percentages are weighted; parenthetical ranges represent 95% CIs.
b Body mass index was calculated as weight in kilograms divided by height in meters squared.
c The SE is >30% of the estimate.

The glycemia-specific prevalence data for all persons by each 0.5% difference in HbA1c was fitted with a logistic regression model and adjusted for all other covariates. Probabilities of DME prevalence were estimated from our analysis the criterion concerning a history of antidiabetic medication use, the overall prevalence of DME seemed to be the same (3.8%; 95% CI, 2.7%-4.9%).

In this study, non-Hispanic blacks were more likely to have DME than non-Hispanic whites. They represented 16% of prevalent diabetes cases but 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; the MESA also showed a higher prevalence of DME among non-Hispanic blacks than among non-Hispanic whites (4.2-fold higher). In another study, Emanuele and colleagues re-
ported that the odds of having clinically significant macular edema was 2.30 (95% CI, 1.33-4.00) for African Americans vs non-Hispanic whites.

In the current study, we did not observe a higher prevalence of DME in Hispanics than in non-Hispanic whites in either crude analyses (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 showed an OR of 2.30 (95% CI, 1.35-3.92) for clinically significant macular edema in Hispanic vs non-Hispanic white patients.39 Although our point estimate of 5.1% suggests that the prevalence of DME may be higher in Hispanics than in non-Hispanic whites (2.6%), the small sample size resulted in a large SE, which precludes us from stating with confidence whether the prevalence of DME is indeed higher among Hispanics in our study.

In our 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 toward older persons with less severe disease.

Two risk factors identified in our study, elevated HbA1c levels and longer diabetes duration, were also reported by Klein et al.,20 who studied a non-Hispanic white sample of persons with diabetes in Wisconsin (age at diagnosis, ≥30 years). Our results suggest that the relationship between HbA1c levels and DME prevalence is not linear. The odds for DME prevalence rose sharply for persons with an HbA1c level above 7% (particularly those with a longer history of diabetes), but above 9% the relationship declines. This decline may reflect a survival disadvantage among individuals with a longer duration of diabetes and elevated HbA1c levels; they may be more likely to die and therefore not be fully represented in cross-sectional data.41-42 Furthermore, a few individuals in this group may not have robust statistics for this upper range of elevated HbA1c.

Although current smokers in this study 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 but other studies have found no significant relationship.46-48 An analysis of data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy found that smoking status was not related to the incidence and progression of DR over 4 years. In univariate analyses, pack-years smoked while diabetic was a risk factor for progression to proliferative retinopathy in patients who were older at diabetes onset and used insulin, but this relationship was not significant in multivariate analyses.49 Similarly, a more recent analysis of 25-year data from the same Wisconsin study found a univariate relationship of higher incidence of macular edema in diabetic persons who smoked more than 15 pack-years after diabetes diagnosis; however, this relationship was not significant in multivariate analyses.49

Our current study has several limitations, some of which are inherent to the NHANES data set, 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 condition also limited further subgroup analyses. Furthermore, the prevalence of DME by race/ethnicity should be interpreted with caution. For retinal images, we used only nonmydriatic fundus photography, which may have underestimated the prevalence of DME compared with the use of optical coherence tomography or stereoscopic photography. Finally, the cross-sectional nature of the NHANES precludes us from drawing firm conclusions regarding the temporality of the observed risk factor associations.

Conclusions

In the United States, approximately 1 of every 25 persons aged 40 years or older with diabetes has DME in at least 1 eye, corresponding to approximately 746,000 persons in this age group in 2010. Our results highlight the high burden of DME among non-Hispanic blacks and robust associations with higher HbA1c 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 even more important for those individuals at higher risk for DME.

**ARTICLE INFORMATION**

Submitted for Publication: December 19, 2013; final revision received February 7, 2014; accepted February 12, 2014.


**Author Contributions:** Drs Varma and Selvin had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Varma, Bressler, Doan, Danese, Bower, Dolan, Fine, Colman, Turpcu.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Varma, Doan, Selvin, Dolan, Fine.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Doan, Gleeson, Danese, Bower, Selvin.

Obtained funding: Danese, Fine, Turpcu.

Administrative, technical, or material support: Varma, Doan, Danese, Colman, Turpcu.

Study supervision: Selvin.

Conflict of Interest Disclosures: Dr Varma is a consultant for Allergan, Aquesys, Genentech, Inc, Merck, and Replensh; has received research funding from Genentech, Inc, and Replensh; and has an unrestricted departmental grant from Research to Prevent Blindness. Dr Bressler is principal investigator of grants or agreements at The Johns Hopkins University sponsored by the following entities: Bayer; Genentech, Inc; National Institutes of Health; Novartis Pharma AG; Regeneron Pharmaceuticals, Inc; and the Emmes Corporation. Drs Doan, Gleeson, and Danese are employees of Outcomes Insights, Inc, and paid consultants for Genentech, Inc. Drs Bower and Selvin are coinvestigators for Dr Bressler’s grant at The Johns Hopkins University, sponsored by Genentech, Inc. Dr Dolan is a paid consultant for Genentech, Inc. Drs Turpcu, Fine, and Colman are employees of Genentech, Inc.

Funding/Support: This study was supported by a grant from Genentech/Roche to The Johns Hopkins University through the Office of Research Administration of the Johns Hopkins University School of Medicine. Support for third-party editorial
Diabetic Macular Edema in the United States

Role of the Sponsor: Genentech/Roche (sponsor) employees participated in the design of the study, interpretation of the data, critical revision and approval of the manuscript, and decision to submit the manuscript. They had access to the data before the completion of the analysis but did not participate in the statistical analysis. Data management and data analysis were performed by Outcomes Insights, Inc, independent of Genentech/Roche. An independent statistical analysis was conducted by Johns Hopkins University Bloomberg School of Public Health employees (Dr.Bower and Selvin).

Disclaimer: Dr. Bressler is the editor of JAMA Ophthalmology. He was not involved in the editorial evaluation or the decision to accept this article for publication.


REFERENCES


OPHTHALMIC IMAGES

**Starry Sky**

Vivian Lee, MD; Benjamin J. Kim, MD

A woman in her early 70s with a retinal detachment for 3 months underwent repair, when a subretinal, soft mass was identified. Histopathologic analysis demonstrated birefringent crystals consistent with calcium oxalate, an uncommon finding with chronic detachments (hematoxylin-eosin, original magnification ×10 [A]; polarized light, original magnification ×10 [B]).