# COVID-19 infection and incident diabetes in American Indian and Alaska Native people: a retrospective cohort study

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## Summary

**Background** Evidence suggests an increased risk of new-onset diabetes following COVID-19 infection. American Indian/Alaska Native (AI/AN) people were disparately impacted by the COVID-19 pandemic and historically have had higher diabetes incidence than other racial/ethnic groups in the US. We measured the association between COVID-19 infection and incident diabetes in AI/AN people.

**Methods** We conducted a retrospective cohort study using de-identified patient data from the Indian Health Service's (IHS) National Patient Information Reporting System. We estimated age-adjusted diabetes incidence rates, incidence rate ratios, and adjusted hazard ratios among three cohorts spanning pre-pandemic (1/1/2018–2/28/2020) and pandemic (3/1/2020–12/31/2021) timeframes: 1) pre-pandemic cohort (1,503,085 individuals); 2) no-COVID-19 pandemic cohort (1,344,339 individuals); and 3) COVID-19 cohort (176,483 individuals).

**Findings** The COVID-19 cohort had an increased hazard of diabetes compared to the no-COVID-19 group (adjusted hazard ratio (aHR) = 1.56; 95% CI: 1.50–1.62) and the pre-pandemic group (aHR = 1.27; 95% CI: 1.22–1.32). The association between COVID-19 infection and new-onset diabetes was stronger in those with severe COVID-19 illness. A sensitivity analysis comparing the COVID-19 cohort to members of other cohorts that had acute upper respiratory infections showed an attenuated but higher risk of new-onset diabetes in those with COVID-19.

**Interpretation** AI/AN people diagnosed with COVID-19 had an elevated risk of a new diabetes diagnosis when compared to the no-COVID-19 group and the pre-pandemic group. The increased diabetes risk in the COVID-19 group remained in a sensitivity analysis that limited the comparator groups to individuals with an AURI diagnosis.

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**Keywords:** Incident diabetes; Covid-19; Indigenous populations; Risk factor

## Introduction

American Indians and Alaska Natives (AI/AN), the indigenous peoples of the land that is now the United States (US), experienced a disproportionate burden of COVID-19 disease compared to Non-Hispanic White persons in the US.[1] Limited data suggest that other indigenous populations across the globe were also disproportionately impacted by COVID-19 illness.[2] The underlying causes of these COVID-19 disparities are multifactorial and have their roots in colonization.[3] These circumstances have also led to AI/AN people experiencing elevated rates of chronic diseases, such as diabetes at nearly 3 times the prevalence[4] and 2.3 times the diabetes-related death rate[5] of Non-Hispanic White people in the US.

Growing evidence suggests that COVID-19 infection increases the risk of developing diabetes. A meta-analysis of eight published studies found a type 2 diabetes risk ratio of 1.78 following COVID-19 infection compared to matched or historic controls without

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## Research in context

### Evidence before this study

We searched PubMed for studies published between March 2020 and June 2023 using the terms "COVID-19" and "diabetes", restricted to English language publications. A meta-analysis of eight published studies reported a significant increase in risk of new onset diabetes following COVID-19 infection compared to matched or historic controls without known COVID-19 infection. In studies that included more than 100,000 exposed individuals, type 2 diabetes risk ratios were 1.31–2.66. However, these studies lacked information about differences in risk across populations, and in particular indigenous populations, which experienced greater morbidity and mortality from COVID-19 than non-indigenous populations. We conducted our study in response to a Notice of Special Interest published by the US National Institute of Diabetes and Digestive and Kidney Diseases in 2022 that highlighted the urgent need for additional research into COVID-19 and its association with new onset diabetes in diverse populations.

### Added value of this study

This study involved 176,483 indigenous individuals with documented COVID-19 infection, 1,344,339 indigenous individuals in a contemporary comparison group, and 1,503,085 indigenous individuals in a pre-pandemic comparison group. Our results suggest that American Indian and Alaska Native peoples had increased risk and incidence of diabetes following COVID-19 illness. This risk was greater in individuals with more severe COVID-19 illness. The increased risk of incident diabetes was present in comparisons to the contemporary and pre-pandemic groups and in a sensitivity analysis that used individuals with an acute upper respiratory infection as the comparison group.

### Implications of all the available evidence

Alaska Native and American Indian people experienced a similar increased risk of developing diabetes following COVID-19 illness as reported in other populations. Systems, such as the Indian Health Service, that provide healthcare for indigenous populations should consider COVID-19 infection a risk factor for diabetes and prepare for an increase in demand for diabetes care.

known COVID-19 infection.[6] Studies that included more than 100,000 exposed individuals reported type 2 diabetes risk ratios of 1.31–2.66.[7–10] While these studies indicate the magnitude of risk of new onset diabetes following COVID-19 infection, they lack information about differences in risk across populations, particularly indigenous people. To address this gap, we conducted the current study, which uses electronic health record data from the US Indian Health Service (IHS), which provides healthcare to 2.6 million AI/AN people across the US, to measure the association between COVID-19 infection and incident diabetes in AI/AN people.

## Methods

### Study design and participants

We conducted a retrospective cohort study using de-identified patient data from the IHS National Patient Information Reporting System (NPIRS) database, the central data repository for IHS. NPIRS compiles patient (demographics, tribal membership, benefit class, insurance eligibility, region) and clinical (inpatient, outpatient, laboratory and medication) data from over 500 IHS-affiliated hospitals and clinics that provide healthcare for eligible AI/AN people.[11,12] Power calculations based on the IHS active user population and estimated incidence of new onset diabetes determined that the study would have ample power (0.80) to detect even a modest association between COVID-19 and incident diabetes. We report our study according to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[13]

Within the IHS user population, we constructed three cohorts spanning pre-pandemic and pandemic timeframes: 1) pre-pandemic cohort (1/1/2018–2/28/2020); 2) no-COVID-19 cohort (3/1/2020–12/31/2021); and 3) COVID-19 cohort (also 3/1/2020–12/31/2021). For each of the two timeframes, we used a three-year lookback to identify the active AI/AN user population, defined as all users with at least one inpatient or outpatient encounter during the 3-year period.[14] For the pre-pandemic cohort the three-year lookback covered 1/1/2015–12/31/2017, and for the pandemic cohorts it covered 3/1/2017–2/28/2020. We then restricted the study population to individuals who were free from documented diabetes during the three-year lookback period based on a validated algorithm that combines diabetes diagnosis codes, medications, and lab results.[15] Diabetes was determined when any of the following criteria were met: diagnosis code of E08-E13 (≥1 inpatient diagnosis (primary or secondary position) OR ≥2 outpatient diagnoses (must occur on separate days)); ≥1 dispensing of a diabetes medication; ≥2 elevated labs occurring on separate days (A1c ≥ 6.5%; fasting glucose ≥126 mg/dL; random glucose ≥200 mg/dL). The population of active IHS users free from documented diabetes in the lookback period formed the three study cohorts.

Within the pandemic cohorts, we identified all individuals with documented COVID-19 based on an ICD-10 (International Classification of Diseases, 10th revision) code for COVID-19 (B97.21, B97.29, U07.1, J12.82, M35.81, U09.9) or documentation of a positive

lab test for SARS-CoV-2. The no-COVID-19 cohort included all individuals without a documented COVID-19 infection.

These categorizations resulted in the three main cohorts used in our analysis (Fig. 1): the pre-pandemic cohort, the pandemic cohort with no documentation of COVID-19 infection (no-COVID-19 cohort), and the pandemic cohort with documented COVID-19 infection (COVID-19 cohort).

This study was reviewed and approved by the Alaska Area IRB (2022-07-034) and the Alaska Native Tribal Health Consortium Human Research Review Committee.

### Follow-up

For individuals in COVID-19 cohort, follow-up time started on the date of documented COVID-19 (index date); person-time from the start date of their cohort study period (3/1/2020) until the date of their documented COVID-19 illness was attributed to the no-COVID-19 group (see Fig. 1, pandemic cohorts study period illustration). For individuals in the pre-pandemic cohort and those in the no-COVID-19 cohort, follow-up time started on the first date of the study period. Individuals were followed from their index date to end of study period or the first date in the study period that they met the case definition for incident diabetes.

### Main outcome

Incident (newly diagnosed) diabetes was ascertained during the study period using the same validated algorithm used to identify prevalent cases during the lookback period.[14] An individual met the case definition for diabetes on the first date in the study period that any of the criteria listed in the study participant section were met. Where possible, we differentiated new-onset type 1 diabetes (ICD-10: E10) and type 2 diabetes (ICD-10: E11) using a validated algorithm that relies on diagnosis codes[16,17]; patients with non-specific diabetes-related diagnosis codes (ICD-10: E08, E09, E13) or who met the diabetes case definition on the basis of elevated labs or diabetes medications were classified as 'unspecified diabetes type.'

### Covariates

From the lookback period, we collected covariates to characterize patients in terms of demographics (age, sex, IHS region: East, Northern Plains East, Northern Plains West, Alaska, Southern Plains, Southwest, West), clinical characteristics (baseline A1c, Charlson comorbidity index,[18] hypertension (ICD-9: 401; ICD-10: I10, I11, I12, I13, I14, I15, I16), hyperlipidemia (ICD9: 272.4; ICD10: E78), obesity and overweight (ICD-9: 278.00, 278.01, 278.02, 278.03, V85.30-V85.39, V85.41-V85.45; ICD-10: E66, Z68.3, Z68.4) and prediabetes (ICD-9: 790.29; ICD-10: R73.03)) and healthcare

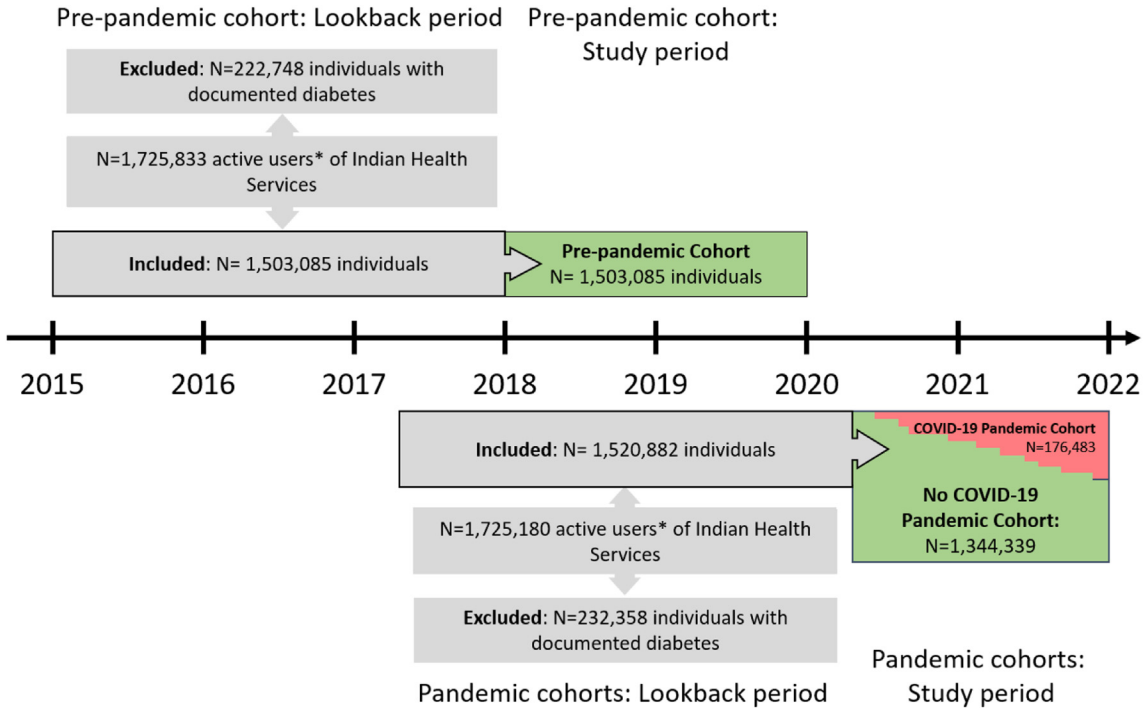



***Fig. 1:* Study flowchart depicting inclusion and exclusion criteria as well as timeframes for cohorts for the overall analysis.** *IHS active user population, all IHS users with at least one inpatient or outpatient encounter during three-year baseline period.

utilization during the lookback period (annualized number of inpatient encounters, number of outpatient encounters, number of A1c measurements). Of note, NPIRS does not contain ethnicity or race information other than an individual's AI/AN status.

### Statistical analyses

We compared baseline characteristics between the COVID-19, no-COVID-19, and pre-pandemic cohorts using chi-squared tests and t-tests for categorical and continuous variables, respectively. Incidence rates of newly diagnosed diabetes were calculated using person-years within each of the three cohorts. Age-adjusted incidence rates were calculated using the direct method and the 2020 United States Census as the standard population.[19] To estimate incidence rate ratios, we fit Poisson regression models taking into account differential follow-up time across the groups.[20] To calculate incidence rate ratios, we used an aggregated dataset that holds all scale parameters constant. We constructed Kaplan–Meier survival curves to estimate diabetes-free survival time across the three cohorts and used the log-rank test to compare survival distributions. The proportional hazards assumption was tested with log–log survival plots and was met. Hazard ratios and 95% confidence intervals (CI) were estimated using Cox proportional hazards models adjusting for baseline characteristics including demographics (age, sex, and IHS region), clinical characteristics (Charlson comorbidity score, prediabetes and obesity/overweight) and healthcare utilization (number of outpatient encounters). Individuals were censored on the date they met the diabetes diagnosis criteria during the study period or at the end of the study period. We report missing data and for analyses using variables with missing data we excluded those individuals and report the number of observations used. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

### Subgroup analyses

We performed subgroup analyses to examine whether findings differed from overall analyses. The first subgroup analysis examined the association between severity of COVID-19 illness and incident diabetes. We classified individuals with a diagnosis of COVID-19 in the inpatient setting as having 'severe COVID-19' and individuals with a diagnosis of COVID-19 only occurring in the outpatient setting or through a positive lab result as having 'mild COVID-19'[21]; these groups, stratified by COVID-19 severity, were compared to the no-COVID-19 and pre-pandemic cohorts. The second subgroup analysis examined potential interaction by sex and presents analyses stratified by sex. The third subgroup analysis restricts all cohorts to individuals with documented prediabetes (ICD-10 code or A1c 5.7–6.4%) during the lookback period. The fourth subgroup analysis examined the association between COVID-19 and new onset diabetes in those with confirmed absence of diabetes during the lookback by restricting to the subset of individuals with a documented A1c <6.5% during the lookback period. This group included individuals with prediabetes (5.7%–6.4%) and individuals with A1c values < 5.7%. Finally, we examined the association between COVID-19 and new onset diabetes among those with documented A1c values < 5.7% during the lookback period. These individuals had neither prediabetes nor diabetes.

### Sensitivity analysis

To assess robustness of our findings to decisions regarding study design, we repeated analyses using a subset of the no-COVID-19 and pre-pandemic comparison groups who had documented acute upper respiratory infection (AURI) during the study period. For this analysis, the COVID-19 cohort remained unchanged. The pre-pandemic and no-COVID-19 cohorts included only individuals with documented AURI during the study period (ICD-9: 460; ICD-10: J00, J01, J02, J03, J04, J05, J06). The start of follow-up for the COVID-19 cohort remained the date of documented COVID-19 infection (index date); the start of follow-up for the AURI comparison cohorts was the date of documented AURI.

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

A total of 1,503,085 individuals comprised the final analytic sample for the historic timeframe (pre-pandemic cohort) and of the 1,520,882 individuals in the pandemic timeframe, 176,483 (11.6%) had documented COVID-19 during the study period (COVID-19 cohort) and 1,344,339 (88.4%) had no documentation of COVID-19 (no-COVID-19 cohort; Fig. 1).

Compared to the no-COVID-19 and pre-pandemic cohorts, individuals in the COVID-19 cohort were older, more likely to be female, more likely to have documented hypertension, hyperlipidemia, obesity/overweight, and prediabetes, and have higher healthcare utilization during the lookback period (Table 1). Characteristics of the AURI cohorts appear in Supplementary Table S1. Between-group differences were less pronounced in the AURI analysis, however, those in the COVID-19 cohort were still more likely to have documented hypertension, hyperlipidemia, overweight/obesity, and prediabetes.

Over the study periods, a total of 2910 individuals in the COVID-19 cohort had documented incident diabetes, while 23,256 and 32,799 individuals in the no-COVID-19 and pre-pandemic cohorts had documented diabetes (Table 2). The majority (>70%) of new

| Baseline characteristics | Pandemic cohorts | | Historic cohort | COVID-19 vs No-COVID-19 | COVID-19 vs Pre-pandemic |
|---|---|---|---|---|---|
| | COVID-19 cohort (N = 176,483) | No-COVID-19 cohort (N = 1,344,339) | Pre-pandemic cohort (N = 1,503,085) | | |
| | 3/1/2017-2/29/2020 | | 1/1/2015-12/31/2017 | p-value | p-value |
| **Demographics**[a] | | | | | |
| Age (years), mean (SD) | 30.0 (18.9) | 29.7 (21.0) | 29.0 (20.5) | <0.0001 | <0.0001 |
| Age (years) category, n (%) | | | | <0.0001 | <0.0001 |
| <18 | 53,492 (30.3) | 470,123 (35.0) | 530,396 (35.3) | | |
| 18–44 | 83,338 (47.2) | 546,260 (40.6) | 621,173 (41.3) | | |
| 45–64 | 30,680 (17.4) | 231,920 (17.3) | 257,763 (17.2) | | |
| 65+ | 8973 (5.1) | 96,026 (7.1) | 93,728 (6.2) | | |
| Missing | 0 (0) | 10 (<1.0) | 25 (<1.0) | | |
| Sex, n (%) | | | | <0.0001 | <0.0001 |
| Male | 78,973 (44.7) | 650,515 (48.4) | 721,435 (48) | | |
| Female | 97,510 (55.3) | 693,582 (51.6) | 781,383 (52) | | |
| Missing | 0 (0) | 242 (<1.0) | 267 (<1.0) | | |
| IHS region, n (%) | | | | <0.0001 | <0.0001 |
| Alaska | 23,339 (13.2) | 156,618 (11.7) | 168,163 (11.2) | | |
| East | 5374 (3) | 43,695 (3.3) | 49,280 (3.3) | | |
| Northern Plains East | 4524 (2.6) | 92,895 (6.9) | 105,676 (7) | | |
| Northern Plains West | 18,448 (10.5) | 160,986 (12) | 183,235 (12.2) | | |
| Southern Plains | 39,545 (22.4) | 334,671 (24.9) | 357,699 (23.8) | | |
| Southwest | 69,812 (39.6) | 359,437 (26.7) | 437,664 (29.1) | | |
| West (outpatient only) | 12,776 (7.2) | 168,629 (12.5) | 181,753 (12.1) | | |
| Missing | 2665 (1.5) | 27,408 (2) | 19,615 (1.3) | | |
| **Clinical** | | | | | |
| Charlson Comorbidity Index,[b] mean (SD) | 1.2 (0.46) | 1.2 (0.43) | 1.2 (0.44) | <0.0001 | <0.0001 |
| Hypertension, n (%) | 24,957 (14.1) | 165,610 (12.3) | 184,566 (12.3) | <0.0001 | <0.0001 |
| Hyperlipidemia, n (%) | 14,986 (8.5) | 104,801 (7.8) | 109,391 (7.3) | <0.0001 | <0.0001 |
| Obesity/overweight, n (%) | 26,308 (14.9) | 128,023 (9.5) | 156,905 (10.4) | <0.0001 | <0.0001 |
| Prediabetes[c], n (%) | 21,779 (12.3) | 104,585 (7.8) | 108,988 (7.3) | <0.0001 | <0.0001 |
| **Healthcare utilization** | | | | | |
| Annual number of outpatient encounters, mean (SD)[d] | 9.2 (11.0) | 6.5 (9.4) | 6.8 (9.6) | <0.0001 | <0.0001 |
| Annual number of inpatient encounters, mean (SD) | 0.05 (0.2) | 0.03 (0.2) | 0.03 (0.2) | <0.0001 | <0.0001 |
| Annual number of HbA1c measures, mean (SD) | 0.3 (0.6) | 0.2 (0.5) | 0.2 (0.4) | <0.0001 | <0.0001 |

Abbreviation: HbA1c, hemoglobin A1c. [a]All demographic variables were ascertained using the last visit for each patient during baseline. [b]Charlson comorbidity index and comorbidities were calculated using all visits during baseline. [c]Includes prediabetes defined by a diagnosis code or A1c lab result. [d]Same day visits removed.

***Table 1:*** **Baseline characteristics of COVID-19, no-COVID-19, and pre-pandemic cohorts among American Indian/Alaska Native people from the Indian Health Service's National Patient Information Reporting System.**

diagnoses of diabetes across all groups were of type 2 diabetes, with roughly 20–25% of cases of unspecified type and the remaining (<2%) classified as type 1 diabetes. Individuals with documented COVID-19 infection had a higher incidence of diabetes than the comparison cohorts. The age-adjusted incidence rate of diabetes in the COVID-19 cohort was 23.6 per 1000 person-years compared to 11.3 per 1000 person-years in the no-COVID-19 cohort and 13.3 in the pre-pandemic cohort. The COVID-19 cohort had an elevated age-adjusted diabetes incidence rate ratio (aIRR) compared to the no-COVID-19 cohort (aIRR = 2.11; 95% CI: 2.03–2.20) and the pre-pandemic cohort (aIRR = 1.82; 95% CI: 1.75–1.89). Analyses restricted to the subset of individuals with prediabetes during the lookback period demonstrated an elevated diabetes aIRR in the COVID-19 cohort, albeit lower than the aIRR estimated for the entire COVID-19 cohort (Supplementary Table S2).

In Kaplan Meier survival curves, the distribution of diabetes-free survival time was significantly different across the COVID-19, no COVID-19 and pre-pandemic cohorts (Fig. 2). In Cox proportional hazards models, the COVID-19 cohort had an increased risk of developing diabetes during the study period in our main analyses as well as in subgroup and sensitivity analyses (Fig. 3). In the overall sample, individuals with documented COVID-19 infection had an increased hazard of new diabetes diagnosis following COVID-19 infection

| Overall | Pandemic cohorts | | Historic cohort | | | | |
|---|---|---|---|---|---|---|---|
| | COVID-19 cohort (N = 176,483) | No-COVID-19 cohort (N = 1,344,339) | Pre-pandemic cohort (N = 1,503,085) | COVID-19 vs No-COVID-19 | | COVID-19 vs Pre-pandemic | |
| | 3/1/2020–12/31/2021 | | 1/1/2018–2/28/2020 | IRR (95% CI) | RD (95% CI) | IRR (95% CI) | RD (95% CI) |
| Incident diabetes diagnosis, n | 2910 | 23,256 | 32,799 | – | – | – | – |
| Diabetes type, n (%) | | | | – | – | – | – |
| Type 1 diabetes | 9 (0.3) | 335 (1.4) | 398 (1.2) | – | – | – | – |
| Type 2 diabetes | 2111 (72.5) | 17,929 (77.1) | 24,519 (74.8) | – | – | – | – |
| Diabetes unspecified | 790 (27.2) | 4992 (21.5) | 7882 (24.0) | – | – | – | – |
| Total person-years of follow-up | 143,391 | 2,619,829 | 3,206,943 | – | – | – | – |
| Average person-years of follow-up, mean (SD) | 0.81 (0.48) | 1.72 (0.34) | 2.13 (0.20) | – | – | – | – |
| Unadjusted incidence rate per 1000 person years | 20.3 | 8.9 | 10.2 | 2.29 (2.20–2.38) | 11.4 (10.5, 12.3) | 1.98 (1.91–2.06) | 10.1 (9.2, 11.0) |
| Age-adjusted incidence rate per 1000 person years | 23.6 | 11.3 | 13.3 | 2.11 (2.03–2.20) | 12.3 (11.3, 13.3) | 1.82 (1.75–1.89) | 10.3 (9.3, 11.3) |
| **AURI** | **Pandemic cohorts** | | Historic cohort | | | | |
| | **COVID-19 cohort (N = 176,483)** | **AURI during pandemic cohort (N = 165,570)** | **AURI pre-pandemic cohort (N = 413,133)** | **COVID-19 vs AURI during pandemic** | | **COVID-19 vs AURI pre-pandemic** | |
| | **3/1/2020–12/31/2021** | | **1/1/2018–2/28/2020** | **IRR (95% CI)** | **RD (95% CI)** | **IRR (95% CI)** | **RD (95% CI)** |
| Incident diabetes diagnosis, n | 2910 | 1979 | 6083 | – | – | – | – |
| Total person-years of follow-up | 143,391 | 180,710 | 539,865 | – | – | – | – |
| Average person-years of follow-up, mean (SD) | 0.81 (0.48) | 0.94 (0.58) | 1.31 (0.66) | – | – | – | – |
| Unadjusted incidence rate per 1000 person years | 20.3 | 10.9 | 11.3 | 1.85 (1.75–1.96) | 9.4 (8.3, 10.5) | 1.80 (1.72–1.88) | 9.0 (8.0, 10.0) |
| Age-adjusted incidence rate per 1000 person years | 23.6 | 15.8 | 18.0 | 1.46 (1.36,1.55) | 7.8 (6.6, 9.1) | 1.31 (1.25–1.37) | 5.6 (4.5, 6.7) |

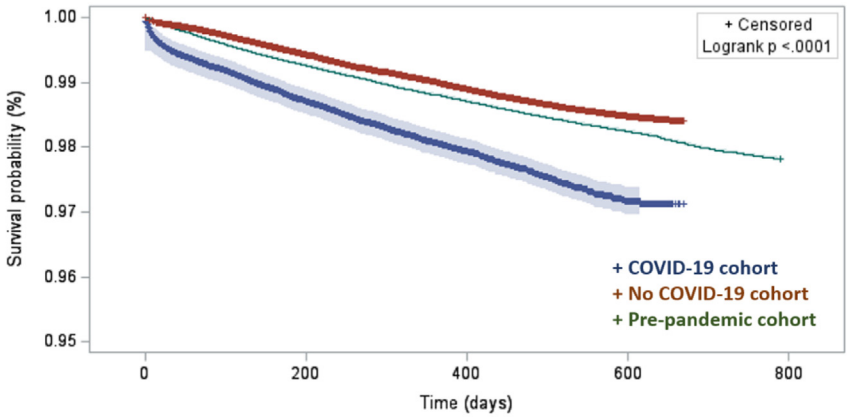
Abbreviations: AURI, Acute upper respiratory infection; IRR, Incidence rate ratio; RD, Risk difference; 95% CI, 95% confidence interval. Age-adjusted estimates used the direct method and the 2020 United States Census as the standard population. Incidence rate ratios and 95% CIs were calculated using Poisson regression.

***Table 2:*** **Comparison of diabetes incidence rates and incidence rate ratios across COVID-19, no-COVID-19, and pre-pandemic cohorts among American Indian/Alaska Native people from the Indian Health Service's National Patient Information Reporting System.**

compared to the no-COVID-19 group (adjusted HR (aHR) = 1.56; 95% CI: 1.50–1.62) and the pre-pandemic group (aHR = 1.27; 95% CI: 1.22–1.32). In a sensitivity analysis comparing the COVID-19 cohort to a subset of individuals from the no-COVID-19 and pre-pandemic cohorts with documented AURI during the study period, the hazard of new-onset diabetes was attenuated but remained higher in those with COVID-19 infection (vs AURI during pandemic cohort aHR = 1.13; 95% CI: 1.06–1.20; and vs AURI pre-pandemic cohort aHR = 1.22; 95% CI: 1.16–1.28). In subgroup analyses, the risk of diabetes was higher in those with severe COVID-19 illness (vs no-COVID-19 aHR = 2.90; 95% CI: 2.67–3.15; vs pre-pandemic aHR = 3.24; 95% CI: 3.00–3.51) than in those with mild COVID-19 (vs no-COVID-19 aHR = 0.97; 95% CI: 0.93–1.01; vs pre-pandemic aHR = 1.09; 95% CI: 1.04–1.13). Risk of new onset diabetes following COVID-19 infection was higher in males than in females (p-value for sex*cohort interaction <0.05). In analyses stratified by sex, the risk of developing diabetes in the COVID-19 vs no COVID-19 cohort was 1.65 (95% CI: 1.56–1.76) in males and 1.49 (95% CI: 1.41–1.57) in females; a similar pattern by sex was observed in the COVID-19 vs pre-pandemic models. Among individuals with prediabetes during the lookback period and among those with documented A1c <6.5% and A1c <5.7% during the lookback period), the risk of new onset diabetes remained significantly higher in the COVID-19 cohort across all comparisons with the exception of the COVID-19 vs pre-pandemic comparison among those with prediabetes (aHR = 0.99; 95% CI: 0.89–1.08).

## Discussion

We measured the association between COVID-19 and incident diabetes in AI/AN people using data from a national IHS healthcare database representing over 1.5 million individuals. Individuals diagnosed with COVID-19 had an elevated incidence of new diabetes diagnoses when compared to those without diagnosed COVID-19 (aIRR = 2.11) and individuals during the pre-pandemic period (aIRR = 1.82). Similarly, the COVID-19 diagnosed group had an elevated risk of a new diabetes




**Number at-risk across follow-up**

| | 0 days | 200 days | 400 days | 600 days | 800 days |
|---|---|---|---|---|---|
| **COVID-19 cohort** | 176,483 | 111,530 | 57,433 | 3,727 | 0 |
| **No COVID-19 cohort** | 1,520,822 | 1,484,562 | 1,395,880 | 1,345,608 | 0 |
| **Pre-pandemic cohort** | 1,503,085 | 1,491,891 | 1,483,667 | 1,476,589 | 0 |

***Fig. 2:*** **Kaplan–Meier survival curves for new onset diabetes across COVID-19, no-COVID-19, and pre-pandemic cohorts among American Indian/Alaska Native people from the Indian Health Service's National Patient Information Reporting System.** Data present Kaplan–Meier survival curves and 95% Hall-Wellner confidence bounds.

diagnosis when compared to the no-COVID-19 group (aHR = 1.56) and the pre-pandemic group (aHR = 1.27). The increased risk of developing diabetes following COVID-19 illness remained in a sensitivity analysis that limited the comparator groups to individuals with an AURI diagnosis. These data add to the very limited literature on post-COVID-19 sequelae in indigenous populations.

The incidence and risk of diabetes following COVID-19 in the AI/AN study population were similar to estimates reported from other populations. In our study we found an unadjusted diabetes incidence rate of 20.3 in the COVID-19 group, which aligns with the estimate (IR = 15.5, 95% CI: 7.9–25.6) from a recent meta-analysis of nine studies.[20] Similarly, the estimated risk of diabetes following COVID-19 in our study population was similar to those from two separate meta-analyses (pooled risk ratios of 1.62[20] and 1.64).[6] Although AI/AN people faced unique challenges during the COVID-19 pandemic,[22] their risk of developing diabetes following COVID-19 infection is comparable in magnitude to the risks reported in other populations.

We conducted a sensitivity analysis limited to individuals with AURI in the comparator groups to control for potential confounders related to healthcare utilization. In this analysis, healthcare utilization was very similar across the three cohorts and diabetes incidence rates were higher in the AURI groups than the overall comparator groups. We found an attenuated diabetes risk (aHR = 1.13 vs no-COVID-19 AURI and aHR = 1.22 vs pre-pandemic AURI) similar to a study from Germany that used an AURI comparison group and reported an aIRR of 1.28 for type 2 diabetes.[23] Daughtery et al. also found a lower COVID-19 diabetes risk when moving from an inclusive pandemic comparison group (HR = 1.83) to a lower respiratory tract infection comparison group (HR = 1.39).[7] The results of our sensitivity analysis may more accurately reflect the excess COVID-19 diabetes risk in the AI/AN population because it mitigated differences in healthcare utilization across the comparator groups.

Severe COVID-19 illness conferred a substantially greater risk of diabetes than mild COVID-19 illness in our study population. A large study using US Veteran's Administration data also reported a graded COVID-19 diabetes risk from non-hospitalized (aHR = 1.21), to hospitalized (aHR = 2.66), and intensive care (aHR = 3.66) patients.[8] Although the pathophysiology underlying the SARS-CoV-2 mediated development of diabetes has not been fully elucidated, more severe COVID-19 illness may result in greater inflammation-mediated insulin resistance and/or viral destruction of pancreatic beta cells.[24] Additionally, or alternatively, individuals recovering from severe COVID-19 may have received more healthcare and laboratory testing than those with mild COVID-19, offering increased opportunities for diabetes detection. Finally, individuals with more severe COVID-19 illness may have also had more diabetes risk factors than individuals with mild COVID-19 disease.

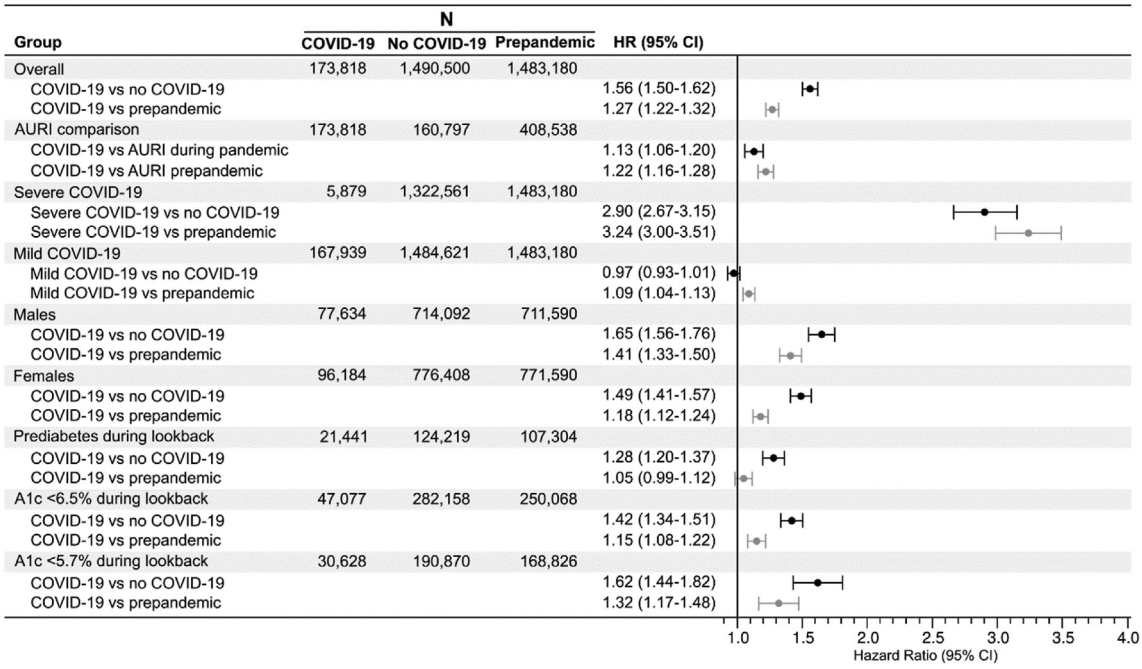



***Fig. 3:*** **Association between COVID-19 infection and new onset diabetes among American Indian/Alaska Native people using de-identified patient data from the Indian Health Service's National Patient Information Reporting System.** Adjusted hazard ratios from Cox proportional hazards model adjusting for demographics (age, sex, and IHS region), clinical characteristics (Charlson comorbidity score, prediabetes and obesity/overweight) and healthcare utilization (number of outpatient encounters). 'AURI comparison' analysis: the pre-pandemic and no-COVID-19 cohorts included only individuals with documented acute upper respiratory infection (AURI) during the study period (ICD-9: 460; ICD-10: J00, J01, J02, J03, J04, J05, J06); the COVID-19 cohort remained unchanged. COVID-19 severity analysis: 'severe COVID-19' was defined as individuals with a diagnosis of COVID-19 in the inpatient setting; 'mild COVID-19' was defined as individuals with a diagnosis of COVID-19 only occurring in the outpatient setting or through a positive lab result. 'Prediabetes' analysis restricted all cohorts to include only individuals with documented prediabetes (ICD-10 code or A1c 5.7–6.4%) during the lookback period. 'A1c <6.5%' analysis restricted all cohorts to those with documented A1c <6.5% during the lookback period. 'A1c <5.7%' analysis restricted all cohorts to those with documented A1c <5.7% during the look back period. Abbreviations: IHS, Indian Health Service; HR, Hazard ratio.

We looked at the association between COVID-19 illness and incident diabetes in individuals with documented prediabetes to explore the hypothesis that COVID-19 infection may serve as a tipping point for the development of diabetes. Although the incidence of diabetes was higher across all three prediabetes cohorts than in the full cohorts, the relative hazards of incident diabetes in the COVID-19 prediabetes subgroup comparisons were of a lesser magnitude than the relative hazards of incident diabetes observed in the full COVID-19 cohort comparisons. In the study conducted by Xie et al.,[8] the relative hazard of new onset diabetes was also less elevated in those with an A1c in the prediabetes range at baseline as compared to those with A1c <5.7%. The explanation for this is unclear and may be due to under-ascertainment of prediabetes in the study population, unmeasured confounders, or factors that influence the process by which COVID-19 leads to diabetes.

Our study is among the first to investigate the association between COVID-19 and new-onset diabetes among AI/AN people, a group disproportionately impacted by the COVID-19 pandemic and diabetes. The large, nationally representative sample supports estimates that are largely generalizable to the AI/AN population who are IHS users, roughly 40% of the overall AI/AN population nationwide. Additionally, our study utilized clinical data (as opposed to claims data) which allowed for inclusion of lab results and thus a more comprehensive ascertainment of diabetes and COVID-19.

Despite these strengths, it is important to acknowledge a number of limitations when interpreting these findings. First, our study relied on clinical data from the IHS data warehouse. Ascertainment of exposure (COVID-19 infection), outcome (new onset diabetes) and clinical covariates relied on these data being documented in an individual's electronic medical record. Under-ascertainment of COVID-19 status because people with mild or asymptomatic infections did not seek testing and because of the transition to home-based testing in 2021 may have misclassified individuals in the no-COVID-19 cohort and potentially weakened the

observed associations. People with more severe illness may have been more likely to seek care and, thus, have conditions documented. This was especially true during the early months of the COVID-19 pandemic when the entire country was under 'stay-at-home' orders and healthcare facilities were largely closed to non-emergent encounters. To address this, we included a historic cohort to ensure findings were robust to any shifts in healthcare utilization that resulted from pandemic-related changes in behavior. Additionally, our data only capture encounters that occurred within the IHS system; if an individual received care outside of an IHS-affiliated facility, this information would not be available for our study. Our analysis was limited to data routinely collected and documented in structured data fields in NPIRS. We do not have reliable data on mortality which would have been valuable to include in our analyses to more accurately portray person-years of follow-up and allow for competing risk of mortality in our Cox proportional hazards models. We were not able to ascertain COVID-19 vaccination status, which has been shown in prior studies to modify the association between COVID-19 infection and diabetes risk.[25] There are no IHS-affiliated inpatient facilities in the West region so our analyses do not include any inpatient data for these patients (~10% of the overall sample). The limited number of incident type 1 diabetes diagnoses in our cohorts precluded stratifying our analyses by diabetes type. Finally, our main analysis included all IHS users who received care during the three-year lookback period to generate robust models widely generalizable to the underlying IHS user population. The study population included active users during the lookback period regardless of whether they had an IHS encounter during the study period. This may have inflated follow-up time for the comparison groups in relation to the COVID-19 cohort, which started on the date of documented COVID-19 infection. To address this, we conducted a sensitivity analysis restricted to individuals with documented AURI in the comparison groups and found that the COVID-19 diabetes risk remained elevated, if somewhat attenuated.

In conclusion, we found a significant increase in risk of new onset diabetes following COVID-19 infection. Our findings were consistent when using various comparison groups (historic, pandemic, AURI) and with adjustment for demographic, clinical and utilization-related variables. Findings in subgroup analyses revealed a dose–response association between COVID-19 severity and risk of diabetes. Our study adds to the growing literature examining the association between COVID-19 infection and new onset diabetes and extends these findings to a previously understudied population, AI/AN individuals.

#### Contributors

MEL and JWK planned the study and obtained funding. SB, MB and UC contributed to the study design. JWK obtained ethics and tribal approvals. SB and IB performed the statistical analyses and MEL advised on analyses. MEL and JWK drafted the manuscript. MB and UC revised the manuscript. All authors approved the version to be published. MEL and JWK are the guarantors of this work.

#### Data sharing statement

IHS NPIRS data are not available to share.

#### Declaration of interests

The authors declare no potential conflicts of interest relevant to this work.

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#### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100727.

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