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Research Article

Incident New Onset Diabetes after COVID-19 Infection: Results from a National Multicenter Cohort

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Abstract

Background It is known that survivors of acute SARS-CoV-2 infection can experience a complex disease known as post-acute sequelae of COVID-19 (PASC). The clinical manifestations of acute COVID-19 have been well characterized; however, less is known about the risk of new-onset diabetes mellitus (DM) in the post-acute phase of COVID-19.

Methods An adult cohort with either confirmed COVID-19 (by diagnosis or positive test) or without COVID-19 was sampled from a large national health research network between January 1st, 2020, and July 8th, 2022. We investigated the outcomes of a new diagnosis of DM (type 1 or 2) occurring after COVID-19 through 12 months after infection. Risk estimates [incidence, relative risk (RR), attributable risk] were used to describe the probability of new post-COVID diabetes. Hazard ratios and 95% confidence intervals were used to describe the risk factors associated with new diabetes.

Findings The 3-month probability of new diabetes was 2.48/1,000 among COVID+, and the RR of new diabetes was highest at 12 months [8.94 (8.54, 9.36)]. Vitamin D deficiency [HR: 1.52 (95% CI: 1.42, 1.63)] was associated with an increased risk of T2DM and having vitamin D deficiency with either obesity (BMI > 30 kg/m^2) or kidney dysfunction (GFR < 60) was associated with more than five times increased risk of T1DM.

Interpretation A large proportion of excess diabetes (type 1 and 2) may be attributed to SARS-CoV-2 infection. Traditional risk factors for diabetes and vitamin D deficiency are associated with an increased risk of new diabetes outcomes. PASC care should involve the identification and management of diabetes.

Keywords: Diabetes Mellitus; Long – COVID; New-onset Diabetes; Post-acute sequelae of COVID-19; PASC

Introduction

The clinical manifestations of acute SARS-CoV-2 infection have been well characterized; It is now well known that beyond the acute phase, individuals with COVID-19 could experience a complex systematic disease known as post-acute COVID-19 syndrome (PASC), lasting weeks to months following the initial infection. [1] PASC involves pulmonary and extra-pulmonary organ system manifestations. [2–4] Diabetes and other glycometabolic abnormalities have been widely reported during the acute phase, and recently studies have tried to shed light on the risk and burden of diabetes mellitus (DM) in the post- COVID. [3-13]

Increasing evidence points towards a reciprocal relationship between COVID-19 and DM. [12] Diabetes has been associated

with poor COVID-19 prognosis and new-onset diabetes has been reported in patients with COVID-19. [13,14] The precise mechanisms behind the development of new-onset diagnosis in people with COVID-19 are not well-known. Several complex and interrelated etiologies are likely responsible, including impairments in both glucose disposal and insulin secretion, stress hyperglycemia, preadmission diabetes, and steroid-induced diabetes. [11,15] Moreover, it is unclear whether new-onset diabetes associated with COVID-19 is type 1, type 2, or a complex subtype of diabetes [16].

It is also worth noting that there is limited biological information regarding predictors and correlates of new-onset diabetes after SARS-CoV-2 infection. [16,17] Few studies have shown that patients with newly diagnosed diabetes have higher inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate, and white blood cells. [18] In addition, people with obesity are also at risk for diabetes and severe outcomes related to COVID-19 [19], with adiposity being a driver for impaired glucose metabolism, immune responses, and inflammation. [6]

SARS‐CoV‐2 may lead to a long-lasting hyper‐inflammatory state, sometimes resulting in proneness to autoimmune reactions, which could explain the findings of new-onset type-1 diabetes cases in children. [20] In addition to that, it should be mentioned that coronavirus-mediated islet cell damage does not seem to be a novel phenomenon, as evidenced by the experience from previous coronavirus (SARS and MERS) epidemics. [21] However, whether the severe COVID-19-induced hyperglycemia noticed in some individuals would remit in the long run, as seen with SARS-CoV-1-induced diabetes, is still unclear. [22-24]

In this study, using TriNetX, a large national health research network that relies on electronic health records from multiple centers across the United States of America, we had two objectives. First, to compare the risk of diabetes after documented COVID-19 infection vs. a cohort who never had COVID-19 infection in the same pandemic time period. Second, to assess the risk factors for development of new onset diabetes after COVID-19 infection, which could help preventive and therapeutic efforts.

Methods

Data Source

This is a retrospective study using the TriNetX database, a large national health research network with data sourced from 71 healthcare organizations (HCOs), including over 106 million patients within the United States (Cambridge, MA, IRB waiver from WCG IRB). TriNetX continuously aggregates de-identified clinical data directly from the electronic medical records (EMR) of participating HCOs, including an extensive data quality and accuracy review. [25] While TriNetX does not identify partner HCOs, a typical partner represents a large academic health center with inpatient, outpatient, and specialty care services.

Patient Selection

We identified all adult patients (aged ≥18 years old) with a HCO encounter, between January 1st, 2020, to Nov 3, 2022 (date of data access). Within this study population, we stratified patients into two cohorts based on COVID-19 infection history, including those with a positive COVID-19 infection (COVID, ICD-10: U07.1, J12.82, U07.2, or positive SARS coronavirus 2 lab result, Supplemental Table 1) and those without a COVID-19 diagnosis, or positive lab result (No COVID). For both cohorts, we excluded patients with a record of diabetes mellitus (ICD-10: E08-E13, metformin use, insulin use, or hypoglycemic agents use, Supplemental Table 1) occurring any time before or up to one month after the study index event (index event: date of positive COVID-19 infection [COVID cohort], Vaccination

Excluding patients with diabetes up to one month after the index event was used to exclude individuals whose diabetes may have gone undiagnosed before the index event due to not being in care. Finally, we excluded all patients without at least one additional HCO encounter occurring up to one year before the index event and one additional HCO encounter occurring up to one year after the index event. For all patients, we collected clinical data, including patient demographics, family history, laboratory findings, medication use, as well as symptoms and diagnoses occurring before and during the study time window. We also specifically collected vitamin D deficiency (defined by ICD-10: E55. 9, or 25 hydroxyvitamin D [25(OJH)D ≤20 ng/mL], the comorbid conditions of obesity and kidney dysfunction, and prediabetes, (defined by ICD-10: R73.03 or Hemoglobin A1c/Hemoglobin. total in Blood, between 5.70 and 6.40 %).

Potential risk factors for new-onset diabetes were further identified within the COVID cohort, including presumed COVID-19 variant (Pre- Delta (or wild-type) variant: COVID-19 infection occurring before July 1st, 2021; Delta variant: COVID-19 infection occurring between July 1st, 2021, to November 30th, 2021; Omicron variant: COVID-19 infection occurring December 1st, 2021, to July 8th, 2022, [26]).

Outcomes

We investigated the outcomes of new-onset diagnosis of diabetes mellitus (ICD-10: E08 – E13), Type 2 diabetes mellitus (ICD-10: E11), and Type 1 diabetes mellitus (ICD-10: E10), occurring up to 3 months, 6 months, and 12 months after the index event. Patient counts for each time window are presented cumulatively.

Statistical Analysis

Data was analyzed data using TriNetX Advanced Analytics. Characteristics of study cohorts were described using mean ± standard deviation for continuous variables and frequency and percentage for categorical variables (Table 1 & 3). Differences between groups were calculated using independent t-test or chi-square. 1:1 propensity score matching using greedy nearest-neighbor method was used to balance cohorts on age, gender, race, BMI, family history of diabetes, and prediabetes. Estimates of incidence (rates per 1,000), relative risk (RR), and attributable risk (risk difference) were used to describe the risk of new diabetes (Table 2) and hazard ratios (HR) and 95% confidence intervals (CIs) were used to describe the risk factors associated with new diabetes (Table 4). P-values less than alpha <.05 were considered statistically significant.

	Before Matching			After Matching*		
	COVID (n=2598548)	**No COVID** (n=31468247)	p-value	**COVID** (n=2598548)	**No COVID** (n=2598548)	p-value
Characteristics	mean ± SD / n (%)			mean ± SD / n (%)		
Demographics						
Age (years)	44.4 ± 17.7	47.4 ± 19.1	<.001	44.4 ± 17.7	47.5 ± 19.1	<.001
Male Gender	1111691 (42.8)	13244523 (42.1)	<.001	1111691 (42.8)	1091332 (42.0)	<.001
Race/edthnicity						
Black	313253 (12.1)	3696112 (11.7)	<.001	313253 (12.1)	307028 (11.8)	<.001
White	1382319 (53.2)	16900978 (53.7)	<.001	1382319 (53.2)	1397769 (53.8)	<.001
Hispanic or Latino	195905 (7.5)	2078700 (6.6)	<.001	195905 (7.5)	171454 (6.6)	<.001
Body Mass Index (kg/m^2)	29.2 ± 6.7	28.2 ± 6.4	<.001	29.2 ± 6.7	28.3 ± 6.4	<.001
Obese (≥30)	211354 (8.1)	931223 (3.0)	<.001	211354 (8.1)	80271 (3.1)	<.001
Overweight (≥25)	361183 (13.9)	1739484 (5.5)	<.001	361183 (13.9)	148979 (5.7)	<.001
Family history of diabetes mellitus	32235 (1.2)	47390 (0.2)	<.001	32235 (1.2)	4063 (0.2)	<.001
Comorbidities						
Prediabetes	29118 (1.1)	122741 (0.4)	<.001	29118 (1.1)	29118 (1.1)	1.00
Ischemic heart disease	65790 (2.5)	357643 (1.1)	<.001	65790 (2.5)	31341 (1.2)	<.001
Hypertion	294650 (11.3)	1651081 (5.2)	<.001	294650 (11.3)	147058 (5.7)	<.001
Hyperlipidemia	135194 (5.2)	748654 (2.4)	<.001	135194 (5.2)	67924 (2.6)	<.001
Vitamin D deficiency	87678 (3.4)	397327 (1.3)	<.001	87678 (3.4)	35960 (1.4)	<.001
Inflammatory Bowel Disease**	13911 (0.5)	72605 (0.2)	<.001	13911 (0.5)	6103 (0.2)	<.001
Celiac disease]	3342 (0.1)	14571 (0.0)	<.001	3342 (0.1)	1190 (0.0)	<.001
Autoimmune Thyroiditis	8577 (0.3)	43083 (0.1)	<.001	8577 (0.3)	3776 (0.1)	<.001
Autoimmune Hepatitis	966 (0.0)	5341 (0.0)	<.001	966 (0.0)	455 (0.0)	<.001

Rheumatoid arthritis	12441 (0.5)	57157 (0.2)	<.001	12441 (0.5)	4872 (0.2)	<.001
Lupus erythematosus	2854 (0.1)	9294 (0.0)	<.001	2854 (0.1)	812 (0.0)	<.001
Medications						
Remdesivir	535 (0.0)	89 (0.0)	<.001	535 (0.0)	10 (0.0)	<.001
Glucocorticoids	350506 (13.5)	1658672 (5.3)	<.001	350506 (13.5)	141621 (5.5)	<.001
Antipsychotics	46461 (1.8)	240928 (0.8)	<.001	46461 (1.8)	20656 (0.8)	<.001
Statins	150017 (5.8)	994589 (3.1)	<.001	150017 (5.8)	87979 (3.1)	<.001
Laboratory						
C-reactive protein (mg/L)	18.0 ± 40.5	10.5 ± 27.7	<.001	18.0 ± 40.5	10.5 ± 27.9	<.001
Erythrocyte sedimentation (mm/h)	19.9 ± 21.0	20.0 ± 20.1	0.12	19.9 ± 21.0	20.2 ± 20.2	0.01
Ferritin (ng/mL)	230.0 ± 625.6	182.4 ± 533.6	<.001	230.0 ± 625.6	177.2 ± 386.6	<.001
D-dimer (mg{FEU}/L)	69.8 ± 393.1	204.7 ± 653.4	<.001	69.8 ± 393.1	204.7 ± 653.4	<.001
Erythrocyte distribution ratio	13.5 ± 2.0	13.6 ± 2.1	<.001	13.5 ± 2.0	13.6 ± 2.1	<.001
Lymphocytes/100	27.8 ± 11.0	28.2 ± 10.6	<.001	27.8 ± 11.0	28.3 ± 10.7	<.001
Neutrophils (10*3/uL)	246.7 ± 1101.1	443.9 ± 1412.0	<.001	246.7 ± 1101.1	444.8 ± 1408.6	<.001
25 (OH)D(ng/mL)	34.2 ± 17.0	34.4 ± 16.1	0.003	34.2 ± 17.0	34.4 ± 16.2	0.27
* Matched on gender, race, BMI, family history of diabetes, and prediabetes **Includes Crohn's disease and ulcerative colitis						

Table 1: Baseline characteristics of patients by COVID-19 status before and after propensity score matching.

	COVID-19	No COVID-19	Relative Risk (95% CIs)	Attributable Risk (risk difference)
	n (risk)			
3-month				
Diabetes (any)	6451 (2.48)	923 (0.36)	6.99 (6.52, 7.49)	2.13
Type 2 diabetes	6223 (2.39)	880 (0.34)	7.07 (6.59, 7.59)	2.06
Type 1 diabetes	160 (0.06)	36 (0.01)	4.44 (3.10, 6.38)	0.05
6-month				
Diabetes (any)	11454 (4.41)	1326 (0.51)	8.64 (8.16, 9.14)	3.90
Type 2 diabetes	11126 (4.28)	1263 (0.49)	8.81 (8.31, 9.34)	3.80
Type 1 diabetes	248 (0.1)	55 (0.02)	4.51 (3.37, 6.04)	0.07
12-month				
Diabetes (any)	17985 (6.92)	2012 (0.77)	8.94 (8.54, 9.36)	6.15
Type 2 diabetes	17481 (6.73)	1917 (0.74)	9.12 (8.70, 9.56)	5.99
Type 1 diabetes	393 (0.15)	81 (0.03)	4.85 (3.82, 6.16)	0.12

Table 2: Risk (rate per 1,000) of new diabetes at 3, 6, and 12-months by COVID status (n=2,598,548).

	Before Matching			After Matching*		
	New Diabetes (n=35406)	**No New Diabetes** (n=2467326)	p-value	**New Diabetes** (n=35406)	**No New Diabetes** (n=35406)	p-value
Characteristics	mean ± SD / n (%)			mean ± SD / n (%)		
Demographics						
Age (years)	55.3 ± 17.3	44.3 ± 17.7	<.001	55.3 ± 17.3	47.3 ± 16.9	<.001
Male Gender	14726 (41.6)	1054635 (42.7)	<.001	14726 (41.6)	14968 (42.3)	0.07
Race/ethnicity						
Black	4974 (14.0)	305828 (12.4)	<.001	4974 (14.0)	4512 (12.7)	<.001
White	26636 (75.2)	1353358 (54.9)	<.001	23636 (75.2)	19790 (55.9)	<.001
Hispanic or Latino	2199 (6.2)	192438 (7.8)	<.001	2199 (6.2)	2797 (7.9)	<.001
Body Mass Index (kg/m^2)	31.8 ± 7.5	29.2 ± 19.1	<.001	31.8 ± 7.5	29.9 ± 6.7	<.001
Obese (≥30)	6349 (17.9)	204037 (8.3)	<.001	6349 (17.9)	3522 (9.9)	<.001
Overweight (≥25)	8775 (24.8)	349607 (14.2)	<.001	8775 (24.8)	5756 (16.3)	<.001
Family history of diabetes mellitus	6830 (19.3)	30221 (1.2)	<.001	6830 (19.3)	536 (1.5)	<.001
Comorbidities						
Prediabetes	2871 (8.1)	26827 (1.1)	<.001	2871 (8.1)	2871 (8.1)	1.00
Ischemic heart disease	7072 (20.0)	61817 (2.5)	<.001	7072 (20.0)	1142 (3.2)	<.001
Hypertension	17782 (50.2)	280565 (11.4)	<.001	17782 (50.2)	5531 (15.6)	<.001
Hyperlipidemia	9860 (27.8)	128840 (5.2)	<.001	9860 (27.8)	2680 (7.6)	<.001
Vitamin D deficiency	4743 (13.4)	84352 (3.4)	<.001	4743 (13.4)	1702 (4.8)	<.001
Inflammatory Bowl Disease**	851 (2.4)	13474 (0.5)	<.001	851 (2.4)	193 (0.5)	<.001
Celiac disease	225 (0.6)	3257 (0.1)	<.001	225 (0.6)	54 (0.2)	<.001
Autoimmune Thyroiditis	300 (0.8)	8310 (0.3)	<.001	300 (0.8)	159 (0.4)	<.001
Autoimmune Hepatitis	106 (0.3)	910 (0.0)	<.001	106 (0.3)	14 (0.0)	<.001
Rheumatoid arthritis	1320 (3.7)	11868 (0.5)	<.001	1320 (3.7)	197 (0.6)	<.001
Lupus erythematosus	439 (1.2)	2728 (0.1)	<.001	439 (1.2)	32 (0.1)	<.001
Medications						
Remdesivir	573 (1.6)	519 (0.0)	<.001	573 (1.6)	10 (0.0)	<.001
Glucocorticoids	15081 (42.6)	338975 (13.7)	<.001	15081 (42.6)	5581 (15.8)	<.001
Antipsychotics	2543 (7.2)	44623 (1.8)	<.001	2543 (7.2)	735 (2.1)	<.001
Statins	9955 (29.1)	142887 (5.8)	<.001	9955 (29.1)	2835 (5.8)	<.001

Laboratory								
C-reactive protein (mg/L)	28.0 ± 52.7	18.1 ± 40.9	<.001	28.0 ± 52.7	19.4 ± 43.5	<.001
Erythrocyte sedimentation (mm/h)	25.5 ± 25.1	19.8 ± 20.9	<.001	25.5 ± 25.1	20.3 ± 20.3	<.001
Ferritin (ng/mL)	394.4 ± 821.5	228.5 ± 632.8	<.001	394.4 ± 821.5	217.9 ± 540.5	<.001
D-dimer (mg{FEU}/L)	140.8 ± 579.6	77.7 ± 413.3	<.001	140.8 ± 579.6	102.6 ± 563.7	0.15
Erythrocyte distribution ratio	14.0 ± 2.6	13.6 ± 2.0	<.001	14.0 ± 2.6	13.6 ± 1.9	<.001
Lymphocytes/100	25.0 ± 11.5	27.7 ± 11.0	<.001	25.0 ± 11.5	27.8 ± 10.9	<.001
Neutrophils (10*3/uL)	135.6 ± 871.0	262.0 ± 1132.9	<.001	135.6 ± 871.0	286.1 ± 1156.1	<.001
25(OH)D (ng/mL)	31.6 ± 17.6	34.2 ± 17.0	<.001	31.6 ± 17.6	34.5 ± 16.3	<.001
* Matched on age and prediabetes **Includes crohn's disease and ulcerative colitis						

Table 3: Characteristics of COVID-19 patients at time of presentation by diabetes outcome.

Table 4. Risk factors associated with new diabetes post-acute COVID (Hazard Ratio & 95% CIs)

	3-month			6-month			12-month		
	Diabetes	**Type 2 diabetes**	**Type 1 diabetes**	**Diabetes**	**Type 2 diabetes**	**Type 1 diabetes**	**Diabetes**	**Type 2 diabetes**	**Type 1 diabetes**
Age > 25 years	**2.14 (2.0, 2.28)**	**2.36 (2.2, 2.53)**	**0.28 (0.23, 0.35)**	**2.31 (2.19, 2.43)**	**2.5 (2.37, 2.64)**	**0.3 (0.25, 0.36)**	**2.46 (2.35, 2.57)**	**2.66 (2.54, 2.78)**	**0.31 (0.27, 0.37)**
Age > 65 years	**2.36 (2.24, 2.48)**	**2.37 (2.25, 2.49)**	1.2 (0.82, 1.76)	**2.38 (2.29, 2.47)**	**2.39 (2.3, 2.48)**	1.08 (0.79, 1.49)	**2.31 (2.24, 2.39)**	**2.32 (2.25, 2.4)**	1.1 (0.85, 1.42)
Family History of Diabetes	**2.47 (2.29, 2.67)**	**2.54 (2.34, 2.75)**	0.92 (0.43, 1.97)	**2.55 (2.41, 2.7)**	**2.6 (2.46, 2.76)**	0.99 (0.52, 1.76)	**2.59 (2.48, 2.71)**	**2.64 (2.53, 2.76)**	1.27 (0.85, 1.89)
Black/African American Race	**1.49 (1.4, 1.59)**	**1.49 (1.4, 1.59)**	**1.58 (1.06, 2.37)**	**1.45 (1.38, 1.52)**	**1.44 (1.37, 1.52)**	**1.55 (1.12, 2.14)**	**1.44 (1.39, 1.5)**	**1.44 (1.38, 1.49)**	**1.55 (1.2, 2.01)**
Vitamin D Deficiency	**1.51 (1.42, 1.62)**	**1.52 (1.42, 1.63)**	0.82 (0.48, 1.4)	**1.59 (1.51, 1.67)**	**1.6 (1.52, 1.68)**	0.81 (0.53, 1.25)	**1.64 (1.57, 1.7)**	**1.64 (1.58, 1.71)**	1.06 (0.78, 1.44)
Black/African American	**0.84 (0.71, 0.99)**	0.83 (0.69, 0.99)	1.25 (0.35, 4.45)	**0.85 (0.75, 0.96)**	0.84 (0.73, 0.95)	0.75 (0.22, 2.53)	**0.87 (0.78, 0.96)**	**0.84 (0.76, 0.94)**	0.89 (0.4, 1.99)
BMI > 30	**1.94 (1.59, 2.36)**	**2.0 (1.64, 2.24)**	**5.29 (1.12, 24.93)**	**2.14 (1.83, 2.49)**	**2.2 (1.88, 2.57)**	**5.26 (1.48, 18.62)**	**2.09 (1.84, 2.37)**	**2.14 (1.88, 2.43)**	**4.13 (1.65, 10.33)**
GFR < 60	**1.32 (1.1, 1.58)**	**1.31 (1.09, 1.58)**	2.7 (0.73, 9.98)	**1.23 (1.07, 1.41)**	**1.22 (1.06, 1.4)**	**2.91 (1.05, 8.08)**	**1.29 (1.16, 1.43)**	**1.27 (1.14, 1.42)**	**2.54 (1.2, 5.37)**
BMI > 30	**2.57 (2.35, 2.8)**	**2.62 (2.4, 2.87)**	1.42 (0.72, 2.81)	**2.68 (2.50, 2.87)**	**2.73 (2.55, 2.93)**	1.18 (0.71, 1.96)	**2.74 (2.59, 2.90)**	**2.80 (2.65, 2.96)**	1.33 (0.91, 1.94)
Delta Variant	**.88 (0.82, 0.94)**	0.85 (0.79, 0.92)	1.33 (0.90, 1.95)	**0.95 (0.90, 0.99)**	**0.93 (0.88, 0.98)**	**1.47 (1.08, 1.99)**	**1.84 (1.56, 2.17)**	**1.86 (1.58, 2.19)**	1.12 (0.28, 4.52)
Omicron Variant	**1.1 (1.04, 1.17)**	**1.1 (1.03, 1.17)**	0.95 (0.64, 1.42)	**1.12 (1.06, 1.18)**	**1.11 (1.05, 1.17)**	1.13 (0.79, 1.61)	**1.12 (1.06, 1.18)**	**1.11 (1.05, 1.17)**	1.13 (0.79, 1.61)
Prediabetes	**2.29 (2.11, 2.48)**	**2.36 (2.17, 2.56)**	0.29 (0.12, 0.70)	**2.49 (2.34, 2.65)**	**2.55 (2.40, 2.71)**	**0.28 (0.13, 0.59)**	**2.56 (2.44, 2.69)**	**2.62 (2.49, 8.59)**	**0.40 (0.24, 0.56)**
Statins	**2.22 (2.10, 2.35)**	**2.24 (2.11, 2.37)**	0.91 (0.56, 1.47)	**2.39 (2.29, 2.49)**	**2.41 (2.31, 2.51)**	1.02 (0.71, 1.47)	**2.39 (2.29, 2.49)**	**2.41 (2.31, 2.51)**	1.02 (0.71, 1.47)
Hypertension	**2.8 (2.66, 2.94)**	**2.84 (2.7, 2.99)**	1.07 (0.75, 1.52)	**2.98 (2.87, 3.09)**	**3.02 (2.91, 3.13)**	1.03 (0.77, 1.38)	**3.09 (3.0, 3.18)**	**3.14 (3.05, 3.24)**	0.99 (0.79, 1.25)
Coronary Artery Disease	**2.65 (2.48, 2.83)**	**2.68 (2.51, 2.86)**	1.16 (0.66, 2.04)	**2.61 (2.48, 2.74)**	**2.63 (2.5, 2.76)**	1.19 (0.76, 1.86)	**2.6 (2.5, 2.7)**	**2.62 (2.51, 2.72)**	1.19 (0.84, 1.69)

Results

Baseline Characteristics: COVID vs. no-COVID

At baseline, 2,598,548 patients with confirmed COVID-19 and 31,468,247 patients without COVID-19 were identified (table1). Among the COVID cohort, 53.2% were white race, the average age was 44.4 ± 17.7 years, and average BMI was 29.2 ± 6.7 kg/m^2. 1.2% (n=32235) had a family history of diabetes, 1.1% (n=29118) had prediabetes, 2.5% (n=65790) had ischemic heart disease, and 5.2% (n=135194) had hyperlipidemia. After matching, patients with COVID had a higher proportion of hypertensive diseases [11.5% (COVID) vs. 5.7% (no COVID); p<.001], vitamin D deficiency [3.4% (COVID) vs. 1.4% (no COVID); p<.001], taking glucocorticoids [13.5% (COVID) vs. 5.5% (no COVID); p<.001], and rosuvastatin [1.1% (COVID) vs. 0.6% (no COVID); p<.001]. Patients without COVID had higher mean hemoglobin A1c [5.7 ± 1.2 (no-COVID) vs. 5.5 ± 0.9 (COVID); p<.001], D-dimer [204.7 ± 653.4 (no-COVID) vs. 69.8 ± 393.1 (COVID); p<.001], and erythrocyte sedimentation [20.2 ± 20.2 (no-COVID) vs. 19.9 ± 21.0 (COVID); p=0.01].

Risk of new diabetes after documented COVID-19

At 3 months, the incidence of type 2 diabetes (T2DM) among patients with COVID-19 was 2.39 per 1,000 (n=6223) compared to 0.39 per 1,000 (n=880) in the no-COVID group [RR: 7.07 (6.59, 7.59)]. The incidence of type 1 diabetes (T1DM) was 0.06 per 1,000 in the COVID group compared to 0.01 in the no-COVID group [RR: 4.44 (3.10, 6.38) (table 2). At 6months, among 11,126 (4.28/1,000) new T2DM cases in the COVID group, 9,863 (3.80/1,000) can be attributed to COVID, and among the 248

(0.1/1,000) incident T1DM cases among patients with COVID, 193 (0.07/1,000) can be attributed to COVID. At 12 months, the incidence of T2DM was 6.73/1,000 (n=17,481) among the COVID group and 0.74/1,000 (n=1,917) in the no-COVID group [RR: 9.12 (95% CI:8.70, 9.56)]. The incidence of T1DM among the COVID group was 0.15/1,000 (n=393) compared to 0.03 (n=81) in the no-COVID group [RR: 4.85 (95% CI: 3.82, 6.16)]. This suggests that among patients with COVID at 12 months, 89.03% of the morbidity from T2DM and 79.39% of the morbidity from T1DM may be attributed to COVID.

Characteristics of COVID patients: new diabetes vs. no new diabetes outcomes

Among COVID+ patients who developed diabetes post-COVID infection (COVID+DM+; n=35,406), the average age was 55.3 ± 17.3 years, 58.4% were female, 75.2% were of white race, 6.2% were Hispanic or Latino, and average BMI was 31.8 ± 7.5 kg/m^2 (Table 3). Among COVID+DM+ group, 19.3% had a family history of diabetes, 8.1% had prediabetes, 20.0% had ischemic heart disease, and 50.0% had hypertension. 27.8% of COVID+ DM+ had hyperlipidemia, 2.4% IBD, 3.4% had rheumatoid arthritis and 1.2% had lupus erythematous compared to 7.6%, 0.4% , 0.6% and 0.1% respectively, in the COVID+ DM- group (p<.001). 29.1% of COVID+DM+ were taking a statin compared to 5.8% in the COVID+DM- group (p<.001). Additionally, in the COVID+DM+ that had recovered, they were taking remdesivir (1.6 %), glucocorticoid (42.6%) and antipsychotics (7.2%) compared to 0%, 15.8%, and 2.1% in the COVID+ DM- group (p<.001). Moreover, in the COVID+DM+ the percentage of people with prior hospitalization was 10.1%, and that of those who needed to be admitted to the ICU was 1.9%, , compared to 5.9% and 0.,6% respectively, in the COVID+DM- group (Supplemental Table 2).There was a higher proportion of vitamin D deficiency among COVID+ DM+ (13.4) compared to COVID+ DM- (4.8; p<.001).

Risk factors associated with new diabetes among COVID

At 3-months, age > 65 years [HR: 2.37 (95% CI: 2.25, 2.49)], family history of diabetes [HR: 2.54 (95% CI: 2.34, 2.75)], having BMI > 30 kg/m^2 and vitamin D deficient [HR: 2.0 (95% CI: 1.64, 2.24)], BMI > 30 [HR: 2.36 (95% CI: 2.2, 2.53)], prediabetes [HR: 2.36 (95% CI: 2.2, 2.53)], statin use [HR: 2.24 (95% CI: 2.11, 2.37)], hyperlipidemia [HR: 2.36 (95% CI: 2.2, 2.53)], hypertension [HR: 2.36 (95% CI: 2.2, 2.53)], and coronary artery disease [HR: 2.36 (95% CI: 2.2, 2.53)] were associated with more than two times greater risk of T2DM compared to no new diabetes. These risk factors were overall consistent at the 6- and 12-month follow-up.

Vitamin D deficiency [HR: 1.52 (95% CI: 1.42, 1.63)], vitamin D deficiency and having GFR < 60 [HR: 1.31 (95%CI: 1.09, 1.58)], and the Omicron (vs. non omicron) variant [HR: 1.1 (95% CI: 1.03, 1.17)] were consistently associated with increased risk of T2DM at each time point. In contrast, having the Delta variant was associated with decreased risk of T2DM and age > 25 years (vs 18-25) and prediabetes were protective against T1DM at all time points. Vitamin D deficiency along with either BMI > 30 or GFR < 60 was associated with more than five times increased risk of T1DM at each follow-up period (Figure 1-3).

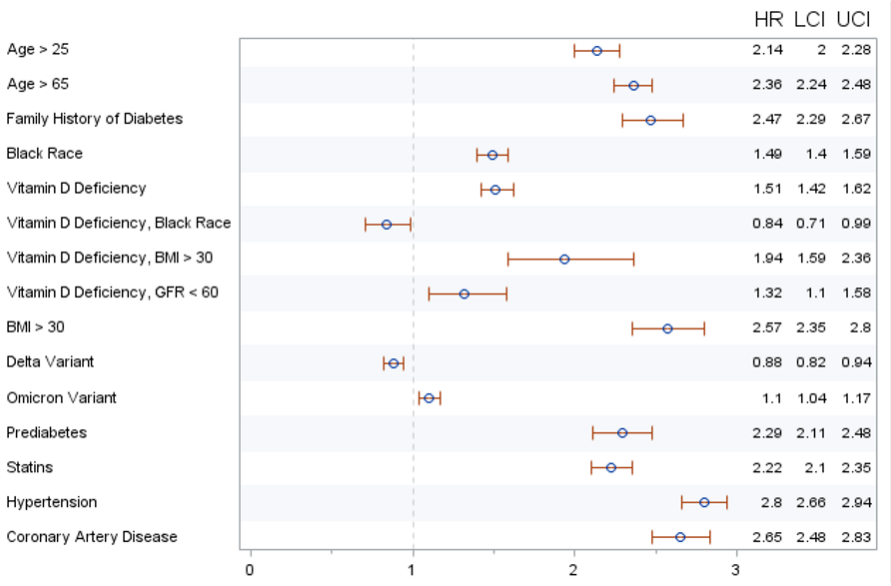

Figure 1: Risk factors associated with new diabetes at 3 months post-acute COVID phase [Hazard Ratio (HR) & 95% Confidence Intervals (CIs)].

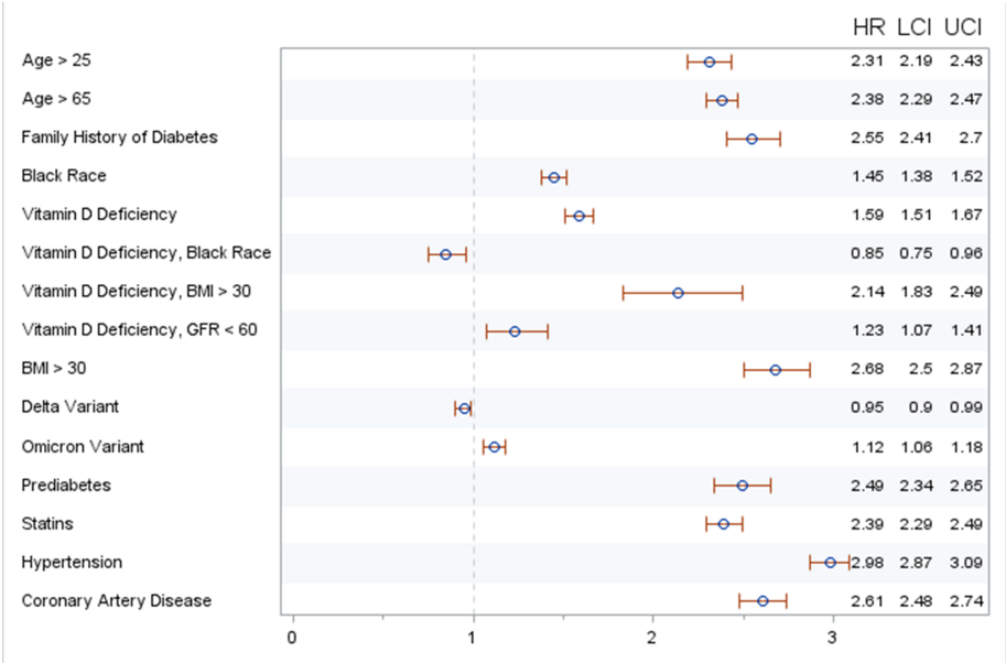

Figure 2: Risk factors associated with new diabetes at 6 months post-acute COVID phase [Hazard Ratio (HR) & 95% Confidence Intervals (CIs)].

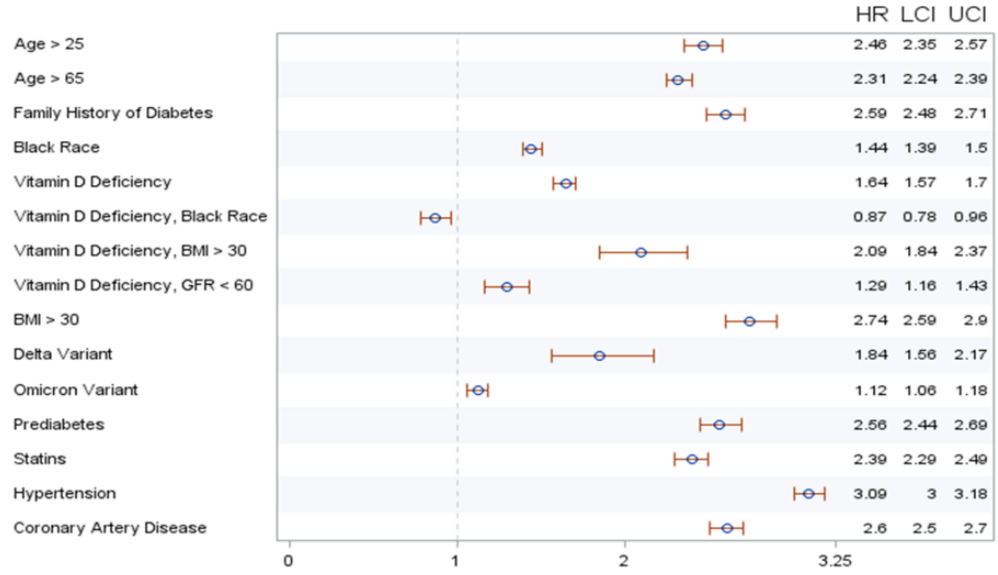

Figure 3: Risk factors associated with new diabetes at 12 months post-acute COVID phase [Hazard Ratio (HR) & 95% Confidence Intervals (CIs)].

Discussion

The COVID-19 outbreak is still increasing rapidly throughout the world. The new virus responsible for this epidemic was named SARS-CoV-2, which has now turned into a global crisis. [27] COVID-19 causes a novel pathophysiological alteration in glucose homeostasis (a combination of severe insulin resistance and insulin insufficiency) that may last longer than the acute phase. [28] On that, several studies indicated that post-COVID incident conditions occur in 20%–30% of patients. [29] Few studies described new-onset cases of incident diabetes mellitus (DM). [30,31] The purpose of this study was not only to determine the frequency of newly diagnosed DM and its different types among COVID-19 survivors but also to capture the risk factors associated with it; by using a large-scale national health record network.

In this study involving both participants with COVID-19 and controls, we provide evidence that suggests that beyond the first 30 days of infection, COVID-19 survivors exhibited an increased risk of incident diabetes and antihyperglycemic use; therefore, diabetes should be considered a serious component of the multifaceted long COVID, also referred to as Post-Acute Sequelae of SARS-CoV-2 or PASC. On that, taking also into consideration the ever-increasing number of people infected with COVID-19 (>750 million people globally as of February 6, 2023) and using our incidence in 12 months, we will be anticipating more than 5 million new diabetes cases. On top of that, knowing that 1 out of every $4 in US healthcare costs is spent on caring for people with diabetes, an unresolved economic crisis in the already affected healthcare systems is in the making. [30,31] Thus, health systems should take measures on screening and management of the glycometabolic outcome of COVID-19. This can be done by bringing awareness on the care of diabetes in many newly developed long COVID clinics around the world. Moreover, it should be noted that we very carefully captured only new DM cases that occurred beyond 30 days after SARS-CoV-2 infection and not any preexisting cases by excluding anyone with a diagnosis of diabetes (ICD-10-CM codes E08–E13) or a laboratory measurement of HbA1C > 6.4, before the time of their COVID diagnosis.

The pathophysiological mechanisms underlying the association between COVID-19 and the risk of diabetes are not entirely clear. COVID-19 infection can cause long-lasting hyperglycemia through several complex but interrelated factors. These include, but are not limited to, the inflammatory response triggered by the virus and subsequent release of counter regulatory hormones, activation of the renin-angiotensinogen system, and destruction of pancreatic beta cells by the virus itself or by the cytokines triggered by the virus. [28,32] Other potential explanations include autonomic dysfunction, hyper activated immune response or autoimmunity, mitochondrial dysfunction, and persistent low-grade inflammation leading to insulin resistance.[29,30,33].

Apart from the above-mentioned lack of understanding of the pathophysiology of incident diabetes, detailing its predictors is also essential but still unknown. Our study sheds light on this and provides evidence of increased risk in adults older than 65 years, in those with a family history of diabetes, and in those with obesity, prediabetes, hyperlipidemia, or coronary artery disease before or at the time of acute COVID-19 infection.

To the best of our knowledge, this is also the first study in a long Covid cohort to assess unique incident DM risk factors beyond the above-mentioned traditional ones. On that, the results of the current study revealed that vitamin D deficiency with and without concomitant kidney dysfunction and the use of statins were consistently associated with increased risk of T2DM at each time point (3, 6, and 12-month follow-up). The use of statins (especially higher potency) has been associated with a slight increase in the incidence of new-onset diabetes in the general population. [34] The exact mechanism of the diabetogenic action of statins is unclear, but it is possible that they may have an effect on beta cell function and insulin resistance. [35] We hypothesize that this effect on insulin regulation also explains the higher rates of incident DM outcomes observed in our study among the COVID group.

In the general population, several studies found an association between lower vitamin D levels and increased incidence of diabetes. [36,37] The beneficial effects of optimal vitamin D status on diabetes incidence may be related to the effect of vitamin D on promoting β-cell function and insulin sensitivity. [38,39] Indeed, supplementation with vitamin D may improve glucose metabolism control in diabetics by reducing insulin resistance and stimulating β-cell function. [40,41] Despite a large number of studies describing the association between vitamin D deficiency with COVID-19 severity, supplementation has failed to affect the severity of the acute illness. The observational studies showing such an association could have been confounded by the presence of obesity or kidney dysfunction, both commonly associated with vitamin D deficiency and with severe COVID outcomes.

However, the effect of vitamin D deficiency on PASC manifestations, including incident diabetes, is largely unknown, and our findings suggest that vitamin D deficiency, with or without the commonly associated obesity or kidney dysfunction, is more common in patients with new-onset diabetes after COVID. This relationship should be further investigated since such a relationship may lead to important preventive strategies.

Assessing the diabetogenic potential of SARS-CoV-2 variants is an additional challenge. The pandemic variants of SARS-CoV-2 have been reported to change the viral characteristics, including transmissibility and antigenicity. However, most of the currently available data were based on studies conducted before the major variants of SARS-CoV-2 were circulated. The Omicron variant is

associated with a more attenuated disease severity compared to previous circulating variants. [42,43] Therefore, tissue tropism of variants and their impact on glycometabolism might be affected. Finally, even though there is a lack of literature in terms of vaccination status among people with newly diagnosed diabetes, one of our previous large studies using the TriNetX network; underlined the importance of vaccination in the prevention of different PASC outcomes, including new-onset diabetes cases. [44] This conclusion emphasizes its importance in the prevention of new DM.

Previous studies have suggested that respiratory viruses may increase the risk of new-onset diabetes. Our study highlights the increased risk of diabetes after COVID-19 infection in adults. Since attempts to prevent COVID-19 transmission thru global masking had caused the influenza season of 2019-2021 to be almost non-existent, we are currently unable to compare head to head the risk of diabetes with COVID-19 versus that with influenza or other respiratory infections. This work would be crucial to do in the future. Nonetheless, our work showing an increased risk of diabetes with COVID-19 highlights the clinical importance of screening for adverse metabolic consequences frequently during the post-acute COVID-19 period.

Compared with the contemporary control group, the risk of post-acute incident diabetes, antihyperglycemic use, and the composite outcome increased according to the severity of the acute infection. Although previous studies have shown that immunizations are highly effective at preventing severe acute COVID-19–associated outcomes, little is known about the effect of vaccination on post-acute outcomes of COVID-19 [17,18]. However, we hypothesize that its effect on reducing the inflammatory responses during the acute phase does also explain the lower rates of all PASC outcomes observed in our study among the vaccinated group

Despite the novelty of our findings, our study has several limitations. First, there are some inherent limitations when EHRs are used to capture data. For instance, since the data are presented as they are recorded, we cannot be sure that there has not been a misreporting of information. Second, although we required a positive COVID-19 test for enrolment in the COVID-19 group; for the control group, it is possible that some of those enrolled might have contracted SARS-CoV-2 but were diagnosed outside of a healthcare system participating in TriNetX. Third, as the pandemic continues, as new variants emerge, and as treatment strategies for acute COVID-19 continue to evolve, it is likely that the epidemiology of PASC, including diabetes, will likely also change over time. Fourth, we were not able to capture the use of glucocorticoids during the acute phase of the infection for the participants included in our study, something that could affect the outcome of incident diabetes. Fifth, one option could have been the use of historical controls. However, the pandemic caused tremendous changes in lifestyle habits, which could have influenced the risk of diabetes and would not be accounted for in the historical controls. Sixth, some testing could have occurred outside of this database - similar to any other EHR-derived analysis – therefore we acknowledge this a potential limitation. Seventh, we recognize that data obtained from electronic health records presents challenges of non-random missingness and employing propensity score matching methods does not remove the possibility of selection bias. However, we carefully selected baseline covariates to match our sample to reduce selection bias and improve the validity of our findings using a national hospitalized and ambulatory cohort, with data available at 3, 6, and 12 months. Our findings should be interpreted in the context of subsequent observational studies. Finally, being an observational study, causation cannot be inferred. Specifically, measurements of vitamin D may have caused a selection bias and the finding with vitamin D could have resulted from such a bias in measurement. Future prospective studies should better define the role of vitamin D in post-COVID incident diabetes.

In summary, the present data show that in the 12 months after COVID-9 infection, there is an increased risk of new diabetes. In addition, risk factors beyond traditional risk factors for diabetes are associated with an increased risk of new diabetes outcome. Taken together, current evidence suggests that diabetes is a piece of the PASC puzzle and that post-acute care strategies for people with COVID-19 should include screening, prevention, and management of diabetes.

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