Prior Glucose-Lowering Medication Use and 30-Day Outcomes Among 64,892 Veterans With Diabetes and COVID-19

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

To identify preinfection risk factors for adverse outcomes among veterans with diabetes and coronavirus disease 2019 (COVID-19) infection.

RESEARCH DESIGN AND METHODS

We identified all Veterans Health Administration patients with diabetes and one or more positive nasal swab(s) for severe acute respiratory syndrome coronavirus 2 (1 March 2020–10 March 2021) (n = 64,892). We examined associations of HbA_{1c} and glucose-lowering medication use with hospitalization, intensive care unit (ICU) admission, and mortality at 30 days using logistic regression models and during 4.4 months of follow-up (range <1–13.1) using proportional hazards models.

RESULTS

Compared with HbA_{1c} <7.0%, HbA_{1c} ≥9.0% was associated with higher odds of hospitalization, ICU admission, and death at 30 days (odds ratio [OR] 1.27 [95% CI 1.19–1.35], 1.28 [95% CI 1.15–1.42], 1.30 [95% CI 1.17–1.44], respectively) as well as higher risk of death over 4.4 months (hazard ratio [HR] 1.22 [95% CI 1.12–1.32]). Insulin use was associated with higher odds of hospitalization, ICU admission, and death (OR 1.12 [95% CI 1.07–1.18], 1.12 [95% CI 1.04–1.22], and 1.18 [95% CI 1.09–1.27], respectively) and higher risk of death (HR 1.12 [95% CI 1.07–1.18]). Sodium–glucose cotransporter 2 inhibitor (SGLT2i), glucagon-like peptide-1 receptor agonist (GLP1-RA), or angiotensin receptor blocker use were associated with lower odds of hospitalization (OR 0.92 [95% CI 0.85–0.99], 0.88 [95% CI 0.81–0.96], and 0.94 [95% CI 0.89–0.99], respectively). Metformin and SGLT2i use were associated with lower odds (OR 0.84 [95% CI 0.78–0.91], 0.82 [95% CI 0.72–0.94], respectively) and risk of death (HR 0.84 [95% CI 0.79–0.89], 0.82 [95% CI 0.74–0.92], respectively).

CONCLUSIONS

Among veterans with diabetes and COVID-19, higher HbA_{1c} and insulin use were directly associated with adverse outcomes, while use of a GLP1-RA, metformin, and SGLT2i was inversely associated.

Diabetes is a risk factor for short-term adverse outcomes from coronavirus disease 2019 (COVID-19) (1). In a recent report, we identified risk factors for

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Table 1—Characteristics of VA veterans diagnosed with diabetes and COVID-19

	Count (*N* = 64,892)	%
Female sex at birth	3,872	6
Age category, years		
19–39	1,296	2
40–49	3,523	5
50–59	10,238	16
60–69	16,506	25
70–79	25,277	39
≥80	8,054	12
White (vs. not White)	42,553	66
Black (vs. not Black)	17,255	27
Hispanic (vs. not Hispanic)	5,812	9
BMI, kg/m^2		
<18.5	268	1
18.5–24.9	5,185	10
25–29.9	14,265	27
30–34.9	16,266	31
35–39.9	9,909	19
≥40	6,617	13
Tobacco use		
Never	17,381	27
Former	31,466	48
Current	16,047	25
HbA_{1c}, %		
<7	32,692	50
7–7.9	15,067	23
8–8.9	8,079	12
≥9	9,056	14
Metformin	29,685	46
Sulfonylurea	12,298	19
Thiazolidinedione	2,075	3
DPP4i	5,810	9
GLP1-RA	4,737	7
SGLT2i	5,542	9
Insulin	18,521	29
ACEi	22,084	34
ARB	12,524	19
Statin	42,083	65
Platelet inhibitor	17,825	27
Hypertension	57,879	89
Cardiovascular disease	38,394	59
Congestive heart failure	12,587	19
eGFR, mL/min/1.73 m^2		
≥90	11,733	20
60–89	25,576	44
45–59	11,096	19
30–44	5,906	10
15–29	2,204	4
<15 or dialysis	1,595	3
Urban/rural/highly rural residence		
Highly rural	739	1
Rural	19,974	31
Urban	44,154	68
Unknown	27	0

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adverse short-term outcomes after COVID-19, including hospitalization, intensive care unit (ICU) admission, and mortality among persons with diabetes by using a large nationwide U.S. cohort of veterans (2). As the pandemic continues, many more individuals with diabetes have been diagnosed with COVID-19. In addition, mortality from COVID-19 has changed over time (3), both of which might impact risk factors for short-term outcomes from COVID-19 among individuals with diabetes. The objective of this report is to expand our previous analysis to identify risk factors for short-term adverse outcomes among veterans with diabetes and COVID-19 infection over additional waves of the epidemic and in a much larger population (*n* = 64,892).

RESEARCH DESIGN AND METHODS

The Veterans Health Administration (VHA) is the largest integrated health care system in the U.S (4). This analysis used data from the Corporate Data Warehouse (CDW), a data repository derived from the VHA's integrated electronic medical record, including a COVID-19 Shared Data Resource containing analytic variables for all VHA enrollees tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (5). We identified enrollees with diabetes and one or more positive nasal swab(s) for SARS-CoV-2 between 1 March 2020 and 10 March 2021 (*n* = 64,892). The index date was defined as the date of the first positive COVID-19 test, most of which were performed in Veterans Affairs laboratories using U.S. Food and Drug Administration–approved RealTime (Abbott Laboratories) or Xpert-Xpress (Cepheid) SARS-CoV-2 assays.

Diabetes was defined as present if any of the following criteria were fulfilled: *1*) two or more abnormal laboratory values from plasma or serum (random glucose >199 mg/dL, fasting glucose >125 mg/dL, 2-h glucose from an oral glucose tolerance test >199 mg/dL) or whole blood (HbA_{1c} >6.4%) (6); *2*) two outpatient or one inpatient *International Classification of Diseases*, Ninth Revision Clinical Modification (ICD-9-CM) or ICD-10-CM codes of 250 or E08–E13; or *3*) receipt of an initial

Table 1—Continued

	Count (*N* = 64,892)	%
Outcomes		
Hospital admission within 30 days	13,315	21
ICU admission within 30 days	4,265	7
Death within 30 days	4,943	8
Death by 10 March 2021	6,931	11

and one refill prescription of a glucose-lowering medication after 1 January 2000, as previously described (2). For each glucose-lowering medication, participants were defined as receiving the medication if they had an active prescription at the index date. The study was approved by the Veterans Affairs Puget Sound Health Care System Institutional Review Board with the requirement for informed consent waived.

We fit logistic regression models and Cox proportional hazards models assessing associations of the following exposures with COVID outcomes: most recent HbA_{1c} in the 2 years before enrollment ($<$7.0%, 7.0–7.9%, 8.0–8.9%, and $\geq$9.0%) and prior glucose-lowering medication use (insulin, metformin, dipeptidyl peptidase 4 inhibitors [DPP4i], glucagon-like peptide-1 receptor agonists [GLP1-RA], sodium–glucose cotransporter 2 inhibitor [SGLT2i], sulfonylureas, or thiazolidinediones). A term for each medication (receipt/no receipt) was included separately in the model such that the odds ratio (OR) or hazard ratio (HR) for each model can be interpreted as the independent association of use of each medication compared with no use of the medication. In addition to terms for most recent HbA_{1c} and prior glucose-lowering medication use, analyses were also adjusted for age, sex, race/ethnicity, BMI, tobacco use, use of an ACE inhibitor (ACEi), angiotensin receptor blocker (ARB), statin, or platelet inhibitor, a history of hypertension, cardiovascular disease, or heart failure defined by ICD-9/ICD-10 codes; and chronic kidney disease (CKD) defined by categories of estimated glomerular filtration rate (eGFR), facility location, month of SARS-CoV-2 diagnosis, and urban/rural residence by home address. We used multiple imputation with 10 sets of imputations for analyses that included BMI or CKD due to ~20% missing values for each of these variables.

Data Resource and Availability

The VHA's and the Department of Veterans Affairs' policies do not permit sharing electronic health record data.

RESULTS

Participants were a mean age of 67.7 years, and 6% (*n* = 3,872) were women. The HbA_{1c} was $<$7.0% in 52% (*n* = 32,692). During the 30 days after the SARS-CoV-2 diagnosis, 21% (*n* = 13,315) were hospitalized, 7% (*n* = 4,265) were admitted to the ICU, and 8% (*n* = 4,943) died (Table 1). Characteristics by timing of the SARS-CoV-2 infection and outcomes by HbA_{1c} category are summarized in Supplementary Tables 1 and 2. The average duration of follow-up was 4.4 months (range $<$1–13.1 months). The average number of days until death was 35.8 (SD 51.2). HbA_{1c} $\geq$9% was associated with 27% higher odds of hospitalization, 28% higher odds of ICU admission, and 30% higher odds of death by 30 days compared with HbA_{1c} $<$7.0% (95% CI 1.19–1.35, 1.15–1.42, and 1.17–1.44, respectively) as well as a 22% (1.12–1.32) greater risk of death over an average 4.4 months of follow-up compared with HbA_{1c} $<$7.0% (Table 2).

Use of a GLP1-RA was associated with lower odds of hospitalization (OR 0.88 [95% CI 0.81–0.96]) by 30 days. Use of an SGLT2i was associated with lower odds of hospitalization and death by 30 days (OR 0.92 [95% CI 0.85–0.99] and 0.82 [95% CI 0.72–0.94], respectively) as well as a lower risk of death during follow-up (HR 0.82 [95% CI 0.74–0.92]). Use of metformin was associated with lower odds of death by 30 days (OR 0.84 [95% CI 0.78–0.91] and lower risk of death during follow-up (HR 0.84 [95% CI 0.79–0.89]). Use of insulin was associated with higher odds of hospitalization, ICU admission, and death by 30 days (OR 1.12 [95% CI 1.07–1.18], 1.12 [95% CI 1.04–1.22], and 1.18 [95% CI 1.09–1.27], respectively) as well as higher risk of death during follow-up (HR 1.20 [95% CI 1.13–1.27]).

Additional factors associated with higher odds of hospitalization included older age (60–69, 70–79, and $\geq$80 years); Black (vs. non-Black) race and Hispanic (vs. non-Hispanic) ethnicity; former or current tobacco use; platelet inhibitor use; history of hypertension, cardiovascular disease, or heart failure; and lower eGFR (30–44, 15–29, or $<$15 mL/min/1.73 m^2 or dialysis). Additional factors associated with lower odds of hospitalization included younger age (19–39 and 40–49 years), higher BMI (25.0–29.9, 30.0–34.9, 35.0–39.9, and $\geq$40.0 kg/m^2), ARB use, and rural or highly rural residence.

Additional factors associated with higher odds of ICU admission included older age (60–69, 70–79, and $\geq$80 years); Black race; Hispanic ethnicity; former or current tobacco use; history of hypertension, cardiovascular disease, or heart failure; and lower eGFR (30–44, 15–29, or $<$15 mL/min/1.73 m^2 or dialysis). Factors associated with lower odds of ICU admission included younger age (40–49 years), White race, and rural residence.

Additional factors associated with higher odds of death by 30 days or risk of death over the follow-up period included older age (60–69, 70–79, and $\geq$80 years), Hispanic ethnicity, BMI $<$18.5 kg/m^2, former or current tobacco use, platelet inhibitor use, history of cardiovascular disease or heart failure, lower eGFR (45–59; 30–44, 15–29, or $<$15 mL/min/1.73 m^2 or dialysis), and highly rural residence. Additional factors associated with lower odds/hazard of death included female sex, younger age (19–39 or 40–49 years), White (vs. non-White) or Black (vs. non-Black) race, higher BMI (25.0–29.9, 30.0–34.9, and 35.0–39.9 kg/m^2), and ACEi, ARB, or statin use.

CONCLUSIONS

In this large national cohort of veterans with diabetes and COVID-19, higher HbA_{1c} (in particular HbA_{1c} $\geq$9.0%) was associated with higher odds of hospitalization, ICU admission, and death by 30 days as well as greater risk of death over an average 4.4 months and up to 13.1 months of follow-up. Use of GLP1-

Table 2—Associations of HbA_{1c} and glucose-lowering medication use with adverse outcomes from COVID-19 among veterans with diabetes

	Hospital admission within 30 days of diagnosis (*n* = 64,892)		ICU admission within 30 days of diagnosis (*n* = 64,865)		Death within 30 days of diagnosis (*n* = 64,892)		Death by 31 December 2020 (*n* = 64,786)	
	OR	95% CI	OR	95% CI	OR	95% CI	HR	95% CI
HbA_{1c}, %								
<7.0	Ref		Ref		Ref		Ref	
7.0–7.9	0.99	0.93–1.04	1.00	0.92–1.09	1.07	0.99–1.16	1.04	0.98–1.11
8.0–8.9	1.03	0.96–1.10	1.05	0.94–1.17	1.07	0.97–1.19	1.05	0.97–1.14
≥9.0	1.27	1.19–1.35	1.28	1.15–1.42	1.30	1.17–1.44	1.22	1.12–1.32
Metformin	0.96	0.92–1.01	0.98	0.91–1.06	0.84	0.78–0.91	0.84	0.79–0.89
Sulfonylurea	1.02	0.96–1.08	1.04	0.95–1.14	1.00	0.92–1.10	0.99	0.93–1.07
Thiazolidinedione	1.04	0.93–1.17	0.97	0.80–1.19	1.07	0.88–1.30	1.06	0.90–1.24
DPP4i	1.00	0.93–1.07	1.00	0.89–1.13	0.99	0.89–1.12	1.03	0.94–1.13
GLP1-RA	0.88	0.81–0.96	0.87	0.76–1.00	0.98	0.86–1.12	0.93	0.84–1.04
SGLT2i	0.92	0.85–0.99	0.93	0.82–1.06	0.82	0.72–0.94	0.82	0.74–0.92
Insulin	1.12	1.07–1.18	1.12	1.04–1.22	1.18	1.09–1.27	1.20	1.13–1.27
Female sex at birth	0.94	0.85–1.04	0.88	0.75–1.04	0.65	0.52–0.80	0.65	0.55–0.78
Age category, years								
19–39	0.81	0.67–0.98	0.72	0.50–1.05	0.39	0.19–0.80	0.26	0.13–0.52
40–49	0.79	0.70–0.90	0.66	0.52–0.83	0.51	0.34–0.76	0.45	0.32–0.63
50–59	Ref		Ref		Ref		Ref	
60–69	1.23	1.14–1.32	1.23	1.09–1.38	2.30	1.94–2.72	2.14	1.87–2.46
70–79	1.34	1.25–1.44	1.48	1.31–1.66	4.36	3.70–5.15	3.74	3.28–4.27
≥80	1.74	1.59–1.90	1.78	1.55–2.05	8.97	7.51–10.70	7.05	6.13–8.10
White (vs. not White)	0.94	0.87–1.01	0.8	0.76–0.96	0.82	0.74–0.92	0.89	0.81–0.97
Black (vs. not Black)	1.40	1.29–1.52	1.21	1.06–1.37	0.80	0.71–0.91	0.84	0.76–0.93
Hispanic (vs. not Hispanic)	1.17	1.08–1.26	1.25	1.11–1.41	1.21	1.08–1.36	1.12	1.02–1.23
BMI category, kg/m^2								
<18.5	0.91	0.71–1.16	1.14	0.80–1.61	1.37	0.99–1.89	1.36	1.10–1.69
18.5–24.9	Ref		Ref		Ref		Ref	
25–29.9	0.86	0.80–0.93	0.95	0.84–1.07	0.88	0.79–0.98	0.83	0.76–0.90
30–34.9	0.81	0.76–0.88	0.98	0.87–1.10	0.87	0.78–0.98	0.77	0.71–0.84
35–39.9	0.82	0.76–0.89	1.01	0.89–1.15	0.82	0.72–0.93	0.76	0.68–0.84
≥40	0.90	0.82–0.99	1.10	0.95–1.28	0.99	0.85–1.15	0.84	0.75–0.95
Tobacco use								
Never	Ref		Ref		Ref		Ref	
Former	1.17	1.11–1.23	1.23	1.12–1.34	1.27	1.17–1.38	1.21	1.13–1.29
Current	1.32	1.25–1.40	1.30	1.18–1.43	1.27	1.15–1.40	1.26	1.16–1.35
ACEi	1.03	0.98–1.08	1.11	1.03–1.20	0.88	0.81–0.95	0.86	0.81–0.92
ARB	0.94	0.89–0.99	1.00	0.92–1.10	0.83	0.76–0.91	0.82	0.76–0.88
Statin	0.94	0.90–0.99	0.94	0.87–1.02	0.83	0.77–0.89	0.81	0.77–0.86
Platelet inhibitor	1.08	1.03–1.13	1.04	0.97–1.12	1.12	1.05–1.21	1.11	1.05–1.18
Hypertension	1.25	1.15–1.36	1.27	1.09–1.48	1.06	0.92–1.22	1.09	0.97–1.22
Cardiovascular disease	1.56	1.48–1.64	1.53	1.40–1.66	1.31	1.20–1.41	1.38	1.29–1.47
Heart failure	1.67	1.59–1.76	1.57	1.46–1.70	1.29	1.20–1.38	1.35	1.28–1.43
eGFR, mL/min/1.73 m^2								
≥90	Ref		Ref		Ref		Ref	
60–89	0.97	0.91–1.03	1.00	0.90–1.12	1.15	1.02–1.29	1.04	0.95–1.144
45–59	1.07	0.99–1.15	1.12	0.99–1.26	1.43	1.26–1.62	1.25	1.14–1.38
30–44	1.20	1.10–1.30	1.27	1.11–1.45	1.70	1.48–1.94	1.52	1.38–1.69
15–29	1.42	1.27–1.58	1.69	1.44–1.99	2.43	2.07–2.86	2.00	1.77–2.25
<15 or dialysis	1.58	1.40–1.79	1.74	1.45–2.08	2.16	1.81–2.58	2.00	1.76–2.28

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Table 2—Continued

	Hospital admission within 30 days of diagnosis (*n* = 64,892)		ICU admission within 30 days of diagnosis (*n* = 64,865)		Death within 30 days of diagnosis (*n* = 64,892)		Death by 31 December 2020 (*n* = 64,786)	
	OR	95% CI	OR	95% CI	OR	95% CI	HR	95% CI
Urban/rural/highly rural residence								
Highly rural	0.64	0.51–0.78	0.81	0.58–1.13	1.58	1.24–2.01	1.45	1.19–1.75
Rural	0.70	0.67–0.73	0.80	0.74–0.87	1.02	0.95–1.09	0.99	0.94–1.05
Urban	Ref		Ref		Ref		Ref	

Cox models did not include individuals who died on the index date. Models additionally adjusted for geographic location by Veterans Integrated Service Network location and by month of COVID-19 diagnosis. Ref, reference.

RA, metformin, or SGLT2i was associated with lower odds or hazard of adverse outcomes, while prior insulin use was associated with higher odds or hazard of all outcomes. Prior use of an ACEi, ARB, or statin were all associated with lower odds of 30-day mortality and lower HR for death.

We previously reported on associations of glycemia and glucose-lowering medication use in a much smaller cohort of veterans with diabetes and COVID-19 (*n* = 13,863) as part of a more comprehensive analysis (2). There are some notable differences between the findings seen in our previous report and those in the current analysis. In particular, in our previous analysis, HbA_{1c} was associated with death but not with hospitalization or ICU admission, and the association was present only among individuals with $HbA_{1c} \geq 9.0\%$. The current study shows a statistically significant association of $HbA_{1c} \geq 9.0\%$ for all outcomes and larger point estimates ranging from 1.22 to 1.32. This is in line with a population-based study of almost 3 million individuals with type 2 diabetes in the U.K. conducted very early in the pandemic, in which, compared with HbA_{1c} of 6.5–7.0%, the HR for COVID-19–related mortality was significantly higher in those with HbA_{1c} of 7.6–8.9% (HR 1.22 [95% CI 1.15–1.30]) and 9.0–9.9% (HR 1.36 [95% CI 1.24–1.50]) (7), very similar to the point estimates from our current report. Our previous analysis showed that insulin use was associated with greater odds of hospital admission at 30 days (OR 1.15 [95% CI 1.03–1.27]) and greater hazard of death (HR 1.18 [95% CI 1.05–1.33]), while sulfonylurea use was associated with greater odds of hospital admission at 30 days (OR 1.13 [95% CI 1.01–1.28]). No significant association was seen between any of the outcomes and treatment with other classes of diabetes antiglycemic medication use, including metformin, thiazolidinediones, DPP4i, GLP1-RA, and SGLT2i. The discrepancy in findings between this analysis and our earlier one is therefore more likely due to differences in study power than to trends in the relationship between HbA_{1c} and mortality over time.

Cardiovascular and glucose-lowering medications, including metformin and statins, have been hypothesized to protect against adverse outcomes from COVID-19 (8), for example, by altering viral entry into cells or reducing cardiovascular or renal events through pathways independent of SARS-CoV-2. Consistent with this, in a nationwide U.K. cohort, adjusted HR for death comparing recorded versus no recorded prescription were 0.77 (95% CI 0.73–0.81) for metformin, 1.42 (95% CI 1.35–1.49) for insulin, 0.82 (95% CI 0.74–0.91) for SGLT2i, 0.94 (95% CI 0.89–0.99) for sulfonylureas, 0.94 (95% CI 0.83–1.07) for GLP1-RA, and 1.07 (95% CI 1.01–1.13) for DPP4i (9), quantitatively very similar estimates to those in the current report. An inverse association of prior GLP1-RA and SGLT2i use with 60-day mortality after COVID-19 compared with prior DPP4i use was also recently reported (OR 0.54 [95% CI 0.37–0.80] and 0.66 [95% CI 0.50–0.86], respectively) in a smaller U.S.-based cohort (10). However, protective associations for these and other premorbid medications are not consistently seen across observational cohorts with COVID-19, which is often attributed to differences in study populations or strategies to adjust for confounding. Another possible explanation is that some of these differences may be due to study power. For example, in our previous report, prior use of a GLP1-RA or SGLT2i was not associated with short-term adverse outcomes in veterans with COVID-19 and diabetes (2) after controlling for confounders including age, BMI, cardiovascular comorbidities, most recent HbA_{1c}, race/ethnicity, and urban/rural/highly rural residence.

Strengths of the current analysis included *1*) a large, well-characterized national sample and *2*) availability of medical care/medications without cost or at low cost to all VHA enrollees, which likely decreases the contribution of unmeasured financial factors to differences in the quality of care received.

Limitations include: *1*) Prescriptions, hospitalizations, or COVID diagnoses that occurred outside VHA were not captured. *2*) Factors related to the diabetes diagnosis, such as duration of diabetes or diabetes subtype (type 1 vs. type 2 diabetes), were not captured, although diabetes in VHA is presumed to predominantly be type 2 diabetes, because persons affected by type 1 diabetes are not eligible for military service. *3*) In both our current and previous analyses, we were unable to evaluate whether a given HbA_{1c} level influenced receipt of a glucose-lowering medication (i.e., was a confounder) or reflected an on-treatment effect (i.e., was a mediator). Associations of prior medication use (GLP1-RA, metformin, SGLT2i, ACEi, ARB, or statin) with short-term outcomes from COVID-19 therefore require further study using rigorous methods to address unmeasured confounding. *4*) Finally, given the timing of this study, we were unable to evaluate mediating or moderating effects of vaccination use due to very

limited vaccination coverage of our population by the index date.

In conclusion, among veterans with diabetes and COVID-19, higher HbA_{1c} (in particular $HbA_{1c} \geq 9\%$) and prior insulin use were associated with adverse outcomes, including hospitalization, ICU admission, and death, while prior use of GLP1-RA, metformin, SGLT2i, ACEi, ARB, or statin were inversely associated with adverse outcomes over up to 13 months of follow-up. Future studies are needed to identify risk factors for long-term adverse outcomes after COVID-19 among individuals with diabetes.

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Author Contributions. P.L.W. conceived the project, designed the overall research plan, and wrote the first draft of the manuscript. E.L. analyzed the data and reviewed and edited the manuscript. L.A.B. reviewed and edited the manuscript. L.T.-P. reviewed and edited the manuscript. A.K. contributed to design and interpretation of the analyses and reviewed and edited the manuscript. A.C.P. contributed to the design and interpretation of the analyses and reviewed and edited the manuscript. S.E.K. contributed to the design of the analyses and reviewed and edited the manuscript. E.J.B. conceived the project, designed the overall research plan, and reviewed and edited the manuscript. P.L.W. and E.J.B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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