Racial and Ethnic Differences in Healthcare Use among Patients with Uncontrolled and Controlled Diabetes

Running head: Racial differences in diabetes healthcare use

Yhenneko J. Taylor, PhD
Center for Outcomes Research and Evaluation, Carolinas HealthCare System,
1540 Garden Terrace, Suite 405, Charlotte, NC 28203
Phone: 704-355-6562/Fax: 704-355-1383
Yhenneko.Taylor@carolinashealthcare.org

Melanie D. Spencer, PhD
Center for Outcomes Research and Evaluation, Carolinas HealthCare System,
1540 Garden Terrace, Suite 406, Charlotte, NC 28203
Phone: 704-355-9886/Fax: 704-355-1383
Melanie.Spencer@carolinashealthcare.org

Rohan Mahabaleshwarkar, PhD
Center for Outcomes Research and Evaluation, Carolinas HealthCare System,
1540 Garden Terrace, Suite 405, Charlotte, NC 28203
Phone: 704-355-9958/Fax: 704-355-1383
Rohan.Mahabaleshwarkar@carolinashealthcare.org

Thomas Ludden, PhD
Department of Family Medicine, Carolinas HealthCare System,
2001 Vail Ave., Suite 400B, Charlotte, NC 28207
Phone: 704-608-2390
Tom.Ludden@carolinashealthcare.org

Corresponding Author

Yhenneko J. Taylor, PhD
Center for Outcomes Research and Evaluation
Carolinas HealthCare System
1540 Garden Terrace, Suite 405
Charlotte, NC 28203
Phone: 704-355-6562
Fax: 704-355-1383
Email: yhenneko.taylor@carolinashealthcare.org

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The authors have no conflicts of interest to report.

Biographical note:

Y.T., M.S. and R.M. drafted the manuscript. R.M. managed the data for this project. R.M. and Y.T. conducted the statistical analyses. Y.T. and M.S. created the figures. T.L. geocoded patient addresses, compiled neighborhood poverty data and critically reviewed the manuscript for important intellectual content. All authors were involved in the design of the study and approved the final version of the manuscript prior to submission.

Abstract (248/300 words)

Objectives: To examine racial/ethnic differences in healthcare use among patients classified as having controlled and uncontrolled diabetes.

Design: Data from the Carolinas HealthCare System electronic data warehouse were used. Glycemic control was defined as glycosylated hemoglobin (HbA1c) < 8% (64mmol/mol) in 2012 (n=9,996). Patients with HbA1c ≥8% (64mmol/mol) in 2012 were classified as uncontrolled (n= 2,576). Race and ethnicity were jointly classified as non-Hispanic Black, non-Hispanic White or Other. Separate mixed effects negative binomial models estimated the independent effect of race/ethnicity on the number of emergency department (ED) visits, hospitalizations and physician office visits in 2013, in each patient group, adjusting for significant confounding variables.

Results: Rates of diabetes-related ED visits were two to three times higher for non-Hispanic Blacks compared to non-Hispanic Whites (uncontrolled rate ratio [RR]: 3.41 95% CI: 1.41 – 8.22; controlled RR: 2.95; 95% CI: 1.78 - 4.91). Similar differences were observed for all-cause ED visits (uncontrolled RR: 1.83, 95% CI: 1.50 - 2.24; controlled RR: 2.45, 95% CI: 2.17 - 2.77). Non-Hispanic Blacks with controlled and uncontrolled diabetes also had lower rates of all-cause physician office visits when compared to non-Hispanic Whites (uncontrolled RR: 0.84, 95% CI: 0.77 - 0.91; controlled RR: 0.81, 95% CI: 0.78 - 0.84).

Conclusion: Notable racial/ethnic disparities exist in the use of emergency services and physician offices for diabetes care. Strategies such as patient education and care delivery changes that address healthcare access issues in racial/ethnic minorities should be considered to offer better diabetes management and address diabetes disparities.

Keywords: health care disparities, HbA1c, health care utilization, glycemic control, emergency services, primary care utilization

Introduction

Racial and ethnic minorities have the highest prevalence of diabetes mellitus in the United States (US), a trend that is expected to continue over the next three decades (Centers for Disease Control and Prevention 2014, Narayan et al. 2006). Non-Hispanic Black adults have one of the highest diabetes prevalence rates. Approximately 13.2% of non-Hispanic Blacks have diagnosed diabetes, a rate that is 73% higher than for non-Hispanic White adults and 3% higher than for Hispanic adults (Centers for Disease Control and Prevention 2014). Racial and ethnic minorities also have higher diabetes mortality, higher risk of diabetes complications and are less likely to receive high quality diabetes care (Spanakis and Golden 2013). For example, both Hispanics and non-Hispanic Blacks with diabetes have lower rates of glycemic and blood pressure control (Division of Diabetes Translation 2015). Recent research suggests that these observed disparities in prevalence of diabetes and rates of glycemic control persist independent of insurance status, income or access to primary care (Heidemann et al. 2016).

Much research has explored factors associated with racial and ethnic disparities in diabetes and strategies for improving outcomes for racial and ethnic minorities. The causes of racial and ethnic disparities in diabetes include individual, healthcare system and environmental factors. Obesity, a prominent risk factor for diabetes, tends to be higher among minority populations (Spanakis and Golden 2013). The higher prevalence of diabetes among minorities may also be related to differences in living conditions that affect nutrition, access to exercise and toxic exposures. One study found that non-Hispanic Black and non-Hispanic White adults living in the same environment had similar prevalence of diabetes (LaVeist et al. 2009). Other factors such as poorer access to healthcare, lower quality of health care, lack of health insurance, poor self-

management of blood glucose, depression and low physical activity may be associated with poorer glycemic control among minorities (Spanakis and Golden 2013). Reviews of strategies to address these disparities identify the healthcare system as an important stakeholder in multifactorial approaches that engage patients and providers and involve community health workers and other types of outreach (Peek, Cargill, and Huang 2007, Peek et al. 2012, Betancourt, Duong, and Bondaryk 2012).

Research available on racial and ethnic differences in use of the healthcare system by patients with diabetes suggest that disparities exist. In one study using self-reported data from a nationally representative sample of 984 adults with diabetes, researchers found that non-Hispanic Blacks with diabetes have fewer primary care visits and fewer prescription refills when compared to non-Hispanic Whites (Lee, Liu, and Sales 2006). Another study examining emergency department use among 8,596 patients in a diabetes management program in Louisiana found that Whites with type 2 diabetes had 19% lower odds of non-urgent emergency department visits compared to Blacks (Chiou et al. 2010). In a representative sample of 3,003 older adults with diabetes in California, researchers using self-reported data found that non-Hispanic Blacks had nearly four times higher odds of emergency department visits for diabetes and half times the odds of seeing a doctor in the previous 12 months compared to non-Hispanic Whites (Kim et al. 2012). Improving glycosylated hemoglobin (HbA1c) values has been associated with lower healthcare utilization and costs for patients with diabetes in U.S. and international studies that did not examine differences by race (McBrien et al. 2016, Afroz et al. 2016, Aagren and Luo 2011). Additional research using clinical databases can determine the impact of improved glycemic control on observed racial/ethnic disparities in the use of healthcare.

The objective of this retrospective cohort study was to investigate racial and ethnic differences in healthcare use among patients classified as having controlled and uncontrolled diabetes. We hypothesized that among patients with similar categories of glycemic control, the number of all-cause and diabetes-related healthcare visits would differ by race/ethnicity. To our knowledge, this is the first study to examine differences in healthcare use by race and glycemic control while controlling for relevant risk factors such as comorbidities and patient demographic characteristics. This study adds important findings to the existing literature on racial and ethnic differences in healthcare use for patients with diabetes by identifying potential areas for interventions to reduce disparities in diabetes management and outcomes.

Methods

Setting and data sources

Carolinas HealthCare System is one of the largest integrated healthcare systems in the US, with over 900 care locations including hospitals, healthcare pavilions, physician practices, surgical and rehabilitation centers, home health agencies, nursing homes, and hospice and palliative care centers located in the states of North Carolina, South Carolina, and Georgia. Data for this study were obtained from the Carolinas HealthCare System electronic data warehouse. The electronic data warehouse contains a wide range of data on: (i) patient demographics such as age, race/ethnicity, gender and health insurance status; (ii) healthcare encounters including admission and discharge dates, and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes; and (iii) laboratory results. The study cohort was defined using data from 2012; primary and secondary outcomes were determined using data from 2013. In addition, patient addresses were geocoded

and linked by census tract to neighborhood poverty rates from the 2006-2010 American Community Survey (ACS) conducted by the US Census Bureau (U.S. Census Bureau 2015).

Study population

The study cohort consisted of patients aged 18 and older, with type 2 diabetes mellitus, who were residents of Mecklenburg County, NC. Patients were included if they had one or more inpatient or outpatient billing records with ICD-9-CM codes for type 2 diabetes (250.x0 and 250.x2) during 2012. Patients with type 1 diabetes (patients with one or more records with ICD-9-CM codes of 250.x1 and 250.x3 during 2012 or 2013) and gestational diabetes (patients with one or more records with ICD-9-CM code of 648.8x during 2012 or 2013) were excluded from the study (n=1,837). We also excluded patients from the study who had HbA1c readings within a span of 30 days that differed by more than 1 unit, due to potential errors in one of these readings (n=181). Finally, patients with missing data on any of the study variables were excluded (n=2,616). The final sample consisted of 2,576 patients with uncontrolled diabetes and 9,996 patients with controlled diabetes. Diabetes control was determined from the average of all HbA1c readings during 2012 and categorized based on diabetes management guidelines from the American Diabetes Association and the European Association for the Study of Diabetes (Inzucchi et al. 2012). While these guidelines recommend a goal of HbA1c < 7% (53mmol/mol) for patients with diabetes, they also state that HbA1c targets may be as high as 8% (64mmol/mol), based on individual circumstances such as increased age, decline in capacity for self-care or reduced cognitive, psychological, or economic status. Therefore, we classified patients with average HbA1c ≥ 8% (64mmol/mol) as having uncontrolled diabetes, whereas those

with average HbA1c < 8% (64mmol/mol) were classified as having controlled diabetes. Approval to conduct this study was obtained from the Carolinas HealthCare System Institutional Review Board.

Measures

Primary outcomes for this study were all-cause and diabetes-related inpatient, emergency department and physician office visits. The values of these variables were determined from 2013 billing data for each care setting. Visits with primary or secondary (i.e. second-listed) diagnosis codes of 250.x0 or 250.x2 were considered diabetes-related. We also examined the following independent variables: race/ethnicity, age, gender, insurance, diabetes-related comorbidities including neuropathy, nephropathy, retinopathy, hypertension, heart disease, stroke, and cancer, body mass index (BMI) and neighborhood poverty rate. Race was categorized as non-Hispanic Black, non-Hispanic White, or other (consisting of Asians, Hawaiians and Pacific Islanders, Hispanics, Native Americans, and individuals with multiple races). Patient age was grouped into one of seven categories: 18-29, 30-39, 40-49, 50-59, 60-69, 70-79 and ≥80 years. Insurance was defined based on the patient's primary payer for their last healthcare visit in 2012 and was categorized as commercial, Medicare, Medicaid, or other (consisting of patients with charity, self-pay, or unknown insurance). Diabetes-related comorbidities were identified based on the ICD-9-CM diagnosis codes appearing on inpatient or outpatient billing records during 2012, and included nephropathy, neuropathy, retinopathy, heart disease, hypertension, stroke and cancer. BMI was categorized as underweight (<18.5), normal (18.5-24.9), overweight (25-29.9), or obese (≥30) as determined from the last weight and height measurement recorded in 2012.

Statistical Analysis

We compared characteristics of patients with controlled and uncontrolled diabetes using chi-square tests for all variables except neighborhood poverty rate, for which a linear mixed model was used. Racial/ethnic differences in the mean number of all-cause and diabetes-related inpatient, emergency department and physician office visits were assessed separately for patients with controlled and uncontrolled diabetes. We used Kruskal-Wallis one-way ANOVA for bivariate analyses of healthcare use and mixed effects negative binomial models for multivariable analyses. Covariates for the multivariable negative binomial models included following variables: age, gender, insurance, diabetes-related comorbidities including neuropathy, nephropathy, retinopathy, hypertension, heart disease, stroke, cancer, BMI and neighborhood poverty rate. We assessed each variable for confounding with race for each of the six outcome measures. The final multivariable model included only variables that resulted in a change of 10% or more in the rate ratio (RR) for race in the fully adjusted model (Mickey and Greenland 1989, Marcinkevage et al. 2013). Means and 95% confidence intervals were reported for continuous variables. Frequencies and percentages were reported for categorical variables. RRs and 95% confidence intervals (CIs) were reported for the negative binomial models. A p-value < 0.05 was considered significant. All analyses were conducted using SAS v9.4 (SAS Institute, Inc., Cary, NC).

Results

Patients with controlled and uncontrolled diabetes differed on a number of characteristics (Table 1). Compared to patients with controlled diabetes, patients with uncontrolled diabetes were more likely to be non-Hispanic Black, male, younger than

60 years old and have a higher prevalence of nephropathy, neuropathy and obesity. Patients with uncontrolled diabetes also had a higher mean neighborhood poverty rate compared to those with controlled diabetes (Table 1).

Comparisons of average healthcare use in 2013 revealed notable differences by race for patients with uncontrolled and controlled diabetes (see supplemental table S1). Among patients with uncontrolled diabetes, non-Hispanic Black patients had higher mean diabetes-related and all-cause emergency department visits than non-Hispanic Whites. Non-Hispanic Black patients with uncontrolled diabetes also had a higher mean number of diabetes-related inpatient stays. Compared to non-Hispanic White patients with uncontrolled diabetes, both non-Hispanic Black and other race patients had a lower mean number of all-cause physician office visits. Results were similar for patients with controlled diabetes. In addition, non-Hispanic Blacks with controlled diabetes had lower mean diabetes-related physician office visits and higher mean all-cause hospitalizations compared to their non-Hispanic White counterparts (all $p<0.05$, see supplemental table S1).

Preliminary analyses revealed few significant confounders. Among patients with uncontrolled diabetes, hypertension and poverty were significant confounders in the relationship between race and diabetes-related emergency department visits, while age and insurance were significant confounders in the relationship between race and all-cause emergency department visits. Age was also a significant confounder in the relationship between race and diabetes-related emergency department visits for patients with controlled diabetes. No other covariates met the criteria for confounding (data not shown).

Following adjustment for significant confounders, associations between race and diabetes-related healthcare use were evident for both groups of patients (Figure 1). Non-

Hispanic Blacks with controlled and uncontrolled diabetes had three times the rate of diabetes-related emergency department visits as non-Hispanic White patients (uncontrolled RR: 3.41, 95% CI: 1.41 - 8.22; controlled RR: 2.95; 95% CI: 1.78 - 4.91). Patients with uncontrolled diabetes of other races also had higher diabetes-related emergency department visits compared to non-Hispanic Whites (RR: 4.06; 95% CI: 1.25 -13.21; Figure 1). Diabetes-related inpatient stays were lower for other race patients compared to non-Hispanic Whites with controlled diabetes, while diabetes-related physician office visits were lower for non-Hispanic Blacks with controlled and uncontrolled diabetes when compared to their non-Hispanic White counterparts.

Regarding all-cause healthcare use (Figure 2), emergency department visits for non-Hispanic Blacks with controlled and uncontrolled diabetes were more than 50% higher than the rate for non-Hispanic Whites (uncontrolled RR: 1.83, 95% CI: 1.50 - 2.24; controlled RR: 2.45, 95% CI: 2.17 - 2.77). Among patients with controlled diabetes, rates of all-cause emergency department visits were also higher for patients belonging to other races compared to non-Hispanic Whites (RR: 1.39, 95%CI: 1.14 - 1.70). Non-Hispanic Blacks with controlled and uncontrolled diabetes had lower adjusted rates of all-cause physician office visits when compared to non-Hispanic Whites (uncontrolled RR: 0.84, 95% CI: 0.77 - 0.91; controlled RR: 0.81, 95% CI: 0.78 - 0.84). Comparisons of mean adjusted all-cause physician office visits versus all-cause emergency department visits demonstrated notable variation by race, however, with smaller distinctions between patients based on diabetes control (Figure 3).

Discussion

Reducing disparities in diabetes has been identified as an important goal given the high prevalence and cost of the disease (Betancourt, Duong, and Bondaryk 2012).

To this end, useful strategies including multifaceted approaches that combine patient, provider, community and health system interventions have been identified (Betancourt, Duong, and Bondaryk 2012, Peek, Cargill, and Huang 2007, Kim et al. 2016). We examined whether racial/ethnic disparities in use of healthcare persist among patients classified as having controlled and uncontrolled diabetes. A new finding of our research is that large and significant differences by race/ethnicity exist in use of healthcare among patients with similar classifications of diabetes control after adjustment for important covariates, such as insurance status and neighborhood poverty. These results add to the literature on disparities in healthcare access and outcomes among patients with diabetes by highlighting distinctly different patterns by race/ethnicity in the settings where patients with diabetes receive care.

We found notably higher rates of diabetes-related emergency department visits among non-Hispanic Black patients with controlled and uncontrolled diabetes when compared to non-Hispanic White patients. A similar result was seen in a study of older adults with diabetes (Kim et al. 2012). Barriers in access to care, low socioeconomic status, greater comorbid burden and greater disease severity are some factors that may contribute to higher use of the emergency department (Kim et al. 2012, Hong, Baumann, and Boudreaux 2007). Among patients with uncontrolled diabetes, higher use of the emergency department may be related to higher HbA1c levels and associated complications. In our sample, mean HbA1c values were slightly higher among non-Hispanic Blacks with uncontrolled diabetes compared to non-Hispanic Whites with uncontrolled diabetes (mean ± standard deviation: 9.77±1.88 vs. 9.24±1.19).

We found slightly lower rates of diabetes-related office visits for non-Hispanic Black patients with controlled and uncontrolled diabetes compared to non-Hispanic Whites. This result differs from that of a previous study, which analyzed self-reported

data from the Indiana Behavioral Risk Factor Surveillance System and found fewer diabetes visits for non-Hispanic Whites with type 2 diabetes compared to non-Hispanic Blacks (Mayo-Gamble and Lin 2014). This difference may reflect differences in data source (self-report vs. electronic medical record) as well as geographic differences in the population examined.

Our finding of higher all-cause emergency department visits and lower all-cause office visits among non-Hispanic Black patients with diabetes, compared to non-Hispanic Whites, is consistent with prior research (Chiou et al. 2010, Kim et al. 2012). Many factors, including barriers to care, lack of a usual source of care, differences in healthcare seeking behavior and mistrust of the healthcare system, influence use of the emergency department by minorities (Blanchard, Haywood, and Scott 2003, Arnett et al. 2016). In our sample, non-Hispanic Black patients with controlled and uncontrolled diabetes had higher comorbidity burden than non-Hispanic Whites, however, adjustment for these factors did not change results notably. Moreover, while glycemic control is associated with lower emergency department use (Chiou et al. 2010), we found that non-Hispanic Black patients with both controlled and uncontrolled diabetes had notably higher emergency department use when compared to their non-Hispanic White counterparts. Prior research has documented practical barriers to accessing primary care that influence use of the emergency department for non-urgent reasons (Rust et al. 2008). Other research suggests that non-Hispanic Blacks are more likely to have no usual source of care or prefer the emergency department as a source of care when compared to non-Hispanic Whites (Brown et al. 2012). Identifying and addressing the root causes of these patterns of healthcare use can inform ways to increase the consistency of care, reduce healthcare costs and improve outcomes for non-Hispanic Black patients with diabetes.

Limitations

Our study had limitations. We collapsed racial/ethnic groups other than non-Hispanic Blacks and non-Hispanic Whites because of small sample sizes and, therefore, were unable to make specific inferences about other groups. Compared to other racial and ethnic minorities, non-Hispanic Blacks have the highest burden of diabetes in the nation (Centers for Disease Control and Prevention 2014, Boyle et al. 2010). We were unable to control for the type of medication patients used to manage their diabetes or changes in glycemic control over the study period. Considering that minority patients have poorer adherence to medications (Shenolikar et al. 2006), controlling for medication use may increase the magnitude of differences observed. Patients classified as having glycemic control at baseline could have become uncontrolled during the one-year study period. Complications from uncontrolled diabetes could have resulted in higher use of the emergency department. If a higher percentage of non-Hispanic Black patients became uncontrolled over the study period, this would suggest a need for interventions to help patients maintain control and thus avoid excess emergency department visits and hospitalizations. Another measure not available for our analysis was whether or not patients had an established primary care provider. While other studies have found that having a regular primary care provider is associated with less use of the emergency department, having a regular source of care does not account for all the racial differences in emergency department use (Blanchard, Haywood, and Scott 2003). We also were not able to account for healthcare use outside of Carolinas HealthCare System. Finally, our data comprised patients from an urban county in the southeastern US and may not be generalizable to rural areas.

Conclusions

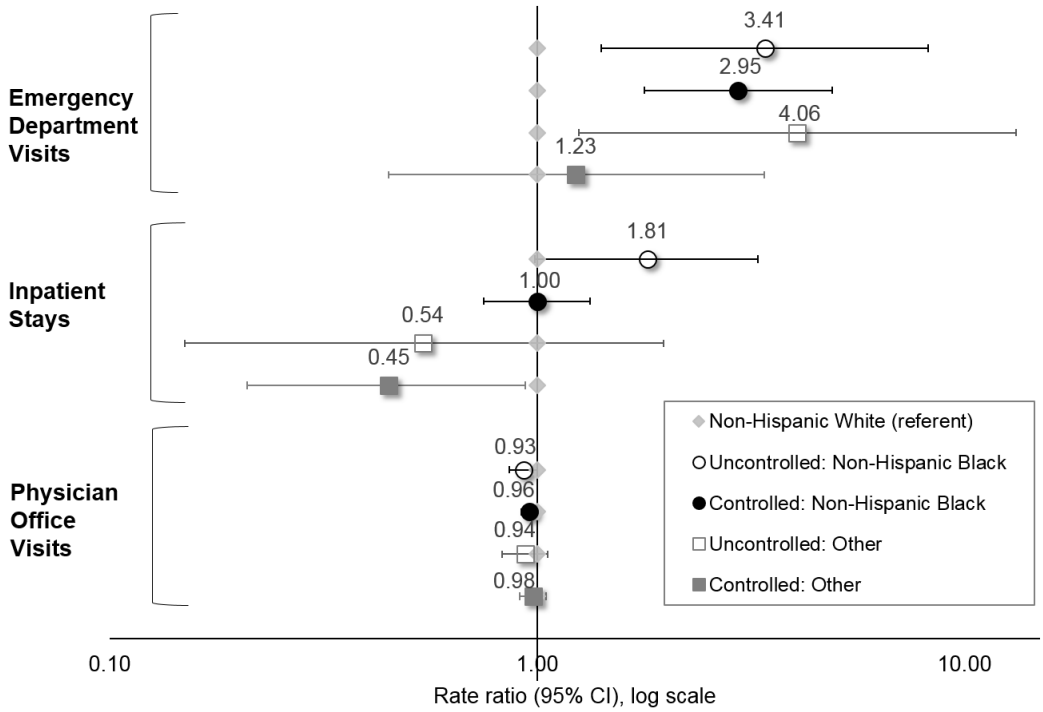
Glycemic control remains an important indicator of health and risk factor for poor diabetes outcomes. However, reaching targets for glycemic control may not change health-seeking behaviors that are associated with poor outcomes. We found that non-Hispanic Blacks with controlled and uncontrolled diabetes had higher rates of all-cause and diabetes-related emergency department visits and lower rates of all-cause doctor's office visits compared to non-Hispanic Whites, in a large sample of patients from an integrated healthcare system. Preventing diabetes adverse outcomes requires a setting of care that can deliver coordinated continuous care and provide support for patient self-management strategies. Future studies should examine the mechanisms that result in diabetes-related emergency department visits for non-Hispanic Blacks. Educational strategies and healthcare delivery changes such as greater care coordination may also be useful in increasing the use of physician offices compared to emergency departments, improving glycemic control and promoting the use of more appropriate settings for chronic disease care.

Table 1. Sample characteristics by level of glycemic control, patients with type 2 diabetes

Characteristic	All (N = 12,572)	Uncontrolled (N = 2,576)	Controlled (N = 9,996)	p-value*
Race, n (%)				<0.001
Non-Hispanic White	5,465 (43.5)	842 (32.7)	4,623 (46.2)	
Non-Hispanic Black	6,072 (48.3)	1,481 (57.5)	4,591 (45.9)	
Other†	1035 (8.2)	253 (9.8)	782 (7.8)	
Age, n (%)				<0.001
18-29	84 (0.7)	32 (1.2)	52 (0.5)	
30-39	426 (3.4)	150 (5.8)	276 (2.8)	
40-49	1,364 (10.8)	455 (17.7)	909 (9.1)	
50-59	3,108 (24.7)	854 (33.2)	2,254 (22.5)	
60-69	3,837 (30.5)	671 (26.0)	3,166 (31.7)	
70-79	2,408 (19.2)	290 (11.3)	2,118 (21.2)	
> 80	1,345 (10.7)	124 (4.8)	1,221 (12.2)	
Female, n (%)	7,064 (56.2)	1,392 (54.0)	5,672 (56.7)	0.014
Insurance, n (%)				<0.001
Commercial	3,331 (26.5)	746 (29.0)	2,585 (25.9)	
Medicaid	636 (5.1)	196 (7.6)	440 (4.4)	
Medicare	6,074 (48.3)	873 (33.9)	5,201 (52.0)	
Other	2,531 (20.1)	761 (29.5)	1,770 (17.7)	
Comorbid Conditions, n (%)				
Nephropathy	326 (2.6)	96 (3.7)	230 (2.3)	<0.001
Neuropathy	1,698 (13.5)	466 (18.1)	1,232 (12.3)	<0.001
Retinopathy	154 (1.2)	44 (1.7)	110 (1.1)	0.012
Heart Disease	3,938 (31.3)	723 (28.1)	3,215 (32.2)	<0.001
Hypertension	10,107 (80.4)	2,056 (79.8)	8,051 (80.5)	0.406
Stroke	848 (6.7)	169 (6.6)	679 (6.8)	0.675
Cancer	965 (7.7)	145 (5.6)	820 (8.2)	<0.001
Body Mass Index, n (%)				<0.001
Underweight (<18.5)	167 (1.3)	32 (1.2)	135 (1.4)	
Normal (18.5-24.9)	1,561 (12.4)	230 (8.9)	1,331 (13.3)	
Overweight: (25-29.9)	3,445 (27.4)	626 (24.3)	2,819 (28.2)	
Obese (≥30)	7,399 (58.9)	1,688 (65.5)	5,711 (57.1)	
Neighborhood poverty rate, mean (95% CI)	17.0 (16.9-17.1)	18.5 (18.3-18.8)	16.7 (16.6-16.8)	<0.001

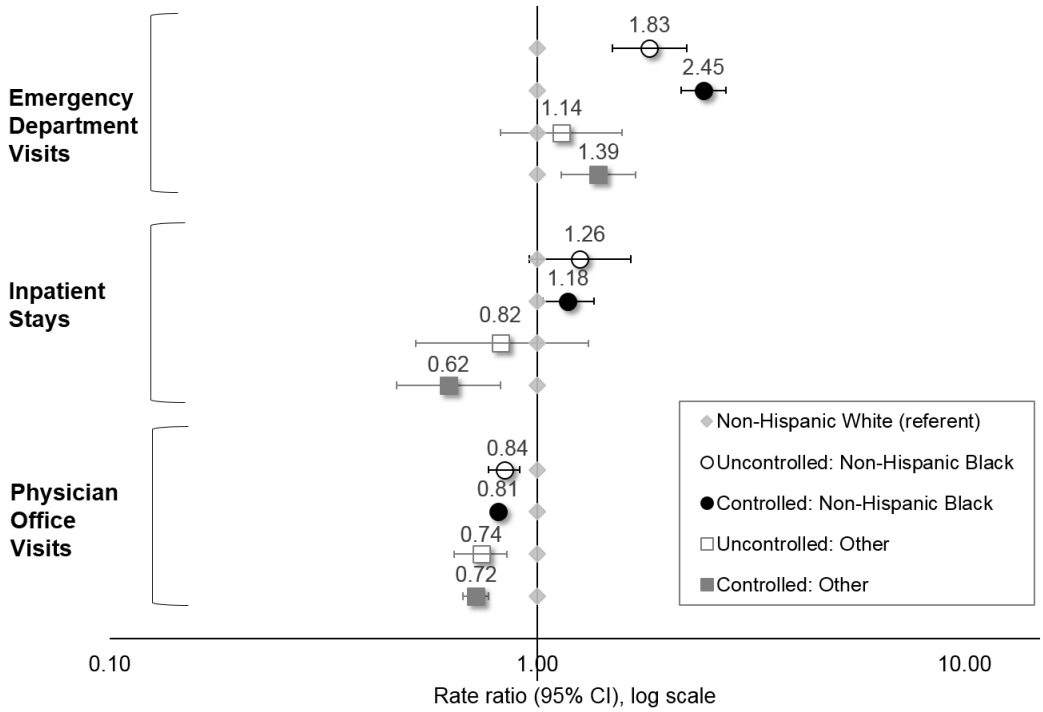
*p-values comparing characteristics of patients with uncontrolled vs. controlled diabetes from chi-square test or linear mixed model (poverty only).
†Other race includes Asians, Hawaiians and Pacific Islanders, Hispanics, Native Americans, and people with multiple races.
CI, confidence interval

Figure 1. Adjusted rate ratios for diabetes-related healthcare visits by visit type and glycemic control*



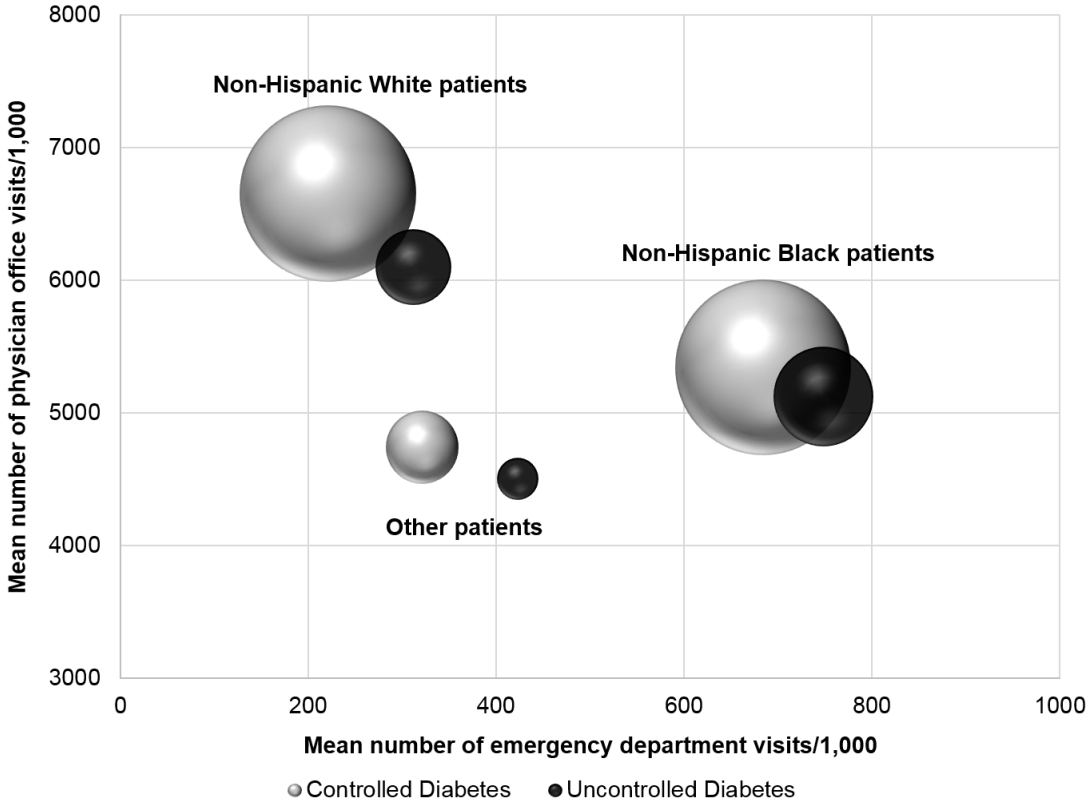
* Models were adjusted for significant confounders from the following list of covariates: age, gender, insurance, neuropathy, nephropathy, retinopathy, heart disease, hypertension, stroke, cancer, body mass index, and neighborhood poverty rate. Other race includes Asians, Hawaiians and Pacific Islanders, Hispanics, Native Americans, and individuals with multiple races.

Figure 2. Adjusted rate ratios for all-cause healthcare visits by visit type and glycemic control*



* Models were adjusted for significant confounders from the following list of covariates: age, gender, insurance, neuropathy, nephropathy, retinopathy, heart disease, hypertension, stroke, cancer, body mass index, and neighborhood poverty rate. Other race includes Asians, Hawaiians and Pacific Islanders, Hispanics, Native Americans, and individuals with multiple races.

Figure 3. Mean adjusted number of emergency department and physician office visits per 1,000 patients with diabetes by race and glycemic control[*]



[*] Predicted values from multivariable regression models adjusted for significant confounders from the following list of covariates: age, gender, insurance, neuropathy, nephropathy, retinopathy, heart disease, hypertension, stroke, cancer, body mass index, and neighborhood poverty rate. Bubble size represents number of patients in the sample. Other race includes Asians, Hawaiians and Pacific Islanders, Hispanics, Native Americans, and individuals with multiple races. Bubble size represents number of patients in sample.

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