Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Sein Lee Date

Evaluating the Association of COVID-19 Vaccination and New-Onset Diabetes as an Outcome

By

Sein Lee
Master of Public Health

Department of Biostatistics and Bioinformatics

_____

Lance Waller, Ph.D.
Committee Chair

_____

Shivani Patel, Ph.D.
Committee Member

Evaluating the Association of COVID-19 Vaccination and New-Onset Diabetes as an Outcome

By

Sein Lee

B.S.
Emory University
2022

Thesis Committee Chair: Lance Waller, Ph.D.

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health in Biostatistics
2024

Abstract

Evaluating the Association of COVID-19 Vaccination and New-Onset Diabetes as an Outcome

By Sein Lee

While the general consensus is that the COVID-19 vaccine is critical for protecting individuals from severe outcomes and is safe, there have been mixed reports of adverse diabetes outcomes and increased risk of new-onset diabetes following vaccination. There are methodological challenges when investigating such an association, such as confounding, surveillance bias, and appropriately addressing COVID-19 vaccination as a time-varying exposure. This study investigates associations between new-onset diabetes and COVID-19 vaccination as a time-varying exposure among adults, and whether this association varies by pre-vaccination demographics and underlying diabetes risk.

This study was based on electronic medical records of adults enrolled in Kaiser Permanente. The outcome of interest is new-onset diabetes, and the exposure is COVID-19 vaccination. Sociodemographic and clinical covariates of interest include sex, age, race, smoking, exercise, BMI, COVID-19 infection, blood pressure, and Social Vulnerability Index (Center for Disease Control and Prevention 2020). Descriptive and exploratory analyses were performed using R and SAS. An unadjusted Cox time-variant proportional hazards model was created with just the exposure variable, and adjusted for all covariates of interest.

Out of 728,120 study participants, 505,763 were vaccinated at some time during the study period of March 2020 and December 2022 and 222,407 were not. 19,477 patients were diagnosed with new-onset diabetes during the study period. The unadjusted Cox time-variant model yielded a hazard ratio of 2.457 (95% CI: 2.322, 2.600) for vaccination. However, in the final Cox time-variant model adjusting for potential confounders, the hazard ratio was 1.144 (95% CI: 0.984, 1.330). Covariates associated with increased risk of new-onset diabetes were COVID-19 infection, BMI, obesity, blood pressure, smoking status, number of pre-pandemic ambulatory visits, age, and SVI percentile.

The findings suggest no association between COVID-19 vaccination and new-onset diabetes during our study period. The results emphasize the importance of control for confounding factors in the study of COVID-19 exposures and diabetes outcomes, especially during the early availability of the vaccine when access was prioritized to those at high risk for severe consequences of COVID-19 infection. There is also a need for careful analysis and clear communication of results regarding the safety of COVID-19 vaccination with respect to risk of new-onset diabetes for public health officials and policymakers.

Evaluating the Association of COVID-19 Vaccination and New-Onset Diabetes as an Outcome

By

Sein Lee

B.S.
Emory University
2022

Thesis Committee Chair: Lance Waller, Ph.D.

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health in Biostatistics
2024

Acknowledgements

I would like to thank both of my advisors, Dr. Lance Waller and Dr. Shivani Patel. They have both been extremely supportive during the entire process. I was able to receive the best guidance and insight in every meeting with Dr. Waller, and Dr. Patel has helped immensely in building this project and overcoming obstacles. I feel honored and incredibly fortunate to have had the opportunity to work with them. I would also like to extend my gratitude to the Kaiser Permanente-Emory research team for their support, resources, and feedback.

Introduction

After the onset of the coronavirus pandemic in 2020, many researchers investigated bidirectional associations between diabetes mellitus and COVID-19. Findings suggest that underlying diabetes mellitus and its complications, such as cardiovascular diseases, heart failure, and chronic kidney disease, are a potential risk factor for adverse COVID-19 outcomes and COVID-19 induced mortality (Lim et al. 2021). Conversely, the occurrence of new onset diabetes in COVID-19 patients suggests the potential diabetogenic action of SARS-CoV-2 as well as incidences of worsened hyperglycemia in patients having been previously diagnosed with diabetes (Domingo et al. 2021). Of particular importance, new-onset diabetes following COVID-19 may represent a chronic disease manifestation of the virus that impacts population health in the longer term.

A related line of research has investigated the association between the coronavirus vaccine and new-onset diabetes. The coronavirus vaccine has shown to be effective in protecting populations that are more vulnerable to COVID-19 morbidities or adverse outcomes (Baden et al. 2020). In people with known diabetes, a lower antibody response and lower frequency of significant side effects compared to the general population has been observed after the vaccination (He et al. 2023).

While the general consensus is that vaccination is critical for protecting individuals from severe outcomes following COVID-19 and is safe, there have been mixed reports of adverse diabetes outcomes induced by the COVID-19 vaccine. For example, reports indicate increased hyperglycemia in type 2 diabetes patients following vaccination (Joob & Wiwanitkit 2023). The multicenter prospective Immune Response to COVID-19 Vaccination in People with Diabetes Mellitus (COVAC- DM) study reports that COVID-19 vaccination per se did not change

glycemic control in people with diabetes. However, on days when side effects were present, a deterioration of glycemia was observed in people with type 1 diabetes (Aberer et al. 2022). From these findings, it can be inferred that while the vaccine prevents adverse COVID-19 outcomes in patients with known diabetes, it may induce adverse diabetes-related outcomes.

A key unanswered question is whether the risk of new-onset diabetes is exacerbated following vaccination for COVID-19. There have been mixed reports regarding the risk of developing diabetes after COVID-19 vaccination for patients previously undiagnosed with diabetes. While there was no observed short term impact of vaccination on diabetes occurrence, there have been reports of patients developing new onset diabetes a few weeks after vaccination (Hromic-Jahjefendic et al. 2023). In contrast, others have reported higher estimated risk of new-onset diabetes in SARS-CoV-2–infected individuals compared to noninfected counterparts, and COVID-19 survivors who received COVID-19 vaccinations experienced a reduced risk of new-onset diabetes, with a dose-dependent effect (Hsieh et al. 2023). In another study where the occurrence of new-onset diabetes was monitored 90 days after COVID-19 infection, COVID-19 infection was associated with increased risk of diabetes, and this risk was higher in unvaccinated than vaccinated patients, supporting the conclusion of the vaccine's ability to prevent newly onset diabetes as a consequence of COVID-19 infection (Kwan et al. 2023). A study that investigated this effect among a pregnant cohort also did not identify an increased risk of GDM associated with receipt of a COVID-19 vaccine (Vesco et al. 2023).

In reviewing these studies, some methodological concerns arise when investigating the relationship between the COVID-19 vaccine and new-onset diabetes. COVID-19 vaccination status is a time-varying exposure within a pandemic setting. Previous studies implemented the methods of conditional logistic modeling (Yan et al. 2022) or Cox proportional hazards modeling

(Hsieh et al. 2023; Xiong et al. 2023) in order to study this association but did not explicitly address the time-varying nature of COVID-19 vaccination exposure and coverage. There is also a concern for potential confounding and surveillance bias. For example, when vaccines first became available, individuals who were at high risk for adverse clinical outcomes and COVID-19 complications were prioritized for vaccine allocation (National Academies of Science, Engineering, and Medicine 2020), possibly leading to a higher number of clinical visits and screenings resulting in a higher number of diagnoses (Tancredi, Cullati & Chiolero 2022). Also, there are some risk factors of diabetes such as blood pressure, age, heart rate, or BMI that correlate with other adverse outcomes of COVID-19 infection (Ceriello & Prattichizzo 2021), which were also correlated with earlier prioritization for vaccination. These important features of the temporal evolution and prioritization of the distribution of COVID-19 vaccination call for a need to account for vaccination as a time-varying exposure and consider a comprehensive set of confounders in the analysis of vaccination and diabetes. Thus, this study attempts to investigate new-onset diabetes as an outcome of COVID-19 vaccination as a time-varying exposure among adults, as well as investigate whether this association persists after accounting for pre-vaccination demographics and underlying diabetes risk.

Methods

Data

This study was based on electronic medical records of adults enrolled in Kaiser Permanente (KP) in three sites: Georgia, Hawaii, and Northwest. Data were obtained as a part of the protocol "Risk of new-onset diabetes following COVID-19: A multiethnic cohort study of 1 million+ individuals across the life course." Electronic medical records were used to derive a retrospective cohort of 728,120 adults who were aged 18 and over who were enrolled during the period of March 1st 2020 to December 31st 2022, out of the entire KP membership consisting of 2,180,699 members at participating sites. Members with prevalent diabetes, indicating diabetes before the study or within 90 days after enrollment, were excluded from the analysis as well as those who experienced pregnancy during the study period.

Study measures

The main outcome of interest is new-onset diabetes, which is defined by having experienced a combination of 2 or more of the following indications of diabetes within a 90 day period: diagnostic code, laboratory records, and two medication fills.

The exposure is COVID-19 vaccination, for which only the first date of vaccination is considered.

Sociodemographic and clinical covariates of interest include sex, age, race, urbanicity, smoking, exercise, body mass index, diagnostic code indicating COVID-19 disease, systolic and diastolic blood pressure, sum and number of comorbidities, number of pre-pandemic ambulatory visits, and census tract-level Social Vulnerability Index score (Center for Disease Control and Prevention 2020).

Analysis

Exploratory analyses including a table of descriptive statistics as well as a Kaplan-Meier plot describing diabetes-free survival by vaccination status were performed in SAS and R. For primary analysis, the bivariate description of new-onset diabetes as a binary outcome (yes vs. no) by covariates of interest was obtained, using ANOVA for numerical covariates and chi-square for categorical covariates to calculate the parametric p-value.

A Cox time-variant survival analysis using the proportional hazards model was performed using the following exposure-outcome groups: those who were unvaccinated throughout the study period and did not experience the outcome, those who were unvaccinated then became vaccinated, those who were vaccinated and did not experience the outcome, those who were unvaccinated throughout the study period and experienced the outcome, and those who were vaccinated and experienced the outcome (Figure 1). An unadjusted model with only the exposure variable (vaccination) was created. Subsequently, a multivariate analysis adjusting for all covariates of interest was deemed the full model.

Results

Table 1 shows the distribution of patient characteristics by vaccination status. Out of 728,120 study participants in the selected cohort, 505,763 were vaccinated at some time during the study period and 222,407 were not vaccinated throughout the study period. Table 2 describes the number of events and person time for each vaccination group. The total person time for the vaccinated group was 474,460,760 person-days. For the unvaccinated group, total person time was 135,220,074 person-days. The number of censored events were 699,300, out of which 484,585 (69.30%) patients were vaccinated and 214,715 (30.70%) were not vaccinated. There were a total of 18,730 patients who were diagnosed with new onset diabetes in the outpatient setting, with 16,125 (86.09%) of them having been vaccinated and 2,605 (13.91%) of them not having been vaccinated. Out of 747 patients were diagnosed with new onset diabetes in the inpatient setting, 548 (73.36%) of them were vaccinated and 199 (26.65%) of them were not vaccinated. There were a total of 9,393 deaths, out of which 4,505 (47.96%) were vaccinated and 4,888 (52.04%) were not vaccinated.

Figure 2 illustrates the Kaplan-Meier plot of diabetes-free survival by vaccination status, not adjusting for other covariates. Survival rates for the vaccinated group remain constant up to December 2020, reflecting that it was before the widespread public distribution of the COVID-19 vaccine. Initially, the vaccinated group has higher survival compared to the unvaccinated group until August 2022, where their survival curves intersect. From August to December 2022, the unvaccinated group shows higher survival rates.

Some other notable patient characteristics from Table 1 are as follows. There were 134,266 patients who were diagnosed with COVID-19 in an outpatient setting, out of which 105,708 were vaccinated and 28,558 were not vaccinated. There were 3,381 patients who were

diagnosed with COVID-19 in an inpatient setting, out of which 2,271 were vaccinated and 1,110 were not. The median age was 46.8 for the entire cohort. However, 49.0 was the median age for the vaccinated group and 38.0 for the unvaccinated group. The majority of the cohort were White patients 377,990 (51.9%). The mean comorbidity sum for the cohort was 0.373 (0.788) for the entire cohort, with the vaccinated group being 0.429 (0.830) and the unvaccinated 0.244 (0.663). The mean number of ambulatory visits in 2019 for all patients was 5.67 (10.6), with the vaccinated group being 6.50 (11.1) and the unvaccinated 3.78 (9.04).

From the distribution of occurrence of new-onset diabetes by patient characteristics in Table 3, out of all patients diagnosed with COVID-19 in an outpatient setting, 2,314 (1.72%) were diagnosed with new-onset diabetes and 131,952 (98.28%) were not. Out of all patients diagnosed with COVID-19 in an inpatient setting, 291 (8.61%) were diagnosed with new-onset diabetes and 3,090 (91.39%) were not. Out of the obesity groups, 0.67% of underweight patients, 0.87% of normal patients, 2.08% of overweight patients, 4.11% of patients in obese class I, and 7.1% of patients in obese class II were diagnosed with new-onset diabetes. As for smoking status, 2.55% of those who never smoked, 3.66% of those who were former smokers, and 3.16% of those who are current smokers were diagnosed with new-onset diabetes. Out of the comorbidity number categories, 2.22% of patients with no comorbidities, 3.4% of patients with 1 comorbidity, and 5.58% of patients with 2 or more comorbidities were diagnosed with new-onset diabetes.

Without adjustment for confounders, the time-variant Cox proportional hazards model containing only exposure and outcome variables, we estimate a hazard ratio of 2.457 (95% CI: 2.322, 2.600) for vaccination. In the final multivariate time-variant Cox proportional hazard

model adjusting for potential confounders, the associated hazard ratio estimate is 1.138 (95% CI: 0.978, 1.323).

In the fully adjusted model, several factors were associated with higher relative hazard of diabetes, including COVID-19 infection, obesity, smoking status, diastolic blood pressure, BMI, and the number of pre-pandemic ambulatory visits. Inpatient COVID-19 diagnosis compared to outpatient had a hazard ratio of 2.219 (95% CI: 1.803, 2.732). Compared to normal patients, patients of obesity class I (HR: 2.417, 95% CI: 1.874, 3.118), obesity class II and higher (reference = normal) (HR: 3.202, 95% CI: 2.331, 4.397), and overweight (HR: 1.614, 95% CI: 1.273, 2.048) demonstrated a positive hazard ratio. Compared to those who never smoked, current smokers had a hazard ratio of 1.326 (95% CI: 1.087, 1.618). The hazard ratio corresponds to the multiplicative increase in hazard associated with a one unit change in the following variables- diastolic blood pressure (HR: 1.009, 95% CI: 1.003, 1.015). BMI (HR: 1.032, 95% CI: 1.020, 1.045), and the number of ambulatory visits in 2019 (HR: 1.004, 95% CI: 1.002, 1.007).

Demographic covariates that demonstrated a positive association with diabetes were race and ethnicity, age, and Social Vulnerability Index. Compared to White, Asian (HR: 1.811, 95% CI: 1.411, 2.325), Hispanic (HR: 1.558, 2.270), Native Hawaiians and Pacific Islanders (HR: 1.974, 95% CI: 1.353, 2.880) had a positive hazard ratio. One unit increase in age corresponds to the hazard ratio of 1.016 (95% CI: 1.011, 1.021). One unit increase in Social Vulnerability Index percentile number corresponds to the hazard ratio of 1.280 (95% CI: 1.038, 1.578).

Discussion

Clarifying any associations between new-onset diabetes and COVID-19 vaccination is an important research topic in order to best communicate risks and benefits of vaccination. While previous studies reported mixed conclusions regarding associations between vaccination and new-onset diabetes, the time-variant survival analysis reveals no excess risk of new-onset diabetes following COVID-19 vaccination after controlling for demographic and underlying risk factors associated with both probability of severe consequences of COVID-19 infection, risk factors associated with diabetes, and factors associated with prioritization for vaccination when supplies were limited. Collectively, the findings suggest that people at increased risk for diabetes were more likely to get vaccinated, and this propensity to get vaccinated leads to a spurious association between vaccination and diabetes incidence.

While vaccination was not associated with new-onset diabetes, our findings indicated that COVID-19 disease was. We also found that pre-pandemic ambulatory care visits, as a proxy for general healthcare seeking behavior and propensity to seek healthcare during the pandemic, was positively associated with new-onset diabetes. This finding emphasizes the importance of controlling for the potential bias in the likelihood of seeking healthcare and getting diagnosed with the disease of interest. In addition, the findings reiterated the importance of well-known risk factors for diabetes, including BMI, obesity, blood pressure, smoking status, and age. Patients with a higher SVI overall percentile ranking also had a greater hazard for new-onset diabetes.

Some limitations of this research include the fact that only the first date of vaccination was considered in this study, while many people have received different numbers of vaccinations over the study period as boosters became available. Future work could investigate associations based on the number of vaccinations received. Another limitation is that the study period defined

in this research is only 3 years long, from March 2020 to December 2022. There may exist longer-term effects following COVID-19 vaccination, also suggesting future research topics. Also, future research can explore the associations between vaccine manufacturer and new-onset diabetes.

In summary, in this analysis of a demographically and regionally diverse population of adults, we found no association between getting vaccinated for COVID-19 and new-onset diabetes after controlling for well-known risk factors for diabetes risk. The findings emphasize the importance of appropriate control for confounding factors in the study of COVID-19 exposures and diabetes outcomes. There is also the need for careful analysis and communication of results regarding the safety of COVID-19 vaccination with respect to risk of new- onset diabetes for public health officials and policymakers.

Appendices

Figure 1. Exposure Groups from Enrollment to End of Follow-up

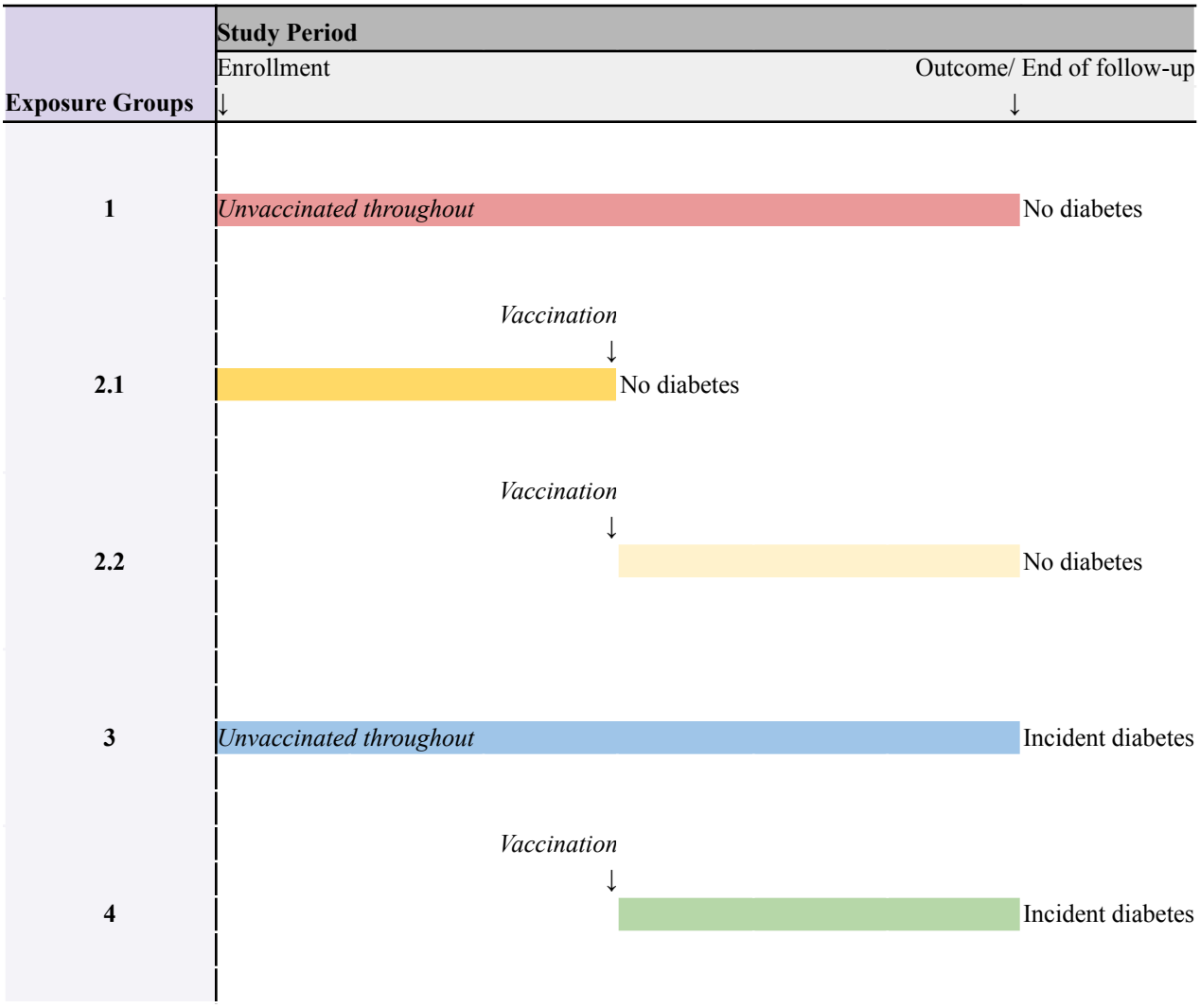

Table 1. Distribution of Patient Characteristics by Exposure Status

	Not vaccinated (N=222407)	Vaccinated (N=505763)	All (N=728170)
Region			
Georgia	70193 (31.6%)	121389 (24.0%)	191582 (26.3%)
Hawaii	51034 (22.9%)	99683 (19.7%)	150717 (20.7%)
Northwest	101180 (45.5%)	284691 (56.3%)	385871 (53.0%)
Diabetes			
Mean (SD)	0.0126 (0.112)	0.0330 (0.179)	0.0267 (0.161)
Median [Min, Max]	0 [0, 1.00]	0 [0, 1.00]	0 [0, 1.00]
COVID-19 Infection			
	192739 (86.7%)	397784 (78.7%)	590523 (81.1%)
Inpatient	1110 (0.5%)	2271 (0.4%)	3381 (0.5%)
Outpatient	28558 (12.8%)	105708 (20.9%)	134266 (18.4%)
Female			
Men	118340 (53.2%)	232297 (45.9%)	350637 (48.2%)
Women	104067 (46.8%)	273466 (54.1%)	377533 (51.8%)
Age			
Mean (SD)	40.8 (16.5)	49.4 (17.3)	46.8 (17.5)
Median [Min, Max]	38.0 [18.0, 108]	49.0 [18.0, 105]	46.0 [18.0, 108]
Missing	10 (0.0%)	18 (0.0%)	28 (0.0%)
Age Categories			
	10 (0.0%)	18 (0.0%)	28 (0.0%)
18-29	70379 (31.6%)	77711 (15.4%)	148090 (20.3%)
30-44	67931 (30.5%)	126448 (25.0%)	194379 (26.7%)
45-64	64613 (29.1%)	193088 (38.2%)	257701 (35.4%)
65-79	14993 (6.7%)	89474 (17.7%)	104467 (14.3%)
80+	4481 (2.0%)	19024 (3.8%)	23505 (3.2%)
Race/Ethnicity			
	46963 (21.1%)	33491 (6.6%)	80454 (11.0%)
Asian	17764 (8.0%)	67925 (13.4%)	85689 (11.8%)
Black or African American	30766 (13.8%)	64606 (12.8%)	95372 (13.1%)
Hispanic	12607 (5.7%)	32736 (6.5%)	45343 (6.2%)
Native American	1634 (0.7%)	3700 (0.7%)	5334 (0.7%)
Native Hawaiians and Pacific Islanders	13004 (5.8%)	23574 (4.7%)	36578 (5.0%)
Other	428 (0.2%)	982 (0.2%)	1410 (0.2%)
White	99241 (44.6%)	278749 (55.1%)	377990 (51.9%)
Urban			
	64300 (28.9%)	113706 (22.5%)	178006 (24.4%)
Rural	15599 (7.0%)	24606 (4.9%)	40205 (5.5%)
Urban	142508 (64.1%)	367451 (72.7%)	509959 (70.0%)
High deductible insurance plan			
No	210159 (94.5%)	486585 (96.2%)	696744 (95.7%)
Yes	12248 (5.5%)	19178 (3.8%)	31426 (4.3%)
BMI			
Mean (SD)	28.9 (7.02)	29.0 (6.80)	29.0 (6.85)
Median [Min, Max]	27.7 [15.0, 87.8]	27.9 [15.0, 89.9]	27.8 [15.0, 89.9]

Missing	70527 (31.7%)	61369 (12.1%)	131896 (18.1%)
Obesity			
	70527 (31.7%)	61369 (12.1%)	131896 (18.1%)
Normal	46754 (21.0%)	128524 (25.4%)	175278 (24.1%)
Obese class I	30202 (13.6%)	90576 (17.9%)	120778 (16.6%)
Obese class II and higher	25178 (11.3%)	72543 (14.3%)	97721 (13.4%)
Overweight	48060 (21.6%)	149174 (29.5%)	197234 (27.1%)
Underweight	1686 (0.8%)	3577 (0.7%)	5263 (0.7%)
Systolic BP			
Mean (SD)	124 (16.8)	125 (17.1)	125 (17.1)
Median [Min, Max]	122 [55.0, 257]	124 [51.0, 245]	124 [51.0, 257]
Missing	47596 (21.4%)	24992 (4.9%)	72588 (10.0%)
Diastolic BP			
Mean (SD)	72.3 (12.0)	73.1 (11.8)	72.9 (11.8)
Median [Min, Max]	72.0 [22.0, 160]	73.0 [20.0, 160]	72.0 [20.0, 160]
Missing	47596 (21.4%)	24992 (4.9%)	72588 (10.0%)
Creatinine			
Mean (SD)	0.892 (0.336)	0.889 (0.330)	0.890 (0.332)
Median [Min, Max]	0.860 [0.160, 24.7]	0.860 [0.100, 27.6]	0.860 [0.100, 27.6]
Missing	104867 (47.2%)	102901 (20.3%)	207768 (28.5%)
Smoke			
	47851 (21.5%)	24741 (4.9%)	72592 (10.0%)
Current	24509 (11.0%)	43537 (8.6%)	68046 (9.3%)
Former	29872 (13.4%)	101618 (20.1%)	131490 (18.1%)
Never	120175 (54.0%)	335867 (66.4%)	456042 (62.6%)
Comorbidity sum			
Mean (SD)	0.244 (0.663)	0.429 (0.830)	0.373 (0.788)
Median [Min, Max]	0 [0, 11.0]	0 [0, 11.0]	0 [0, 11.0]
Charlson Comorbidity Index score			
Mean (SD)	0.294 (0.892)	0.540 (1.18)	0.465 (1.10)
Median [Min, Max]	0 [0, 16.0]	0 [0, 19.0]	0 [0, 19.0]
Comorbidity Number			
>=2	8640 (3.9%)	41609 (8.2%)	50249 (6.9%)
0	183745 (82.6%)	357332 (70.7%)	541077 (74.3%)
1	30022 (13.5%)	106822 (21.1%)	136844 (18.8%)
Ambulatory Care Visits, 2019			
Mean (SD)	3.78 (9.04)	6.50 (11.1)	5.67 (10.6)
Median [Min, Max]	1.00 [0, 376]	3.00 [0, 538]	3.00 [0, 538]
Social Vulnerability Index			
Mean (SD)	0.323 (13.1)	0.361 (9.84)	0.350 (10.9)
Median [Min, Max]	0.493 [-999, 1.00]	0.444 [-999, 1.00]	0.461 [-999, 1.00]
Missing	64299 (28.9%)	113704 (22.5%)	178003 (24.4%)

Table 2. Number of Events and Person Time for Each Vaccination Group

Diabetes event	Vaccine Status		
	Not Vaccinated (N= 222407)	Vaccinated (N=505763)	Total
Diabetes			
Outpatient	2605 (13.91%)	16125 (86.09%)	18730
Inpatient	199 (26.64%)	548 (73.36%)	747
Censor	214715 (30.70%)	484585 (69.30%)	699300
Death	4888 (52.04%)	4505 (47.96%)	9393
Total Person-days	135220074	474460760	609680834

Figure 2. Kaplan Meier Plot of Diabetes-free Survival by Vaccination Status Not Adjusting for Other Covariates

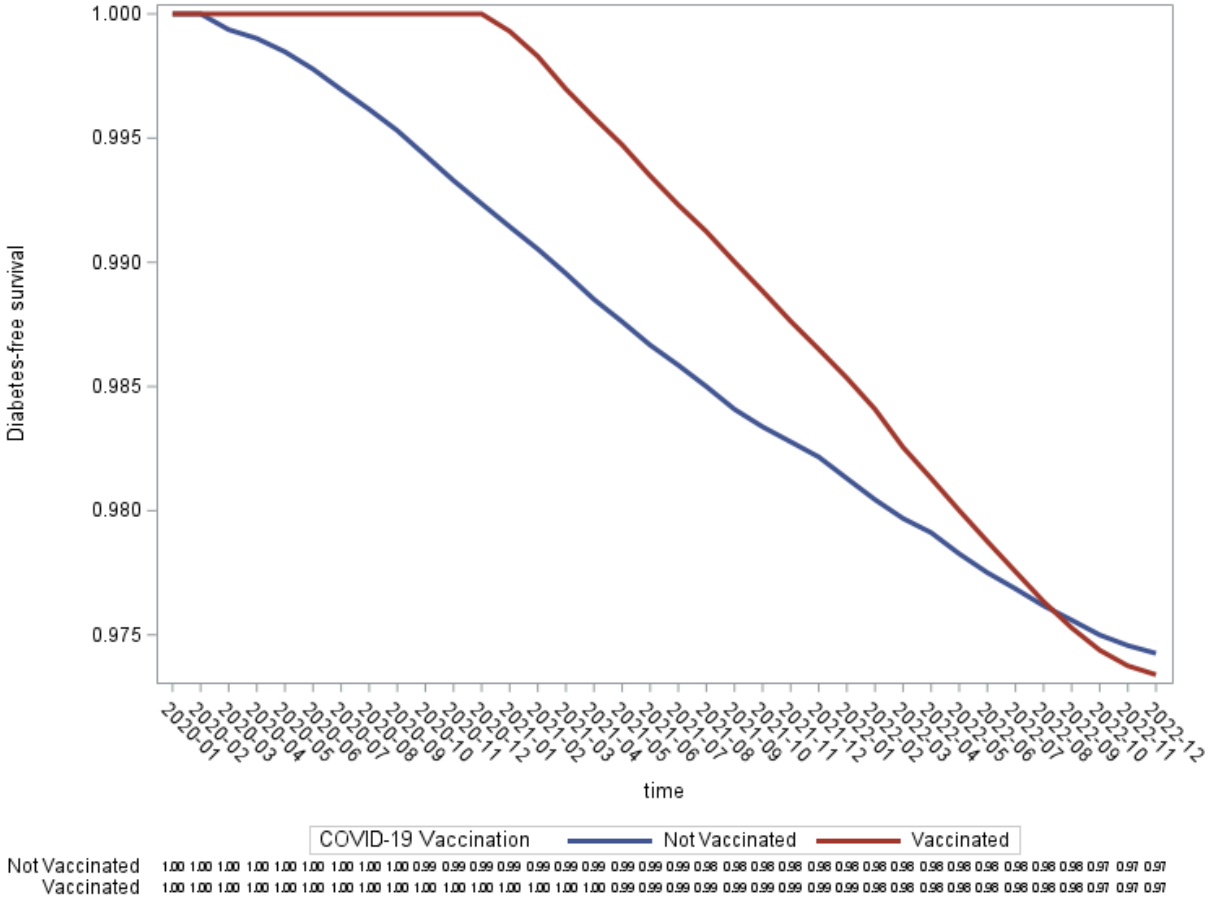

Table 3. Distribution of Occurrence of New-onset Diabetes by Background Characteristics

			New-onset Diabetes		
Covariate	**Statistics**	**Level**	**No N=708693**	**Yes N=19477**	**Parametric P-value***
Region	N (Row %)	Georgia	185441 (96.79)	6141 (3.21)	**<.001**
		Northwest	376957 (97.69)	8914 (2.31)	
		Hawaii	146295 (97.07)	4422 (2.93)	
Vaccination	N (Row %)	No	219603 (98.74)	2804 (1.26)	**<.001**
		Yes	489090 (96.7)	16673 (3.3)	
COVID-19 Infection	N (Row %)	Outpatient	131952 (98.28)	2314 (1.72)	**<.001**
		Inpatient	3090 (91.39)	291 (8.61)	
Female	N (Row %)	Men	341086 (97.28)	9551 (2.72)	**0.012**
		Women	367607 (97.37)	9926 (2.63)	
Age Categories	N (Row %)	18-29	147282 (99.45)	808 (0.55)	**<.001**
		30-44	190781 (98.15)	3598 (1.85)	
		45-64	247677 (96.11)	10024 (3.89)	
		65-79	100189 (95.9)	4278 (4.1)	
		80+	22736 (96.73)	769 (3.27)	
Race/Ethnicity	N (Row %)	White	369007 (97.62)	8983 (2.38)	**<.001**
		Black or African American	91706 (96.16)	3666 (3.84)	
		Hispanic	43903 (96.82)	1440 (3.18)	
		Asian	82896 (96.74)	2793 (3.26)	
		Native American	5149 (96.53)	185 (3.47)	
		Native Hawaiians and Pacific Islanders	35058 (95.84)	1520 (4.16)	
		Other	1388 (98.44)	22 (1.56)	
Urban	N (Row %)	Rural	39157 (97.39)	1048 (2.61)	**0.017**
		Urban	495622 (97.19)	14337 (2.81)	
High deductible insurance plan	N (Row %)	No	677797 (97.28)	18947 (2.72)	**<.001**
		Yes	30896 (98.31)	530 (1.69)	
Obesity	N (Row %)	Underweight	5228 (99.33)	35 (0.67)	**<.001**
		Normal	173755 (99.13)	1523 (0.87)	
		Overweight	193137 (97.92)	4097 (2.08)	
		Obese class I	115817 (95.89)	4961 (4.11)	
		Obese class II and higher	90782 (92.9)	6939 (7.1)	
Smoke	N (Row %)	Never	444398 (97.45)	11644 (2.55)	**<.001**

		Former	126683 (96.34)	4807 (3.66)	
		Current	65897 (96.84)	2149 (3.16)	
Comorbidity Number	N (Row %)	0	529062 (97.78)	12015 (2.22)	**<.001**
		1	132186 (96.6)	4658 (3.4)	
		>=2	47445 (94.42)	2804 (5.58)	

* The parametric p-value is calculated by ANOVA for numerical covariates and chi-square test for categorical covariates.

Table 4. Unadjusted Cox Time-Variant PH Model Results Testing the Association between Vaccination and New-Onset Diabetes

Parameter	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Vaccination	0.89904	0.02882	972.9027	<.0001	2.457	2.322	2.600

Table 5. Fully Adjusted Cox Time-Variant PH Model Results Testing the Association between Vaccination and New-Onset Diabetes

Parameter		Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Vaccination		0.12887	0.07719	2.7876	0.0950	1.138	0.978	1.323
Region (Georgia)	Hawaii	-0.60749	0.16009	14.3996	0.0001	0.545	0.398	0.745
	Northwest	-0.48422	0.07277	44.2759	<.0001	0.616	0.534	0.711
COVID-19 Infection (Outpatient)	Inpatient	0.79719	0.10603	56.5263	<.0001	2.219	1.803	2.732
Female		-0.27319	0.06121	19.9226	<.0001	0.761	0.675	0.858
Age		0.01594	0.00235	46.1812	<.0001	1.016	1.011	1.021
Race/Ethnicity (White)	Asian	0.59386	0.12749	21.6975	<.0001	1.811	1.411	2.325
	Black or African American	0.14737	0.08387	3.0875	0.0789	1.159	0.983	1.366
	Hispanic	0.63177	0.09599	43.3155	<.0001	1.881	1.558	2.270
	Native American	0.48319	0.27055	3.1896	0.0741	1.621	0.954	2.755
	Native Hawaiians and Pacific Islanders	0.68017	0.19263	12.4681	0.0004	1.974	1.353	2.880
	Other	0.53068	0.70900	0.5602	0.4542	1.700	0.424	6.823
Urban (Rural)	Urban	0.31394	0.17448	3.2374	0.0720	1.369	0.972	1.927
High deductible insurance plan (No)	Yes	-0.01108	0.19227	0.0033	0.9540	0.989	0.678	1.442
BMI		0.03158	0.00611	26.7047	<.0001	1.032	1.020	1.045
Obesity (Normal)	Obese class I	0.88268	0.12990	46.1727	<.0001	2.417	1.874	3.118
	Obese class II and higher	1.16367	0.16186	51.6871	<.0001	3.202	2.331	4.397
	Overweight	0.47898	0.12136	15.5782	<.0001	1.614	1.273	2.048
	Underweight	-0.52243	1.00589	0.2697	0.6035	0.593	0.083	4.259
Systolic BP		0.00304	0.00222	1.8726	0.1712	1.003	0.999	1.007
Diastolic BP		0.00875	0.00313	7.7906	0.0053	1.009	1.003	1.015
Creatinine_first		-0.03392	0.06754	0.2522	0.6155	0.967	0.847	1.103
Smoke (Never)	Current	0.28198	0.10152	7.7155	0.0055	1.326	1.087	1.618
	Former	0.08254	0.06771	1.4862	0.2228	1.086	0.951	1.240
Comorbidity Sum		0.11386	0.10266	1.2300	0.2674	1.121	0.916	1.370
Charlson score		-0.02802	0.05985	0.2192	0.6397	0.972	0.865	1.093
Comorbidity Number (0)	1	-0.07791	0.09344	0.6953	0.4044	0.925	0.770	1.111

	>=2	-0.19824	0.20009	0.9816	0.3218	0.820	0.554	1.214
Exercise		-0.0003431	0.0002060	2.7739	0.0958	1.000	0.999	1.000
Number of Ambulatory Visits 2019		0.00440	0.00144	9.2661	0.0023	1.004	1.002	1.007
Social Vulnerability Index Percentile		0.24249	0.10919	4.9318	0.0264	1.274	1.029	1.579

References

Aberer, F., Moser, O., Aziz, F., Sourij, C., Ziko, H., Lenz, J., Abbas, F., Obermayer, A. M., Kojzar, H., Pferschy, P. N., Müller, A., Unteregger, C., Leitner, M., Banfic, T., Eckstein, M. L., Wachsmuth, N., Kaser, S., Mader, J. K., Tripolt, N. J., … for the COVAC-DM Study Group. (2021). Impact of COVID-19 Vaccination on Glycemia in Individuals With Type 1 and Type 2 Diabetes: Substudy of the COVAC-DM Study. *Diabetes Care*, *45*(2), e24–e26. https://doi.org/10.2337/dc21-1563

Baden, L. R., El Sahly, H. M., Essink, B., Kotloff, K., Frey, S., Novak, R., Diemert, D., Spector, S. A., Rouphael, N., Creech, C. B., McGettigan, J., Khetan, S., Segall, N., Solis, J., Brosz, A., Fierro, C., Schwartz, H., Neuzil, K., Corey, L., … COVE Study Group. (2021). Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *The New England Journal of Medicine*, *384*(5), 403–416. https://doi.org/10.1056/NEJMoa2035389

Centers for Disease Control and Prevention/ Agency for Toxic Substances and Disease Registry/ Geospatial Research, Analysis, and Services Program. (2020). *CDC/ATSDR Social Vulnerability Index*.

Ceriello, A., & Prattichizzo, F. (2021). Variability of risk factors and diabetes complications. *Cardiovascular Diabetology*, *20*(1), 101. https://doi.org/10.1186/s12933-021-01289-4

Făgărășan, I., Rusu, A., Cristea, M., Bala, C.-G., Vulturar, D.-M., Cristea, C., & Todea, D.-A. (2022). Predictors of New-Onset Diabetes in Hospitalized Patients with SARS-CoV-2 Infection. *International Journal of Environmental Research and Public Health*, *19*(20), 13230. https://doi.org/10.3390/ijerph192013230

He, Y.-F., Ouyang, J., Hu, X.-D., Wu, N., Jiang, Z.-G., Bian, N., & Wang, J. (2023). Correlation between COVID-19 vaccination and diabetes mellitus: A systematic review. *World Journal of Diabetes*, *14*(6), 892–918. https://doi.org/10.4239/wjd.v14.i6.892

Hromić-Jahjefendić, A., Barh, D., Uversky, V., Aljabali, A. A., Tambuwala, M. M., Alzahrani, K. J., Alzahrani, F. M., Alshammeri, S., & Lundstrom, K. (2023). Can COVID-19 Vaccines Induce Premature Non-Communicable Diseases: Where Are We Heading to? *Vaccines*, *11*(2), 208. https://doi.org/10.3390/vaccines11020208

Hsieh, T. Y. J., Chang, R., Yong, S.-B., Liao, P.-L., Hung, Y.-M., & Wei, J. C.-C. (2023). COVID-19 Vaccination Prior to SARS-CoV-2 Infection Reduced Risk of Subsequent Diabetes Mellitus: A Real-World Investigation Using U.S. Electronic Health Records. *Diabetes Care*, *46*(12), 2193–2200. https://doi.org/10.2337/dc23-0936

Joob, B., & Wiwanitkit, V. (2023). COVID-19 vaccination and diabetic ketoacidosis. *World Journal of Diabetes*, *14*(5), 560–564. https://doi.org/10.4239/wjd.v14.i5.560

Kwan, A. C., Ebinger, J. E., Botting, P., Navarrette, J., Claggett, B., & Cheng, S. (2023). Association of COVID-19 Vaccination With Risk for Incident Diabetes After COVID-19 Infection. *JAMA Network Open*, *6*(2), e2255965–e2255965. https://doi.org/10.1001/jamanetworkopen.2022.55965

Lim, S., Bae, J. H., Kwon, H.-S., & Nauck, M. A. (2021). COVID-19 and diabetes mellitus: From pathophysiology to clinical management. *Nature Reviews. Endocrinology*, *17*(1), 11–30. https://doi.org/10.1038/s41574-020-00435-4

National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Board on Health

Sciences Policy; Committee on Equitable Allocation of Vaccine for the Novel Coronavirus. (2020). *Framework for Equitable Allocation of COVID-19 Vaccine* (B. Kahn, L. Brown, W. Foege, & H. Gayle, Eds.). National Academies Press (US). http://www.ncbi.nlm.nih.gov/books/NBK562672/

Nørgård, B. M., Zegers, F. D., Juhl, C. B., Kjeldsen, J., & Nielsen, J. (2023). Diabetes mellitus and the risk of post‐acute COVID‐19 hospitalizations—A nationwide cohort study. *Diabetic Medicine*, *40*(2), e14986. https://doi.org/10.1111/dme.14986

Puig-Domingo, M., Marazuela, M., Yildiz, B. O., & Giustina, A. (2021). COVID-19 and endocrine and metabolic diseases. An updated statement from the European Society of Endocrinology. *Endocrine*, *72*(2), 301–316. https://doi.org/10.1007/s12020-021-02734-w

Tancredi, S., Cullati, S., & Chiolero, A. (2022). [Surveillance bias: When appearances are misleading]. *Revue Medicale Suisse*, *18*(790), 1412–1415. https://doi.org/10.53738/REVMED.2022.18.790.1412

Vesco, K. K., Denoble, A., Lipkind, H. S., Kharbanda, E., Desilva, M. B., Daley, M. F., Getahun, D., Zerbo, O., Naleway, A., Jackson, L., Williams, J., Boyce, T. G., Fuller, C., & Vazquez Benitez, G. (2023). 1184-P: No Increased Risk of Gestational Diabetes Mellitus (GDM) Diagnosis after COVID-19 Vaccination. *Diabetes*, *72*(Supplement_1). https://doi.org/10.2337/db23-1184-P

Wu, Y., Ding, Y., Tanaka, Y., & Zhang, W. (2014). Risk Factors Contributing to Type 2 Diabetes and Recent Advances in the Treatment and Prevention. *International Journal of Medical Sciences*, *11*(11), 1185–1200. https://doi.org/10.7150/ijms.10001

Xiong, X., Lui, D. T. W., Chung, M. S. H., Au, I. C. H., Lai, F. T. T., Wan, E. Y. F., Chui, C. S. L., Li, X., Cheng, F. W. T., Cheung, C.-L., Chan, E. W. Y., Lee, C. H., Woo, Y. C., Tan, K. C. B., Wong, C. K. H., & Wong, I. C. K. (2023). Incidence of diabetes following COVID-19 vaccination and SARS-CoV-2 infection in Hong Kong: A population-based cohort study. *PLOS Medicine*, *20*(7), e1004274. https://doi.org/10.1371/journal.pmed.1004274

Yan, V. K. C., Wan, E. Y. F., Ye, X., Mok, A. H. Y., Lai, F. T. T., Chui, C. S. L., Li, X., Wong, C. K. H., Li, P. H., Ma, T., Qin, S., Wong, V. K. C., Tsang, T. C., Tsui, S. H., Chui, W. C. M., Cowling, B. J., Leung, G. M., Lau, C. S., Wong, I. C. K., & Chan, E. W. Y. (n.d.). Effectiveness of BNT162b2 and CoronaVac vaccinations against mortality and severe complications after SARS-CoV-2 Omicron BA.2 infection: A case–control study. *Emerging Microbes & Infections*, *11*(1), 2304–2314. https://doi.org/10.1080/22221751.2022.2114854