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Predictors of mortality in patients with serious mental illness and co-occurring type 2 diabetes

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Abstract

Persons with serious mental illness (SMI) have higher rates of chronic medical conditions such as type 2 diabetes and mortality than the general population. We assessed demographic and health-related factors in the prediction of all-cause mortality among SMI patients with diabetes and a comparison group of diabetic patients without SMI. From 1999 to 2002, 201 patients with type 2 diabetes and SMI were recruited from community mental health centers and 99 persons with type 2 diabetes and no identified mental illness were recruited from nearby primary clinics. Deaths over an average seven-year period after baseline assessment were identified using the Social Security Administration's Death Master File. Twenty-one percent in each group died over follow-up. Age, smoking status, duration of diabetes, and diabetes-related hospitalization in the 6 months prior to baseline assessment predicted mortality in all patients. Among the non-SMI patients, those who were prescribed insulin had over a four-fold greater odds of mortality whereas this association was not found in the SMI patients. Diabetes likely contributes to mortality in persons with SMI. Providers need to be especially vigilant regarding mortality risk when patients require hospitalization for diabetes and as their patients age. Smoking cessation should also be aggressively promoted.

Keywords

insulin; smoking

1. Introduction

Persons with serious mental illness (SMI) such as schizophrenia or a major mood disorder have a higher mortality rate than the general population (Felker et al., 1996) that is only partially explained by higher rates of suicide (Harris and Barraclough, 1998). As in the general population, heart disease is the leading cause of mortality among persons with serious mental

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illness (Colton and Manderscheid, 2006; Jemal et al., 2008). Two other important mortality risk factors among those with SMI are obesity and cigarette smoking which occur at higher rates among those with SMI compared to the general population (Brown et al., 2000; Dickerson et al., 2006). Lack of emotional support and social networks, low socioeconomic status, sedentary lifestyle, and substance abuse are also risk factors that may contribute to mortality in people with SMI (Barreira, 1999; Dixon and Wohlheiter, 2003).

Type 2 diabetes, often leading to cardiovascular or cerebrovascular complications (Moss et al., 1991, Weiderpass et al., 2001), is another leading cause of death in the United States and has recently been associated with a 2.5-fold increase in the odds of mortality over the first 5 years from diagnosis (Guzder et al., 2007). And while the age-standardized death rate for all causes in the United States general population declined from 1970 to 2002 by about 32%, the age-standardized death rate for diabetes increased by 3.2% (Jemal et al., 2005). The death rate for diabetes has been increasing since the late 1980's, likely reflecting dramatic increases in obesity.

Furthermore, estimates of the prevalence of treated diabetes among individuals with schizophrenia ranges from 9 to 14 percent which is 2 to 4 times greater than estimates for the general U.S. adult population (Dixon et al., 2000). Although not entirely understood, biologic predisposition in combination with lifestyle factors (e.g., poor nutrition, physical inactivity) and treatment with psychotropic medications associated with weight gain and metabolic abnormalities (e.g. certain second-generation antipsychotic medications) likely contribute to the higher risk of diabetes in patients with SMI (American Diabetes Association, 2004).

Few studies have examined mortality among those with co-morbid diabetes and serious mental illness. The goals of this study were: first, to examine the rate and predictors of all-cause mortality among patients with diagnosed type 2 diabetes and co-occurring SMI over an average follow-up time of 6.9 years; and second, to compare how these factors were similar or different from predictors of mortality in a parallel cohort of individuals from the same metropolitan area with type 2 diabetes but without SMI.

2. Methods

2.1 Study setting and sample

A total of 201 persons with SMI (100 with a schizophrenia-spectrum disorder, 101 with a major mood disorder) and 99 persons without mental illness in the prior year, all of whom had type 2 diabetes, were recruited from September 1999 until September 2002. Mental illness and type 2 diabetes diagnoses were based on patient medical charts. A lack of mental illness was defined as no record of psychiatric treatment or medication in the patient's medical chart in the prior year. This was verified with the patient during recruitment. Participants of the study met the following additional criteria: age 18 to 65 years, English language fluency, and ability to provide informed consent. All participants provided written informed consent.

The participants with SMI were recruited from six public and private outpatient mental health clinics in urban and suburban communities across the Baltimore metropolitan area to represent a broad range of patients receiving outpatient care. Participants with type 2 diabetes and without SMI were recruited from three primary care clinics near the psychiatric clinics.

2.2 Baseline assessment

Each participant met in person with research staff for approximately 2.5 hours at the baseline assessment. Each participant's height, weight, blood pressure, and glycosylated hemoglobin (HbA1c) were measured at baseline. HbA1c was measured using the Bayer DCA 2000+. Individuals with a systolic blood pressure reading greater than or equal to 130 or a diastolic

blood pressure reading greater than or equal to 80 were classified as having current elevated blood pressure. Patients were also asked if they had ever been diagnosed with high blood pressure. Individuals with elevated blood pressure or who self-reported a diagnosis of high blood pressure were classified as having current hypertension. Patients were also asked if a doctor ever told them that they had heart problems. Body Mass Index (BMI) was calculated from the patient's height and weight measurements.

Participants were interviewed regarding various aspects of their diabetes, non-diabetes, and mental health history, and service utilization. These self-report interview questions were derived from items on the National Health Interview Survey (NHIS, U.S. Department of Health and Human Services, 1998), the National Health and Nutrition Examination Survey III (NHANES III) (U.S. Department of Health and Human Services, 1994), and the Schizophrenia Patient Outcomes Research Team (PORT) client survey (Lehman et al., 1998). Diabetes service use items asked patients how many diabetes-related outpatient visits, inpatient hospitalizations, and emergency department visits they had had over the six month period preceding the baseline assessment. Information about prescribed medications was obtained from chart review. The Colorado Symptom Index (CSI) (Shern et al., 1994) was used to assess anxiety and depression symptoms (higher scores reflecting more frequent symptoms).

Research assistants met weekly throughout the study to ensure standardization of the interview procedures. The Institutional Review Boards of the University of Maryland School of Medicine and of each participating facility approved the study. Further details regarding the study setting, sample, and baseline assessments are provided in Dixon et al., 2004.

2.3 Identifying decedents

On June 9, 2008 we searched the Social Security Administration's (SSA's) Death Master File (DMF) at website www.rootsweb.ancestry.com to identify study participants who had died since their baseline assessment. Studies have shown that searches of the SSA's DMF through commercial internet websites have good sensitivity and specificity for identifying decedents (Sesso et al., 2000; Hill, 2001).

We used the following search algorithm for which Hauser and Ho (2001) reported 82% sensitivity and 100% specificity: Social security numbers (SSN's) provided by study participants were entered into the search page of the aforementioned website. If the name and date of birth returned by the search page matched that of the participant in question, then this was considered to be a verified death (positive match). If the name and date of birth did not match, then the participant's last name was entered and the resulting first names and dates of birth were examined. For these participants, if a match by name and date of birth was found but the SSN did not match, the participant's assessment and medical chart were reviewed to check whether the SSN recorded from patient interviews was correct. A negative match occurred if no matches were found for participants with known name, date of birth, and verified SSN. Decedents were identified independently by two research assistants with 100% agreement. Vital status was unavailable for five patients who did not provide social security numbers. Cause of death was unavailable. Follow-up times varied according to recruitment date. Assuming a 6-month lag-time for mortality records to be accessible, average follow-up time was 6.9 years (range: 5.2–8.1).

2.4 Data analysis

We first identified patient characteristics that would potentially predict mortality. These variables can be grouped into three domains: (1) demographics (*age*, *race* (Non-Caucasian versus Caucasian), *gender*, *high school graduate* (yes/no); (2) diabetes characteristics (*duration of diabetes*, *prescribed insulin* (yes/no), *diabetes-related hospitalization* in the past

6 months (yes/no), *HbA1c level*); and (3) other health factors (*current smoker, obese (BMI ≥ 30), self-reported heart problem or hypertension diagnosis, CSI depression score, prescribed ACE inhibitor or statin medication, and non-diabetes-related hospitalization in the past 6 months (yes/no)*). We computed summary statistics for these variables to describe the SMI patient group and to compare them to the non-SMI group using t and χ^2 tests.

Secondly, from the above set of variables we identified individual predictors of mortality separately in the SMI and non-SMI samples. These analyses were conducted with a series of logistic regressions in order to examine the bivariate association between the baseline variables and mortality while adjusting for length of follow-up time.

Lastly, we constructed a multivariate logistic regression model applied to the full sample to identify baseline predictors of mortality over follow-up, after adjusting for the other predictor variables. In order to screen variables for entry into this model as main effects, variables were required to have a bivariate association with mortality in the combined sample at the 0.10 significance level (i.e. p -value < 0.10). To identify potential patient group interactions, a binary group indicator variable, *SMI* (yes/no), was constructed to identify patients who had and did not have SMI. If a predictor variable was associated with mortality in one of the patient groups (p -value $< .10$ screen criteria) but not the other, the corresponding variable-by-*SMI* interaction was formally tested in the combined sample using logistic regression adjusting for follow-up time. Interaction terms with p -values less than 0.10 were then included in the multivariate model. Finally, variables in the multivariate model with p -values greater than 0.20 were removed to produce a more parsimonious model.

Statistical significance was defined as a p -value less than 0.05 in the bivariate and multivariate models. All tests were two-sided.

Cox proportional hazards regression was attempted for the analysis of time to death following study recruitment adjusting for age and produced similar results; however, the proportional hazards assumption was violated for several predictors (Schoenfeld, 1982), hence we reverted to logistic regression analysis with adjustment for length of follow-up time.

3. Results

3.1 Baseline characteristics and mortality rates

Baseline characteristics of the SMI and non-SMI patient groups are presented in Table 1. The SMI group was slightly younger and had a lower proportion of non-Caucasians. The two groups did not significantly differ in proportion that were male or graduated from high school. A significantly higher proportion of those with SMI were current smokers at baseline and they also had higher depression scores. Of note, a far lower percentage of those with SMI were prescribed an ACE inhibitor or statin medication (Kreyenbuhl et al., 2006). The SMI group also had greater control of their blood sugar levels as indicated by mean HbA1c (Dixon et al., 2004). Of the 101 non-Caucasians in the SMI group, 90 were African American and of the 68 non-Caucasians in the non-SMI group, 65 were African American.

Forty-two of the 201 (20.9%) individuals with SMI and 21 of the 99 (21.2%) individuals without SMI died over the follow-up period.

3.2 Baseline predictors of mortality: bivariate analyses

In analyses unadjusted for covariates except length of follow-up, the odds of death in the SMI group was: 8% greater per year of age at baseline, 6% greater per year duration of diabetes at baseline, more than three times greater among those who had had versus had not had a diabetes-

related hospitalization, about double for non-Caucasians versus Caucasians, and more than double for smokers versus non-smokers, as shown in Table 2.

Among those without SMI, prediction was very similar for age, duration of diabetes, and having had a diabetes-related hospitalization, but the associations of race and smoking with mortality were not found in these patients. There was, however, over a five-fold greater odds of death among those who were versus who were not prescribed insulin, a finding not observed among those with SMI.

Based on the bivariate analyses, variable-by-SMI interactions were tested for the following variables in the combined sample: *race*, *gender*, *high school graduate*, *current smoker*, and prescribed *insulin*. The *insulin-by-SMI* interaction was significant (Wald $\chi^2 = 6.96$, $df = 1$, $P = 0.008$). Although *current smoker* at baseline predicted death only in the SMI group, the *current smoker-by-SMI* interaction was not significant (Wald $\chi^2 = 3.27$, $df = 1$, $P = 0.071$). All other interactions were non-significant.

3.3 Baseline predictors of mortality: multivariate analysis

Age, *race*, *gender*, *high school graduate*, *duration of diabetes*, and *diabetes-related hospitalization* were entered into the preliminary multivariate logistic regression model as main effects having met the $P < .10$ criteria in the bivariate analysis of the combined sample. Interaction terms meeting the $P < .10$ criteria and entered into the model included: *insulin-by-SMI* and *current smoker-by-SMI*. In the multivariate model, both *high school graduate* and the *smoker-by-SMI* interaction terms had p-values greater than 0.20 and hence were removed. Results from the final model are presented in table 3. Independent predictors of mortality across both groups included *age*, *duration of diabetes*, *diabetes-related hospitalization*, and *current smoker*. *Race* and *gender* were not significant after adjustment for the other covariates.

The *prescribed-insulin-by-SMI* interaction remained significant after covariate adjustment so that in the group without SMI those prescribed insulin had about a four-fold greater adjusted odds of dying over the follow-up than those not prescribed insulin (adjusted odds ratio (AOR): 4.1, 95% confidence interval (CI): (1.3, 13.3)). In contrast, the adjusted odds of death was not significantly greater among those who were prescribed insulin versus those who were not prescribed insulin in the SMI group (AOR = 0.53, 95% CI: (0.19, 1.45)).

Finally, we examined the association of specifically African American race and mortality. Relatively few of the non-Caucasians were not African American (11 in the SMI group and 3 in the NSMI group.) In secondary analyses, we deleted the $n = 14$ non-Caucasians who were not African American and performed analyses on the sample with Caucasians and African Americans only. Unlike in the total sample, in the re-fitted multivariate model African American race was significantly associated with mortality after adjustment for covariates (AOR = 2.19, 95% CI: (1.07, 4.48), $P = .031$). There was no interaction between group and African American race.

4. Discussion

This study both validates anticipated findings and also provides unexpected findings that merit further consideration regarding the mortality risk of diabetes among persons with SMI. First, it is to be expected that mortality is associated with advanced age, and with indicators of severity of diabetes including duration of diabetes and recent hospitalization for diabetes as we found in the group with and the group without SMI. Not surprisingly, our data suggest that older persons and those with more severe diabetes require more aggressive monitoring.

Of the remaining diabetes factors, neither HbA1c level nor prescription of insulin predicted mortality in the SMI group. In contrast, prescription of insulin was a strong predictor of mortality in the non-SMI group and this interaction between insulin and group remained significant after adjusting for the other predictors of mortality in the multivariate model. The result in the non-SMI group is consistent with prior general population epidemiological research (de Marco et al., 1999). The prescription of insulin for Type 2 diabetes is often initiated when the patient is unable to control the disease with diet or oral hypoglycemics. Difficulty managing diabetes over time can result in complications and poorer health outcomes that could lead to premature death, thus prescription of insulin may be a marker for illness severity and mortality risk. It has also been shown that among patients with diabetes and advanced heart disease, patients treated with insulin have a significantly greater mortality risk (Beckman et al., 2002; Smooke et al., 2005).

It is not clear why prescription of insulin at baseline did not predict mortality among those with SMI. Prescription of insulin may not mark severity in diabetes the same way among those with SMI as it does among those without SMI. One explanation for this may involve physician prescribing patterns and the possibility that physicians take different factors into consideration in prescribing insulin to patients with versus without SMI. Another plausible explanation might stem from differences in patients' acceptance and adherence to their diabetes medication regimens between those with and without SMI. A third explanation for the differential association with insulin might stem from as yet unknown clinical differences in diabetes between those with and without SMI.

Of the non-diabetes health related factors only *current smoker* (at baseline) was a significant predictor of mortality in the total sample after adjusting for other factors. These findings are consistent with a large body of literature. There was also a higher proportion of smokers in the SMI group than the non-SMI group which is consistent with other studies which have shown a greater prevalence of nicotine addiction among those with SMI. Patients with SMI are also more likely to be "heavy" smokers (≥ 30 cigarettes/day) and have higher nicotine dependence than persons without SMI (de Leon and Diaz, 2005; Mortensen and Juel, 1993). These findings underscore the hazards of smoking in individuals with SMI and diabetes who are at high cardiovascular risk and for whom aggressive treatment of nicotine addiction is of paramount importance.

Other than age, no other demographic variable significantly predicted mortality after adjusting for other factors. However, the analysis of the sample that included only African Americans and Caucasians found that race was a significant predictor of mortality after adjusting for other factors with African Americans having about double the odds of mortality compared to Caucasians. This result is consistent with multiple studies indicating that African Americans versus Caucasians with diabetes have a higher burden of illness and mortality (e.g. Karter et al., 2002 and Heisler et al., 2003.)

Strengths of the study include that, to our knowledge, this is the first investigation to study mortality prospectively in a relatively large cohort of individuals with diagnosed type 2 diabetes and SMI who were extensively characterized at baseline, and to make comparisons to a local comparison group of individuals with type 2 diabetes who did not have SMI. Study limitations include that the specific causes of mortality and the extent to which mortality was directly related to diabetes were unknown. Also the sample size was smaller in the non-SMI group than the SMI group, therefore there was less power to detect associations in the former group. Overall, the sample size and number of deaths limited the number of predictors of mortality that could be entered into the multivariate logistic regression model, hence we were not able to adjust for all baseline differences. However the variables excluded from the model were not associated with mortality and therefore would have had limited influence on the regression

coefficient estimates for the variables that were included the model. Also, it is possible that our reliance on self-reported alcohol and drug use led to under-reporting of such use.

The high percentage of deaths (21%) in both the SMI and NSMI groups over the follow-up period is striking. Based on previous research, we might have expected higher rates of mortality among those with SMI. The lack of excess deaths among this group may be due to the fact that those with SMI were younger, had better control of blood glucose, and were less obese. On the other hand, more of the patients with SMI smoked. Overall, given that diabetes is 2–4 times more prevalent among individuals with SMI than those in the general population, our findings are generally consistent with previous research (Brown et al., 2000) showing that diabetes contributes to excess mortality among those with SMI. To better address this problem, clinicians caring for persons with SMI need to be especially vigilant regarding mortality risk when their patients require hospitalization for diabetes and as their patients age. Furthermore, it is important that smoking cessation be aggressively promoted among persons with SMI and diabetes to reduce the risk of morbidity and mortality from cardiovascular disease. Mental and physical health care should be better linked within health care delivery systems given the co-occurring clinical needs of persons with serious mental illness and diabetes.

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Table 1

Baseline characteristics of study sample of type 2 diabetes patients with versus without co-occurring serious mental illness (SMI).

	Patients with SMI N = 201	Patients without SMI N = 99			
VARIABLE	% (n)^I	% (n)^I	Test statistic	df's	P
Age	50.1 +/- 8.7	53.1 +/- 8.9	$t = -2.82$	298	0.005
Non-Caucasian Race ²	50.7 (102)	68.7 (68)	$\chi^2 = 7.98$	1	0.005
Male Gender	48.3 (97)	52.5 (52)	$\chi^2 = 0.33$	1	0.57
High School Graduate	66.2 (133)	66.7 (66)	$\chi^2 = 0.00$	1	>0.99
Current smoker	53.2 (107)	34.3 (34)	$\chi^2 = 8.76$	1	0.003
Obese (BMI ≥ 30)	66.5 (133)	78.1 (75)	$\chi^2 = 3.66$	1	0.056
Heart Problem or hypertension	82.6 (166)	87.9 (87)	$\chi^2 = 1.03$	1	0.31
Depression score (CSI)	2.0 +/- 1.2	1.0 +/- 1.0	$t = 7.38$	297	<0.001
Prescribed ACE inhibitor or statin	35.3 (71)	68.7 (68)	$\chi^2 = 29.7$	1	<0.001
Hospitalized for non-diabetes-related condition past 6 mo's	18.4 (37)	18.6 (18)	$\chi^2 = 0.00$	1	>0.99
Duration diabetes (years)	7.4 +/- 7.3	8.4 +/- 8.2	$t = -1.05$	292	0.29
Prescribed insulin	26.9 (54)	26.3 (26)	$\chi^2 = 0.00$	1	>0.90
Hospitalized for diabetes past 6 mo's	8.0 (16)	10.2 (10)	$\chi^2 = 0.18$	1	0.67
HbA1c	7.85 +/- 2.18	8.64 +/- 2.43	$t = -2.81$	291	0.005

^I Mean +/- standard deviation provided for continuous variables. Sample size varies slightly for some variables due to missing values.

² Of the 101 non-Caucasians in the SMI group 90 were African American and of the 68 non-Caucasians in the Non-SMI group 65 were African American.

Table 2

Within group odds ratios of association between predictor variables and mortality from univariate logistic regression analyses adjusted for follow-up time.

Variable	Variable Levels	Patients with SMI ¹ (N = 201)				Patients without SMI (N = 99)			
		OR	95% CI	Wald χ^2 Statistic ²	P	OR	95% CI	Wald χ^2 Statistic ²	P
Age	--	1.08	(1.03, 1.14)	10.3	0.001	1.10	(1.02, 1.18)	6.35	0.012
Race	1 non-Caucasian	2.04	(1.00, 4.17)	3.86	0.049	1.06	(0.33, 3.33)	0.01	0.92
	0 Caucasian								
Gender	1 male	2.01	(0.98, 4.12)	3.63	0.057	1.13	(0.39, 3.27)	0.05	0.82
	0 female								
High School Graduate	1 yes	0.52	(0.26, 1.06)	3.26	0.071	0.61	(0.22, 1.65)	0.96	0.33
	0 no								
Current smoker	1 current smoker	2.33	(1.13, 4.82)	5.24	0.022	0.72	(0.25, 2.06)	0.38	0.54
	0 not curr. smoker								
Obese (BMI > 30)	1 yes	0.69	(0.34, 1.40)	1.05	0.31	0.67	(0.22, 2.06)	0.49	0.48
	0 no								
Heart Problem or Hypertension	1 yes	1.31	(0.50, 3.41)	0.30	0.59	3.38	(0.41, 27.9)	1.28	0.26
	0 no								
Hospitalized: non-diabetes condition ³	1 yes	1.04	(0.43, 2.48)	0.01	0.94	0.74	(0.19, 2.88)	0.18	0.67
	0 no								
Prescribed ACE inhibitor or statin	1 yes	0.71	(0.33, 1.54)	0.74	0.39	1.65	(0.54, 5.03)	0.77	0.38
	0 no								
Depression score (CSI)	--	0.83	(0.63, 1.10)	1.71	0.19	1.09	(0.68, 1.75)	0.13	0.72
HbA1c	--	1.04	(0.89, 1.22)	0.29	0.59	1.05	(0.85, 1.28)	0.20	0.66
Duration of diabetes	--	1.06	(1.02, 1.11)	9.37	0.002	1.07	(1.00, 1.14)	4.48	0.034
Prescribed insulin	1 yes	0.82	(0.37, 1.81)	0.25	0.62	5.46	(1.85, 16.1)	9.41	0.002
	0 no								
Hospitalized: diabetes-related condition ³	--	3.42	(1.18, 9.84)	5.17	0.023	4.38	(1.12, 17.1)	4.52	0.033

¹ Serious Mental Illness

² Degrees of freedom for each Wald χ^2 test is 1.

³ During the 6 months prior to baseline

Table 3Multivariate logistic regression model for probability of death during follow-up in combined sample ($N=293$).¹

Baseline Variables	Variable Levels	Estimate	SE ²	Wald χ^2 Statistic ³	P	AOR ⁴	95% CI ⁵ for AOR
Intercept	--	-10.4	2.35	19.5	<0.001	--	--
SMI ^{6,7}	1 yes	0.84	0.46	3.39	0.066	--	--
	0 no	--	--	--	--	--	--
Length of follow-up	--	0.25	0.21	1.42	0.23	1.29	0.85,1.95
Age	--	0.12	0.026	20.0	<0.001	1.13	1.07,1.18
Race	1 Non-Cauc	0.68	0.36	3.57	0.059	1.98	0.97,4.00
	0 Caucasian	--	--	--	--	--	--
Gender	1 male	0.67	0.35	3.65	0.056	1.95	0.97, 3.9
	0 female	--	--	--	--	--	--
Duration of diabetes (yrs)	--	0.050	0.021	5.50	0.019	1.05	1.01,1.10
Hospitalized for diabetes related condition	1 yes	1.69	0.53	10.4	0.001	5.44	1.94,15.2
	0 no	--	--	--	--	--	--
Prescribed insulin ⁷	1 yes	1.42	0.60	5.69	0.017	--	--
	0 no	--	--	--	--	--	--
Current Smoker	1 yes	0.72	0.36	3.94	0.047	2.06	1.01, 4.20
	0 no	--	--	--	--	--	--
SMI-by-Prescribed insulin ⁸	--	2.06	0.77	7.17	0.007	--	--

¹ Seven observations were dropped from the regression analysis due to missing values.² Standard Error³ Degrees of freedom for each Wald χ^2 test is 1.⁴ Adjusted Odds Ratio⁵ Confidence Interval⁶ Serious Mental Illness⁷ Simple adjusted odds ratio and 95% confidence interval not interpretable due to interaction between indicator variables for serious mental illness and prescribed insulin.⁸ Adjusted odds ratios are provided in the text for comparing those prescribed versus not prescribed insulin within the serious mental illness group and within the no serious mental illness group.