Risk factors for adverse outcomes among 35 879 veterans with and without diabetes after diagnosis with COVID-19

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ABSTRACT

Introduction Risk factors and mediators of associations of diabetes with COVID-19 outcomes are unclear.
Research design and methods We identified all veterans receiving Department of Veterans Affairs healthcare with ≥1 positive nasal swab for SARS-CoV-2 (28 February–31 July 2020; n=35 879). We assessed associations of diabetes (with and without insulin use) with hospitalization, intensive care unit (ICU) admission, or death at 30 days, and with hazard of death until the censoring date. Among participants with diabetes (n=13 863), we examined associations of hemoglobin A1c and antihyperglycemic medication use with COVID-19 outcomes. We estimated mediation between diabetes and outcomes by comorbidities (cardiovascular disease, heart failure, and chronic kidney disease), statin or ACE inhibitor/angiotensin receptor blocker (ARB) use, and cardiac biomarkers (brain natriuretic peptide and troponin).
Results Diabetes with and without insulin use was associated with greater odds of hospitalization, ICU admission, and death at 30 days, and with greater hazard of death compared with no diabetes (OR 1.73, 1.76 and 1.63, and HR 1.61; and OR 1.39, 1.49 and 1.33, and HR 1.37, respectively, all p<0.0001). Prior sulfonylurea use was associated with greater odds of hospitalization and prior insulin use with hospitalization and death among patients with diabetes; among all participants, statin use was associated with lower mortality and ARB use with lower odds of hospitalization. Cardiovascular disease-related factors mediated <20% of associations between diabetes and outcomes.
Conclusions Diabetes is independently associated with adverse outcomes from COVID-19. Associations are only partially mediated by common comorbidities.

Significance of this study

What is already known about this subject?
► Diabetes has been previously linked to a higher risk of COVID-19 related adverse outcomes including hospitalization, ICU admission, and death, but risk factors and mediators remain unclear.

What are the new findings?
► Diabetes with and without insulin use was associated with greater odds of adverse outcomes compared with no diabetes.
► Among all participants statin or angiotensin receptor blocker use was associated with lower odds of adverse outcomes. Among individuals with diabetes, prior sulfonylurea or insulin use was associated with greater odds of adverse outcomes among patients with diabetes. Cardiovascular disease-related factors mediated <20% of associations between diabetes and outcomes.
► Given that the associations of diabetes with adverse outcomes from COVID-19 are only partially mediated by cardiovascular disease-related factors, other downstream consequences of diabetes including hyperglycemia and/or metabolic decompensation at presentation or during admission, altered inflammatory responses, and increased coagulation activity should be evaluated as potential intermediates.

How might these results change the focus of research or clinical practice?
► Studies using prospective treatment assignment are needed to assess the role of potentially modifiable factors such as statin use in preventing adverse outcomes from COVID-19.

INTRODUCTION

Diabetes complicates more than 25% of hospitalized SARS-CoV-2/COVID-19 cases and has been repeatedly associated with an excess risk of severe outcomes, defined as hospitalization, intensive care unit (ICU) admission, and death.[1–7] In the Veterans Health Administration, nearly one in four enrollees has diabetes,[8] comprising a far greater share than in the general population of US adults.[9] In addition, common comorbidities or sequelae of diabetes including hypertension (HTN), cardiovascular disease (CVD), heart failure (HF), and chronic kidney disease (CKD), which are prevalent among Veterans Affairs (VA) enrollees, have consistently been associated with higher risk of COVID-19 related adverse outcomes;[10 11] however, whether associations of diabetes with adverse

outcomes from COVID-19 are mediated by the presence of these common cardiovascular and renal comorbidities is not established, and to our knowledge, independent associations of prior glycemic control and individual antihyperglycemic medication use with COVID-19 outcomes have not been evaluated in a large nationwide US cohort with diabetes.

To address these knowledge gaps, we used national data from the VA healthcare system to rigorously address three goals: (1) to quantify the independent association of diabetes with adverse outcomes from COVID-19, (2) to identify risk factors for adverse COVID-19 outcomes among veterans with diabetes, and (3) to quantify how much, if any, of this association is mediated by common cardiovascular and renal comorbidities including common complications of diabetes (CVD, HF, and CKD), concurrent use of commonly prescribed medications for diabetes-associated conditions (ACE inhibitors, angiotensin receptor blockers (ARB), and statins), and biomarkers of cardiac injury measured at the time of COVID-19 diagnosis.

METHODS
Study setting and study population
The Veterans Health Administration is the largest integrated healthcare system in the USA, providing care at 170 medical centers and 1074 outpatient sites.[12] For this analysis, we used data from the Corporate Data Warehouse, a data repository derived from the VA's integrated electronic medical record including a COVID-19 Shared Data Resource, which contains analytic variables for all VA enrollees tested for SARS-CoV-2.[13] We identified every enrollee with one or more positive nasal swabs for SARS-CoV-2 between 1 March and 31 July 2020, comprising the analytic sample (n=35 879). The index date was defined as the date of the first positive COVID-19 test. Most tests were performed in VA laboratories using US Food and Drug Administration approved RealTime (Abbott Laboratories) or Xpert-Xpress (Cepheid) SARS-CoV-2 assays. A small number were sent to outside laboratories. The requirement for informed consent was waived.

Exposures
Diabetes was defined as two or more abnormal lab values from plasma or serum (random glucose >199 mg/dL, fasting glucose >125 mg/dL, 2-hour glucose from an oral glucose tolerance test >199 mg/dL) or whole blood (hemoglobin A1c >6.4%)[14]; two outpatient or one inpatient International Classification of Diseases and Related Health Problems, Ninth Revision Clinical Modification or Tenth Revision (ICD-9-CM or ICD-10) codes of 250 or E08-E13, or receipt of an initial and one refill prescription of an antihyperglycemic medication. Diabetes status was further categorized by whether insulin was prescribed for treatment in outpatient VA pharmacy records.

Covariates
We collected data on age, sex, and race/ethnicity, VA facility location, and urban versus rural/highly rural status using a validated classification scheme that has been previously described.[15] Body mass index (BMI) was defined as weight (kg) divided by height (m^2). Smoking status was classified as current, former, or never. Comorbidities (HTN, CVD, and HF) were identified using ICD-9-CM and ICD-10 codes entered after 1 October 1999, the date when the Veterans Health Administration (VHA) began using a universal electronic health record.[16] We defined CKD as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2[17] using the most recent creatinine at least 3 days, but not more than 1 year, before the index date. We collected data on commonly prescribed medications including ACE/ARB, nitrates, beta-blockers, calcium-channel blockers, diuretics, statins, and antihyperglycemic medications, during the 6 months prior to COVID-19 diagnosis. For individuals with data available on markers of cardiac injury (troponin-I, troponin-T, B-type natriuretic peptide (BNP), and N-terminal prohormone BNP (NT-proBNP)) at time of COVID-19 diagnosis, we dichotomized troponin values as normal or elevated based on cut points provided for each assay at the testing site because a variety of assays for these biomarkers are used across the VA healthcare system (n=5904). We categorized BNP and NT-proBNP values into quartiles (n=4023).

Outcomes
We collected data on hospitalizations and ICU admissions occurring between 1 March and 31 August 2020, and deaths occurring through 31 December 2020.

Statistical analyses
Baseline characteristics were summarized for the overall group and by presence of diabetes. We used multiple imputation with 20 sets of imputations for analyses that included BMI or CKD due to approximately 20% missing values for each of these variables. We used DAGitty[18] to generate a directed acyclic graph (DAG) to assist in model selection for confounder adjustment and for mediation analysis selecting variables based on literature review (online supplemental figure 1). We fit logistic regression models testing the association of diabetes with and without insulin use with occurrence of hospitalization, ICU admission, and death, adjusting for the minimal sufficient adjustment set for estimating the total effect of diabetes according to our DAG (age, sex, race/ethnicity, BMI, smoking status, facility location, and urban/rural status). We also fit Cox proportional hazards models to estimate hazard of death (data administratively censored on 31 December 2020),\ and examined the residuals to confirm that it was reasonable to assume proportional hazards. To facilitate quantitative comparison of the effect sizes in the current report with those in previous studies, we conducted a sensitivity analysis in which we fit models that additionally adjusted for covariates that

are frequently included (ACE/ARB use, statin use, platelet inhibitor use, HTN, CVD, HF, and CKD). We also conducted sensitivity analyses excluding individuals with a diagnostic code for type 1 diabetes.

Among participants with diabetes (n=13 863), we fit models assessing associations of hemoglobin A1c (<7%, 7%–7.9%, 8%–8.9%, and ≥9%) and prior antihyperglycemic medication use (insulin, metformin, dipeptidyl peptidase (DPP) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, sodium-glucose contransporter-2 (SGLT2) inhibitors, sulfonylureas, and thiazolidinediones) with the same COVID-19 outcomes as in the larger sample adjusted for age, sex, race/ethnicity, BMI, tobacco use, ACE use, ARB use, statin use, platelet inhibitor use, HTN, CVD, HF, CKD, facility location, month of diagnosis, and urban/rural residence.

For diabetes and CVD-related variables that we hypothesized might mediate the association of diabetes with adverse outcomes from COVID-19 (CVD, HF, CKD, ACE/ARB use, statin use, BNP or NT-pro BNP in the upper quartile, or elevated troponin), we estimated the total effect of diabetes on adverse outcomes from COVID-19 at 30 days, which can be decomposed into two components: the average direct effect from diabetes and the average causal mediation effect (ACME) that is due to the mediating variable of interest. These quantities are expressed as risk differences. Where possible, we included both clinical (eg, HF) and biochemical (eg, BNP) measures. When applicable, we also reported the proportion mediated (which can be conceptualized as ACME/total effect).[19 20] To identify statistically significant mediating effects, we tested the null hypothesis that ACME=0 and estimated 95% CIs using bias-corrected and accelerated bootstrapping with 1000 replicates. For mediation models, we analyzed only complete cases (n=28 933). Analyses were conducted in Stata V.16.1 (College Station, Texas, USA) and R V.4.0.2, with the *mediation* package.[19] All tests were two sided, and p<0.05 was considered significant.

RESULTS

Participants were 60.3 years old (±17.0) on average, and 11% were female (n=3886). Thirty-nine per cent (n=13 863) had diabetes: 10% (n=3508) had diabetes treated with insulin, while 29% (n=10 355) had diabetes not on insulin. During the 30 days after diagnosis, 19% (n=6775) were hospitalized, 6% were admitted to the ICU (2313), and 7% died (n=2404) (table 1). Average number of days until death was 17 (IQR 8–47). In models testing for interactions of sex with diabetes status, tests for multiplicative first-order interactions were not significant; therefore, OR and HR are presented for models including men and women together. Diabetes treated with insulin was associated with 73% greater odds of hospital admission, 76% greater odds of ICU admission, and 63% greater odds of death at 30 days, as well as a 61% greater hazard of death occurring before the censoring date compared with no diabetes (all p<0.0001) (table 2). Diabetes without

use of insulin was associated with 39% greater odds of hospital admission, 49% greater odds of ICU admission, 33% greater odds of death at 30 days, and a 37% greater hazard of death compared with no diabetes (all p<0.0001) (table 2). Other characteristics associated with higher risk of adverse outcomes were greater age and former and current smoking for all outcomes; black race for hospital or ICU admission within 30 days; Hispanic ethnicity and hospitalization or death within 30 days; BMI ≥40 kg/m² for all outcomes except hazard of death; BMI 30.0–39.9 kg/m² for ICU admission within 30 days; and BMI <18.5 kg/m² for hazard of death. Characteristics associated with lower risk of adverse outcomes include rural residence for all outcomes: white race for hospital or ICU admission within 30 days; BMI 25.0–34.9 kg/m² and 30-day mortality and hazard of death; and BMI 35.0–39.9 kg/m² and hazard of death. A sensitivity analysis that additionally adjusted for ACE/ARB use, statin use, platelet inhibitor use, HTN, CVD, HF, and CKD showed substantially attenuated ORs for hospital and ICU admission and, to a lesser extent, mortality (online supplemental table 1).

Diabetes characteristics including baseline hemoglobin A1c (<7%, 7%–7.9%, 8%–8.9% and ≥9%) and antihyperglycemic medication use (n (%)) are shown in online supplemental table 2). Analysis of glycemic control as reflected by hemoglobin A1c among individuals with diabetes suggest that hemoglobin A1c ≥9% was associated with greater odds of death at 30 days (OR 1.25 (95% CI 1.02 to 1.54)) compared with A1c <7% but was not significantly related to hospital or ICU admission within 30 days of diagnosis or hazard of death (table 3). Female sex at birth was associated with lower odds of death at 30 days as well as lower hazard of death (OR 0.61 (95% CI 0.41 to 0.91); and HR 0.65 (95% CI 0.48 to 0.88), respectively). We did not find evidence of statistically significant multiplicative first-order interactions of age or sex with hemoglobin A1c with hospitalization, ICU admission, or death. Insulin use was associated with greater odds of hospital admission at 30 days (OR 1.15 (95% CI 1.03 to 1.27)) and greater hazard of death (HR 1.18 (95% CI 1.05 to 1.33)), while sulfonyurea use was associated with greater odds of hospital admission at 30 days (OR 1.13 (95% CI 1.01 to 1.28)). No significant association was seen between any of the outcomes and treatment with other classes of diabetes antiglycemic medication use including metformin, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors. ARB use was associated with lower odds of hospital admission and lower hazard of death (OR 0.82 (95% CI 0.73 to 0.92) and HR 0.85 (95% CI 0.74 to 0.97)). Statin use was associated with lower odds of death at 30 days and lower hazard of death (OR 0.76 (95% CI 0.66 to 0.88) and HR 0.76 (95% CI 0.68 to 0.84)) (table 3). Other characteristics significantly associated with higher risk of adverse outcomes in persons with diabetes were greater age, CVD, and eGFR <45 mL/min/1.73 m² for all outcomes; black race for hospital or ICU admission; BMI

Table 1 Characteristics of VA veterans diagnosed with COVID-19 between 1 January and 31 July 2020, overall and stratified by diabetes diagnosis

	Overall	No diabetes	Diabetes treated with insulin	Diabetes not treated with insulin
	n=35 879	n=22 016	n=3508	n=10 355
Age category, years				
19–39	16 (5571)	24 (5233)	2 (69)	3 (269)
40–49	11 (4098)	15 (3258)	5 (185)	6 (655)
50–59	17 (6217)	18 (3954)	18 (638)	16 (1625)
60–69	21 (7498)	17 (3777)	29 (1022)	26 (2699)
70–79	23 (8414)	16 (3623)	36 (1257)	34 (3534)
80+	11 (4081)	10 (2171)	10 (337)	15 (1573)
Sex at birth, female	11 (3886)	14 (2993)	5 (175)	7 (718)
Race/ethnicity				
White	55 (19812)	57 (12500)	53 (1857)	53 (5455)
Black	35 (12560)	32 (7026)	40 (1418)	40 (4116)
Hispanic	14 (4877)	15 (3304)	12 (404)	11 (1169)
Other	7 (2606)	8 (1794)	5 (183)	6 (629)
Body mass index category, kg/m²				
<18.5	1 (242)	1 (155)	0	1 (79)
18.5–24.9	15 (4324)	17 (2857)	9 (285)	13 (1182)
25–29.9	32 (4324)	34 (5784)	26 (850)	29 (2578)
30–34.9	29 (8373)	29 (4847)	31 (1021)	28 (2505)
35–39.9	15 (4311)	13 (2170)	20 (651)	17 (1490)
≥40	8 (2453)	6 (1060)	13 (435)	11 (958)
Tobacco use				
Never	35 (12460)	41 (9039)	23 (824)	25 (2597)
Former	40 (14313)	34 (7471)	52 (1837)	48 (5005)
Current	25 (9106)	25 (5506)	24 (847)	27 (2753)
Urban/rural/highly rural residence				
Highly rural	0 (106)	0 (58)	0	0 (34)
Rural	15 (5288)	14 (3112)	17 (605)	15 (1571)
Urban	67 (24089)	68 (15037)	64 (2246)	66 (6806)
Unknown	18 (6396)	17 (3809)	18 (643)	19 (1944)
Hypertension	62 (22371)	46 (10056)	94 (3294)	87 (9021)
Cardiovascular disease	40 (14457)	28 (6228)	64 (2254)	58 (5975)
Heart failure	12 (4155)	5 (1208)	26 (909)	20 (2038)
Estimated glomerular filtration rate, mL/min/1.73 m²				
≥90	28 (7955)	33 (5357)	18 (601)	22 (1997)
60–89	47 (13325)	50 (8044)	38 (1260)	45 (4021)
45–59	14 (3983)	11 (1755)	19 (644)	18 (1584)
30–44	6 (1823)	4 (606)	13 (443)	9 (774)
15–29	2 (703)	1 (160)	7 (226)	4 (317)
<15 or dialysis	2 (597)	1 (99)	5 (159)	4 (339)
Medication use				
ACE inhibitor	19 (6657)	11 (2492)	40 (1397)	27 (2768)
ARB	10 (3718)	6 (1290)	25 (872)	15 (1556)
Statin	36 (12781)	22 (4803)	78 (2721)	51 (5257)
Nitrate	3 (1231)	2 (353)	10 (352)	5 (5257)
Beta-blocker	22 (7724)	14 (3058)	48 (1680)	29 (2986)
Calcium channel blocker	19 (6951)	14 (3063)	36 (1275)	25 (2613)
Thiazide diuretic	13 (4648)	10 (2145)	22 (785)	17 (1718)

Continued

Table 1 Continued

	Overall	No diabetes	Diabetes treated with insulin	Diabetes not treated with insulin
	n=35 879	n=22 016	n=3508	n=10 355
Potassium-sparing diuretic	3 (1170)	2 (463)	7 (259)	4 (448)
Loop diuretic	7 (2672)	3 (762)	24 (825)	10 (1085)
Fibrate	1 (325)	1 (117)	2 (87)	1 (121)
Digitalis	0 (144)	0 (44)	1 (35)	1 (65)
Amiodarone	1 (222)	0 (75)	1 (48)	1 (99)
Platelet inhibitor	15 (5472)	8 (1716)	41 (1438)	22 (2318)
Anticoagulant	7 (2468)	4 (968)	14 (477)	10 (1023)
Cardiac biomarkers				
Troponin elevated at COVID-19 diagnosis	12 (719)	9 (223)	17 (166)	14 (330)
Upper quartile of BNP or NT-pro BNP at COVID-19 diagnosis	3 (1008)	1 (281)	6 (213)	5 (514)
Hospital admission within 30 days	19 (6775)	14 (3091)	29 (1031)	26 (2653)
ICU admission within 30 days	6 (2313)	4 (937)	11 (394)	9 (982)
Death within 30 days	7 (2404)	5 (1012)	10 (361)	10 (1031)
Death by 31 December 2020	11 (3781)	7 (1575)	16 (555)	16 (1651)

Data are presented as mean (SD) for continuous variables and % (n) for categorical variables
P values for global differences in participant characteristics across categories of diabetes status from analysis of variance or χ2 tests were all <0.001
ARB, angiotensin receptor blockers; BNP, B-type natriuretic peptide; ICU, intensive care unit; NT-proBNP, N-terminal prohormone BNP; VA, Veterans Affairs.

$\geq$40 kg/m^2 for ICU admission and death within 30 days; BMI <18.5 kg/m^2 for 30-day and mortality hazard; and HF and former and current tobacco use for all outcomes except death at 30 days. Besides female sex at birth, lower risk of adverse outcomes in persons with diabetes was seen for BMI 25.0–39.9 kg/m^2 for mortality hazard and all outcomes except 30-day mortality for rural residence. Results from sensitivity analyses excluding individuals with type 1 diabetes (n=1364) were quantitatively very similar (data not shown).

Of the seven mediating variables we tested, CVD, HF, CKD, prior statin use, BNP in the upper quartile at COVID-19 diagnosis, and elevated troponin (based on site-specific cutpoints) at COVID-19 diagnosis partially mediated the estimated effect of diabetes on hospital admission as demonstrated by an ACME significantly different from the null value of zero. CVD, HF, CKD, BNP, and troponin partially mediated the estimated effect of diabetes on ICU admission, and every candidate mediator partially mediated the estimated effect of diabetes on mortality. For most of these mediators, however, the mediating effect was small. Mediation effects estimated by ACME through CVD and CHF were generally of largest magnitude, accounting for about 18% of the total estimated effect of diabetes on death, but no mediator contributed more than a 1.1% greater risk to any adverse outcome (table 4).

CONCLUSIONS

In this cohort of US veterans with COVID-19 (n=35 879), diabetes with and without use of insulin was independently associated with greater odds of hospital admission, ICU admission, and death compared with no diabetes. Point estimates of ORs and HRs for all outcomes were higher in diabetes treated with insulin compared with no treatment with insulin. Among veterans with diabetes (n=13 878), we found that hemoglobin A1c $\geq$9% was associated with greater odds of death at 30 days, while female sex at birth was inversely associated with adverse outcomes from COVID-19. Prior use of insulin or sulfonylureas was directly associated with adverse outcomes from COVID-19, while prior use of an ARB or statin was associated with a lower risk of some adverse outcomes. To our knowledge, this is the largest study of risk factors for adverse outcomes from COVID-19 in a cohort of individuals with and without diabetes in the USA as well as the first to formally assess whether the association of diabetes with adverse COVID-19 outcomes is mediated by cardiovascular and renal disease related factors including prevalent cardiovascular conditions, CKD, medications, or markers of cardiovascular injury. CVD-related factors (including CVD, HF, and elevated troponin levels at COVID-19 diagnosis) partially mediated the total estimated effects of diabetes on adverse outcomes from COVID-19, but mediation effects were small.

Prior studies report variable magnitude of the association of diabetes with adverse COVID-19 outcomes,[2 3 5–7] which may be due to differences in confounder adjustment or to heterogeneity of the populations studied. One important confounder is BMI. Given that BMI is strongly and positively associated with incident type 2 diabetes and demonstrates a J-shaped association with mortality from COVID-19,[21 22] estimates not adjusted for BMI might overestimate or underestimate the magnitude of the association between diabetes and adverse COVID-19

Table 2 ORs/HRs from regression models testing the association of diabetes with adverse outcomes from COVID-19 in US veterans, n=35 879

	Hospital admission within 30 days of diagnosis		ICU admission within 30 days of diagnosis		Death within 30 days of diagnosis		Death by 31 December 2020	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
No diabetes	ref		ref		ref		ref	
Diabetes treated with insulin	1.73	1.58 to 1.89	1.76	1.54 to 2.00	1.63	1.42 to 1.88	1.61	1.45 to 1.78
Diabetes not treated with insulin	1.39	1.31 to 1.49	1.49	1.35 to 1.64	1.33	1.21 to 1.47	1.37	1.28 to 1.48
Sex at birth, female	0.72	0.65 to 0.81	0.64	0.52 to 0.78	0.58	0.44 to 0.78	0.60	0.48 to 0.74
Age category, years								
19–39	0.37	0.32 to 0.43	0.35	0.27 to 0.45	0.06	0.02 to 0.16	0.11	0.06 to 0.20
40–49	0.66	0.58 to 0.75	0.63	0.51 to 0.79	0.34	0.21 to 0.56	0.34	0.23 to 0.50
50–59	ref		ref		ref		ref	
60–69	1.42	1.30 to 1.55	1.45	1.25 to 1.68	2.79	2.21 to 3.53	2.77	2.31 to 3.31
70–79	1.92	1.76 to 2.11	2.15	1.86 to 2.49	6.98	5.58 to 8.73	6.18	5.20 to 7.34
≥80	2.54	2.28 to 2.83	2.49	2.10 to 2.95	20.01	15.89 to 25.19	15.75	13.31 to 18.91
White (vs not white)	0.89	0.80 to 0.98	0.85	0.73 to 1.00	0.90	0.76 to 1.05	0.98	0.87 to 1.11
Black (vs not black)	1.52	1.37 to 1.70	1.38	1.17 to 1.63	0.95	0.80 to 1.13	0.97	0.85 to 1.10
Hispanic (vs not Hispanic)	1.17	1.07 to 1.29	1.14	0.98 to 1.32	1.19	1.01 to 1.41	1.01	0.89 to 1.15
Body mass index category, kg/m²								
<18.5	1.07	0.78 to 1.45	0.87	0.53 to 1.43	1.35	0.92 to 1.99	1.50	1.17 to 1.92
18.5–24.9	ref		ref		ref		ref	
25–29.9	0.94	0.86 to 1.03	1.11	0.96 to 1.29	0.87	0.77 to 0.99	0.81	0.74 to 0.89
30–34.9	0.93	0.84 to 1.02	1.18	1.01 to 1.36	0.84	0.72 to 0.98	0.74	0.66 to 0.83
35–39.9	1.04	0.93 to 1.16	1.36	1.14 to 1.62	0.90	0.75 to 1.08	0.79	0.69 to 0.91
≥40	1.31	1.15 to 1.49	1.64	1.34 to 1.99	1.40	1.12 to 1.74	1.04	0.88 to 1.22
Tobacco use								
Never	ref		ref		ref		ref	
Former	1.23	1.15 to 1.32	1.30	1.16 to 1.46	1.21	1.08 to 1.36	1.16	1.06 to 1.26
Current	1.34	1.24 to 1.45	1.33	1.17 to 1.50	1.31	1.14 to 1.50	1.35	1.22 to 1.49
Urban/rural/highly rural residence								
Highly rural	0.66	0.37 to 1.17	1.02	0.47 to 2.25	1.27	0.63 to 2.55	0.91	0.50 to 1.65
Rural	0.66	0.60 to 0.73	0.80	0.70 to 0.92	0.85	0.74 to 0.97	0.85	0.77 to 0.94
Urban	ref		ref		ref		ref	
Unknown	1.42	1.33 to 1.52	1.32	1.19 to 1.47	1.07	0.95 to 1.20	1.16	1.07 to 1.25

Models additionally adjusted for geographic location by Veterans Integrated Service Network location.
n=35 879 for logistic regression models, n=35 817 for Cox proportional hazards model.
ICU, intensive care unit.

Table 3 Associations of hemoglobin A1c and antidiabetic medication use with adverse outcomes from COVID-19 among veterans with diabetes, n=13 863

	Hospital admission within 30 days of diagnosis		ICU admission within 30 days of diagnosis		Death within 30 days of diagnosis		Death by 31 December 2020	
	OR	95% CI	OR	95% CI	OR	95% CI	HR	95% CI
Sex at birth, female	0.91	0.76 to 1.09	0.75	0.55 to 1.00	0.61	0.41 to 0.91	0.65	0.48 to 0.88
Age category, years								
19–39	0.78	0.55 to 1.09	0.92	0.54 to 1.57	0.14	0.02 to 1.01	0.08	0.01 to 0.56
40–49	0.75	0.60 to 0.93	0.74	0.52 to 1.07	0.67	0.35 to 1.27	0.57	0.35 to 0.95
50–59	ref		ref		ref		ref	
60–69	1.18	1.03 to 1.35	1.18	0.96 to 1.44	2.58	1.88 to 3.53	2.12	1.68 to 2.66
70–79	1.23	1.07 to 1.42	1.31	1.07 to 1.61	4.75	3.48 to 6.47	3.46	2.76 to 4.33
≥80	1.36	1.15 to 1.62	1.34	1.04 to 1.73	9.43	6.76 to 13.15	6.17	4.85 to 7.84
White (vs not white)	0.97	0.83 to 1.13	0.95	0.76 to 1.19	0.92	0.73 to 1.15	1.02	0.86 to 1.20
Black (vs not black)	1.42	1.20 to 1.67	1.27	1.00 to 1.61	0.87	0.69 to 1.11	0.92	0.77 to 1.09
Hispanic (vs not Hispanic)	1.07	0.93 to 1.23	0.97	0.79 to 1.20	1.15	0.93 to 1.43	1.01	0.86 to 1.18
Body mass index category, kg/m²								
<18.5	0.97	0.59 to 1.61	0.90	0.45 to 1.80	1.80	1.05 to 3.09	1.63	1.16 to 2.29
18.5–24.9	ref		ref		ref		ref	
25–29.9	0.98	0.85 to 1.13	1.10	0.90 to 1.36	0.97	0.80 to 1.17	0.85	0.75 to 0.97
30–34.9	0.90	0.77 to 1.04	1.13	0.92 to 1.40	0.95	0.78 to 1.16	0.77	0.67 to 0.88
35–39.9	0.96	0.82 to 1.12	1.20	0.94 to 1.52	0.95	0.74 to 1.22	0.79	0.66 to 0.94
≥40	1.08	0.90 to 1.29	1.32	1.03 to 1.71	1.45	1.12 to 1.88	0.99	0.81 to 1.20
Tobacco use								
Never	ref		ref		ref		ref	
Former	1.16	1.04 to 1.29	1.27	1.08 to 1.49	1.19	1.01 to 1.41	1.18	1.04 to 1.34
Current	1.23	1.10 to 1.39	1.33	1.12 to 1.60	1.14	0.94 to 1.39	1.19	1.03 to 1.37
Hemoglobin A1c, %								
<7	ref		ref		ref		ref	
7–7.9	0.90	0.81 to 1.01	0.94	0.80 to 1.11	1.04	0.88 to 1.22	0.98	0.87 to 1.10
8–8.9	0.92	0.79 to 1.06	0.95	0.76 to 1.17	1.09	0.88 to 1.34	1.00	0.86 to 1.17
≥9	1.10	0.96 to 1.25	1.04	0.85 to 1.27	1.25	1.02 to 1.54	1.09	0.94 to 1.27
Metformin	1.00	0.91 to 1.10	1.13	0.98 to 1.30	1.03	0.89 to 1.21	0.93	0.83 to 1.04
Sulfonyurea	1.13	1.01 to 1.28	1.13	0.96 to 1.34	0.87	0.72 to 1.06	0.96	0.83 to 1.11
Thiazolidinedione	0.89	0.69 to 1.16	1.02	0.70 to 1.49	0.95	0.60 to 1.48	0.95	0.67 to 1.34

Continued

Table 3 Continued

	Hospital admission within 30 days of diagnosis		ICU admission within 30 days of diagnosis		Death within 30 days of diagnosis		Death by 31 December 2020	
	OR	95% CI	OR	95% CI	OR	95% CI	HR	95% CI
DPP-4 inhibitor	0.94	0.80 to 1.10	0.99	0.78 to 1.24	1.05	0.83 to 1.34	1.01	0.84 to 1.22
GLP-1 receptor agonist	1.11	0.92 to 1.33	1.06	0.81 to 1.38	1.31	0.99 to 1.74	1.00	0.79 to 1.26
SGLT2 inhibitor	0.87	0.73 to 1.05	0.78	0.59 to 1.03	0.76	0.55 to 1.05	0.81	0.63 to 1.04
Insulin	1.15	1.03 to 1.27	1.12	0.96 to 1.31	1.11	0.94 to 1.30	1.18	1.05 to 1.33
ACE inhibitor	1.01	0.91 to 1.11	1.01	0.87 to 1.17	0.92	0.78 to 1.07	0.90	0.80 to 1.01
ARB	0.82	0.73 to 0.92	0.89	0.75 to 1.06	0.89	0.74 to 1.07	0.85	0.74 to 0.97
Statin	1.00	0.91 to 1.10	0.91	0.79 to 1.04	0.76	0.66 to 0.88	0.76	0.68 to 0.84
Platelet inhibitor	1.01	0.91 to 1.11	0.93	0.81 to 1.07	1.02	0.88 to 1.18	1.03	0.93 to 1.14
Hypertension	1.17	1.00 to 1.37	1.22	0.95 to 1.58	0.89	0.69 to 1.15	1.03	0.84 to 1.26
Cardiovascular disease	1.53	1.38 to 1.69	1.52	1.31 to 1.76	1.32	1.13 to 1.54	1.39	1.23 to 1.56
Heart failure	1.56	1.41 to 1.73	1.50	1.30 to 1.72	1.12	0.98 to 1.29	1.24	1.12 to 1.36
Estimated glomerular filtration rate, mL/min/1.73 m²								
≥90	ref		ref		ref		ref	
60–89	0.93	0.83 to 1.05	0.93	0.78 to 1.11	1.15	0.92 to 1.42	0.99	0.85 to 1.16
45–59	1.04	0.90 to 1.20	1.11	0.90 to 1.37	1.39	1.09 to 1.78	1.16	0.98 to 1.38
30–44	1.22	1.03 to 1.44	1.32	1.04 to 1.68	1.77	1.36 to 2.30	1.47	1.22 to 1.77
15–29	1.35	1.09 to 1.68	1.49	1.11 to 2.01	2.40	1.75 to 3.27	1.82	1.48 to 2.24
<15 or dialysis	1.36	1.09 to 1.70	1.49	1.11 to 2.00	1.62	1.16 to 2.26	1.57	1.26 to 1.95
Urban/rural/highly rural residence								
Highly rural	0.68	0.32 to 1.43	1.31	0.54 to 3.16	2.00	0.88 to 4.54	1.33	0.69 to 2.58
Rural	0.66	0.58 to 0.75	0.82	0.68 to 0.98	0.91	0.76 to 1.10	0.86	0.75 to 0.99
Urban	ref		ref		ref		ref	
Unknown	1.26	1.14 to 1.40	1.05	0.91 to 1.21	1.03	0.88 to 1.19	1.10	0.99 to 1.22

Models additionally adjusted for geographic location by Veterans Integrated Service Network location and by month of COVID-19 diagnosis.
n=13 863 or logistic regression models, n=13 825 for Cox proportional hazards model.
ARB, angiotensin receptor blockers; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide 1; ICU, intensive care unit; SGLT2, sodium–glucose contransporter-2.

Table 4 Risk differences comparing the expected probability of adverse outcomes (hospital admission, ICU admission, or death) from COVID-19 at 30 days due to the total effect from diabetes, effect through the mediator (average causal mediation effect (ACME)), and direct effect due to diabetes (average direct effect (ADE)) for candidate cardiovascular disease-related mediators in veterans (28 February 2020–31 July 2020)

Candidate mediators	Cardiovascular disease	Heart failure		Chronic kidney disease		ACE inhibitor or ARB use		Statin use		Upper quartile of BNP or NT-pro BNP at COVID-19 diagnosis		Elevated troponin at COVID-19 diagnosis	
	Risk difference (%)	Risk difference (%)	95% CI	Risk difference (%)	95% CI	Risk difference (%)	95% CI	Risk difference (%)	95% CI	Risk difference (%)	95% CI	Risk difference (%)	95% CI
Hospital admission													
Total effect	1.9	1.9	1.3 to 2.5	2.0	1.4 to 2.6	1.8	1.2 to 2.4	1.8	1.2 to 2.4	1.6	−0.7 to 4.2	1.1	−0.8 to 3.1
Average causal mediation effect	0.3	0.3	0.2 to 0.4	0.4	0.3 to 0.5	−0.1	−0.2 to 0.1	−0.2	−0.4 to −0.1	0.4	0.1 to 0.7	0.2	0.1 to 0.6
Average direct effect	1.6	1.6	0.9 to 2.2	1.6	1.0 to 2.2	1.9	1.3 to 2.5	2.0	1.4 to 2.6	1.2	−1.1 to 3.9	0.9	−1.0 to 2.8
Proportion mediated*	14.7	16.0	10.5 to 30.0	19.8	13.9 to 33.5	*		*		*		*	
ICU admission													
Total effect	3.1	3.1	2.4 to 3.8	3.2	2.5 to 4.0	3.1	2.4 to 3.8	3.1	2.4 to 3.8	3.7	0.7 to 6.3	3.5	1.4 to 5.9
Average causal mediation effect	0.4	0.5	0.4 to 0.6	0.3	0.2 to 0.4	0.0	−0.1 to 0.2	0.0	−0.1 to 0.2	0.3	0.0 to 0.7	0.1	0.0 to 0.4
Average direct effect	2.7	2.6	1.8 to 3.3	2.9	2.2 to 3.7	3.1	2.4 to 3.8	3.0	2.3 to 3.7	3.4	0.4 to 5.9	3.4	1.2 to 5.7
Proportion mediated*	13.2	15.2	11.7 to 23.3	9.2	6.2 to 14.0	*		*		*		3.8	1.2 to 31.0
Death													
Total effect	5.8	5.7	4.7 to 6.8	5.7	4.7 to 6.8	5.8	4.7 to 6.8	5.8	4.8 to 6.8	3.6	0.6 to 6.0	7.7	4.9 to 11.1
Average causal mediation effect	1.1	1.0	0.9 to 1.3	0.6	0.4 to 0.8	0.2	0.0 to 0.4	0.4	0.2 to 0.7	0.2	0.0 to 1.0	0.2	0.0 to 0.5
Average direct effect	4.7	4.7	3.6 to 5.7	5.2	4.1 to 6.3	5.6	4.5 to 6.7	5.4	4.3 to 6.5	3.4	0.4 to 6.0	7.6	4.7 to 10.9
Proportion mediated*	18.2	18.3	15.0 to 25.2	10.2	7.5 to 14.6			6.7	2.8 to 12.1			2.3	0.6 to 7.7

Models run using 1000 simulations with bootstrapped CIs.

Models additionally adjusted for sex, age group, race/ethnicity, BMI category, smoking status, station, and urban/rural status.

n=28 933 with data available on CVD, HF, CKD, ACE inhibitor or ARB use, and statin use; n=3803 with data available on BNP; n=5503 with data available on troponin.

*Proportion mediated is not reported when ACME or ADE is not significant or when the CI for the proportion mediated includes numbers >100% or <0%, which occurs when the ADE and ACME have possibly opposite effects (ie, one negative and one positive).

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CKD, chronic kidney disease; CVD, cardiovascular disease; HF, heart failure; ICU, intensive care unit; NT-pro BNP, N-terminal pro BNP.

outcomes, since the association between BMI and adverse outcomes in our analyses demonstrated both higher and lower risks, depending on BMI level. The associations we observed between overweight or obese BMI and lower mortality risk is another demonstration of the frequently described obesity paradox.[23] Consistent with this supposition, ORs for diabetes-related mortality in COVID-19 from a large population-based study and a meta-analysis that did not adjust for BMI[2 6] were 2.03 (95% CI 1.97 to 2.09) and 2.68 (95% CI 2.09 to 3.44), respectively, relatively greater than the estimates reported here. McGurnaghan *et al*,[7] however, reported an OR of 1.39 (95% CI 1.28 to 1.47) for type 2 diabetes not adjusted for BMI in a predominantly white Scottish population-based cohort suggesting that factors such as differences in racial/ethnic makeup of cohorts may also contribute to variation in the magnitude of observed associations.

The current analysis adjusted for potential confounders (such as BMI) but not for potential intermediate variables (such as cardiovascular comorbidities of diabetes) using a minimal adjustment set derived from a directed acyclic graph (online supplemental figure 1). Prior studies have adjusted for a number of comorbid conditions, especially cardiovascular conditions,[22] which in many cases may be downstream consequences of longstanding or poorly controlled diabetes. Because these variables might be intermediates of the association of diabetes with adverse COVID-19 outcomes, this adjustment might attenuate observed associations. For example, Tartof *et al*[22] reported an OR for diabetes with A1c ≥7.5% of 1.22 (95% CI 0.81 to 1.84) with death while Shi *et al*[24] reported an HR for diabetes of 1.58 (95% CI 0.84 to 2.99) with death after adjustment for covariates including HF, renal disease, and history of myocardial infarction or CVD. In a sensitivity analysis, we fit models that also included ACE/ARB use, statin use, platelet inhibitor use, HTN, CVD, CHF, and CKD, which substantially attenuated ORs for hospital and ICU admission (online supplemental table 1). Risk estimates for mortality were also attenuated but to a lesser extent.

Our results demonstrate a direct association between prior use of insulin or sulfonylureas and higher risk of adverse outcomes from COVID-19, while prior use of an ARB or statin was inversely associated with adverse outcomes. We did not, however, demonstrate an association of prior metformin use with COVID-19 outcomes, in contrast to prior work.[25–27] Sex-stratified analyses from previous research reports an inverse association of COVID-19 and mortality present in women but not men,[27] which might explain why no metformin association was seen in this predominantly male cohort. Insulin use has been significantly associated with risk of mortality among Italian emergency department COVID-19 patients,[28] as also seen in the current study. Prior statin use was associated with a lower hazard of death (HR 0.72; 95% CI 0.69 to 0.75) among English patients with diabetes independent of age and comorbid CVD.[10] The magnitude of this association is similar in the current report (OR

for death at 30 days 0.76 (95% CI 0.66 to 0.88); and HR for death 0.76 (95% CI 0.68 to 0.84)). The lower COVID-19 mortality risk among statin users, however, is not a universal finding. In fact, in French inpatients with diabetes, prior statin use was associated with higher odds of death at 28 days (OR 1.46 (95% CI 1.08 to 1.95)) in both unadjusted and adjusted analyses.[29] Reasons for these disparate findings are unclear but may be due to differences in confounder adjustment as well as differences in severity of illness in the cohorts under study, as the French cohort mortality of about 21% at 28 days was considerably higher than our overall 30-day mortality rate of about 7%. Lastly, white race was associated with lower odds of hospitalization or ICU admission, while black race was associated with higher odds of these outcomes; however, neither white nor black race was significantly associated with mortality. The direction of the association is consistent with multiple previous reports, although the magnitude of the observed association appears somewhat attenuated than previous studies (OR hospitalization black vs white 2.0 (95% CI 1.6 to 2.4)), unadjusted rate ratio for hospitalization 3.9 (95% CI 3.7 to 4.2)).[30 31] The diminished strength of the association in the current report may be due to the availability of VHA care without cost or to the fact that income and socioeconomic status are lower in VHA on average than the general population across strata of race[32]; however, reasons for the persistent, though attenuated, odds of adverse outcomes among black individuals are unclear and warrant further study.

We evaluated whether CVD-related factors mediate the association of diabetes with COVID-19 outcomes and found that cardiovascular-related factors mediated only small, incremental increases in risk. Given that the associations of diabetes with adverse outcomes from COVID-19 are only partially mediated by CVD-related factors, other downstream consequences of diabetes should be evaluated as potential intermediates, such as the presence of hyperglycemia and/or metabolic decompensation at presentation or during admission,[28] altered inflammatory responses, and increased coagulation activity.

Our study has several strengths, most importantly a large, well characterized national sample. Second, we used a DAG to guide the adjustment strategy designed to estimate the direct effect of diabetes on COVID-19 outcomes. Third, we were able to show that in a system with equal access to care, veterans of color did not have an increased risk of death compared with white veterans after admission. Last, within VA, most enrollees receive medical care and medications without cost, which likely decreases the contribution of unmeasured financial factors to differences in the quality of care received. Our results should be considered within the context of several limitations. The VA population is generally older, with lower income and socioeconomic status[32] than the US population as a whole, and our findings may not be generalizable to non-VA populations. Additionally, the proportion of women was low (11%); however, although women comprised only a small proportion of the sample,

the number of female participants (n=3886) is adequate for robust statistical inference. We were also unable to capture hospitalizations or some outpatient prescriptions that occurred outside the VA, although the VA asks that veterans provide notification within 72 hours of an outside hospital admission and when possible will attempt to transfer patients to a VA facility, which would be captured here. We were unable to capture time since diabetes diagnosis, which might confound associations in the analyses restricted to individuals with diabetes. Lastly, we were unable to distinguish type 1 and type 2 diabetes, a major limitation; however, results from sensitivity analyses excluding individuals with a diagnostic code for type 1 diabetes were quantitatively very similar to results in the full cohort. The relative prevalence of diabetes subtype in the VA population has not been reported; however, it is presumed to overwhelmingly be type 2 diabetes, as type 1 mainly occurs in childhood with incidence declining after age 14 years, and persons affected by type 1 diabetes in childhood or adolescence are not eligible for military service as adults.[33]

In conclusion, diabetes is independently associated with risk of adverse outcomes from COVID-19 in US veterans. Statin use was associated with lower odds of death. Associations are partially but not completely mediated by the presence of CVD-related factors that are frequently comorbid with diabetes. Future studies using prospective treatment assignment are needed to assess the role of potentially modifiable factors such as statin use in preventing adverse outcomes from COVID-19 in the general population and among individuals with diabetes.

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