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Demographic and Metabolic Risk Factors Associated with Development of Diabetic Macular Edema among Persons with Diabetes Mellitus

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Purpose: Diabetic macular edema (DME), a leading cause of visual impairment, can occur regardless of diabetic retinopathy (DR) stage. Poor metabolic control is hypothesized to contribute to DME development, although large-scale studies have yet to identify such an association. This study aims to determine whether measurable markers of dysmetabolism are associated with DME development in persons with diabetes.

Design: Retrospective cohort study.

Participants: Using data from the Sight Outcomes Research Collaborative (SOURCE) repository, patients with diabetes mellitus and no preexisting DME were identified and followed over time to see what factors associated with DME development.

Methods: Cox proportional hazard modeling was used to assess the relationship between demographic variables, diabetes type, smoking history, baseline DR status, blood pressure (BP), lipid profile, body mass index (BMI), hemoglobin A1C (HbA1C), and new onset of DME.

Main Outcome Measures: Adjusted hazard ratio (HR) of developing DME with 95% confidence intervals (CIs).

Results: Of 47 509 eligible patients from 10 SOURCE sites (mean age 63 ± 12 years, 58% female sex, 48% White race), 3633 (7.6%) developed DME in the study period. The mean ± standard deviation time to DME was 875 ± 684 days (~2.4 years) with those with baseline nonproliferative DR (HR 3.67, 95% CI: 3.41−3.95) and proliferative DR (HR 5.19, 95% CI: 4.61−5.85) more likely to develop DME. There was no difference in DME risk between type 1 and type 2 patients; however, Black race was associated with a 40% increase in DME risk (HR 1.40, 95% CI: 1.30−1.51). Every 1 unit increase in HbA1C had a 15% increased risk of DME (HR 1.15, 95% CI: 1.13−1.17), and each 10 mmHg increase in systolic BP was associated with a 6% increased DME risk (HR 1.06, 95% CI: 1.02−1.09). No association was identified between DME development and BMI, triglyceride levels, or high-density lipoprotein levels.

Conclusions: These findings suggest that in patients with diabetes modifiable risk factors such as elevated HbA1C and BP confer a higher risk of DME development; however, other modifiable systemic markers of dysmetabolism such as obesity and dyslipidemia did not. Further work is needed to identify the underlying contributions of race in DME.

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Diabetic macular edema (DME) is a common cause of vision loss for patients with diabetes and affects nearly 750 000 people in the United States.[1−3] In the United States, prevalence of DME in adults ≥40 years has been reported between 4% and 10% with variability based on racial/ethnic background and diabetes duration.[1,4,5] Diabetic macular edema results from swelling of the macula caused by fluid leaking from damaged retinal blood vessels and may occur with any stage of diabetic retinopathy (DR) or diabetes type.[6] Patients with DME require frequent monitoring by an eye care professional to identify when treatment with intraocular injections of anti-VEGF agents and, less commonly, laser photocoagulation, is needed.[7−9] Once intraocular injections are started, patients may need treatments as often as monthly and potentially indefinitely.

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Development and progression of DR have been shown to be associated with diabetes duration and glycemic control[1,10] and so it is well accepted in ophthalmic practice that control of diabetes, hypertension, and serum lipids is foundational for DR management. Yet these comorbidities are often managed by an internist or endocrinologists, and not all ophthalmologists systematically consider these systemic markers of disease in clinical decision making for DME. Although the development of DME has been associated with increased diabetes mellitus (DM) duration and hypertension,[5] recent data revealed systolic blood pressure (SBP), not current hemoglobin A1C (HbA1C), a marker of recent glycemic control, was associated with receiving anti-VEGF intraocular therapy in patients with diabetes.[11,12]

It has been hypothesized that clinical and pathophysiologic heterogeneity seen in DME may stem from underlying variations in individual metabolic control. A recent study broadly assessing glucose, blood pressure (BP), and lipid control in patients with diabetes found that the presence of DR and DME increased when a combination of factors were present.[13] Chronic local inflammation has been hypothesized to contribute to underlying neurovascular pathology in DME[14] and may even precede vascular changes.[15–18] Metabolic syndrome (MetS) characterized by the presence of central obesity, insulin resistance, hypertension, and dyslipidemia, represents a state of low-grade, chronic systemic inflammation and is a well-described risk factor for macrovascular diseases such as stroke and cardiovascular disease,[19] although its role in microvascular diseases such as DR or DME is unclear.[20–23]

The purpose of this study is to leverage a large multicenter repository of nearly 50 000 patients with DM across multiple health systems in the United States to look for associations between components of systemic metabolic dysfunction associated with MetS[24,25] and new onset of DME.

Methods

Data Source and Collection

Data were derived from the Sight Outcomes Research Collaborative (SOURCE) Ophthalmology Data Repository. Sight Outcomes Research Collaborative captures the electronic health record (EHR) data of all patients receiving any eye care at academic health systems participating in this consortium from the time each site went live on the EPIC EHR until the present. This study used data from 10 active SOURCE sites, each of whom contributed 5 to 12 years of data. Sight Outcomes Research Collaborative captures information on patient demographics and all ocular and nonocular diagnoses (identified from International Classification of Diseases [ICD] billing codes), vital signs, outpatient laboratory data, along with eye examination findings from every clinic visit. The data in SOURCE are deidentified, but privacy-preserving software (Datavant Inc.) permits researchers to follow patients longitudinally over time and across institutions while still protecting patients' identities.[26,27] The University of Michigan Institutional Review Board approved this study and waived the need for informed consent. This study was conducted in accordance with the Health Insurance Portability and Accountability Act and follows the tenets set forth by the Declaration of Helsinki.

Identifying Patients with DM

We identified adults with DM using a validated algorithm[28] based on ICD Ninth Edition (ICD-9) and Tenth Edition (ICD-10) codes, medication data, and HbA1C values (Table S1, available at www.ophthalmologyscience.org). The algorithm employs the following criteria: (1) ≥1 ICD-10 code for DM (E08–E13) and/or ICD-9 codes for DM (250.xx, 366.41, 357.2, 362.xx) or (2) receipt of ≥1 outpatient antidiabetic medication prescription or (3) ≥1 abnormal HbA1C level measured as ≥6.5% (48 mmol/mol). We also required each of these patients to have ≥1 documented BP measurement, fasting lipid profile, body mass index (BMI), and HbA1C. Among these eligible patients with DM, we excluded patients with preexisting DME as identified during their first 2 years in SOURCE. We also excluded patients if they had any other coexisting condition that could contribute to macular edema such as retinal vein occlusion, uveitis/pars planitis, pseudophakic cystoid macular edema, exudative age-related macular degeneration, or retinitis pigmentosa (Table S2, available at www.ophthalmologyscience.org). Baseline DR status (i.e., no DR, nonproliferative DR [NPDR], or proliferative DR [PDR]) was obtained for each included individual using ICD-9 and ICD-10 codes (Table S3, available at www.ophthalmologyscience.org). As a sensitivity analysis to confirm absence of DME at baseline, we required at least one record of an eye visit by Current Procedural Terminology code during the baseline period (Table S4, available at www.ophthalmologyscience.org). Demographic information such as an individual's age at baseline, sex, race, ethnicity, type of diabetes, and smoking status as recorded in the EHR were also collected for analysis.

Identifying Patients with DME

A diagnosis of DME was determined by ICD-9 and ICD-10 billing codes, which included ICD-9 362.07 and ICD-10 E08.3X1X, E09.3X1X, E10.3X1X, E11.3X1X, and E13.3X1X (Table S2, available at www.ophthalmologyscience.org). Codes for "retinal edema" (i.e., ICD-9 362.83 and ICD-10 H35.8) were included if a DR code was also present and all exclusion criteria were met (Table S2, available at www.ophthalmologyscience.org).

Statistical Analysis

All statistical analyses were performed using SAS version 9.4 software (SAS Institute) and R, version 4.3.2 (R Foundation for Statistical Computing). Continuous variables are reported as mean ± standard deviation or median and compared using an unpaired 2-tailed *t* test. Categorical variables are reported as frequencies and percentages and compared using chi-square tests. A Kruskal–Wallis rank sum test was conducted to detect differences in the population median across baseline DR status and development of DME. A Cox proportional hazards regression model was used to identify variables associated with development of DME. Covariates of interest included demographics, diabetes type, smoking status, SBP, pulse pressure (difference between SBP and diastolic BP), lipids, HbA1C, baseline DR status (i.e., no DR, NPDR, and PDR), and BMI. Patients were followed from the index date (2 years after entry into SOURCE) until the patient developed the outcome of interest, died, or reached the end of their time in SOURCE. For patients with multiple measures of BP, lipids, and BMI, we took the value closest to the index date for the analysis. Given the presumed importance of HbA1C and how it can change over time, we treated this as a time-dependent covariate in the model. The subset of included patients that were identified by metformin use alone (n = 9917), which we used as a surrogate for early or prediabetes, were input into the statistical model separately

from those cases with a formal diagnosis of type 2 diabetes. To demonstrate the utility of a potential risk calculator, covariates were estimated for 4 example patient scenarios and fitted to the Cox regression model and reported as the probability of DME developing at index date. For all analyses, a P value <0.05 was considered statistically significant.

Results

Across 10 participating eye centers within the SOURCE repository, a total of 47 509 individuals with DM met our study inclusion criteria during the defined baseline period (Tables S1 and S2, available at www.ophthalmologyscience.org). Patients were, on average, 63 ± 12 years of age and included female (n = 27 731, 58.4%) and non-Hispanic (n = 40 415, 85.1%) participants. Included individuals were 48.2% White (n = 22 896), 30.6% Black (n = 14 499), 6.4% Asian (n = 3057), 0.5% American Indian (n = 238), 0.3% Hawaiian (n = 150), and 14.0% Other or Not Available (n = 6669). Most were diagnosed with type 2 diabetes (n = 31 302, 65.9%) or metformin use alone (n = 9917, 20.9%) followed by type 1 diabetes (n = 5487, 11.5%) and other forms of DM such as monogenic diabetes or maturity-onset diabetes of the young (n = 803, 1.7%). Analysis of billing codes showed that 80% of included individuals had no recorded history of DR (n = 37 918) in the baseline period, whereas 17% had a diagnosis of NPDR (n = 8134) and 3% PDR (n = 1457) (Table S3, available at www.ophthalmologyscience.org). Just under half of the included patients had a history of current or prior tobacco smoking (n = 22 166, 46.7%). Approximately 68% of total eligible patients (n = 32 160) had a record of at least one eye examination within the baseline period (Table S4, available at www.ophthalmologyscience.org).

There were 3633 (7.6%) patients who were newly diagnosed with DME during the follow-up period. The average time to DME development in at least one eye was 875 ± 684 days (~2.4 years) with a median time of 730 days (2 years) (Fig S1, available at www.ophthalmologyscience.org). Median time to DME varied significantly by baseline DR status with time to DME longest in those with no DR (median = 846 days), followed by NPDR (median = 632 days), and then PDR (median = 563 days) ($P < 0.001$) (Fig S2, available at www.ophthalmologyscience.org). Baseline demographic characteristics were clinically similar with a mean age of 62 ± 12 years in those who developed DME versus 63 ± 13 years in the group who did not develop DME ($P < 0.001$), and both groups were more female (1992 [55%] vs. 25 739 [59%], $P < 0.001$) (Table 5). The proportion of non-Hispanic ethnicity who did and did not develop DME were similar (3214 [88%] vs. 37 201 [85%], $P < 0.001$); the number of patients who did and did not develop DME varied by race in White participants (1638 [45%] vs. 21 258 [49%]) and minorities such as Black (1332 [37%] vs. 13 167 [30%]) and Asian participants (208 [5.7%] vs. 2849 [6.5%]). Smoking status was no different between groups with less than half of the patients with and without DME having a history of current or prior smoking (1674 [46%] vs. 20 492 [47%], $P = 0.2$) (Table 5). Most patients had a diagnosis of type 2 diabetes regardless of DME development; however, those identified by metformin use alone were less likely to develop DME compared with a formal type 2 diagnosis within the chart (Table 5). Incidence of DME varied based on the SOURCE sites ranging from 3.2% to 12.8% (Table S6, available at www.ophthalmologyscience.org) with data obtained over 9 ± 2 years from the 10 sites based on the availability of their EHR.

Metabolic Variables at Index Date

Metabolic markers of interest were measured at a time point closest to the index date for all individuals (Fig 3). Those who developed DME had a higher mean HbA1C compared with those who did not develop DME (8.3 ± 2.1 vs. 7.2 ± 2.1, $P < 0.001$) (Fig 4). Mean SBP (135 ± 20 vs. 132 ± 18, $P < 0.001$) was higher in those who developed DME. Elevated diastolic BP (74 ± 12 vs. 74 ± 11, $P = 0.024$) and triglyceride (TG) values (153 ± 132 vs. 153 ± 121 mg/dL, $P = 0.031$) were statistically significant in those developing DME, whereas BMI (32 ± 7 vs. 32 ± 7 kg/m^2, $P = 0.5$) and high-density lipoprotein (HDL) values (50 ± 16 vs. 50 ± 15 mg/dL, $P = 0.14$) were similar among patients who did and did not develop DME (Fig 4).

Demographic and Metabolic Factors Associated with Development of DME

Using a multivariable Cox regression analysis, Black patients had a 40% increased hazard of DME (hazard ratio [HR] 1.40, 95% confidence interval [CI]: 1.30−1.51, $P < 0.001$) compared with White patients. There was no significant difference in hazard of DME between patients with type 1 versus type 2 diabetes; however, those diagnosed as having diabetes in our study by metformin use alone had a 55% decreased risk of DME compared with those with type 1 DM (HR 0.45, 95% CI: 0.39−0.53, $P < 0.001$). We found no statistically significant association between cigarette smoking (HR 0.98, 95% CI: 0.92−1.05) or sex (HR 1.06, 95% CI: 0.98−1.13) and development of DME (Fig 5). Increased risk of DME was associated with age, where each additional 5 years of age conferred a 2% increased risk of DME (HR 1.02, 95% CI: 1.01−1.04, $P < 0.01$).

Individuals with NPDR at the index date had a 270% increased hazard risk of DME (HR 3.67, 95% CI: 3.41−3.95), whereas those with PDR at the index date had a 420% increased hazard risk of DME (HR 5.19, 95% CI: 4.61−5.85) compared with those without DR at baseline (Fig 5). Every 1 unit increase in HbA1C was associated with a 15% increased hazard of DME (HR 1.15, 95% CI: 1.13−1.17, $P < 0.001$). For every 10 mmHg increase in SBP, the hazard of DME increased 6% (HR 1.06, 95% CI: 1.02−1.09, $P < 0.001$). No association with DME was identified for BMI (HR 0.99, 95% CI: 0.99−1.00, $P = 0.25$), dyslipidemia measured by TG (HR 0.99, 95% CI: 0.99−1.00, $P = 0.11$), or HDL (HR 0.99, 95% CI: 0.99−1.00, $P = 0.96$) levels. A sensitivity analysis was performed by repeating the Cox regression model on the subset of patients who developed DME that had an eye

Table 5. Baseline Patient Characteristics Measured at Index Date for Those with Diabetes Who Do and Do Not Develop Diabetic Macular Edema

	No DME (N = 43 876)	New DME Dx (N = 3633)	*P* Value
Age, yrs, mean (SD)	63 (13)	62 (12)	**<0.001**
Sex, n (%)			**<0.001**
Female	25 739 (59)	1992 (55)	
Male	18 137 (41)	1641 (45)	
Race, n (%)			**<0.001**
White	21 258 (48.5)	1638 (45.1)	
Black	13 167 (30)	1332 (36.7)	
Asian	2849 (6.5)	208 (5.7)	
American Indian	222 (0.5)	16 (0.4)	
Hawaiian	137 (0.3)	13 (0.4)	
Other	4985 (11.3)	343 (9.4)	
N/A	1258 (2.9)	83 (2.3)	
Ethnicity, n (%)			**<0.001**
Non-Hispanic	37 201 (84.8)	3214 (88.5)	
Hispanic	4986 (11.4)	326 (9.0)	
Unknown/refused	1689 (3.8)	93 (2.5)	
Type of diabetes, n (%)			**<0.001**
Type 1 diabetes	4824 (11)	663 (18.2)	
Type 2 diabetes	28 703 (65.4)	2599 (71.5)	
Metformin use	9663 (22)	254 (7.1)	
Other (MODY, monogenic, etc)	686 (1.6)	117 (3.2)	
Baseline DR status, n (%)			**<0.001**
No DR	36 109 (82)	1809 (50)	
NPDR	6681 (15)	1453 (40)	
PDR	1086 (3)	371 (10)	
Smoking status, n (%)			0.2
Never	22 838 (52.1)	1925 (52.9)	
Current or prior	20 492 (46.7)	1674 (46.1)	
Unknown	546 (1.2)	34 (1)	

Data combined from all 10 participating centers. *P* values were calculated with Pearson chi-squared test and Wilcoxon rank sum test. Bolded *P* value indicates statistical significance.
DME = diabetic macular edema; DR = diabetic retinopathy; Dx = diagnosis; MODY = maturity-onset diabetes of the young; N/A = not applicable; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; SD = standard deviation.

examination recorded in the baseline period (n = 2602) (Fig S6, available at www.ophthalmologyscience.org). There were no substantive changes in the results of the original model when the added requirement of a baseline eye visit was considered.

Discussion

It is well accepted that management of systemic disease with stringent regulation and treatment of hyperglycemia, hypertension, and hyperlipidemia is the first step in delaying onset and/or progression of DR. However, modifiable systemic markers do not currently play a defined role in DME monitoring or management, and the role of metabolic dysfunction in the development of DME is not well understood. In this cohort study of 47 509 patients with diabetes, Black race, and elevated SBP in addition to systemic hyperglycemia as measured by HbA1C and severity of baseline DR status were associated with development of DME. Interestingly, other systemic markers of metabolic dysfunction such as BMI and dyslipidemia measured by HDL and TG levels at the index date were not associated with development of DME in our model.

By evaluating documented EHR laboratory and vital sign measurements rather than diagnosis codes or medication list, we could more accurately assess a patient's baseline metabolic control regardless of treatment or diagnosis. Those identified as having diabetes by metformin use alone, which likely represents milder blood glucose dysregulation, showed a decreased risk of DME development. We confirm previous reports of elevated SBP with increased risk of DME in patients with diabetes.[1,5] Our study adds to the growing body of literature that BP control is an important risk factor for the development of DME when accounting for baseline DR status. We also show that the significance of these risk factors can be appreciated sometimes years in advance of DME development as, on average, DME developed 2.4 years after the index date and independent of other markers of metabolic dysfunction. Elevated BP and associated fluctuations of both diastolic BP or SBP are hypothesized to directly affect peripheral retinal arterial pressure and arterial wall stiffness, which subsequently decreases retinal vasculature integrity, leading to DME.[29–31] An interruption between hydrostatic and oncotic pressures is also hypothesized to contribute to DME development, thus, elevated SBP may also indirectly increase the risk of DME through its systemic effects on

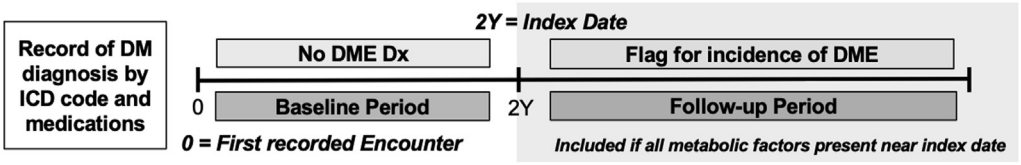

Figure 3. Use of Sight Outcomes Research Collaborative for cohort development to identify individuals who develop diabetic macular edema (DME). A record of diabetes mellitus (DM) diagnosis (Dx) by international classification code (ICD) or medications was used to identify adult patients (>18 years of age). A 2-year baseline period from first encounter (0) to index date (2Y) was employed to include those without DME and exclude those with preexisting macular edema of any type or known diagnosis of DME. Patients were then followed for the development of DME in the follow-up period. All included individuals had at least one record of blood pressure, high-density lipoprotein, and triglyceride levels, body mass index, and hemoglobin A1C captured at time point closest to index date.

kidney function and overall fluid status.[32,33] This work emphasizes the importance of early guidance to patients with diabetes on BP control by eye care providers in conjunction with primary care providers and need for further mechanistic studies to understand the effects of BP on DME development.

In our analysis, baseline values of BMI and measured markers of dyslipidemia were not clinically different between those who did and did not develop DME and did not associate with DME development; however, average values measured in both groups were elevated above normal for both BMI and TG levels (i.e., BMI > 29 kg/m^2 and TG > 150 mg/dL). The role of BMI and lipid levels, including treatment of these markers, on development of DR and DME has been fairly mixed.[34–39] Even though measured 2 years before development of DME in some individuals in this study, BMI and lipid levels are unlikely to significantly fluctuate over this time frame, and thus, we interpret our findings to suggest that these markers are not drivers for DME development regardless of diabetes type or baseline DR status. Abnormal baseline values of the studied variables may still represent a state of low-lying inflammation as hypothesized in MetS; however, our data suggest that DME development is more dependent on elevations in BP and blood glucose levels specifically. Although fenofibrate, a peroxisome proliferator-activated receptor alpha agonist that reduces TGs and low-density lipoprotein and increases HDL levels, is currently being investigated in DR and DME, available data suggest that any benefit is independent of effect on serum lipid levels and instead acts through a secondary mechanism of antiinflammatory and antiapoptotic pathways.[40,41] Although we did not see increases in BMI or measured markers of dyslipidemia associated with MetS correspond with new-onset DME in this study, these variables have been shown to contribute to other macrovascular and microvascular comorbidities of diabetes, and patients should be counseled on treatment based on available recommendations.

Although the study aim focused on dysmetabolism and DME, our data stress important racial disparities in DME development. Like prior reports,[1,4,42] we show that Black patients are more likely to develop DME when compared with White patients and most strikingly, that race held a similar risk of developing DME as a 3 unit increase in HbA1C even when accounting for baseline DR status in our model and at least a 2-year timeframe of access to care. Importantly, Black patients were overrepresented in our cohort at 30.5% compared with the 2023 US census report of 14% in

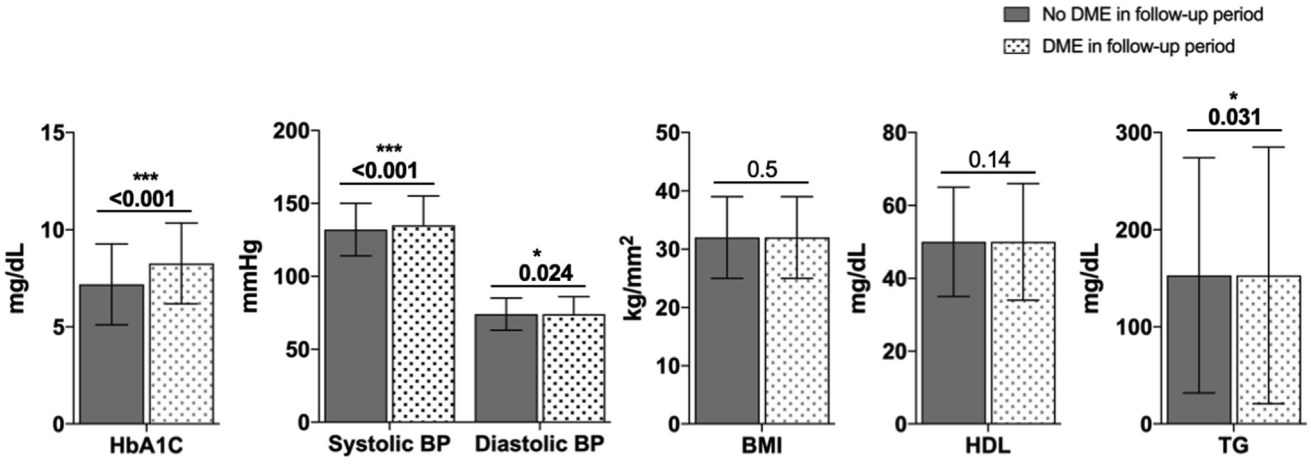

Figure 4. Baseline metabolic variables at index date for those who develop diabetic macular edema (DME) compared those with diabetes mellitus (DM) who do not develop DME. Metabolic values (mean ± standard deviation) measured at record closest to the index date for each included individual comparing those with DM that do (dot pattern bars) and do not (gray bars) develop DME in the follow-up period. BMI = body mass index; BP = blood pressure; HbA1C = hemoglobin A1C; HDL = high-density lipoprotein; TG = triglyceride levels. In the figures, * indicates $P < 0.05$, ** indicates $P < 0.01$, *** indicates $P < 0.001$.

	Adj HR Ratio	Lower 95% CI	Upper 95% CI	*P* value
Age	1.02	1.01	1.04	**0.006**
Male Gender	1.06	0.98	1.13	0.13
Black Race	**1.40**	1.30	1.51	**<0.001**
Type 2 DM	0.93	0.84	1.02	0.12
Metformin Use	**0.45**	0.39	0.53	**<0.001**
Smoking	0.98	0.92	1.05	0.53
NPDR	**3.67**	3.41	3.95	**<0.001**
PDR	**5.19**	4.61	5.85	**<0.001**
HbA1C	**1.15**	1.13	1.17	**<0.001**
Systolic BP	**1.06**	1.02	1.09	**<0.001**
BMI	0.99	0.99	1.00	0.25
HDL	0.99	0.99	1.00	0.11
TG	0.99	0.99	1.00	0.96

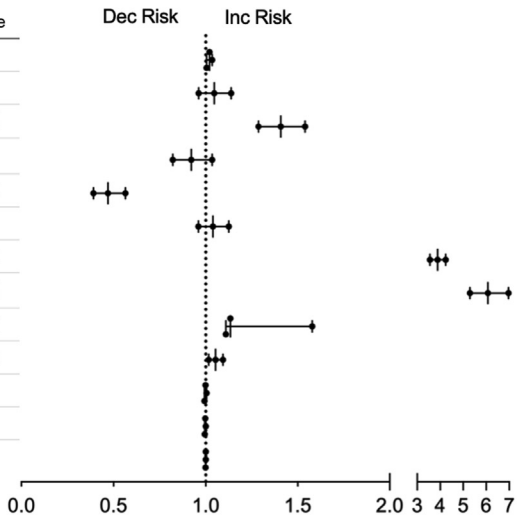

Figure 5. Risk factors for developing diabetic macular edema (DME) in patients with diabetes mellitus (DM) identified by multivariable regression. Forest plots of adjusted hazard ratios from a multivariate Cox regression analysis of demographic and metabolic risk factors on a new diagnosis of DME with corresponding 95% confidence interval (CI). Reference group is female for gender, White for race, no diabetic retinopathy (DR) for baseline DR, no history of smoking for smoking status, and type 1 DM for diabetes type. For continuous variables, risk is associated with 1 corresponding unit except for age, which has increments of 5 years, and systolic blood pressure, which has increments of 10 mmHg. adj HR = adjusted hazard ratio; BMI = body mass index; BP = blood pressure; Dec = decreased; HbA1C = hemoglobin A1C; HDL = high-density lipoprotein; Inc = increased; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; TG = triglyceride levels.

the general population,[43] and it is likely the implications of these finding are explained by work showing disparities in DR screening and DME treatment based on race.[44,45] A recent study also identified modifiable socioeconomic factors rather than race itself predicted visually threatening DR.[46] Although further investigation is necessary to determine whether Black race itself is an independent risk factor or a marker of health care inequities, lifestyle, environment, or other stresses, this study emphasizes the need for resources focused on early identification, close monitoring, and follow-up for DME in Black patients.[44,47]

A direct application of this report is a scalable, scoring risk algorithm for patients with DM for the development of this sight-threatening condition to help identify those who require more frequent visits and ultimately improve allocation of limited health resources. In our cohort of nearly 50 000 patients with DM, 7.6% developed DME within the 9 ± 2 years studied, which suggests that a small number of patients are at the greatest risk of vision loss. Identifying those at risk early allows for more aggressive risk factor management and focused use of resources to prevent future vision loss. For example, this Cox regression analysis could be used to create a risk calculator tool to identify risk of DME (Table 7). Although a calculator of this type requires validation, Table 7 demonstrates the intricacy of the studied variables in predicting risk of DME at index date for different clinical scenarios and highlights the important context of baseline DR status in this prediction. We anticipate that a validated tool could help an eye care provider more accurately determine a safe follow-up timeframe and better utilization of limited resources. Future directions of this work also include determining how metabolic variables identified in this study are associated with the need for intraocular treatment burden, which is well-known to be both invasive and expensive.[48]

Limitations

There are several limitations of this study inherent to retrospective data collection. Both our inclusion and exclusion criteria (Tables S1 and S2, available at www.ophthalmologyscience.org) may have captured patients inaccurately coded or missed patients with diabetes who developed DME. We used a validated methodology to identify patients with diabetes, although with a wide net criterion for the diagnosis of diabetes, we may have overestimated the total number of individuals with diabetes. However, this allowed us to best capture a baseline diabetes population despite variable coding patterns between providers and institutions. Per prior reports,[28] we used medication use alone to help identify our cohort, but we recognize certain antidiabetic medications such as metformin and mifepristone can be used for indications outside of diabetes. Despite this, most off-label uses of metformin relate to diabetes and/or obesity such as prediabetes, antipsychotic-induced weight gain, gestational DM, and polycystic ovarian syndrome, and thus, inclusion may still be applicable to this population.

Furthermore, because of the scope of the SOURCE database and the cohort size included in this study, manual chart review was not possible to confirm the diagnostic codes used or even clinical cohort characteristics such as diabetes duration, a considerable risk factor for the development of DME. To address this, we included severity of DR (i.e., no DR, NPDR, or PDR) identified during the baseline period as a proxy for diabetes duration. We also

Table 7. Example Risk Calculator for Diabetic Macular Edema Development Incorporating Baseline Metabolic and Demographic Risk Factors

Metabolic and Demographic Factor Identified at Index Date	No Baseline DR		Baseline NPDR		Baseline PDR	
	Predicted Risk of DME at Index Date (%)	*95% CI*	*Predicted Risk of DME at Index Date (%)*	*95% CI*	*Predicted Risk of DME at Index Date (%)*	*95% CI*
45-year-old Black, non-Hispanic woman, with type 1 DM (HbA1C 8.9, SBP 135, PP 30, BMI 22, HDL 40, TG 167, current smoker)	7.25	(7.23–7.28)	24.14	(24.12–24.16)	32.36	(32.34–32.38)
75-year-old White, non-Hispanic man with type 2 DM (HbA1C 7.6, SBP 140, PP 40, BMI 30, HDL 50, TG 153, and history of smoking)	6.19	(6.16–6.21)	20.88	(20.86–20.91)	28.22	(28.22–28.24)
65-year-old Asian, non-Hispanic man with type 2 DM (HbA1C 6.6, SBP 155, PP 50, BMI 28, HDL 35, TG 140, never smoker)	11.82	(11.79–11.85)	36.96	(36.94–36.98)	47.95	(47.94–47.97)
48-year-old Hispanic woman with metformin use only (HbA1C 6.6, SBP 160, PP 50, BMI 32, HDL 45, TG 170, unknown smoker status)	6.05	(6.03–6.08)	20.48	(20.45–20.50)	27.70	(27.68–27.72)

BMI = body mass index (kg/m^2); CI = confidence interval; DM = diabetes mellitus; DME = diabetic macular edema; DR = diabetic retinopathy; HbA1C = hemoglobin A1C (%); HDL = high-density lipoprotein (mg/dL); NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; PP = pulse pressure (difference of systolic and diastolic blood pressure in mmHg); SBP = systolic blood pressure (mmHg); TG = triglycerides (mg/dL).

performed a sensitivity analysis on the subset of patients with a recorded eye examination in the baseline period, who are thus more likely to have accurately coded eye findings that confirmed the reported results. Additionally, our findings such as the association with Black race, baseline DR status, and glycosylated hemoglobin closely corroborate with existing knowledge and previously published studies.[1,4,42] Thus, we anticipate the highlighted findings are clinically applicable despite the absence of diabetes duration in our model; however, further studies are necessary to confirm this.

Finally, although our study design allowed us to accurately identify patients who developed DME and captures how HbA1C changes over time, we were not able to capture fluctuations in the other metabolic markers that may be important in DME development. We chose to define dyslipidemia in this study using HDL and TG rather than cholesterol and low-density lipoprotein based on the criteria used for MetS. Thus, this study cannot comment on the effect of statin use or baseline cholesterol levels in DME development.

Evaluation of patients receiving eye care from tertiary centers throughout the United States showed that Black race and elevated SBP in addition to elevated systemic hyperglycemia associated with an increased likelihood of developing DME in patients with diabetes, whereas other metabolic variables such as BMI and HDL and TG levels did not. Collaboration with and education of internists and/or endocrinologists on BP control in these patients may help reduce the risk of vision loss from DME.

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Analysis and interpretation: Haliyur, Marwah, Stein, Shah

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Abbreviations and Acronyms:
BMI = body mass index; **BP** = blood pressure; **CI** = confidence interval; **DR** = diabetic retinopathy; **DM** = diabetes mellitus; **DME** = diabetic macular edema; **EHR** = electronic health record; **HbA1C** = hemoglobin A1C; **HDL** = high-density lipoprotein; **HR** = hazard ratio; **ICD** = International Classification of Diseases; **MetS** = metabolic syndrome; **NPDR** = nonproliferative diabetic retinopathy; **PDR** = proliferative diabetic retinopathy; **SBP** = systolic blood pressure; **SOURCE** = Sight Outcomes Research Collaborative; **TG** = triglyceride.

Key words:
Black race, Blood pressure, Diabetic macular edema, Diabetic retinopathy, Metabolic syndrome.

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