Association Between Diabetes Severity and Risks of COVID-19 Infection and Outcomes

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BACKGROUND: Little is known about whether diabetes increases the risk of COVID-19 infection and whether measures of diabetes severity are related to COVID-19 outcomes.

OBJECTIVE: Investigate diabetes severity measures as potential risk factors for COVID-19 infection and COVID-19 outcomes.

DESIGN, PARTICIPANTS, MEASURES: In integrated healthcare systems in Colorado, Oregon, and Washington, we identified a cohort of adults on February 29, 2020 ($n = 1{,}086{,}918$) and conducted follow-up through February 28, 2021. Electronic health data and death certificates were used to identify markers of diabetes severity, covariates, and outcomes. Outcomes were COVID-19 infection (positive nucleic acid antigen test, COVID-19 hospitalization, or COVID-19 death) and severe COVID-19 (invasive mechanical ventilation or COVID-19 death). Individuals with diabetes ($n = 142{,}340$) and categories of diabetes severity measures were compared with a referent group with no diabetes ($n = 944{,}578$), adjusting for demographic variables, neighborhood deprivation index, body mass index, and comorbidities.

RESULTS: Of 30,935 patients with COVID-19 infection, 996 met the criteria for severe COVID-19. Type 1 (odds ratio [OR] 1.41, 95% CI 1.27–1.57) and type 2 diabetes (OR 1.27, 95% CI 1.23–1.31) were associated with increased risk of COVID-19 infection. Insulin treatment was associated with greater COVID-19 infection risk (OR 1.43, 95% CI 1.34–1.52) than treatment with non-insulin drugs (OR 1.26, 95% 1.20–1.33) or no treatment (OR 1.24; 1.18–1.29). The relationship between glycemic control and COVID-19 infection risk was dose-dependent: from an OR of 1.21 (95% CI 1.15–1.26) for hemoglobin A1c (HbA1c) < 7% to an OR of 1.62 (95% CI 1.51–1.75) for HbA1c ≥ 9%. Risk factors for severe COVID-19 were type 1 diabetes (OR 2.87; 95% CI 1.99–4.15), type 2 diabetes (OR 1.80; 95% CI 1.55–2.09), insulin treatment (OR 2.65; 95% CI 2.13–3.28), and HbA1c ≥ 9% (OR 2.61; 95% CI 1.94–3.52).

CONCLUSIONS: Diabetes and greater diabetes severity were associated with increased risks of COVID-19 infection and worse COVID-19 outcomes.

KEY WORDS: diabetes; insulin; hemoglobin A1c; COVID-19; epidemiology

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INTRODUCTION

Reports of hospitalized patients with COVID-19 during the early months of the global pandemic noted a high proportion of patients with diabetes, and also that diabetes was an independent risk factor for progression to acute respiratory distress syndrome and death.[1–4] Later studies have reaffirmed these findings. For instance, in the COVID-19-Associated Hospitalization Surveillance Network, 33% of hospitalized patients with COVID-19 had diabetes compared with 11% of the US population,[5] and diabetes was an independent risk factor for intensive care unit admission and death.[6] The excess mortality related to diabetes and COVID-19 has been staggering. In England, deaths in the first half of 2020 compared with historical figures were 51% higher among individuals with type 1 diabetes and 64% higher among individuals with type 2 diabetes; two-thirds of these excess deaths were attributed to COVID-19 on death certificates.[7]

Although it is now well established that diabetes is a potent risk factor for COVID-19 mortality, there are major gaps in our understanding of this relationship. Nearly all studies of diabetes and COVID-19 have included only hospitalized patients,[8,9] which is likely to introduce selection bias that can result in spurious associations or obscure genuine ones. This study design also precludes an examination of diabetes as a potential risk factor for COVID-19 infection, rather than complications such as critical illness or mortality.[10] In addition, little is known about factors that might

explain variability in COVID-19 risk among individuals with diabetes, such as glycemic control and obesity. A review of the epidemiology of diabetes and COVID-19 at the outset of the pandemic noted the lack of population- or community-based studies addressing these questions.[11] More than 2 years into the pandemic, they remain largely unanswered.[12]

In the setting of three large integrated healthcare systems with comprehensive information on diagnoses, hospitalizations, laboratory test results, and out-of-hospital deaths, we conducted a population-based cohort study to investigate diabetes and measures of diabetes severity as risk factors for two outcomes: COVID-19 infection and severe COVID-19. In contrast with previous studies, which have studied intensive care unit admission as a surrogate for severe COVID-19, we used a validated algorithm for invasive mechanical ventilation and state death certificate data to define this outcome. Because of the important role obesity plays in the development of both diabetes and COVID-19 complications, we also investigated the independent relationship between body mass index (BMI) and study outcomes in patients with diabetes after adjustment for several diabetes severity measures.

METHODS

Population

This study included adults aged 18 years or greater who were members of Kaiser Permanente (KP)—an integrated health care delivery system providing both health care and insurance coverage—in one of three KP regions: Colorado, Washington, and Northwest (includes Oregon and southwest Washington). Cohort inclusion criteria were continuous enrollment for at least 6 months and no COVID-19 prior to the cohort entry date of February 29, 2020. Data sources included electronic health records (EHRs) and laboratory test results from outpatient, emergency department, and inpatient facilities; health system administrative and billing information; and state death certificates. Individuals were followed until the time of their first COVID-19 outcome, loss of enrollment, death, or end of follow-up on February 28, 2021. KP Institutional Review Boards approved the study.

Outcomes

The two outcomes in this study were COVID-19 infection and severe COVID-19. COVID-19 was defined as the first occurrence of a (1) positive nucleic acid antigen test (NAAT) for SARS-CoV-2, (2) hospitalization with an International Classification Diseases version 10 (ICD-10) diagnosis code for COVID-19 (B342, B9721, B9729, U071, U072), or (3) death certificate with COVID-19 listed as a cause of death. Severe COVID-19 was defined as the first occurrence of a COVID-19 hospitalization involving invasive mechanical ventilation or a COVID-19 death. COVID-19 hospitalizations included hospitalizations with an ICD-10 code for COVID-19 and any hospitalization within 28 days of the initial COVID-19 diagnosis. COVID-19 death was defined as a COVID-19 hospitalization with a discharge status of death, a death with COVID-19 listed as a cause of death, or any death within 28 days of an initial COVID-19 diagnosis. In a previous publication, we reported results of a validation study ($n=76$): the positive predictive (PPV) value for confirmed COVID-19 infection from hospitalizations with COVID-19 diagnosis codes was 96% (95% confidence interval [CI] 89–99%), and the PPV for invasive mechanical ventilation identified through diagnosis and procedure codes was 100% (95% CI 86–100%).[13]

Exposures

The exposures of interest were diabetes, glycemic control, treatment intensity, presence of diabetes complications, and BMI. The definition of diabetes, assessed prior to cohort entry and updated at the start of each month of follow-up, was adapted from a previous study: an ICD-9 or ICD-10 diagnosis code for diabetes mellitus (250.x, E10, E11, E13) in an inpatient or at least 2 outpatient claims, a laboratory measure of hemoglobin A1c (HbA1c) $\geq 6.5\%$, or a pharmacy fill of a diabetes medication.[14] Type 1 diabetes was defined as the presence of an ICD-9 (250.$\times$1 or 250.$\times$3) or ICD-10 code (E10) for type 1 diabetes; all other diabetes was considered type 2. Diabetes with complications was defined using ICD-9 and ICD-10 codes from the Charlson index (250.4–250.63, E10.2-E10.5, E10.61-E10.619, E11.2-E11.5, E11.61-E11.619, E13.2-E13.4, E13.61-E13.619).[15] HbA1c was assessed each month based on the most recent measure in the prior 12 months and categorized as $<7\%$, $7-<9\%$, $\geq 9\%$, or missing. Current treatment (insulin, non-insulin diabetes medication only, no medication) was determined each month based on whether the days' supply overlapped with the start of the month for non-insulin medications, and whether the medication was filled in the prior 6 months for insulin.

Covariates

As described previously,[13] demographic variables at cohort entry were ascertained from the EHR: age, sex, self-reported race/ethnicity, and neighborhood deprivation index (NDI).[16] Smoking status was categorized as current, former, or never (including individuals with no smoking information recorded). BMI at cohort entry was categorized as underweight, normal, overweight, and obese class I, II, and III based on the ranges <18.5, $18.5-<25$, $25-<30$, $30-<35$, $35-<40$, and ≥ 40 kg/m^2. The following comorbidities were ascertained from ICD-10 codes in the 12 months prior to cohort entry: hypertension, myocardial infarction, peripheral vascular disease, cerebrovascular disease, heart failure, atrial fibrillation and flutter, liver disease, asthma, chronic obstructive pulmonary disease,

rheumatological disease, dementia, and cancer.[13,15] Pharmacy records were used to assess time-varying measures of medication use including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, and systemic corticosteroids. All covariates, as well as KP region and month of follow-up, were included as adjustment variables in all statistical models. Age was parameterized with natural cubic splines; other adjustment covariates were categorical.

Statistical Analysis

We estimated odds ratios (ORs) and 95% CIs from a series of covariate-adjusted logistic regression models relating COVID-19 outcomes in each month of follow-up to exposure variables assessed at the start of that month. These models incorporated inverse probability weights to account for missing data on race/ethnicity, NDI, and BMI, and to account for censoring due to disenrollment during follow-up. We estimated logistic regression model parameters using weighted generalized estimating equations with a working correlation matrix and with standard errors calculated via the sandwich estimator to account for the missing data and censoring weights and within-person correlation across time.[17,18] We first fit models for the outcome of COVID-19 infection and then repeated the same models for the outcome of severe COVID-19. All models were estimated in the entire study population and compared individuals with the exposure of interest (diabetes or category of severity measure) with a referent group of individuals without diabetes. HbA1c levels were also fit with natural cubic splines to allow for estimation of a smooth, potentially non-linear relationship between HbA1c and odds of study outcomes. For analyses of BMI, we restricted our sample to individuals with diabetes and estimated covariate-adjusted models relating COVID-19 outcomes to BMI categories, before and after adjustment for all diabetes severity measures. For analyses of the outcome of severe COVID-19, because of the limited number of events, we used fewer age spline parameters and combined two race/ethnicity categories.

Before June 2020, NAAT testing for SARS-CoV-2 was not widely available in all geographic regions included in this study. To evaluate the impact of testing bias, we conducted sensitivity analyses in which observation for COVID-19 outcomes began on June 1, 2020, and individuals with COVID-19 before that date were excluded. We also evaluated a definition of type 1 diabetes that excluded individuals who used non-insulin glucose-lowering medications and we estimated associations for severe COVID-19 restricted to individuals with COVID-19 infection, an approach that has been used often in previous studies but may be susceptible to collider bias.[10] All analyses were conducted using R, version 4.0.2.

RESULTS

Of 1,086,918 eligible individuals (33.2% Colorado, 38.3% Northwest, 28.5% Washington), 53.2% were female, 13.1% had diabetes, and 92.7% were enrolled for at least 12 months at cohort entry. Compared with individuals who did not have diabetes, individuals with diabetes were older (mean age 62.8 vs 48.7 years), more likely to be Black (5.8 vs 3.6%) or Hispanic/Latino (12.2 vs 8.7%), and more likely to live in the highest quartile of NDI (29.8 vs 23.6%), indicating greater social deprivation. Individuals with diabetes also had a higher mean BMI (33.0 vs 28.4 kg/m^2) and a greater burden of comorbidities (Table 1). Among individuals with diabetes, 5.9% were classified as type 1 diabetes, 35.7% had diabetes complications, the mean HbA1c was 7.1%, and 16.8% did not have information on HbA1c. Most received some form of diabetes treatment (36.7% non-insulin drugs only, 20.8% insulin). Among the 907,263 (83.5%) individuals with complete data on race/ethnicity, NDI, and BMI, 560,946 NAAT tests for COVID-19 were done; the prevalence of diabetes among individuals with positive tests was 16.4%, and among those with only negative tests it was 15.0%. Censoring due to loss of enrollment or non-COVID death occurred in 112,248 (12.4%) individuals, 30,935 (3.4%) had COVID-19 including 3906 hospitalizations, and 996 (0.1%) met criteria for severe COVID-19 including 752 COVID-19 deaths.

Compared with the reference group with no diabetes, diabetes was associated with an increased risk of COVID-19 (OR of 1.27; 95% CI, 1.23–1.31, Table 2). Odds ratios for adjustment variables are displayed in Appendix Table 1. There was strong statistical evidence the ORs for COVID-19 infection differed based on the presence of diabetes complications, treatment intensity, and HbA1c levels ($P < 0.001$ for each measure), although the differences in these ORs were not large in magnitude. For instance, individuals receiving insulin treatment had a greater risk of COVID-19 (OR 1.43; 95% CI, 1.34–1.52) than individuals receiving only non-insulin treatment (OR 1.26; 95% CI, 1.20–1.33) and untreated individuals (OR 1.24; 95% CI, 1.18–1.29). The relationship between COVID-19 risk and HbA1c category was dose-dependent; cubic spline modeling suggested a linear relationship up to an HbA1c of approximately 8% and then a plateau (Fig. 1a).

Associations with diabetes and diabetes severity measures were greater in magnitude for severe COVID-19. Compared with the reference group with no diabetes, diabetes was associated with nearly twofold increased risk of severe COVID-19 (OR 1.85; 95% CI, 1.59–2.14, Table 3). Odds ratios for adjustment variables are displayed in Appendix Table 2. Type 1 diabetes was associated with a greater increased risk (OR 2.87; 95% CI, 1.99–4.15) than type 2 diabetes (OR 1.80; 95% CI, 1.55–2.09). Insulin use was associated with a greater increased risk (OR 2.65; 95% CI, 2.13–3.28) than use of only non-insulin drugs (OR 1.69; 95% CI, 1.36–2.09) and no treatment (OR 1.68; 95% CI, 1.41–2.01), which had

Table 1 Characteristics of study population at cohort entry

	No diabetes (*N* = 944,578)	**Diabetes (*N* = 142,340)**	**Overall (*N* = 1,086,918)**
Kaiser Permanente region			
Colorado	312,446 (33.1%)	48,375 (34.0%)	360,821 (33.2%)
Northwest	359,734 (38.1%)	56,260 (39.5%)	415,994 (38.3%)
Washington	272,398 (28.8%)	37,705 (26.5%)	310,103 (28.5%)
Female	503,780 (53.3%)	74,112 (52.1%)	577,892 (53.2%)
Age (years), mean (SD)	48.7 (18.0)	62.8 (14.7)	50.6 (18.2)
Age (years), categories			
18–24	93,924 (9.9%)	1429 (1.0%)	95,353 (8.8%)
25–34	155,493 (16.5%)	5120 (3.6%)	160,613 (14.8%)
35–44	165,514 (17.5%)	11,097 (7.8%)	176,611 (16.2%)
45–54	157,253 (16.6%)	19,751 (13.9%)	177,004 (16.3%)
55–64	161,798 (17.1%)	32,988 (23.2%)	194,786 (17.9%)
65–74	133,419 (14.1%)	41,308 (29.0%)	174,727 (16.1%)
75–84	57,212 (6.1%)	23,152 (16.3%)	80,364 (7.4%)
85+	19,965 (2.1%)	7495 (5.3%)	27,460 (2.5%)
Race/Ethnicity			
White	654,522 (69.3%)	97,304 (68.4%)	751,826 (69.2%)
Hispanic / Latino	82,442 (8.7%)	17,304 (12.2%)	99,746 (9.2%)
Asian American	61,160 (6.5%)	9763 (6.9%)	70,923 (6.5%)
Black / African American	33,952 (3.6%)	8256 (5.8%)	42,208 (3.9%)
Indigenous American / Alaskan	6711 (0.7%)	1577 (1.1%)	8288 (0.8%)
Native Hawaiian / Pacific Islander	5729 (0.6%)	1475 (1.0%)	7204 (0.7%)
Multiple	3435 (0.4%)	878 (0.6%)	4313 (0.4%)
Other	16,560 (1.8%)	2276 (1.6%)	18,836 (1.7%)
Missing	80,067 (8.5%)	3507 (2.5%)	83,574 (7.7%)
Health plan enrollment			
<1 year	69,363 (7.3%)	4945 (3.5%)	74,308 (6.8%)
1–<3 years	257,952 (27.3%)	22,628 (15.9%)	280,580 (25.8%)
3–<6 years	188,097 (19.9%)	23,799 (16.7%)	211,896 (19.5%)
6+years	429,166 (45.4%)	90,968 (63.9%)	520,134 (47.9%)
Neighborhood Deprivation Index (NDI)			
First quartile	244,975 (25.9%)	27,344 (19.2%)	272,319 (25.1%)
Second quartile	242,919 (25.7%)	33,941 (23.8%)	276,860 (25.5%)
Third quartile	227,772 (24.1%)	37,882 (26.6%)	265,654 (24.4%)
Fourth quartile (worst)	223,375 (23.6%)	42,383 (29.8%)	265,758 (24.5%)
Missing	5537 (0.6%)	790 (0.6%)	6327 (0.6%)
Current smoker	60,491 (6.4%)	10,669 (7.5%)	71,160 (6.5%)
Body mass index (BMI), kg/m^2			
Underweight (<18)	10,425 (1.1%)	572 (0.4%)	10,997 (1.0%)
Normal (18–<25)	253,972 (26.9%)	16,909 (11.9%)	270,881 (24.9%)
Overweight (25–<30)	278,173 (29.4%)	37,678 (26.5%)	315,851 (29.1%)
Obese I (30–<35)	155,462 (16.5%)	36,987 (26.0%)	192,449 (17.7%)
Obese II (35–<40)	66,212 (7.0%)	24,028 (16.9%)	90,240 (8.3%)
Obese III (40+)	43,846 (4.6%)	22,898 (16.1%)	66,744 (6.1%)
Missing	136,488 (14.4%)	3268 (2.3%)	139,756 (12.9%)
Diabetes type			
Type 1		8409 (5.9%)	
Type 2		133,931 (94.1%)	
Diabetes complications			
No		91,581 (64.3%)	
Yes		50,759 (35.7%)	
Diabetes treatment			
Diabetes, no treatment		60,513 (42.5%)	
Non-insulin diabetes drugs only		52,217 (36.7%)	
Any insulin		29,610 (20.8%)	
HbA1c (highest in past 12 months)			
<7%		67,740 (47.6%)	
7–<9%		37,348 (26.2%)	
≥9%		13,402 (9.4%)	
Missing		23,850 (16.8%)	
Comorbidities			
Hypertension	149,959 (15.9%)	76,468 (53.7%)	226,427 (20.8%)
Myocardial infarction	11,781 (1.2%)	8541 (6.0%)	20,322 (1.9%)
Peripheral vascular disease	39,988 (4.2%)	22,400 (15.7%)	62,388 (5.7%)
Cerebrovascular disease	13,768 (1.5%)	7994 (5.6%)	21,762 (2.0%)
Congestive heart failure	11,556 (1.2%)	10,736 (7.5%)	22,292 (2.1%)
Atrial fibrillation or flutter	24,319 (2.6%)	12,769 (9.0%)	37,088 (3.4%)

Table 1 (continued)

	No diabetes ($N = 944,578$)	Diabetes ($N = 142,340$)	Overall ($N = 1,086,918$)
Kidney disease	34,606 (3.7%)	29,548 (20.8%)	64,154 (5.9%)
Liver disease	3526 (0.4%)	2252 (1.6%)	5778 (0.5%)
Asthma	66,815 (7.1%)	15,851 (11.1%)	82,666 (7.6%)
COPD	20,347 (2.2%)	9537 (6.7%)	29,884 (2.7%)
Rheumatologic disease	10,474 (1.1%)	2978 (2.1%)	13,452 (1.2%)
Dementia	8347 (0.9%)	4450 (3.1%)	12,797 (1.2%)
Cancer	25,953 (2.7%)	8885 (6.2%)	34,838 (3.2%)
Medication use			
ACEI/ARB	105,816 (11.2%)	72,832 (51.2%)	178,648 (16.4%)
Statins	111,700 (11.8%)	78,443 (55.1%)	190,143 (17.5%)
Systemic corticosteroids	7279 (0.8%)	2755 (1.9%)	10,034 (0.9%)
Missing race, BMI, or NDI	172,631 (18.3%)	7024 (4.9%)	179,655 (16.5%)

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *COPD* chronic obstructive pulmonary disease, *SD* standard deviation

similar risks. There was a strong, dose-dependent relationship between A1c category and risk of severe COVID-19. Cubic spline modeling suggested a linear relationship between an HbA1c of approximately 6 to 8%, with slightly greater risks below 6% and a plateau above 8% (Fig. 1b).

In analyses restricted to individuals with diabetes, we evaluated associations between BMI categories and COVID-19 outcomes. Compared with the reference group of normal BMI (18 to < 25 kg/m^2), there was a graded relationship between BMI category and COVID-19 risk (Wald $P < 0.001$, Table 4), ranging from OR 1.10 (95% CI, 1.00–1.22) for overweight (BMI 25 to < 30 kg/m^2) to OR 1.32 (95% CI, 1.19–1.47) for obese III (BMI 40 ≥ kg/m^2). BMI was also associated with an increased risk of severe COVID-19 in a dose-dependent manner ($P < 0.001$), and the associations were greater in magnitude, ranging from an OR 1.03 (95% CI, 0.76–1.41) for overweight to OR 2.30 (95% CI, 1.59–3.33) for obese III. When analyses were repeated adjusting for all diabetes severity measures, associations were unchanged for both outcomes.

Sensitivity analyses that excluded the period when NAAT testing for SARS-CoV-2 was not widely available yielded estimates that were slightly attenuated but statistically significant for COVID-19 infection, and estimates that were

Table 2 Associations of diabetes and diabetes severity measures with COVID-19 of any severity

Group	No. (%) of individuals		Odds ratio* (95% CI)	*P* value**
	COVID-19 infection	No COVID-19 infection		
Diabetes				
No	24,916 (3.3%)	741,252 (96.7%)	1 [Reference]	
Yes	6019 (4.3%)	135,076 (95.7%)	1.27 (1.23–1.31)	
Type				0.053
Type 1	369 (4.7%)	7528 (95.3%)	1.41 (1.27–1.57)	
Type 2	5650 (4.2%)	127,548 (95.8%)	1.27 (1.23–1.31)	
Complications				< 0.001
No	3859 (4.2%)	88,239 (95.8%)	1.23 (1.19–1.28)	
Yes	2160 (4.4%)	46,837 (95.6%)	1.40 (1.32–1.47)	
Treatment				< 0.001
None	2551 (4.3%)	57,135 (95.7%)	1.24 (1.18–1.29)	
Non-insulin only	2083 (4.0%)	49,783 (96.0%)	1.26 (1.20–1.33)	
Insulin	1385 (4.7%)	28,158 (95.3%)	1.43 (1.34–1.52)	
HbA1c				< 0.001
Missing	1313 (4.1%)	30,772 (95.9%)	1.17 (1.10–1.24)	
< 7%	2316 (3.9%)	57,087 (96.1%)	1.21 (1.15–1.26)	
7 to < 9%	1580 (4.4%)	34,704 (95.6%)	1.40 (1.33–1.48)	
≥ 9%	810 (6.1%)	12,513 (93.9%)	1.62 (1.51–1.75)	

*No diabetes is the reference group for each odds ratio. **P value for two-sided Wald test of whether odds of COVID-19 infection differs across levels of severity measures. *CI* confidence interval. Percentages are for counts within rows. Odds ratios adjusted for Kaiser Permanente region, month of follow-up, age, sex, race/ethnicity, neighborhood deprivation index, smoking status, body mass index, comorbidities, and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, and systemic corticosteroids

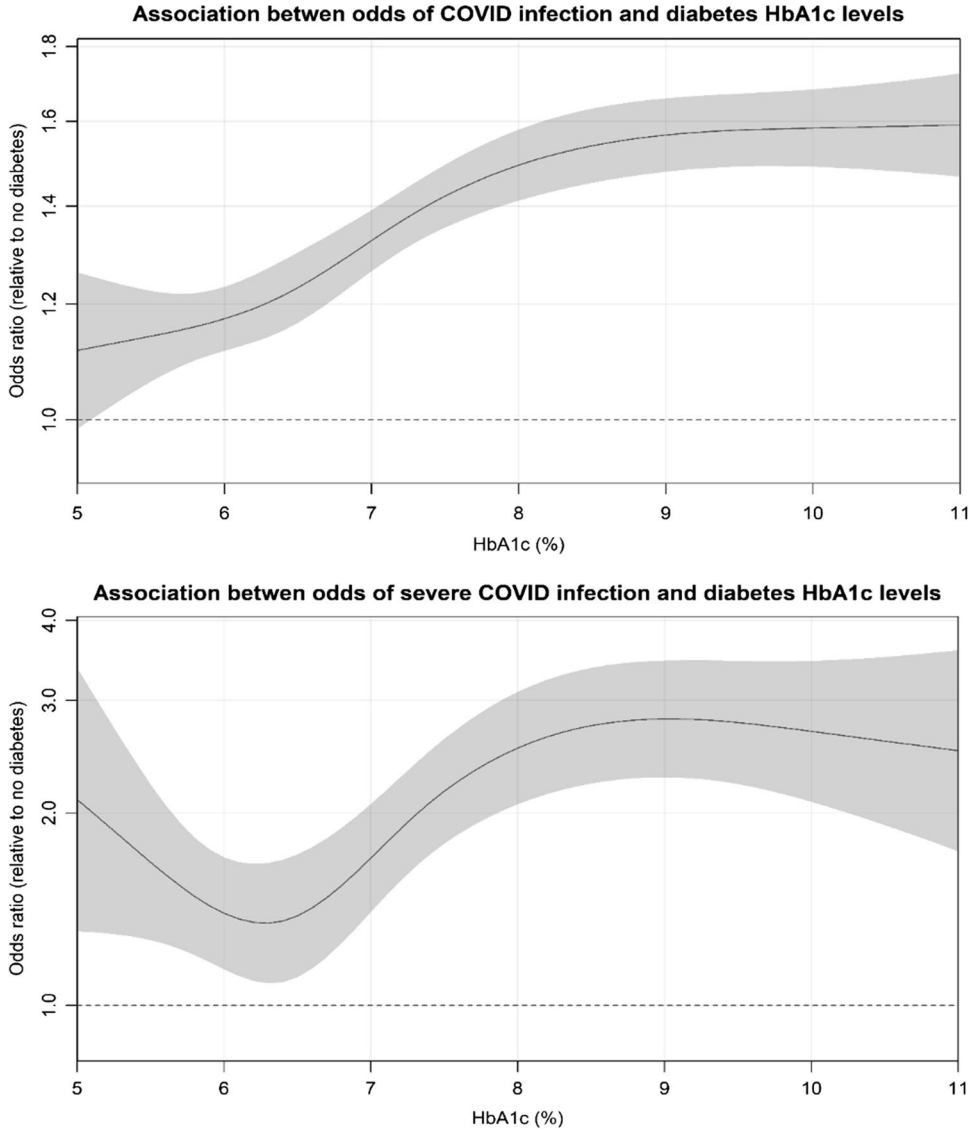

Fig. 1 Association of hemoglobin A1c levels with a COVID-19 of any severity, and b severe COVID-19. Modeled with cubic splines, confidence intervals shaded in gray. The reference group is individuals without diabetes

slightly greater in magnitude for severe COVID-19 (Appendix Tables 3 and 4). Excluding individuals classified as type 1 diabetes who used non-insulin glucose-lowering medications ($n=961$) resulted in similar results (Appendix Table 5). Analyses of severe COVID-19 that included only individuals with COVID-19 infection yielded slightly attenuated associations compared to the primary analysis (Appendix Tables 6 and 7).

DISCUSSION

In this community-based study of COVID-19 outcomes conducted in three large integrated healthcare systems, diabetes was not only a strong risk factor for severe COVID-19 but also independently associated with COVID-19 infection of any severity, after adjustment for demographic factors, neighborhood measures of socioeconomic status, BMI, and comorbidities. Among individuals with diabetes, several diabetes markers of severity were associated with substantial increases in risk, especially for the outcome of severe COVID-19. Even individuals with good glycemic control (HbA1c < 7%) according to current treatment guidelines[19] had an increased risk of COVID-19 and severe COVID-19 compared to individuals without diabetes. We also identified a strong dose-dependent relationship between BMI and COVID-19 outcomes among individuals with diabetes after adjusting for all diabetes severity measures, supporting evidence from Mendelian randomization experiments that obesity is an important etiologic factor for adverse COVID-19 outcomes.[20,21]

Our results are consistent with findings from previous studies of severe COVID-19, all of which included data from early in the global pandemic (through mid-2020). Two population-based studies from England found evidence of

Table 3 Associations of diabetes and diabetes severity measures with severe COVID-19

Group	No. (%) of individuals		Odds ratio* (95% CI)	*P* value**
	Severe COVID-19 infection	No severe COVID-19 infection		
Diabetes				
No	525 (0.1%)	765,643 (99.9%)	1 [Reference]	
Yes	471 (0.3%)	140,624 (99.7%)	1.85 (1.59–2.14)	
Type				0.011
Type 1	36 (0.5%)	7861 (99.5%)	2.87 (1.99–4.15)	
Type 2	435 (0.3%)	132,763 (99.7%)	1.80 (1.55–2.09)	
Complications				0.045
No	185 (0.2%)	91,913 (99.8%)	1.66 (1.39–2.00)	
Yes	286 (0.6%)	48,711 (99.4%)	2.04 (1.71–2.43)	
Treatment				< 0.001
None	208 (0.3%)	59,478 (99.7%)	1.68 (1.41–2.01)	
Non-insulin only	123 (0.2%)	51,743 (99.8%)	1.69 (1.36–2.09)	
Insulin	140 (0.5%)	29,403 (99.5%)	2.65 (2.13–3.28)	
HbA1c				< 0.001
Missing	98 (0.3%)	31,987 (99.7%)	1.88 (1.50–2.36)	
< 7%	165 (0.3%)	59,238 (99.7%)	1.46 (1.20–1.78)	
7 to < 9%	153 (0.4%)	36,131 (99.6%)	2.32 (1.90–2.84)	
≥ 9%	55 (0.4%)	13,268 (99.6%)	2.61 (1.94–3.52)	

*No diabetes is the reference group for each odds ratio. **P value for two-sided Wald test of whether odds of sever COVID-19 differs across levels of severity measures. *CI* confidence interval. Percentages are for counts within rows. Odds ratios adjusted for Kaiser Permanente region, month of follow-up, age, sex, race/ethnicity, neighborhood deprivation index, smoking status, body mass index, comorbidities, and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, and systemic corticosteroids

a graded relationship between HbA1c levels and the risk of COVID-19 death.[7,22] A study of national health records from Scotland found that diabetes, HbA1c levels, and number of diabetes medications prescribed were associated with increased risks of fatal or intensive care unit (ICU)-treated COVID-19.[23] Among veterans receiving healthcare from the Department of Veterans Affairs with a positive NAAT test for SARS-CoV-2, diabetes was associated with increased risks of hospitalization, ICU admission, and death within 30 days, and the risks were greater among individuals

Table 4 Associations of body mass index (BMI) with COVID-19 outcomes among individuals with diabetes

	COVID-19 infection risk			
	Restricted to individuals with diabetes		Restricted to individuals with diabetes, adjusted for severity measures*	
	Odds ratio	95% CI	Odds ratio	95% CI
BMI categories (kg/m^2)				
Underweight (< 18)	0.92	0.57–1.49	0.93	0.58–1.49
Normal (18 to < 25)	1 (reference)		1 (reference)	
Overweight (25 to < 30)	1.10	1.00–1.22	1.10	1.00–1.22
Obese I (30 to < 35)	1.27	1.15–1.40	1.26	1.14–1.40
Obese II (35 to < 40)	1.31	1.18–1.45	1.30	1.17–1.45
Obese III (≥ 40)	1.32	1.19–1.47	1.31	1.18–1.47
	Severe COVID-19 infection risk			
	Restricted to individuals with diabetes		Restricted to individuals with diabetes, adjusted for severity measures*	
	Odds ratio	95% CI	Odds ratio	95% CI
BMI categories (kg/m^2)				
Underweight (< 18)	1.25	0.49–3.18	1.28	0.50–3.25
Normal (18 to < 25)	1 (reference)		1 (reference)	
Overweight (25 to < 30)	1.03	0.76–1.41	1.03	0.76–1.41
Obese I (30 to < 35)	1.47	1.08–2.01	1.45	1.06–1.97
Obese II (35 to < 40)	1.66	1.16–2.37	1.61	1.12–2.29
Obese III (≥ 40)	2.30	1.59–3.33	2.20	1.52–3.19

CI confidence interval. All models adjusted for Kaiser Permanente region, month of follow-up, age, sex, race/ethnicity, neighborhood deprivation index, smoking status, body mass index, comorbidities, and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, and systemic corticosteroids. *Additionally adjusted for diabetes type, presence of diabetes complications, treatment intensity category, and hemoglobin A1c category

receiving insulin treatment.[24] In contrast with earlier reports that severe COVID-19 outcomes are similar among individuals with type 1 and type 2 diabetes,[23,25] we found that type 1 diabetes was associated with 2.9-fold (95% CI 2.0–4.2) risk of severe COVID-19 compared with a 1.8-fold (95% CI 1.6–2.1) risk for type 2 diabetes ($P = 0.01$ for difference).

Our study is one of the few to evaluate diabetes and diabetes severity measures as risk factors for a validated severe COVID-19 outcome, without conditioning on an initial COVID-19 diagnosis or hospitalization, which can generate biased estimates of association.[10] In the absence of a consensus definition of severe COVID-19,[26,27] previous studies have included hospitalizations or ICU admissions, criteria which may vary considerably across geographic locations and even by hospital. Criteria for providing these levels of care have also varied over time during the pandemic. Because of concerns about the reproducibility and relevance of these subjective outcomes, we created and validated an algorithm for severe COVID-19 that included death or treatment with invasive mechanical ventilation, which is more likely to reflect respiratory and end organ failure.

Several potential mechanisms have been proposed that may link diabetes with an increased susceptibility to COVID-19 infection and severe outcomes after an infection, including a direct effect of elevated glucose levels SARS-CoV-2 replication, upregulation of harmful immune and inflammatory responses, hypercoagulability, and activation of the renin–angiotensin–aldosterone system.[28] In addition, other comorbidities that associate with diabetes and the cardiovascular complications that results from diabetes are also potent risk factors for adverse COVID-19 outcomes. Whether or not diabetes has a direct biological effect on COVID-19 outcomes, it is clear that diabetes and measures of the severity of diabetes are important risk factors that can be used to identify the most patients most susceptible to infection and severe outcomes.

Obesity has been identified as a key risk factor for COVID-19-related mortality. A study of people enrolled in Kaiser Permanente Southern California and diagnosed with COVID-19 identified a strong relationship between BMI and COVID-19 death, even after adjustment for diabetes and other comorbidities.[29] This finding has been replicated in the UK.[30] Because of the causal role obesity plays in the development of diabetes,[31,32] studies that evaluate the relationship between BMI and COVID-19 outcomes in populations with diabetes can help to disentangle the effects of these cardiometabolic risk factors on disease risk. In the national study of diabetes and COVID-19 mortality from Scotland, there was evidence of a J-shaped relationship; BMI < 20 kg/m^2 and all BMI categories greater than the reference category of 20 to < 25 kg/m^2 were associated with an increased risk of COVID-19 death.[23] We found evidence of a strong, graded relationship between BMI and both COVID-19 infection of any severity and severe COVID-19. Because of the small number of individuals in the underweight category (BMI < 18 kg/m^2), our study was underpowered to detect differences in risk compared to individuals with a normal BMI.

Our study is one of only a few to evaluate diabetes and diabetes severity measures as risk factors for developing COVID-19 of any severity. We used rich EHR data from integrated healthcare systems that provide both healthcare and insurance coverage to members, with long periods of prior enrollment and near-complete capture of COVID-19 outcomes. This rigorous study design allowed us to estimate population-based associations of diabetes risk factors with severe COVID-19, without conditioning on the presence of a COVID-19 infection or hospitalization as previous studies have done. Detailed laboratory and pharmacy data allowed for ascertainment of several diabetes severity measures. Additional strengths of this study include the community-based design representing three geographic regions of the USA, the validated definition of severe COVID-19, and adjustment for comorbidities and several sociodemographic factors as potential confounding variables.

Our study also had limitations. Although we included more recent data than previous studies of diabetes and COVID-19, widespread vaccination against COVID-19 had not yet occurred and information on the delta and omicron variants is lacking.[33] Also, a true physiologic endpoint of severe COVID-19 based on oxygenation levels in large-scale observational studies remains elusive. Residual confounding from factors associated with diabetes and COVID-19 outcomes and were not measured is a possibility, and associations may not reflect causal risk estimates.[20,21] For example, individual-level social determinants such as income and lack of access to effective medical care may underlie some of the risk attributed to diabetes in this study. Because autoantibody testing results and age at onset of diabetes were not available, some individuals with type 2 diabetes may have been misclassified as having type 1 diabetes, and vice versa. Also, many asymptomatic and mildly symptomatic cases of COVID-19 that did not result in diagnostic testing were most likely not captured.

Patients with diabetes suffer a large proportion of the severe morbidity and mortality associated with COVID-19. Within this heterogeneous population, we have demonstrated that the magnitude of risk differs by type and severity of diabetes. Our study confirms several observations from previous population-based studies of risk factors for COVID-19 mortality and provides new evidence about how diabetes, diabetes severity measures, and obesity related to the risk of developing COVID-19 of any severity. As new SARS-CoV-2 variants emerge and new treatments and risk mitigation interventions are developed,[34–36] these findings may help to allocate scarce resources among individuals at greatest risk and with the greatest potential to benefit from these interventions. Additional community- or population-based studies are needed to extend these findings to time periods when different SARS-CoV-2 variants predominate.

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Declarations

Conflict of Interest *The authors declare no competing interests.*

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