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Evaluating the Risk of Adverse Events After COVID-19 Diagnosis

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List of Acronyms and Abbreviations

AE	adverse event
AESI	adverse event of special interest
AMI	acute myocardial infarction
ASD	absolute standardized difference
BEST	Biologics Effectiveness and Safety
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CKD	chronic kidney disease
COVID-19	coronavirus disease 2019
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
ED	emergency department
ESRD	end-stage renal disease
FDA	US Food and Drug Administration
GBS	Guillain-Barré syndrome
HIV	human immunodeficiency virus
HR	hazard ratio
HS	hemorrhagic stroke
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, 10th Revision, Procedure Coding System
ITP	immune thrombocytopenia
LTC	long-term care
MSA	metropolitan statistical area
PE	pulmonary embolism
Q1, Q3	first and third quartiles
RI	relative incidence
RR	risk ratio
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCRI	self-controlled risk interval
SD	standard deviation
sIPT	stabilized inverse probability of treatment
sIPTW	stabilized inverse probability of treatment weighted
SNF	skilled nursing facility
SSD	Shared Systems Data
TTS	thrombosis with thrombocytopenia syndrome
US	United States
VAERS	Vaccine Adverse Event Reporting System

Executive Summary

Background and Introduction

The coronavirus disease 2019 (COVID-19) pandemic is a global outbreak caused by the novel strain of coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with transmission well established and ongoing in the United States (US) and other countries throughout the world. COVID-19 severity may range from asymptomatic to fatal and may be associated with a variety of sequelae. There is currently a lack of data from large US data sources quantifying the risk of many known or potential adverse events (AEs) associated with COVID-19. A number of these AEs are currently monitored after exposure to COVID-19 vaccines by the US Food and Drug Administration (FDA) and in other ongoing studies in large administrative claims databases as part of active surveillance of COVID-19 vaccines. Thus, we aimed to assess the risk of AEs after a COVID-19 diagnosis before the first eligible COVID-19 vaccination in 2 large US data sources.

Study Objectives

The objective of this study was to estimate the association of 16 AEs with a COVID-19 diagnosis compared with not having a COVID-19 diagnosis in adults aged 18 years or older in the US.

Approach

Data Sources

This study was performed in 2 data sources participating in the FDA Center for Biologics Evaluation and Research (CBER) Biologics Effectiveness and Safety (BEST) Initiative: Merative™ MarketScan® Commercial Database and US Centers for Medicare & Medicaid Services Medicare fee-for-service data. Both are US administrative claims databases. All analyses were performed separately in the 2 databases following a common protocol.

Study Design and Definitions

This study used 2 study designs: (1) a cohort design comparing individuals with COVID-19 diagnoses and matched comparators without a COVID-19 diagnosis; and (2) a self-controlled risk interval (SCRI) design comparing a risk window immediately following COVID-19 diagnosis with reference windows within the same individuals before their COVID-19 diagnosis or after the risk window. The study population in MarketScan included adults aged 18 to 64 years; Medicare included individuals aged 65 years or older. The study period for the cohort design began on 1 April 2020 (the date the *International Classification of Diseases, Tenth Revision, Clinical Modification* [ICD-10-CM] code for COVID-19 was introduced), and the study period for the SCRI design began on 1 June 2020 (after healthcare utilization in the US returned to pre-pandemic levels after COVID-19-related disruptions). The study period for both designs ended on 10 December 2020, the day before the introduction of COVID-19 vaccines in the US.

The primary exposure of interest for both the cohort and SCRI designs was a recorded diagnosis of COVID-19. The date of the diagnosis was used as Time 0. For the cohort design, a comparator group of individuals without a COVID-19 diagnosis was identified through individual-level matching on calendar date and key demographic and clinical characteristics. For the SCRI design, periods of risk after the COVID-19 diagnosis exposure (the “risk window”) and comparator periods within the same individual (“reference windows”) were identified.

The outcomes of interest for this study included 16 AEs that have previously been identified, evaluated, or proposed as potential AEs associated with COVID-19 or COVID-19 vaccination. Adverse events included Guillain-Barré syndrome (GBS), Bell's palsy, encephalitis/encephalomyelitis, narcolepsy, appendicitis, nonhemorrhagic stroke, hemorrhagic stroke, acute myocardial infarction, myocarditis/pericarditis, deep vein thrombosis, pulmonary embolism (overall, and inpatient only), disseminated intravascular coagulation, immune thrombocytopenia, transverse myelitis, unusual site thrombosis with thrombocytopenia syndrome (TTS), and common site TTS. Covariates included baseline demographic characteristics, conditions identified as increasing an individual's risk of specific AEs, comorbidities, healthcare utilization, and other characteristics. Covariates were identified to describe patient characteristics in both the SCRI and cohort designs. Additionally, covariates were used to describe differences between exposure groups and were included in propensity score models in the cohort design.

Statistical Methods

In the cohort analyses, the overall incidence of each AE (with follow-up including Time 0) was evaluated and compared between the 2 exposure groups within AE-specific analysis sets defined after application of AE-specific exclusion criteria to the matched cohorts. Stabilized inverse probability of treatment (sIPT) weights were estimated and applied to address differences in measured covariates between groups. Weighted overall hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. Cumulative incidence curves and time period–specific HRs were estimated to describe changing risk over time. Negative control outcome analyses were performed with 4 outcomes to evaluate potential residual bias.

In the SCRI design, the overall occurrence of each AE during the AE-specific risk windows (including Time 0) after COVID-19 diagnosis was compared with the occurrence in pre- and postexposure reference windows separated from the risk window by pre- and postexposure buffers. Relative incidence (RI) and 95% CIs were estimated with conditional Poisson regression models; we used standard Poisson models, extended models accounting for outcome-dependent observation windows, and extended models adjusting for seasonality. Attributable risks were also estimated using the extended models accounting for outcome-dependent observation periods with adjustment for seasonality. Adverse events with high case fatality rates were not evaluated using the SCRI design because of violations of underlying assumptions of the SCRI design.

In both study designs, subgroup analyses were performed by sex, age group, immunocompromised status, hospitalization on Time 0, and calendar time (cohort design only). Also, sensitivity analyses were performed further excluding those with a previous diagnosis of pneumonia or lower respiratory tract infection to reduce the impact of potential misclassification of COVID-19 status. The risk of AEs on Time 0 was evaluated, and analyses were performed with alternative risk windows/follow-up periods (i.e., starting follow-up/risk period on day 1 rather than Time 0). Additionally in the SCRI, another analyses evaluated the RI in a 7-day pre-exposure window (i.e., during the pre-exposure buffer) and in the postexposure buffer because of uncertainty about the course of COVID-19 illness relative to the recorded diagnosis.

Results

The results generally suggested some association of a COVID-19 diagnosis with most AEs, although the strength of the overall estimates and consistency across AEs and data sources varies widely. HR estimates in the overall Medicare cohort analysis ranged from 0.59 (95% CI, 0.25-1.43) for transverse myelitis to 2.73 (95% CI, 2.43-3.07) for disseminated intravascular coagulation. In MarketScan, HR estimates ranged from 1.70 (95% CI, 0.28-10.19) for transverse myelitis to 10.69 (95% CI, 1.38-82.74) for Guillain-Barré syndrome. RI estimates in the overall Medicare SCRI analysis (extended, seasonality-adjusted model) ranged from 1.94 (95% CI, 1.71-

2.21) for Bell's palsy to 11.73 (95% CI, 10.05-13.69) for myocarditis/pericarditis. In MarketScan, RI estimates ranged from 1.87 (95% CI,1.08-3.26) for narcolepsy to 100.95 (95% CI, 67.05-151.97) for pulmonary embolism (restricted to inpatient diagnoses only). The highest and most consistent effect measure estimates were observed in the cardiac/thrombotic outcomes, including stroke, acute myocardial infarction, pulmonary embolism, myocarditis/pericarditis, deep vein thrombosis, thrombosis with thrombocytopenia syndrome, and disseminated intravascular coagulation. Neurologic or immune-mediated adverse events also showed strong to moderate associations with COVID-19 diagnosis, including Guillain-Barré syndrome and immune thrombocytopenia. Estimates for other AEs were milder, imprecise, or inconsistent across data sources and study designs.

There were large numbers of AEs identified on Time 0 for many outcomes; in the cohort analyses, the distribution of AEs between exposure groups varied, with larger numbers of AEs on Time 0 in the comparator group for more severe, hospitalized outcomes, and larger numbers of AEs on Time 0 in the COVID-19-diagnosed groups for AEs not requiring hospitalization. Additionally, subgroup analyses by hospitalization status on Time 0 also demonstrated strong heterogeneity; in the cohort analyses, those hospitalized on Time 0 were more likely to have AEs in the comparator group on Time 0, leading to lower HR estimates in that subgroup (the opposite effect was observed in the SCRI, with generally increased RI estimates in the hospitalized subgroup). For some AEs, the overall analyses suggested null associations or HR estimates below 1.00, but these findings were generally not robust across analyses; subgroup analyses or analyses with alternative risk periods addressing potential sources of bias (e.g., conditioning on hospitalization status resulting in overrepresentation of severe, hospitalized outcomes on Time 0) resulted in effect measure estimates suggesting some positive association. For other estimates with very large overall HR and SCRI estimates, alternative risk period analyses excluding Time 0 and starting follow-up on day 1 resulted in more attenuated HR and RI estimates.

Discussion

The study used 2 separate designs and differing analytic approaches in 2 large data sources with study populations that differed by age to estimate the association between a COVID-19 diagnosis and various AEs. Using 2 complementary approaches and a variety of sensitivity analyses, alternative risk periods, and subgroup analyses allowed evaluation of the associations while accounting for multiple potential issues, some of which may be unique to a time period of COVID-19-related healthcare disruptions. The results generally found increased risks of most AEs in overall analyses, but secondary, sensitivity, and subgroup analyses demonstrated some considerations related to AEs on Time 0 and hospitalization status affecting most AEs and both study designs. For many of the AEs analyzed, a substantial number of patients experienced an AE on the same day that they were diagnosed with COVID-19, and among those hospitalized on Time 0, a substantial number of comparators experienced an AE on the day they were matched to a patient with COVID-19. Additionally, a number of AE estimates showed paradoxical effect measure associations below 1.00 for COVID-19 diagnosis among patients who were hospitalized on Time 0. Alternative risk period analyses removing Time 0 (the day of the COVID-19 diagnosis or matching) from follow-up resulted in generally more attenuated estimates closer to the null, regardless of whether the overall estimate was above or below the null initially.

Conclusion

COVID-19 diagnoses were associated with multiple AEs, with strong and consistent associations noted for GBS, nonhemorrhagic stroke, hemorrhagic stroke, acute myocardial infarction, myocarditis/pericarditis, deep vein thrombosis, pulmonary embolism, disseminated intravascular coagulation, immune thrombocytopenia, and

common site TTS. Potential associations with the other AEs cannot be ruled out. The strengths of the observed associations varied somewhat by data source, study design, and analytic approach, but increases in relative and absolute risk were consistently observed with many AEs, particularly vascular/thrombotic events. For some of the more common AEs (e.g., thrombotic events in the older Medicare population), even relatively modest increased relative risks translated into larger absolute risks. These associations were only evaluated in the time period before the introduction of COVID-19 vaccines. Subsequent changes in predominant circulating viral variants, COVID-19 vaccinations, and healthcare utilization patterns may reduce the generalizability of these results to more recent time periods. However, these results suggest that COVID-19 diagnoses contributed to potentially large numbers of serious AEs in the US population.

1. Background

The coronavirus disease 2019 (COVID-19) pandemic is a global outbreak caused by the novel strain of coronavirus called SARS-CoV-2, with transmission well established and ongoing in the United States (US) and countries throughout the world. The first COVID-19 case was reported in China in December 2019,[1] and the first non–travel related US case was confirmed in February 2020 in a California resident.[2] COVID-19 initially spread aggressively throughout the US population, and cases could be severe in some individuals and high-risk groups.[3] COVID-19 ranged in severity from asymptomatic to fatal, and wide variations in individuals' perception of COVID-19 risk and severity have been demonstrated in the US.[4-7]

Multiple COVID-19 vaccines in the US have been granted emergency use authorization or approval. Post-authorization safety monitoring during the COVID-19 pandemic vaccination program aims to continuously evaluate the safety of COVID-19 vaccines to rapidly detect potential safety concerns. Inferential studies evaluate signals from monitoring programs, such as the US Food and Drug Administration (FDA) and US Centers for Disease Control and Prevention's (CDC) Vaccine Adverse Event Reporting System (VAERS), and FDA's active surveillance systems—the Biologics Effectiveness and Safety (BEST) Initiative. Inferential studies provide the analytical framework to assess the risk of adverse events (AEs) following immunization. Many of the postvaccination AEs being evaluated, either observed or hypothesized, may also be associated with COVID-19 illness. Previous studies from several countries have evaluated the association between various definitions of COVID-19 (e.g., COVID-19 hospitalization, diagnosis, or positive test) and select AEs using cohort,[8-14] case-control,[15] and self-controlled[10,13,14,16-18] study designs. These studies have demonstrated increased risks of numerous AEs[8-19] associated with COVID-19 in various populations. A number of these AEs are currently monitored after exposure to COVID-19 vaccines by FDA in large administrative claims databases as part of active safety surveillance. Additional evidence quantifying the risk of many known or potential AEs associated with COVID-19 illness is needed to provide context for the findings of vaccine safety surveillance activities and to inform the risk-benefit analyses of COVID-19 vaccines. Thus, we aimed to assess the risk of AEs after a COVID-19 diagnosis in adults in 2 large US data sources covering populations of different ages.

An accurate understanding of the potential sequelae of COVID-19 illness is important to inform public health messaging and mitigation strategies and contextualize the results from COVID-19 vaccine safety studies assessing the risk of AEs after COVID-19 vaccination.

2. Objective

The objective of this study was to estimate the risk of specified AEs associated with a COVID-19 diagnosis in adults aged ≥ 18 years in the US.

3. Methods

To accomplish the study objective, this study used 2 separate study designs: a cohort design comparing individuals with COVID-19 diagnoses and matched comparators without a prior COVID-19 diagnosis (methods described in Section 3.3); and a self-controlled risk interval (SCRI) design comparing a risk window after COVID-19 diagnosis with reference windows within the same individuals before the COVID-19 diagnosis and after the risk window (methods described in Section 3.4).

3.1. Data Sources

This study was performed in 2 administrative claims databases participating in the FDA CBER BEST Initiative: the Merative™ MarketScan® Commercial Database[i] and the US Centers for Medicare & Medicaid Services Medicare database. All analyses were performed separately in the 2 databases according to a common protocol.[20] The study included data from 2 April 2019 for the cohort or 2 June 2019 for the SCRI to 10 December 2020.

Diagnoses were identified with ICD-10-CM codes, and pharmacy dispensing of medications was identified with National Drug Codes. Procedures were assessed with Current Procedural Terminology, Healthcare Common Procedure Coding System, or *International Classification of Diseases, Tenth Revision, Procedure Coding System* (ICD-10-PCS) codes.

3.1.1. MarketScan Commercial Claims

The MarketScan Commercial Database contains person-level clinical utilization, expenditure, and enrollment information from inpatient, outpatient, prescription drug, and carve-out services (i.e., services managed under separate contracts than the primary plan). The MarketScan Commercial Database contains insurance claims and enrollment data for employees, Consolidated Omnibus Budget Reconciliation Act continuees, spouses, and dependents with employer-based commercial insurance from large employers, health plans, and government and public organizations throughout the US. Only those aged 18 to 64 years were included in the analyses for this data source.

3.1.2. US Medicare Fee-for-Service Claims

Medicare is a federal program providing health insurance coverage to individuals aged 65 years and older and individuals aged younger than 65 years who have end-stage renal disease (ESRD) or are disabled. This study used Medicare medical claims and enrollment data from individuals aged 65 years and older only with fee-for-service Medicare Part A (inpatient hospital care) and Part B (outpatient care and physician services). Medicare fee-for-service enrollment was assessed using the Medicare Enrollment Database and Common Medicare Environment, and individuals' medical services and diagnoses were assessed with the Shared Systems Data (SSD). Additionally, nursing home stays were identified through SSD and assessment data in the Minimum Data Set.

3.2. Definitions

Exposure, outcome, and covariate variables were consistent across the cohort and SCRI designs, which are described in Section 3.2.1, Section 3.2.2, and Section 3.2.3.

Details of the study populations, eligibility criteria, study designs, and analyses differed between the cohort and SCRI designs; they are described separately in Section 3.3 (cohort) and Section 3.4 (SCRI).

3.2.1. Exposure Assessment

The primary exposure of interest for both the cohort and SCRI designs was a recorded diagnosis of COVID-19 (ICD-10-CM code U07.1) in claims from inpatient, emergency department (ED), outpatient, or professional/provider claims, in any diagnosis position, but excluding hospital admitting diagnoses in Medicare; these initial diagnoses upon hospital presentation are typically less reliable than discharge diagnoses. The service date when the diagnosis was recorded, as appropriate for each source of data (e.g., the admission date for facility-level diagnoses, the service date for provider-level diagnoses) was considered as the

[i] Merative and MarketScan are trademarks of Merative Corporation in the US, other countries, or both.

diagnosis date. Validation studies have reported that the ICD-10-CM code for COVID-19 has reasonably high validity, particularly for hospitalized COVID-19.[21-30] However, some individuals with COVID-19 may not seek care and may not have received a recorded diagnosis of COVID-19 in a medical setting; thus, this study could only evaluate recorded COVID-19 diagnoses rather than all COVID-19 infections.

For the cohort design, a comparator group of individuals without a COVID-19 diagnosis was identified. For the SCRI design, periods of exposure (the "risk window") and nonexposure ("reference windows") were identified among individuals with a COVID-19 diagnosis (Section 3.4.2.4).

For both designs, the date of the COVID-19 diagnosis was Time 0 for the analysis, and eligibility criteria were evaluated relative to that date (Section 3.3.2.3; Section 3.4.2.3).

3.2.2. Outcome Definition and Assessment

The outcomes of interest for this study, along with their associated washout windows and risk windows, include those that have previously been identified, evaluated, or proposed as potential AEs after COVID-19 vaccination[31-34] so that the results of these studies may contribute to the interpretation of vaccine safety surveillance and inform benefit-risk evaluation of vaccines. Adverse events evaluated in this study, a description of the composite outcomes, and the required care settings, along with their proposed postexposure risk windows and washout windows (or "clean windows" before AE occurrence to ensure identification of a new-onset event) are shown in Table 1. Because some AEs may have high case fatality rates (approximately 10% or greater), violating a key assumption of the SCRI (Section 3.4.1), not all AEs were evaluated with the SCRI design. Some AEs were evaluated with the SCRI in MarketScan but not in Medicare due to higher case fatality rates in the older Medicare population compared to the younger commercially insured population in MarketScan.

AE-specific washout windows—time periods during which the AE is not permitted to occur to ensure identification of new-onset AEs—are also shown in Table 1. The cohort study applied the washout window before the date of COVID-19 diagnosis or matched Time 0 (exposure), and the SCRI applied the washout window before the date of the AE (outcome). The risk windows for the AEs shown in Table 1 all contain day 0 (i.e., Time 0, the date of the COVID-19 diagnosis in the exposed group) because some COVID-19 diagnoses may be identified within the same encounter as the AE secondary to individuals seeking care for the AE; this differs from many studies of AEs following receipt of COVID-19 vaccines that start the risk window on day 1 to ensure temporal ordering of vaccine and AEs.[33] However, analyses of alternative risk periods in both designs were performed evaluating the risk on Time 0 (the day of COVID-19 diagnosis or matched comparator date) and starting the risk window on day 1 (cohort, Section 3.3.3.4; SCRI, Section 3.4.3.3).

Table 1. Adverse Events and Their Associated Washout Windows and Risk Windows

Adverse events	Care setting	Washout window (days)	Risk window (days)	Evaluated with cohort design [a]	Evaluated with SCRI design, MarketScan	Evaluated with SCRI design, Medicare
Guillain-Barré syndrome	IP	[−365 to −1]	[0, 41]	X	X	X
Bell's palsy	IP, OP/PB	[−183 to −1]	[0, 41]	X	X	X
Encephalitis/encephalomyelitis	IP	[−183 to −1]	[0, 41]	X		
Narcolepsy	IP, OP/PB	[−365 to −1]	[0, 41]	X	X	X
Appendicitis	IP, OP-ED	[−365 to −1]	[0, 41]	X	X	X
Nonhemorrhagic stroke	IP	[−365 to −1]	[0, 27]	X		
Hemorrhagic stroke	IP	[−365 to −1]	[0, 27]	X		
Acute myocardial infarction	IP	[−365 to −1]	[0, 27]	X		
Myocarditis/pericarditis	IP, OP/PB	[−365 to −1]	[0, 41]	X	X	X
Deep vein thrombosis	IP, OP/PB	[−365 to −1]	[0, 27]	X	X	X
Pulmonary embolism [b]	IP	[−365 to −1]	[0, 27]	X	X	
Disseminated intravascular coagulation	IP, OP/PB	[−365 to −1]	[0, 27]	X	X	
Immune thrombocytopenia	IP, OP-ED	[−365 to −1]	[0, 41]	X	X	X
Transverse myelitis	IP, OP/PB	[−365 to −1]	[0, 41]	X	X	X
Unusual site thrombosis with thrombocytopenia syndrome ▪ Unusual site thrombosis (intracranial or intra-abdominal venous thrombosis, such as in portal, renal, and other veins) AND ▪ Thrombocytopenia within ≤ 14 days	Thrombosis: IP, OP-ED Thrombocytopenia: IP, OP/PB	[−365 to −1]	[0, 41]	X		
Common site thrombosis with thrombocytopenia syndrome ▪ Common site thrombosis (AMI, HS, NHS, DVT, PE) AND ▪ Thrombocytopenia within ≤ 14 days	AMI, HS, and NHS: IP DVT, PE, and thrombocytopenia: IP, OP/PB	[−365 to −1]	[0, 41]	X		

AMI = acute myocardial infarction; DVT = deep vein thrombosis; ED = emergency department; HS = hemorrhagic stroke; IP = inpatient; ITP = immune thrombocytopenia; NHS = nonhemorrhagic stroke; OP = outpatient; PB = professional/provider; PE = pulmonary embolism; SCRI = self-controlled risk interval.

[a] Evaluated with cohort design in both MarketScan and Medicare.

[b] Evaluated separately in inpatient settings only, and in any setting (in combined inpatient, outpatient, or provider claims settings).

3.2.3. Covariate Definitions and Assessment

Covariates were identified in individuals' data before and on Time 0. These variables were used to describe patient characteristics (both cohort and SCRI design), to describe differences between exposure groups (cohort design), and as covariates in propensity score models (cohort design). Covariates included demographic characteristics, conditions identified as increasing individuals' risk of specific AEs, comorbidities, healthcare utilization, and other characteristics relevant to exposure, outcome, and observation. All covariates were identified for each individual to describe the study population. Adverse event-specific risk factors and potential confounders were curated from the full list of covariates for inclusion in AE-specific propensity score models, as appropriate for each AE (Appendix A, Table A-2). Identified covariates included the following:

- Demographic characteristics on Time 0
    - Age (recorded both as a continuous variable and categorized as 18-34 years, 35-49 years, 50-64 years, 65-79 years, and ≥ 80 years)
    - Sex, as reported in database enrollment information
    - County and state of residence, Medicare; metropolitan statistical area (MSA) (or residence outside an MSA) and state of residence, MarketScan
    - US geographic region (Northeast, North Central, South, West, unknown)
    - Race or ethnicity (categorized as American Indian/Alaska Native, Asian, Black or African American, Hispanic/Latin American/Latinx, White, a race/ethnicity not listed, not provided) (available in Medicare only)
    - Dual Medicare/Medicaid eligibility status (available in Medicare only)
    - Reason for entering Medicare (aged-in, disability, ESRD) (available in Medicare only)
- Healthcare setting on Time 0
    - Hospitalization status on Time 0 (hospitalized on Time 0 in MarketScan; hospital admission date on Time 0 in Medicare)
    - Skilled nursing facility (SNF)/long-term care (LTC) status on Time 0 (identified in Medicare only)
- Conditions increasing individuals' risk of specific AEs, other comorbidities, and frailty indicators,[35] in the 365 days before Time 0 (unless otherwise noted)
    - Animal exposure/bites or rabies
    - Antiphospholipid syndrome
    - Autoimmune disorders (i.e., inflammatory bowel disease, multiple sclerosis, psoriasis, rheumatic arthritis, systemic lupus erythematosus, other)
    - Brain lesions related to secondary narcolepsy
    - Cancer
    - Chronic lymphocytic leukemia
    - Chronic kidney disease (CKD) or other renal disease (any CKD in MarketScan; CKD other than ESRD in Medicare)
    - ESRD (identified in Medicare only)
    - Chronic liver disease
    - Chronic lung diseases (e.g., asthma, chronic obstructive pulmonary disease, cystic fibrosis, pulmonary embolism)
    - Dementia or other neurologic conditions

- Diabetes mellitus, type 1 or 2
- Disseminated intravascular coagulation (DIC; this will serve as an exclusion criterion for analyses of DIC as an outcome, but will serve as a covariate for the analysis of other AEs)
- Heart conditions (e.g., heart failure, coronary artery disease, arrhythmias, rheumatic heart disease)
- Hemiplegia or paraplegia
- Herpes simplex virus infection
- Hypertension
- Immunocompromised state (i.e., human immunodeficiency virus [HIV], hematological malignancy, immune deficiency, solid malignancy, rheumatological/inflammatory disorder, organ transplant)
- Infections associated with Guillain-Barré syndrome (GBS) (i.e., *E. coli*, campylobacter, H. influenzae, Japanese encephalitis, Chikungunya, Zika, Varicella, hepatitis E, HIV, cytomegalovirus, M. pneumoniae, Epstein-Barr, influenza)
- Viral infections associated with immune thrombocytopenia (ITP) (i.e., varicella, HIV, cytomegalovirus)
- Infections associated with myocarditis/pericarditis[36,37] (i.e., adenovirus, campylobacter, coxsackieviruses, cytomegalovirus, diphtheria, echovirus, *E. coli*, Epstein-Barr, HIV, Lyme disease, parvovirus, rickettsia, rubella, staphylococcus, streptococcus, viral hepatitis)
- Inpatient surgery (evaluated in the 90 days before but not including Time 0)
- Lipid abnormality
- Mental health conditions
- Nutritional deficiencies
- Obese or severely obese
- Peripheral vascular disease
- Pneumonia or other lower respiratory tract infection
- Pregnancy (evaluated in the 280 days before and including Time 0, in MarketScan only)
- Sepsis
- Sickle cell disease or thalassemia
- Smoking/nicotine dependency
- Stroke or cerebrovascular disease
- Thromboembolism (this covariate has some overlap with some outcome definitions that also serve as outcome-specific exclusion criteria, but it will serve as a covariate for the analysis of other AEs)
- Thrombophilia
- Trauma (evaluated in the 90 days before but not including Time 0)
- Tuberculosis

- Healthcare utilization measured in the 365 days before Time 0
  - Inpatient hospital stays (0, 1-2, 3+)
  - ED visits (0, 1-2, 3+)
  - Outpatient visits (0, 1-2, 3-5, 6-10, 11+)
  - SNF/LTC stay (only SNF identified in MarketScan only)
  - Influenza vaccination

3.3. Cohort Design

3.3.1. Study Design

The cohort design identified an exposure group of individuals who were diagnosed with COVID-19, and a comparator group of individuals without a diagnosis of COVID-19 on or before their matching date with individual-level matching based on key demographic and clinical characteristics (Section 3.3.2.2).

3.3.2. Study Population

Adults aged 18 to 64 years with commercial insurance or aged 65 years or older enrolled in Medicare fee-for-service with an incident COVID-19 diagnosis (identified in inpatient or outpatient/provider claims settings) and matched individuals without a COVID-19 diagnosis were identified for the analyses. One overall, descriptive study cohort was identified within each database, and then individual outcome-specific analysis sets were identified for the analysis of each AE.

3.3.2.1. Study Period

The cohort entry period, the timeframe in which individuals were eligible to enter the study cohort and the timeframe during which all Time 0s must occur, began on 1 April 2020 (the date on which the ICD-10-CM code for COVID-19 [U07.1] was introduced) and ended on 10 December 2020 (the day before the first COVID-19 vaccine was authorized for use in the US), inclusive. This approach allowed for evaluation of AEs before the introduction of COVID-19 vaccines so that rates of AEs were unaffected by vaccine-related events.

For individuals included in the study cohort, additional data from before the cohort entry period—back to 2 April 2019 (i.e., 365 days before the earliest possible index date)—were used to evaluate eligibility criteria, washout windows, and covariates.

3.3.2.2. Cohort Entry

The exposure group (i.e., those with a COVID-19 diagnosis) was identified on the date of a COVID-19 diagnosis, and then a matched comparator group was identified.

Time 0 in the Exposure Group

Exposed individuals with a COVID-19 diagnosis were identified at their first recorded diagnosis of COVID-19 (Section 3.2.1) during the cohort entry period, and the date of the COVID-19 diagnosis became Time 0 for the exposure group. Eligibility criteria were evaluated relative to Time 0 (Section 3.3.2.3). All individuals meeting the eligibility criteria were included in the exposure group.

Matching for Comparator Group

Comparator individuals without a prior COVID-19 diagnosis were matched to individuals in the COVID-19-diagnosed group to account for changes in COVID-19 incidence, COVID-19 testing availability and practice, seasonality of AEs, healthcare utilization patterns, and individual risk of COVID-19 and AEs. Eligible comparator individuals were 1:1 exact matched, with replacement, to eligible exposure individuals on the following characteristics:

- Age, in years, in approximately 5-year increments (18-24 years, 25-29, 30-34, 35-39, etc.)
- Sex
- Geographic region of residence (county of residence or adjoining county in Medicare; MSA of residence and state or non-MSA residence and state in MarketScan)
- Immunocompromised status (yes/no)

- Hospitalization status on Time 0 (yes/no) (matched on admission date for Medicare; matched on evidence of any inpatient claims on Time 0 for MarketScan)
- SNF/LTC residence on Time 0 (yes/no) (identified in Medicare only)

Individuals with missing values for any of the matching variables were not matched. The exposed and comparator individuals successfully matched on the calendar date were included in the final matched cohort. The calendar date of Time 0 for the exposed individual was assigned as the calendar date of Time 0 for the matched comparator.

Comparator individuals were matched with replacement, and those who were successfully matched on a previous calendar date continued to be considered for the exposure and comparator groups on all future calendar dates on which they met eligibility criteria. Thus, a comparator individual may be selected multiple times for different COVID-19 exposed individuals who received a COVID-19 diagnosis on the same or different dates.

3.3.2.3. Eligibility Criteria

All eligibility criteria were evaluated relative to Time 0 for all members of the cohort in either exposure group (Figure 1).

Figure 1. Eligibility Assessment, Covariate Assessment, and Follow-up Windows Relative to Time 0 for the Cohort Design

AE = adverse event; COVID-19 = coronavirus disease 2019; LTC = long-term care; SNF = skilled nursing facility.

[a] Gaps in insurance coverage of a maximum of 31 days are permitted in MarketScan.

[b] Pregnancy status identified in MarketScan only.

[c] Adverse event-specific washout windows were applied only to analyses of individual AEs, not to the base study cohort.

[d] Bell's palsy and encephalitis/encephalomyelitis.

[e] All AEs other than Bell's palsy and encephalitis/encephalomyelitis.

[f] Occurrence of the event of interest or censoring at the earliest of the following: disenrollment from the database (gaps in insurance coverage of a maximum of 31 days are permitted in MarketScan); death (available in Medicare only); end of the study period (10 Dec 2020); or the day before COVID-19 diagnosis in comparators for both the comparator and the individual with COVID-19 to whom they were matched.

Note: The cohort entry period (the time during which all Time 0 dates must occur) began on 1 April 2020, but lookback periods may have extended before 1 April 2020, as far back as 2 April 2019.

To be eligible for inclusion, individuals must have met the following criteria:

- Inclusion criteria
    - Be aged ≥ 18 years and < 65 years on Time 0 in MarketScan; aged ≥ 65 years on Time 0 in Medicare fee-for-service
    - Had continuous enrollment in insurance plan for a minimum of 1 year before Time 0, days [−365 to −1] (gaps in insurance coverage of a maximum of 31 days were permitted only in MarketScan)
    - Had ≥ 1 healthcare claim in the year before Time 0, days [−365 to −1]
- Exclusion criteria
    - Had a diagnosis of COVID-19 or a diagnosis indicative of COVID-19 (e.g., COVID-19, SARS-associated coronavirus as the cause of disease, other coronavirus as the cause of disease) before Time 0 using all available study data back to 1 January 2020
    - Had a diagnosis of select respiratory infections potentially indicating COVID-19 (e.g., pneumonia due to SARS-associated coronavirus), between 20 February 2020 and Time 0, to exclude those with potential COVID-19 infections before COVID-19-specific coding was available

All eligible matched individuals were included in the overall matched cohort for descriptive analyses. Adverse event-specific washout windows were applied to the overall cohort to define AE-specific analysis sets (Section 3.2.2) for AE-specific analyses.

3.3.2.4. Follow-up

Follow-up for each AE began on Time 0, inclusive. Follow-up continued until the first occurrence of 1 of the following:

- First occurrence of the AE of interest
- Censoring for 1 of the following occurrences:
    - Disenrollment from the database (gaps in insurance coverage of a maximum of 31 days were permitted in MarketScan only)
    - Death (available in Medicare only)
    - End of the study period (10 December 2020)
    - The day before a diagnosis of COVID-19 (comparator group only); both members of a matched pair were censored when a comparator is censored because of a COVID-19 diagnosis to avoid disproportionate accumulation of follow-up time in later time periods in the exposure group

3.3.3. Statistical Methods

All statistical analyses were performed separately in each data source. Descriptive analyses were performed in the overall matched cohort, and AE-specific analyses were performed separately in AE-specific analysis sets.

3.3.3.1. Descriptive Analyses

Attrition of the study population by application of the eligibility criteria was reported. The characteristics of individuals with a COVID-19 diagnosis who were retained after matching and those who failed to match were reported.

The baseline covariates of the matched cohort were described by exposure group, after matching but before weighting. Continuous values were summarized by mean, standard deviation (SD), median, and first and third

quartiles (Q1, Q3). Categorical values were summarized with counts and percentages. Absolute standardized differences (ASDs)[38] were calculated for variables both before and after weighting to describe the relative balance of the covariates across exposure groups. For multilevel categorical variables, a single ASD value across all levels of the categorical variable was calculated.[39]

3.3.3.2. Analysis Sets

Adverse event-specific analysis sets were created as subsets of the overall matched cohort by excluding individuals with occurrence of the outcome of interest within the outcome-specific washout window before Time 0 (Table 2). This was done to ensure identification of only incident events occurring after Time 0 rather than continuing care for pre-existing conditions or recurrent events.

Table 2. Analysis Set for Each Specified Outcome and Definition

AE-specific analysis set	Those excluded from AE-specific analysis set
Guillain-Barré syndrome	Those with Guillain-Barré syndrome within 365 days before Time 0
Bell's palsy	Those with Bell's palsy within 183 days before Time 0
Encephalitis/encephalomyelitis	Those with encephalitis/encephalomyelitis within 183 days before Time 0
Narcolepsy	Those with narcolepsy within 365 days before Time 0
Appendicitis	Those with appendicitis within 365 days before Time 0
Nonhemorrhagic stroke	Those with nonhemorrhagic stroke within 365 days before Time 0
Hemorrhagic stroke	Those with hemorrhagic stroke within 365 days before Time 0
Acute myocardial infarction	Those with acute myocardial infarction within 365 days before Time 0
Myocarditis/pericarditis	Those with myocarditis/pericarditis within 365 days before Time 0
Deep vein thrombosis	Those with deep vein thrombosis within 365 days before Time 0
Pulmonary embolism[a]	Those with pulmonary embolism within 365 days before Time 0
Disseminated intravascular coagulation	Those with disseminated intravascular coagulation within 365 days before Time 0
Immune thrombocytopenia	Those with immune thrombocytopenia within 365 days before Time 0
Transverse myelitis	Those with transverse myelitis within 365 days before Time 0
Unusual site thrombosis with thrombocytopenia syndrome	Those with unusual site thrombosis with thrombocytopenia syndrome within 365 days before Time 0
Common site thrombosis with thrombocytopenia syndrome	Those with common site thrombosis with thrombocytopenia syndrome within 365 days before Time 0

AE = adverse event.

[a] Evaluated separately in inpatient settings only, and in combined inpatient, outpatient, or provider claims settings; both AE definitions were evaluated in the same analysis set.

Application of the AE-specific exclusion criteria may have resulted in the exclusion of an exposed or comparator individual while their corresponding matched pair is retained in the analysis set, thus breaking the matched pair. This situation was not expected to be problematic because most AE-specific exclusion criteria were expected to be rare,[34] and all matching factors were included in propensity score models to ensure that the balance of matching factors was retained after exclusions and weighting.

3.3.3.3. Outcome Analyses

Each specific AE was analyzed within the AE-specific analysis set (Table 2). For each AE, propensity scores were estimated using logistic regression with exposure group status on Time 0 as the response variable and the matching factors and prespecified covariates for each AE as the independent variables. Lists of AE-specific prespecified covariates include variables that are associated with both COVID-19 diagnosis and the AE,

selected based on risk factors and disease etiology (Appendix A, Table A-2). Propensity score distributions were plotted by exposure group to visualize the degree of overlap.

Stabilized inverse probability of treatment (sIPT) weights were calculated separately for each AE-specific analysis set from the AE-specific propensity scores[40] and were truncated below the 1st percentile and above the 99th percentile to reduce the influence of extreme weights. The distribution of the truncated sIPT weights was described by exposure group.[41] The ASD values were plotted before and after sIPT weighting in each analysis set to observe the covariate imbalance between exposure groups.

Kaplan-Meier estimates of survival over time were estimated in the crude and sIPT-weighted exposure and comparator groups.[42] Robust variance estimation was used to estimate the 95% confidence interval (CI) in the unweighted and sIPT-weighted cohorts to account for some individuals being included multiple times.[43] Cumulative incidence curves were plotted displaying the cumulative incidence estimates for each day of follow-up as 1 minus the Kaplan-Meier survival estimator and 95% CI.

Hazard ratios (HRs) and 95% CIs were estimated with Cox proportional hazards models. Weighted HRs and 95% CIs were estimated by applying the sIPT weights to the Cox model with robust sandwich variance estimators.

To evaluate potentially changing risk over time, daily cumulative incidence estimates and time-specific HRs were reported on Time 0 (to evaluate AEs occurring on the same day as COVID-19 diagnosis), on the end of the AE-specific risk period (either day 27 or 41, depending on the AE, Table 1), on day 90, and on day 180.

3.3.3.4. Secondary Analyses

Subgroup Analyses

Subgroup analyses evaluated the risk of each AE within the following subgroups:

- Sex
- Age group
    - 18-34 years
    - 35-49 years
    - 50-64 years
    - 65-79 years
    - ≥ 80 years
- Immunocompromised status
- Hospitalization on Time 0
- Calendar time period (corresponding to time periods of different healthcare utilization, testing practices or intensity[34,44]), defined as individuals who have Time 0 in the following date ranges:
    - 1 Apr 2020-31 May 2020
    - 1 Jun 2020-10 Dec 2020

Propensity scores and sIPT weights were re-estimated within each subgroup, and sIPT-weighted HRs were estimated.

Sensitivity Analysis With Expanded Exclusion Criteria

To assess the sensitivity of our results to potential misclassification of exposed cases as unexposed, we excluded anyone with a diagnosis of pneumonia or other lower respiratory tract infection with an unknown organism before Time 0 (days [1 January 2020, −1]) to reduce even further the potential inclusion of

individuals with undiagnosed COVID-19. The overall HRs and 95% CIs were estimated for each AE within the further restricted sample.

Alternative Follow-up Excluding Time 0

Some COVID-19 infections may be recognized and diagnosed because of patients seeking care for an AE, thus increasing the probability of co-occurring AE diagnoses on Time 0 with COVID-19 diagnoses that would have otherwise gone undiagnosed in the absence of an AE (i.e., reverse causality).[45] Additionally, because hospitalization status was a matching criterion, the matched, hospitalized patients in the comparator group without a COVID-19 diagnosis may be more likely to be hospitalized for serious events (such as the AEs being evaluated), with the diagnoses recorded on Time 0 (the day of hospital admission). To evaluate the potential impacts of these biases on Time 0, an analysis was performed in a new analysis set where Time 0 was removed from the follow-up period and was included in the outcome washout period, and follow-up began on day 1. For these alternate time period analyses, propensity scores and sIPT weights were re-estimated, as the composition of the analysis sets differed from the overall analyses. Overall and time period-specific analyses were performed for the alternative risk period analyses.

Negative Control Analysis

Negative control analyses were performed to investigate the possibility of residual unmeasured confounding by differences between the COVID-19-diagnosed group and the comparator group by healthcare-seeking behavior in which individuals who are likely to seek care for COVID-19 are also more likely to seek care for AEs, or by comorbidity status in which individuals at higher risk of COVID-19 are also at higher risk of AEs because of worse underlying health status. These analyses[46] evaluated the relationship between a COVID-19 diagnosis and AEs not expected to be caused by COVID-19 infection. The identified potential negative control outcomes were acute events, some of which have been used in other studies of vaccination safety/effectiveness or COVID-19 infection,[31,47] that included the following:

- Colonic diverticulitis
- Laceration of hand or finger
- Gout
- Arm/leg cellulitis

Incidence of each negative control outcome was evaluated separately in AE-specific analysis sets with AE-specific sets of covariates in propensity score models; thus, the adequacy of confounding control and bias reduction was evaluated in each AE-specific analysis set. The first occurrence of each negative control outcome was identified during all available follow-up in each AE-specific analysis set. HRs and 95% CIs were estimated for each negative control outcome in the overall time period in the crude and sIPT-weighted exposure groups. HR and 95% CI estimates consistent with an estimate other than 1.00 were considered non-null results, potentially suggestive of residual bias.

3.3.4. Statistical Power and Sample Size Determination

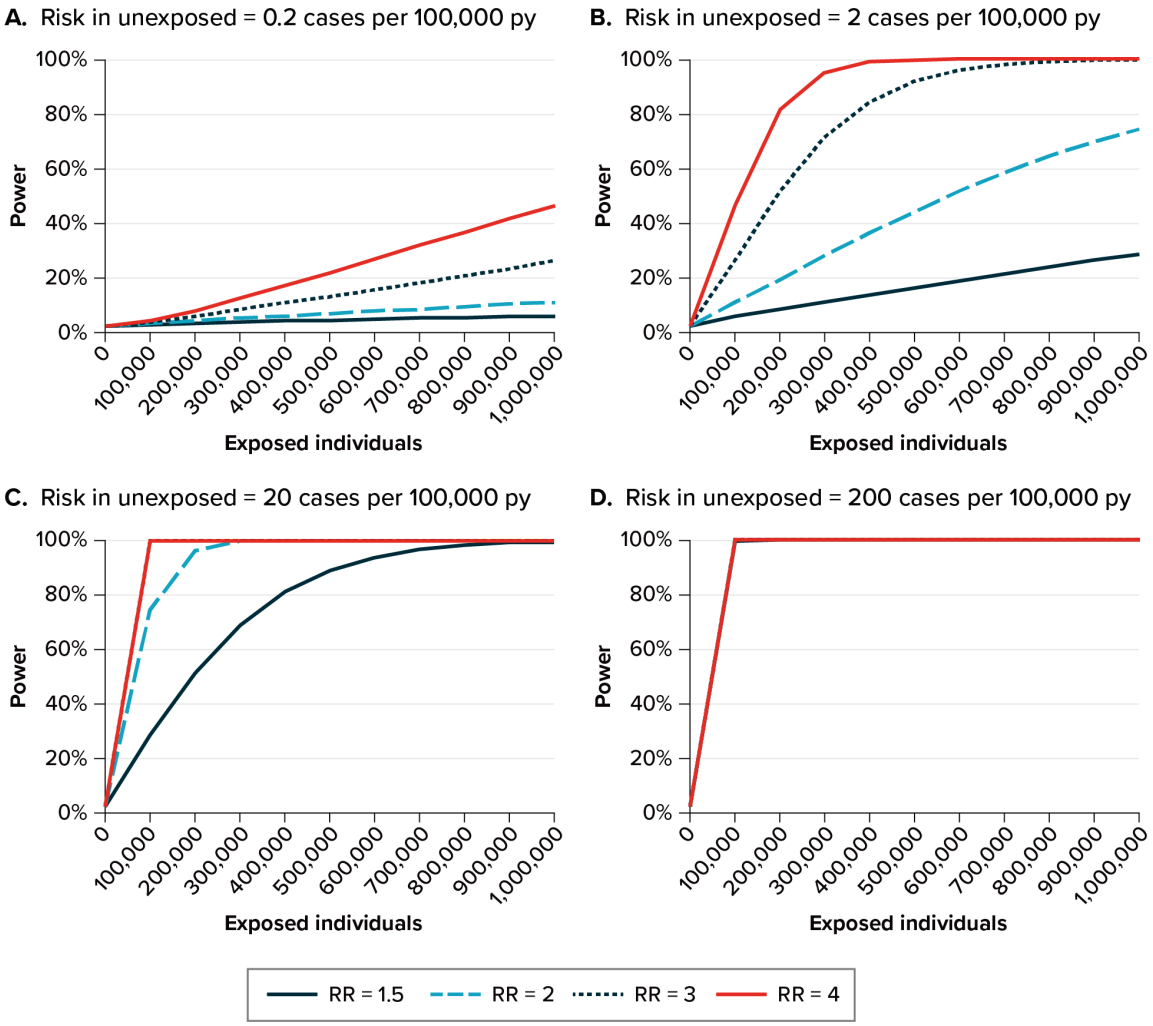
The analyses included all available observations that met the specified inclusion criteria (Section 3.3.2.3).[48] This study included a large number of outcomes with varying incidence and possible strengths of association. To estimate the precision of effect measure estimates for this study, precision estimates were based on the following assumptions:

- A range of potential effect measure estimates was assumed, with risk ratios (RRs) of 1.5, 2, 3, and 4.

- Power was estimated as the probability that the 95% CI would exclude a null value of 1.0 under the assumed RR size.
- A 1:1 ratio of exposure to comparator individuals is assumed because of the 1:1 matching used for selection into the primary study cohorts for the exposure versus comparator comparisons, with total assumed sample sizes (exposure and comparator groups combined) ranging up to 1,000,000 individuals.
- Assumptions of the baseline risk of outcomes in the comparator group were based on a recent evaluation of background rates of the AEs of interest in the MarketScan and Medicare fee-for-service databases.[34] Estimates were generated with expected annual incidence rates among the comparator group of 0.2, 2, 20, and 200 cases per 100,000 person-years.

Figure 2 displays the estimated power for various combinations of AE incidence rates, effect sizes, and sample sizes under these assumptions.

Figure 2. Estimated Power for Cohort Evaluations of Associations of COVID-19 Diagnosis With Adverse Events Under an Array of Possible Sample Sizes, Underlying Risks, and Strengths of Association



COVID-19 = coronavirus disease 2019; py = person-years; RR = risk ratio.

Note: In plots of 200 cases per 100,000 py, not all curves are visible because the plotted curves are generally overlapping.

3.4. Self-Controlled Risk Interval Design

3.4.1. Study Design

The SCRI is an exposure-anchored design that identifies individuals with a diagnosis of COVID-19; risk windows after the COVID-19 diagnosis and reference windows of nonexposure are then defined within the same individuals. The occurrences of the AEs during the risk windows after COVID-19 diagnosis were compared with the occurrence of AEs within reference windows from the same individual. The only individuals who contributed analytically to the SCRI analysis were those who had a COVID-19 diagnosis and experienced an AE during a risk or reference window.[49,50]

3.4.2. Study Population

Adults aged 18 to 64 years with commercial insurance, or those aged 65 years or older enrolled in Medicare fee-for-service with an incident COVID-19 diagnosis were identified for the SCRI analysis. One overall study population was identified, and then individual AE-specific analysis sets were identified including those who experienced the AE during the risk or reference windows.

3.4.2.1. Study Period

Individuals were eligible for inclusion in the SCRI analysis if they had a diagnosis of COVID-19 during the study entry period from 1 June 2020 to 10 December 2020, inclusive.

Disruptions in healthcare utilization early in the pandemic led to reduced recorded diagnoses of many conditions in the US.[34,44,51] Because one of the underlying assumptions of the SCRI is that characteristics, such as outcome misclassification, do not vary over time,[49] the study period was restricted to the time period after 1 June 2020, after incidence rates of most AEs based on healthcare claims information returned to pre-pandemic rates.[34,44] Similar to the cohort design, the study period ended before the introduction of the first COVID-19 vaccine in the US to avoid inclusion of vaccine-associated AE events in the analysis.

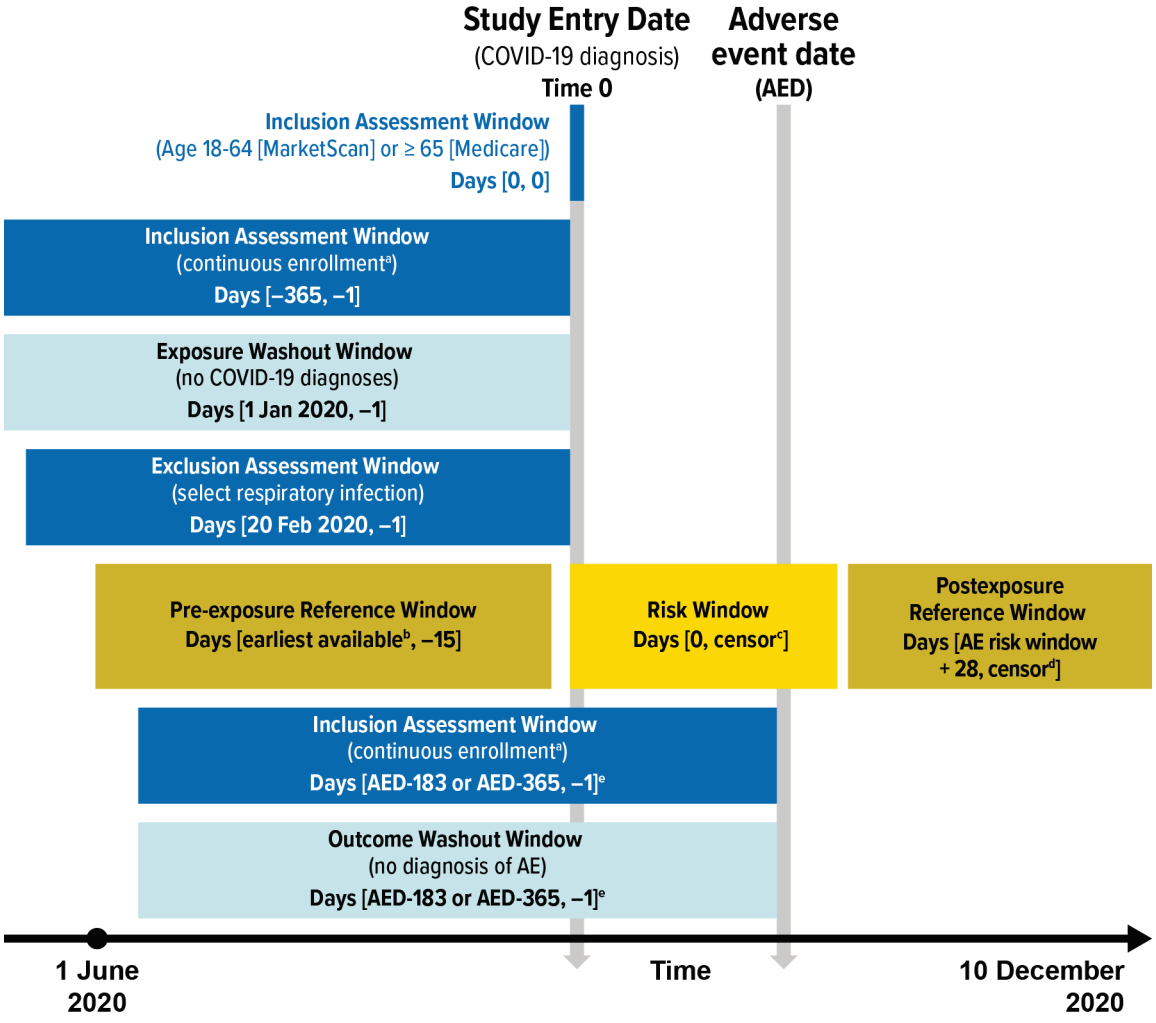
For individuals included in the SCRI study, additional data from before the study entry period—365 days before the first possible AE date—were used to evaluate eligibility criteria, washout windows, and covariates.

3.4.2.2. Study Entry

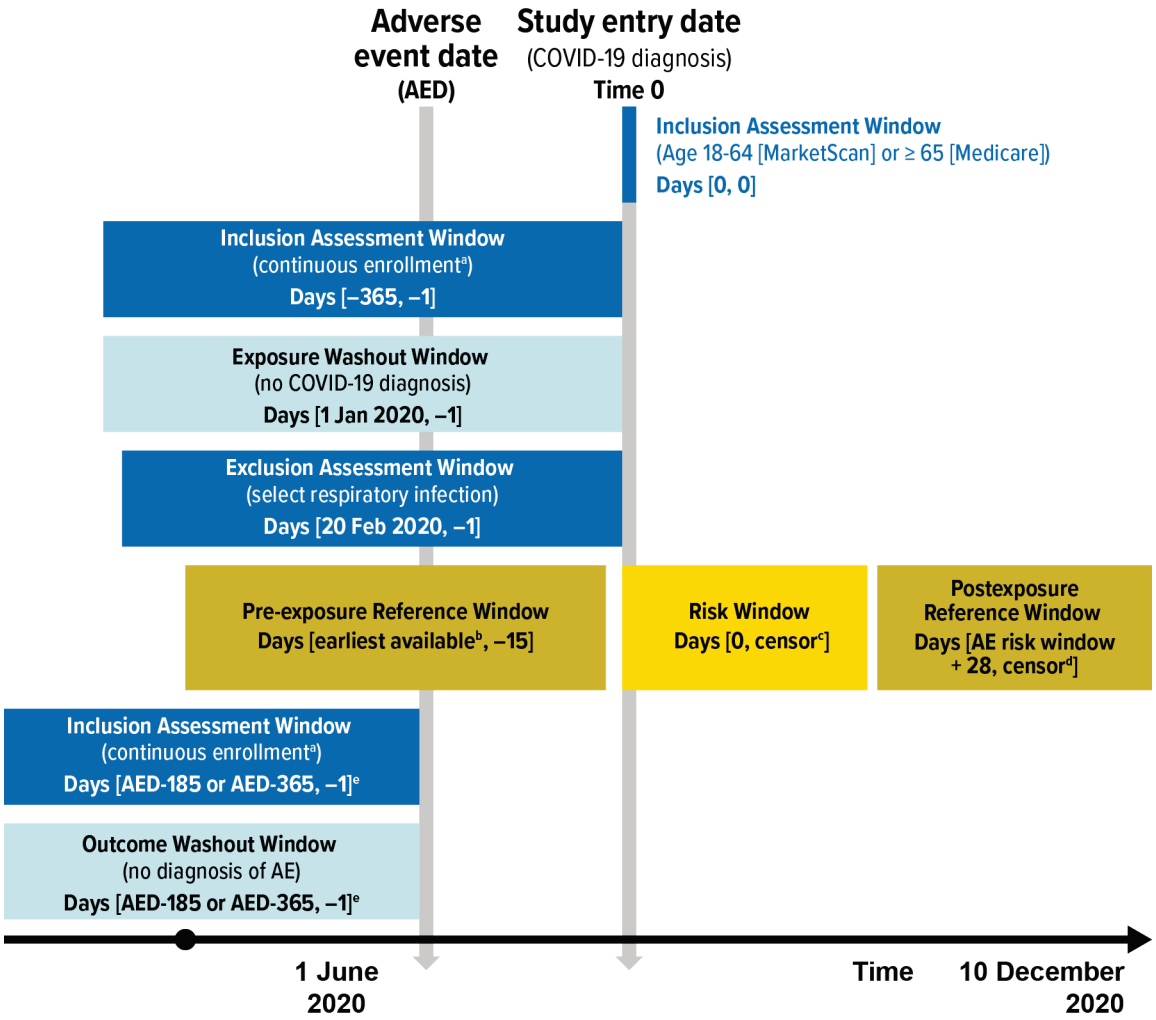
Individuals' first recorded diagnosis of COVID-19 (Section 3.2.1) during the cohort entry period was defined as Time 0. Eligibility criteria were evaluated relative to Time 0 (Figure 3), and all individuals meeting all eligibility criteria were included in the study population.

Figure 3. Eligibility Assessment, Covariate Assessment, Risk Windows, and Reference Windows Relative to Time 0 for the Self-Controlled Risk Interval Design

A. AE occurring after time 0 (in risk window or postexposure reference window)



B. AE occurring before time 0 (in pre-exposure reference window)



AE = adverse event; AED = adverse event date; COVID-19 = coronavirus disease 2019.

[a] Gaps of up to 31 days are permitted in MarketScan.

[b] Latest of the following: 365 days after the beginning of continuous enrollment; beginning of the study period (1 June 2020).

[c] Earliest of the following: end of the AE-specific risk window (Table 1); disenrollment from the database (gaps in insurance coverage of a maximum of 31 days were permitted); death (available in Medicare only); end of the study period (10 December 2020).

[d] Earliest of the following: 365 days; disenrollment from the database (gaps insurance coverage of a maximum of 31 days were permitted); death (available in Medicare only); end of the study period (10 December 2020).

[e] Length of AE-specific washout window varies by AE. See Table 1.

Note: Covariates for descriptive purposes were evaluated relative to Time 0 using the same process and assessment windows used for the cohort design (Section 3.2.3; Figure 1).

Note: The study entry period (the calendar time during which all Time 0 dates must have occurred) began on 1 June 2020. However, lookback periods may have extended before 1 June 2020.

3.4.2.3. Eligibility Criteria

The following eligibility criteria were evaluated relative to Time 0 (Figure 3) for entry into the SCRI study population:

- Inclusion criteria
  - Was aged ≥ 18 years and < 65 years on Time 0 in MarketScan; aged ≥ 65 years on Time 0 in Medicare fee-for-service.
  - Had continuous enrollment in insurance plan for a minimum of 1 year before Time 0, days [−365 to −1], to ensure adequate lookback time to evaluate all washout windows. Gaps in insurance coverage of a maximum of 31 days were permitted (MarketScan only).
  - Had at least 1 day of follow-up in the pre-exposure reference window (Section 3.4.2.4).
- Exclusion criteria
  - Had a diagnosis of COVID-19 or a diagnosis indicative of COVID-19 (e.g., COVID-19, SARS-associated coronavirus as the cause of disease, other coronavirus as the cause of disease) before Time 0 using all available study data back to 1 January 2020 [1 January 2020 to −1].
  - Had a diagnosis of select respiratory infection potentially indicating COVID-19 (e.g., pneumonia due to SARS-associated coronavirus), between 20 February 2020 and Time 0, [20 February 2020 to −1] to exclude those with potential COVID-19 infections before COVID-19 coding was available.

Each AE was evaluated separately in AE-specific analysis sets; additional AE-specific eligibility criteria were applied to the overall study population for each AE to determine eligibility for each analysis set, including the following:

- Inclusion criteria
  - Had an occurrence of the AE of interest during the AE-specific risk window (Table 1) or reference windows.
  - Had continuous enrollment in insurance plan for the duration of the AE-specific washout window (Table 1) before the date of the first occurrence of the AE in a risk or reference window, to ensure adequate lookback time to evaluate the washout windows. Gaps in insurance coverage of a maximum of 31 days were permitted (MarketScan only). Note that for AEs occurring in a pre-exposure reference window, this may have required more continuous enrollment than the 365-day criterion before Time 0.
- Exclusion criteria
  - Had an occurrence of the AE during the AE-specific washout window (Table 1) before the date of the AE.

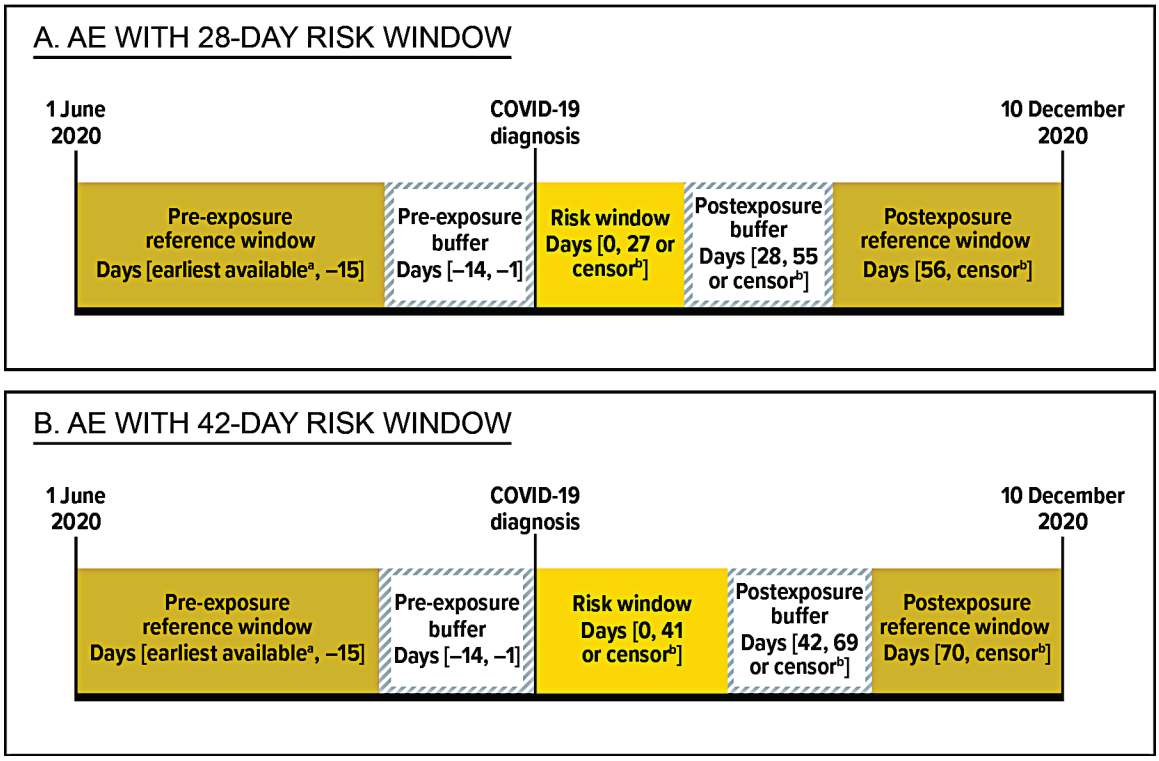
3.4.2.4. Risk and Reference Window Assignment

All of an individual's continuous enrollment in the database during the study period from 1 June 2020 through 10 December 2020 was assigned to risk windows, reference windows, and buffers (Figure 4), as follows:

- The pre-exposure reference window, beginning at the earliest possible date (later of 1 June 2020 or 365 days after beginning of continuous database enrollment) and ending 15 days before Time 0.

- A 14-day pre-exposure buffer before Time 0, as the timing of the onset of COVID-19 infection relative to the diagnosis date is unknown.
- The risk window, beginning on Time 0 (inclusive) and continuing until the end of the AE-specific risk window (Table 1).
- A 28-day postexposure buffer after the risk window, as the timing of resolution of COVID-19 infection relative to the diagnosis date is unknown.
- The postexposure reference window, beginning the day after the postexposure buffer until the end of available data (10 December 2020, end of continuous database enrollment), or until the censoring of having a COVID-19 diagnosis.

Figure 4. Assignment of Risk and Reference Windows Relative to COVID-19 Diagnosis (Time 0) for Adverse Events With 28-Day or 42-Day Risk Windows



AE = adverse event; COVID-19 = coronavirus disease 2019.

[a] Latest of the following: 1 June 2020 or 365 days after the beginning of continuous database enrollment.

[b] Earliest of the following: 365 days; disenrollment from the database (insurance coverage gaps of a maximum of 31 days were permitted in MarketScan only); death (available in Medicare only); end of the study period (10 December 2020); COVID-19 diagnosis.

3.4.2.5. Outcome Identification

One overall SCRI study population was identified, and the risk and reference windows were defined for all members of the study population; the occurrence of all AEs (Table 1) was identified during the risk windows, reference windows, and pre-AE washout windows. AEs occurring during pre-exposure or postexposure buffers were not included as outcomes for the SCRI, but they were considered as exclusion criteria if they occurred during a pre-AE washout window for an AE identified in the risk or reference windows. Subsequently, AE-specific analysis sets were defined as subsets of the overall study population based on the occurrence of AEs and AE-specific exclusion criteria.

3.4.3. Statistical Methods

All statistical analyses were performed separately in each data source. Descriptive analyses were performed in the overall cohort identified in each data source, but AE-specific analyses were performed separately in each AE-specific analysis set.

3.4.3.1. Descriptive Analyses

The attrition of the participants in the overall SCRI study population was described. Included individuals' demographic characteristics and healthcare setting were described. Continuous values were summarized by mean, SD, median, and first and third quartiles. Categorical values were summarized with counts and percentages.

For each AE, all individuals in the overall SCRI study population with the AE occurring during a risk or reference window were identified, and those without an AE occurring in a risk or reference window were excluded. For each identified event in a risk or reference window, previous occurrences of the event were evaluated during the AE-specific washout window (Table 1) anchored on the date of AEs occurring during the risk or reference windows (Figure 3) to ensure identification of new-onset AEs instead of continuing care for or recurrence of previous events. Those with a previous diagnosis of the AE occurring during the washout window were excluded from the AE-specific analysis set. The number of individuals in each AE-specific analysis set was reported, along with the count of individuals with AE events in a risk or reference window.

3.4.3.2. Outcome Analyses

Within each AE-specific analysis set, the relative incidence (RI) and 95% CI[50,52] for the association between the AE and a COVID-19 diagnosis was estimated using Poisson regression conditional on the number of events observed for each individual and accounting for the variable length of follow-up in the risk and reference windows.[45] Because some AEs may increase the risk of mortality, the assumption of having no event-dependent censoring may be violated,[45] an extended Poisson model accounting for event-dependent observation windows was used[53] to estimate RI and 95% CI. COVID-19 diagnosis itself may increase the risk of mortality and introduce exposure-dependent observation windows, thereby further violating the assumptions of the extended method.[45,54] Thus, both the extended Poisson model for event-dependent observation windows and standard conditional Poisson regression model were used. Additionally, a model using the extended method was further adjusted for seasonality by calendar month to account for potential seasonality and time trends in outcome incidence. For most AEs, conclusions from the SCRI are based on the results of the extended, seasonality-adjusted models to ensure that potential biases and time-varying confounding were addressed.

To contextualize the RI observed in the SCRI analysis, attributable risk (the number of excess cases of the AE observed because of COVID-19 diagnosis) was estimated using the following formula adapted from Yih and colleagues[55] and Ammann and colleagues[56]:

$$attributable\ risk = \frac{AE\ cases\ in\ risk\ window}{number\ of\ eligible\ COVID\text{-}19\ cases\ in\ analysis} \times \left(1 - \frac{1}{RI}\right)$$

Where *RI* is the RI estimated in the overall SCRI analysis.

3.4.3.3. Secondary Analyses

Subgroup Analyses

For AEs with sufficient case counts in each subgroup, the SCRI analysis using the extended Poisson model for event-dependent observation windows and adjusted for seasonality was repeated within the following subgroups:

- Sex, as reported in database enrollment information
    - Female
    - Male
- Age group
    - 18-34 years
    - 35-49 years
    - 50-64 years
    - 65-79 years
    - ≥ 80 years
- Immunocompromised status (measured in the 365 days before Time 0)
- Hospitalization status on Time 0

Sensitivity Analyses with Expanded Exclusion Criteria

To assess the sensitivity of our results to potential misclassification of exposed cases as unexposed, we applied additional exclusion criteria, further excluding anyone with a diagnosis of pneumonia or other lower respiratory tract infection with an unknown organism before Time 0 (days [1 Jan 2020, −1]), because these infection diagnoses may represent undiagnosed COVID-19, thus resulting in misspecification of the timing of the COVID-19 diagnosis. Within the more restricted population, the RI and 95% CI using the extended Poisson model for event-dependent observation windows and adjusted for seasonality were estimated for each AE.

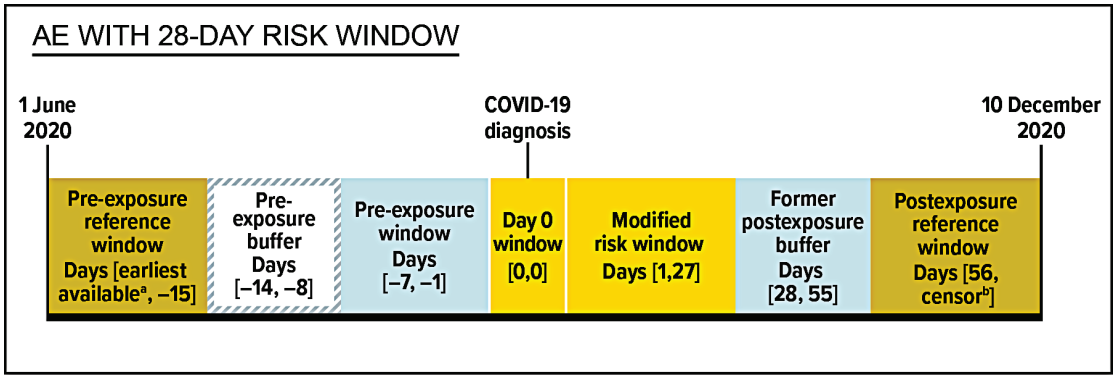
Evaluating Alternative Risk Windows

The true date of COVID-19 infection onset relative to COVID-19 diagnosis was unknown, but it likely preceded the recorded COVID-19 diagnosis. Additionally, the date of COVID-19 resolution relative to the recorded diagnosis was unknown. To evaluate whether increased AE risk extended before or after the prespecified risk window and whether COVID-19 cases may be diagnosed secondary to seeking treatment for AEs,[45] the following alternative windows (Figure 5) were defined and evaluated as separate risk windows with the extended Poisson model for event-dependent observation windows in the alternative risk period analyses:

- A 7-day pre-exposure window
- Time 0
- The prespecified risk window, although with Time 0 removed and follow-up beginning on day 1
- The former postexposure buffer

The analytic macro for the extended Poisson model for event-dependent observation windows[53] could not accommodate the analysis of the 1-day Time 0 risk period, thus the alternative risk period analyses were conducted with modified interval boundaries to estimate the RI for each period.

Figure 5. Risk Window, Additional Risk Windows, and Reference Windows for Alternative Risk Period Analyses of the Self-Controlled Risk Interval Design



AE = adverse event; COVID-19 = coronavirus disease 2019.

Note: Example shown with an AE with a prespecified 28-day risk window.

[a] Latest of the following: 1 Jun 2020 or 365 days after the beginning of continuous database enrollment.

[b] Earliest of the following: 365 days; disenrollment from the database (insurance coverage gaps of a maximum of 31 days were permitted in MarketScan only); death (available in Medicare only); end of the study period (10 Dec 2020); COVID-19 diagnosis.

3.4.4. Statistical Power and Sample Size Determination

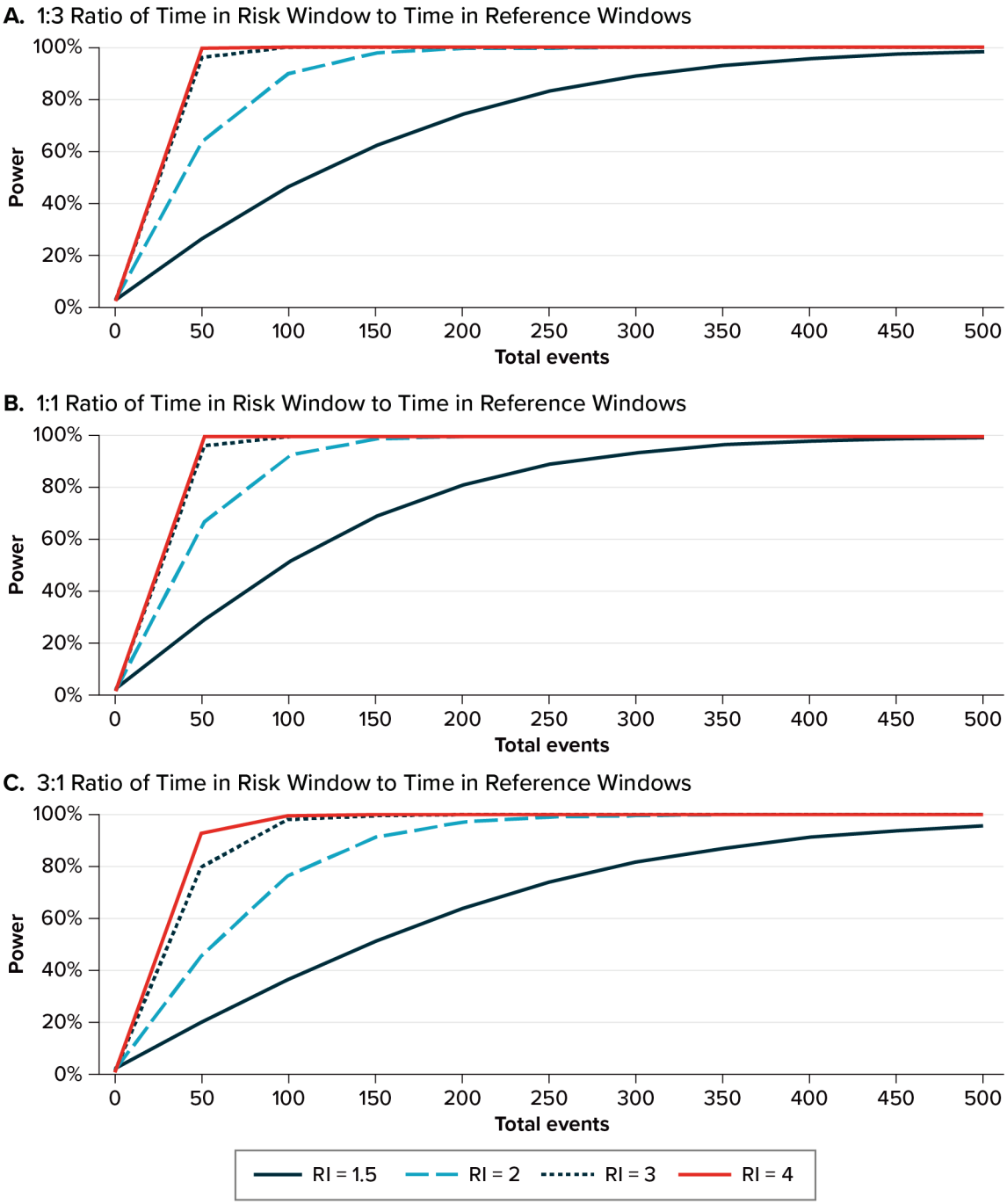
All individuals with a COVID-19 diagnosis and an AE during a risk or reference window who met all eligibility criteria were included in the AE-specific analyses.

The anticipated power of the resulting effect measure estimates from these analyses was estimated under varying assumptions of the expected number of outcomes included, the relative time distribution in the risk and reference windows, and the anticipated magnitude of the strength of the effect measure estimates.[57] This study included a large number of outcomes with varying incidence and possible association strengths. To estimate the precision of effect measure estimates for this study, the following assumptions were included in precision estimates[57]:

- We assumed a range of potential effect measure estimates, with RRs of 1.5, 2, 3, and 4 to account for differential effect measure estimates across the outcomes.
- Power was estimated as the probability that the 95% CI would exclude a null value of 1.0 under the assumed RR size.
- Although the risk windows were of fixed lengths (either 28 or 42 days), the reference windows were of variable lengths, and censoring was possible. Thus, an array of ratios of time spent in risk and reference windows was possible. We estimated power under 3 scenarios of risk-to-reference window time distributions: 1:3 (25% of time in risk windows compared with reference windows); 1:1 (50% of time in risk windows); and 3:1 (75% of time in risk windows).

Figure 6 displays the estimated power for various combinations of AEs, effect sizes, and distribution of risk and referent window time.

Figure 6. Estimated Power for Self-Controlled Risk Interval Evaluations of Associations of COVID-19 Diagnosis With Outcomes Under an Array of Possible Case Counts, Risk-to-Reference Time Distributions, and Strengths of Association



COVID-19 = coronavirus disease 2019; RI = relative incidence.

Some of the AEs being evaluated are very rare, and AEs with fewer than 10 identified individuals with both COVID-19 and an AE may have had limited power to identify increased risks, regardless of the strength of the effect measure estimate or distribution of risk and reference window time. Additionally, AEs with weak associations with COVID-19 (e.g., an RR < 2.0) may have had limited power. Having less time in reference

windows than in the risk window tended to result in decreased power estimates. However, for most AEs with relatively strong expected associations and larger case counts, the anticipated power was reasonable.

3.5. Study Conduct

All analyses were conducted with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.1.2 and 4.1.3 (R Core Team 2021). The study was performed according to the approved protocol[20] and the internal standard operating procedures of the participating research partners, and was conducted consistent with the International Society for Pharmacoepidemiology's *Guidelines for Good Pharmacoepidemiology Practices*[58] and FDA's *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.*[59] The study ensured that processes and deliverables were documented, reviewed, and validated in sufficient detail to allow for subsequent re-examination or replication.

This surveillance activity was conducted as part of the FDA public health surveillance mandate; thus, Institutional Review Board approval and oversight were not required by FDA.

4. Results

4.1. Descriptive Analyses

The attrition and descriptive results of both data sources are described together in the following sections in the overall cohort and SCRI populations.

4.1.1. Cohort Analyses

In the final, matched cohorts across both data sources, we identified 1,261,123 eligible individuals with a COVID-19 diagnosis during the study period and an equal number of matched comparators without a prior COVID-19 diagnosis. In MarketScan, we identified 358,306 eligible individuals aged 18 through 64 years with new-onset COVID-19. After matching, 319,300 (89.11%) eligible adults in the COVID-19-diagnosed group could be matched to an individual without a recorded COVID-19 diagnosis on or before the index date. In Medicare, we identified 1,085,418 eligible adults with new-onset COVID-19. Of these eligible adults, 1,017,410 (93.7%) could be matched to a comparator without a prior COVID-19 diagnosis. Among the 68,008 patients with a COVID-19 diagnosis who could not be matched, the majority (99.6%) were hospitalized at Time 0. Further details of the cohort attrition by eligibility criteria and AE-specific cohorts for the cohort study are shown in Table B-1-MarketScan and Table B-1-Medicare.

The characteristics of the individuals with a COVID-19 diagnosis and matched comparators are shown in Table B-2-MarketScan and Table B-2-Medicare (the characteristics of individuals with a COVID-19 diagnosis who were not included in the analytic cohorts because of failing to match are shown in Table B-3-MarketScan and Table B-3-Medicare). A summary of selected characteristics across both data sources is shown in Table 3.

In the MarketScan cohort, the mean age of both COVID-19 exposure groups was 41.8 years (SD 13.6), with 56.0% of the cohort being female. In Medicare, the mean age in both COVID-19 exposure groups was 77.7 years (SD 8.6 years), and 58.0% were female. The largest proportion of both the MarketScan and Medicare samples (46.9% and 37.8%, respectively) came from the southern US region. Generally, the younger MarketScan cohort was relatively healthy, with most major comorbidities being uncommon, except for hypertension, lipid abnormalities, and mental health conditions (≥ 20% in both COVID-19 exposure groups). In contrast, both exposure groups in Medicare displayed frequent occurrences of comorbidities. Over half of the Medicare cohort reported heart conditions (≥ 59%) and hypertension (≥ 79%). All comorbidities were more

common in the older Medicare cohort in comparison to the MarketScan cohort. Additionally, healthcare utilization was more common in Medicare than in MarketScan: hospitalization at Time 0 (16.3% vs. 1.3%); LTC or SNF stay (≥ 28% vs. ≥ 0.05%); and influenza vaccination (≥ 56% vs. ≥ 28%).

In both data sources, the characteristics of the COVID-19-diagnosed group and the comparator group were largely similar and well balanced, with ASDs less than 0.1 for almost all measured characteristics (Table B-2-MarketScan, Table B-2-Medicare). The only categories with an ASD larger than 0.1 in both data sources was the occurrence of pneumonia or lower respiratory tract infection (ASD = 0.13 in MarketScan, ASD=0.12 in Medicare, prevalence higher in the COVID-19-diagnosed group), and outpatient provider visits (ASD= 0.19 in MarketScan, ASD = 0.17 in Medicare, higher visit count in the COVID-19-diagnosed group). In the MarketScan cohort, recorded obesity diagnoses were also more common in the COVID-19-diagnosed group (ASD = 0.11).

For each AE-specific cohort, the relatively substantial overlap of the propensity scores (Figure B-1-MarketScan, Figure B-1-Medicare) and the similar distributions of sIPT weights (Table B-4-MarketScan, Table B-4-Medicare) by COVID-19 exposure indicated that the covariates were largely well balanced across the COVID-19 and comparator groups. After sIPT weighting, the balance of covariates across exposure groups was largely improved, as evidenced by ASDs closer to 0 (Figure B-2-MarketScan, Figure B-2-Medicare).

Table 3. Selected Characteristics of Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis Included in the Cohort Study

Characteristic	MarketScan COVID-19 diagnosis (exposure) group	MarketScan comparator group	MarketScan ASD	Medicare COVID-19 diagnosis (exposure) group	Medicare comparator group	Medicare ASD
Total selected observations[a] (unique individuals)	319,300 (319,300)	319,300 (312,282)		1,017,410 (1,017,410)	1,017,410 (930,513)	
Demographic characteristics						
Age, years						
Mean (SD)	41.8 (13.6)	41.8 (13.6)	0.00	77.7 (8.6)	77.7 (8.6)	0.00
Median (Q1, Q3)	43 (30, 53)	43 (30, 53)		76 (71, 84)	76 (71, 84)	
Sex, n (%)			0.00			0.00
Female	178,975 (56.1)	178,975 (56.1)		590,584 (58.0)	590,584 (58.0)	
Male	140,325 (43.9)	140,325 (43.9)		426,826 (42.0)	426,826 (42.0)	
US geographic region, n (%)			0.00			0.00
Northeast	62,215 (19.5)	62,224 (19.5)		218,277 (21.5)	218,107 (21.4)	
North central	71,170 (22.3)	71,149 (22.3)		250,139 (24.6)	250,130 (24.6)	
South	149,868 (46.9)	149,880 (46.9)		385,012 (37.8)	385,108 (37.9)	
West	36,037 (11.3)	36,037 (11.3)		161,002 (15.8)	161,085 (15.8)	
Unknown	10 (0.0)	10 (0.0)		2,980 (0.3)	2,980 (0.3)	
Hospitalized on Time 0, n (%)	4,046 (1.3)	4,046 (1.3)	0.00	166,154 (16.3)	166,154 (16.3)	0.00
SNF/LTC[b] residence on Time 0, n (%)	NA	NA		250,193 (24.6)	250,193 (24.6)	0.00
Comorbidities, n (%)						
Autoimmune disorders	12,677 (4.0)	12,973 (4.1)	0.00	93,071 (9.1)	89,588 (8.8)	0.01
Cancer	13,421 (4.2)	14,271 (4.5)	0.01	272,867 (26.8)	283,933 (27.9)	0.02
Chronic kidney disease or renal disease (other than end-stage renal disease)	6,052 (1.9)	5,101 (1.6)	0.02	276,654 (27.2)	262,576 (25.8)	0.03
End-stage renal disease[b]	NA	NA	NA	20,229 (2.0)	14,209 (1.4)	0.05
Chronic lung diseases	32,616 (10.2)	25,419 (8.0)	0.08	293,426 (28.8)	265,622 (26.1)	0.06
Diabetes, Type 1 or 2	33,117 (10.4)	25,491 (8.0)	0.08	406,448 (39.9)	364,235 (35.8)	0.09
Heart conditions	37,470 (11.7)	31,315 (9.8)	0.06	614,855 (60.4)	586,102 (57.6)	0.06
Hypertension	78,717 (24.7)	69,065 (21.6)	0.07	823,414 (80.9)	800,051 (78.6)	0.06
Immunocompromised state	37,672 (11.8)	37,672 (11.8)	0.00	438,954 (43.1)	438,954 (43.1)	0.00

Characteristic	MarketScan COVID-19 diagnosis (exposure) group	MarketScan comparator group	MarketScan ASD	Medicare COVID-19 diagnosis (exposure) group	Medicare comparator group	Medicare ASD
Pneumonia or lower respiratory tract infection	41,355 (13.0)	28,356 (8.9)	0.13	237,118 (23.3)	188,874 (18.6)	0.12
Pregnancy	2,616 (0.8)	2,288 (0.7)	0.01	NA	NA	NA
Stroke or cerebrovascular disease	4,730 (1.5)	4,021 (1.3)	0.02	228,802 (22.5)	221,952 (21.8)	0.02
Thromboembolism	3,531 (1.1)	2,885 (0.9)	0.02	77,562 (7.6)	75,096 (7.4)	0.01
Healthcare utilization, n (%)						
SNF/LTC stay[c]	341 (0.1)	158 (0.0)	0.02	295,527 (29.0)	286,390 (28.1)	0.02
Influenza vaccination in previous year	90,018 (28.2)	95,167 (29.8)	0.04	570,066 (56.0)	572,746 (56.3)	0.01

ASD = absolute standardized difference; COVID-19 = coronavirus disease 2019; LTC = long-term care; NA = not applicable; Q1 = first quartile, Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] A unique individual may be included multiple times because of matching with replacement, and an individual may be included in both the exposure and comparator groups. This table counts each instance of an individual's entry separately as distinct observations; the number of unique individuals is reported separately.

[b] Only available in Medicare.

[c] SNF and LTC both identified in Medicare; SNF identified in MarketScan.

4.1.2. SCRI Analyses

Across both data sources, 1,185,864 individuals were identified with an eligible COVID-19 diagnosis. In MarketScan, we identified 509,875 individuals with a COVID-19 diagnosis during the study period. Of those identified individuals, 330,799 (64.87%) were eligible for inclusion based on age, enrollment, and no prior respiratory infection. In Medicare, we identified 1,571,901 adults with new-onset COVID-19 during the study period; of these, 855,065 (54.4%) were eligible for SCRI analyses based on the study inclusion criteria. Further information regarding the attrition of the AE-specific analysis sets for the SCRI study are shown in Table B-10-MarketScan and Table B-10-Medicare.

The characteristics of the overall SCRI population are shown in Table 4. This overall population represents all individuals potentially eligible for inclusion in the AE-specific SCRI analyses. However, because each AE-specific analysis is restricted to only individuals experiencing the AE in a risk or reference window, the included individuals of each AE-specific analysis set differ; characteristics of each AE-specific analysis set are shown in Table B-11-MarketScan and Table B-11-Medicare.

In MarketScan, the mean age of individuals with a COVID-19 diagnosis was 41.4 years (SD 13.7), with 54.7% of the cohort being female. In Medicare, the mean age was 77.4 years (SD 8.4 years), and 56.9% were female. The largest proportion of both the MarketScan and Medicare samples (52.0% and 41.6%, respectively) came from the southern US region. The individuals in Medicare were predominantly white (84.4%) (race and ethnicity were not reported in MarketScan). Hospitalization at Time 0 was more common in Medicare than in MarketScan (21.4% vs. 3.1%), as was immunocompromised state (41.8% vs. 10.9%).

After restricting to the AE-specific analysis sets, the largest analysis sets in both MarketScan and Medicare data sources were DVT (n = 1,013 and n = 17,046, respectively), myocarditis and pericarditis (n = 339 and n = 1,605, respectively (Table B-11-MarketScan , Table B-11-Medicare). In MarketScan, pulmonary embolism (n = 1,444) was the largest AE-specific analysis set; however, pulmonary embolism analyses were not performed in Medicare because of the higher case fatality rate in older adults and the resulting violation of the assumptions of the SCRI (Table 1).

In the overall SCRI population (before restricting to AE-specific analysis sets), 54.7% of the MarketScan population were women, and 56.9% of the Medicare population were women. However, the sex distribution for most of the AE-specific analysis sets tended to differ. In MarketScan, women represented a larger majority of the transverse myelitis (71.4%) and narcolepsy (74.4%) analysis sets. In contrast, women represented a minority of the MarketScan AE analysis sets for DIC (40.5%), GBS (41.7%), DVT (41.8%), myocarditis/pericarditis (43.1%), appendicitis (45.3%), and pulmonary embolism (45.9%). In Medicare, women also represented a minority of the analysis sets for GBS (29.8%), ITP (46.5%), myocarditis/pericarditis (48.1%), and appendicitis (48.5%). Immunocompromised individuals represented the minority of both MarketScan (10.9%) and Medicare (41.8%) overall SCRI populations (Table B-11-MarketScan, Table B-11-Medicare). However, for all AE-specific analysis sets in both Medicare and MarketScan, the proportions of individuals who were immunocompromised were higher than in the overall SCRI population. Immunocompromised individuals represented the majority of those who experienced ITP (MarketScan = 69.2%, Medicare = 76.6%) and transverse myelitis (MarketScan = 71.4%, Medicare = 72.7%). In comparison to the overall SCRI population (MarketScan = 3.1%, Medicare = 21.4%), those hospitalized at Time 0 represented a larger proportion of the MarketScan cohorts who experienced DIC (40.5%) and pulmonary embolism (32.7), and Medicare cohorts who experienced transverse myelitis (63.6%) and myocarditis/pericarditis (55.6%). Additionally, residents of LTC facilities or SNFs represented a larger proportion of individuals in Medicare who experienced transverse myelitis (40.9%),

narcolepsy (30.5%), and DVT (29.0%), in comparison to the overall SCRI population (21.8%). Race/ethnicity and US region of those who experienced AEs largely reflected the makeup of the overall SCRI cohort.

Table 4. Characteristics of Individuals With a COVID-19 Diagnosis Included in the Self-Controlled Risk Interval Analysis Study Population, Overall

Characteristic	MarketScan N = 330,799	Medicare N = 855,065
Age, years		
Mean (SD)	41.4 (13.7)	77.4 (8.4)
Median (Q1, Q3)	42 (29, 53)	76 (70, 83)
Age groups, n (%)		
18-34 years	113,978 (34.5)	NA
35-49 years	103,886 (31.4)	NA
50-64 years	112,935 (34.1)	NA
65-79 years	NA	539,002 (63.0)
≥ 80 years	NA	316,063 (37.0)
Sex, n (%)		
Female	180,800 (54.7)	486,381 (56.9)
Male	149,999 (45.3)	368,684 (43.1)
US geographic region, n (%)		
Northeast	44,345 (13.4)	125,327 (14.7)
North central	69,166 (20.9)	233,154 (27.3)
South	172,142 (52.0)	355,853 (41.6)
West	44,841 (13.6)	138,058 (16.1)
Unknown	305 (0.1)	2,673 (0.3)
Race/ethnicity, n (%)[a]		
American Indian/Alaska Native	NA	7,165 (0.8)
Asian	NA	12,648 (1.5)
Black or African American	NA	67,441 (7.9)
Hispanic/Latin American/Latinx	NA	21,394 (2.5)
White	NA	722,056 (84.4)
A race/ethnicity not listed	NA	10,840 (1.3)
Not provided	NA	13,521 (1.6)
Hospitalized on Time 0, n (%)	10,129 (3.1)	182,913 (21.4)
SNF/LTC[a] residence on Time 0, n (%)	NA	186,367 (21.8)
Immunocompromised state, n (%)	35,924 (10.9)	357,587 (41.8)

COVID-19 = coronavirus disease 2019; LTC = long-term care; NA = not applicable; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] Only available in Medicare.

4.2. Outcome Analyses

The results of all the analyses (both cohort and SCRI designs) are presented separately, by AE, in the following sections. Within each AE-specific section, all performed cohort and SCRI analyses were summarized on forest plots. Complete analytic output for each AE is given in Appendix B, as follows:

- Cohort analyses

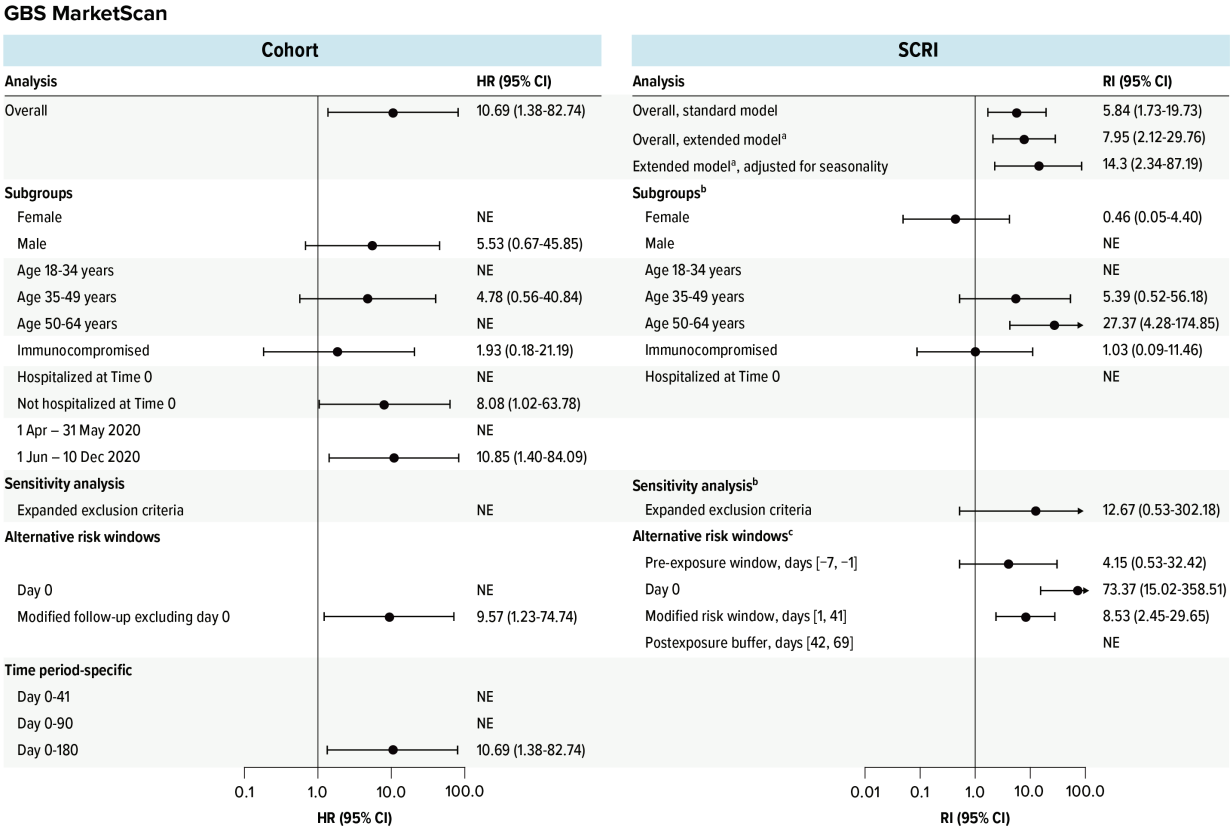
- Unweighted and weighted cumulative incidences are shown in Figure B-3-MarketScan and Figure B-3-Medicare.
- HR estimates overall and in specific follow-up time periods are shown in Table B-5-MarketScan and Table B-5-Medicare.

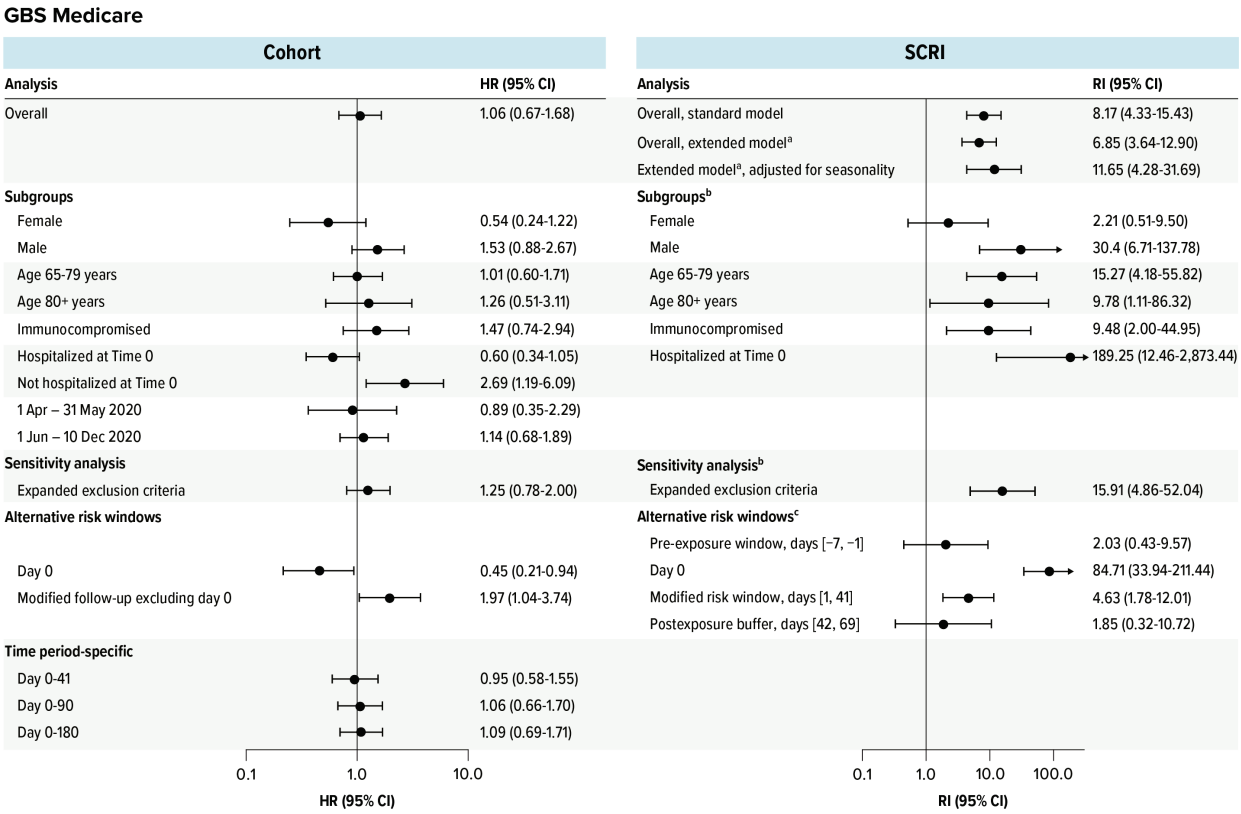
- SCRI analyses
  - RI estimates using both the standard and extended Poisson models are shown in Table B-12-MarketScan and Table B-12-Medicare.
  - RI estimates for subgroup analyses are shown in Table B-13-MarketScan and Table B-13-Medicare.
  - RI estimates for alternative risk windows are shown in Table B-14-MarketScan and Table B-14-Medicare.

4.2.1. Guillain-Barré Syndrome

GBS was evaluated using both the cohort design and the SCRI design in both data sources. An overview of the results of all the outcome analyses is shown in Figure 7.

Figure 7. Estimated Association of a COVID-19 Diagnosis With GBS, All Analyses and Data Sources





CI = confidence interval; GBS = Guillain-Barré Syndrome; HR = hazard ratio; NE = not estimable; RI = relative incidence; SCRI = self-controlled risk interval.

[a] Extended Poisson models accounting for event-dependent observation windows.

[b] Evaluated using the extended Poisson models accounting for event-dependent observation windows and adjustment for seasonality.

[c] Evaluated using a modified extended Poisson models accounting for event-dependent observation windows to allow for 1-day intervals and adjustment for seasonality.

4.2.1.1. Overall Outcome Analyses

In the cohort analyses, the weighted cumulative incidence of GBS by COVID-19 exposure group over follow-up is shown in Figure 8. GBS was very rare in both data sources, with cumulative incidences of less than 0.01% (except for the Medicare comparator group with a steep increase in cumulative incidence driven by small case counts at the end of follow-up) (Figure 8). For adults aged 18 to 64 years in MarketScan, the COVID-19-diagnosed group had a consistently higher cumulative incidence of GBS throughout all of follow-up, and all the GBS cases in the COVID-19-diagnosed group occurred in the first 90 days of follow-up. Among adults aged 65 years or older in Medicare, the comparator group had more GBS cases identified on Time 0 (i.e., the day of COVID-19 diagnosis or matched date) and the cumulative incidence of GBS was much higher in the comparator group in the older Medicare cohort than in the younger MarketScan cohort (Table B-5-MarketScan.A, Table B-5-Medicare.A).

The overall HR across all of follow-up and at prespecified time periods is shown in Figure 7. For the overall cohort analyses in MarketScan, the COVID-19-diagnosed group was substantially more likely to experience GBS in comparison to the comparator group (HR = 10.69; 95% CI, 1.38-82.74). However, in the overall cohort analysis in the larger and older Medicare cohort, the HR estimate was much smaller (HR = 1.06; 95% CI, 0.67-1.68). Notably, the total sample size, follow-up time, and number of recorded GBS events during the risk

period were smaller in the MarketScan cohort analysis (ages 16-64 years) in comparison to the Medicare cohort (ages ≥ 65 years).

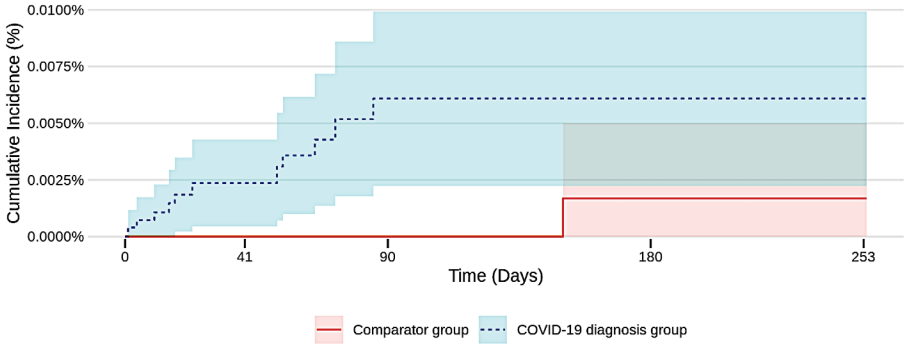
For the overall SCRI analyses, the RI estimates and 95% CI during days 0-41 after COVID-19 diagnosis are summarized in Figure 7. The SCRI RI and 95% CI intervals were estimated with the standard Poisson model, the extended Poisson models accounting for event-dependent observation periods, and the extended model adjusted for seasonality. The estimates from the 3 models were generally consistent in both data sources, although the extended model adjusted for seasonality reported the highest RI estimates. In both data sources, the extended regression model with adjustment for seasonality suggested an increased risk of GBS after being diagnosed with COVID-19: RI = 14.3 (95% CI, 2.34-87.19) in MarketScan; RI = 11.65 (95% CI, 4.28-31.69) in Medicare.

In MarketScan, both the overall cohort and SCRI analyses suggest substantially increased relative risk of GBS associated with a COVID-19 diagnosis, although GBS was rare. In Medicare, the overall cohort and SCRI analyses differed, with the cohort HR being close to the null and quite high SCRI RIs. The magnitude of both the HR and RI estimates in the younger MarketScan were generally greater than those in Medicare.

Time period–specific HRs were also estimated in the cohort analyses. In the MarketScan cohort, the sample sizes were too small to estimate the HRs for the day 0 to 41 and day 0 to 90 time periods. The day 0 to 180 time period HR was consistent with the overall MarketScan cohort HR. In Medicare, the time period–specific HRs were all consistent with the overall estimate (Figure 7).

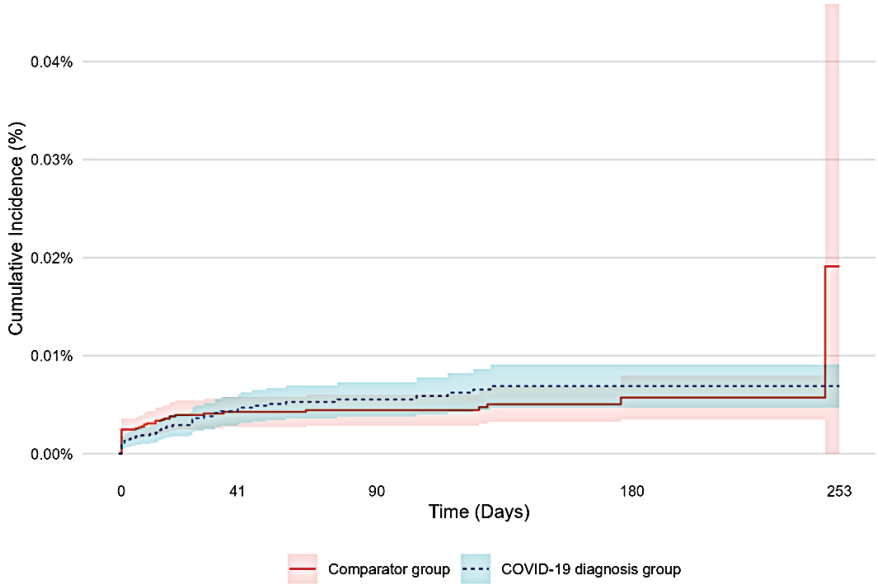
Figure 8. Weighted Cumulative Incidence of Guillain-Barré Among Individuals With a COVID-19 Diagnosis and Comparators Without a COVID-19 Diagnosis

A. MarketScan



Comparator group					
At Risk	318556	187743	128056	37008	541
Censored	4472	132782	191610	281796	318555
Events	0	0	0	1	1
COVID-19 diagnosis group					
At Risk	319279	187288	127083	36261	527
Censored	4476	133980	193290	283240	319267
Events	1	7	12	12	12

B. Medicare



Comparator group					
At Risk	1015672	598068	409943	154215	1889
Censored	16195	423788	608951	862438	1015627
Events	25	40	41	44	45
COVID-19 diagnosis group					
At Risk	1015994	550786	372865	136057	1521
Censored	18316	471179	646181	880805	1015948
Events	11	37	42	46	46

COVID-19 = coronavirus disease 2019.
Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

4.2.1.2. Subgroup Analyses

The HRs and RIs for individual subgroups in both the cohort and SCRI analyses are shown in Figure 7.

In the MarketScan cohort analyses, sample sizes were too small to estimate subgroups in females, the youngest and oldest age groups, those hospitalized at Time 0, and during the earlier calendar time period. In those subgroup analyses that could be performed, the HR estimates were consistently elevated, except for the immunocompromised group, where it was attenuated (HR = 1.93; 95% CI, 0.18-21.19). In Medicare, all subgroup HRs were generally similar to the overall estimate, except for the increased estimate in the nonhospitalized at Time 0 (HR = 2.69; 95% CI, 1.19-6.09) subgroup and the reduced estimates in women (HR = 0.54; 95% CI, 0.24-1.22) and those hospitalized at Time 0 (HR = 0.60; 95% CI, 0.34-1.05).

In the MarketScan SCRI analysis, sample sizes were too small to estimate subgroups in males, the 18-34 year age group, and those hospitalized at Time 0. Similar to the MarketScan cohort analysis, in the subgroups that could be estimated, the RI estimate for those aged 35-49 years was consistent with the overall estimate, and the estimate in the immunocompromised group was attenuated. In contrast with the MarketScan overall SCRI estimate, the 50-64 year age subgroup had an increased although highly imprecise RI estimate (RI = 27.37; 95% CI, 4.28-174.85), and the female subgroup had a reduced RI estimate (RI = 0.46; 95% CI, 0.05-4.40). In the Medicare SCRI analysis, the RI estimates for most subgroups were generally consistent with the overall RI,

except for the attenuated estimate in women (RI = 2.21; 95% CI, 0.51-9.50) and the elevated although highly imprecise estimates in men (RI = 30.4; 95% CI, 6.71-137.78) and those hospitalized at Time 0 (RI = 189.25; 95% CI, 12.46-2,873.44).

The trends in the RIs of the Medicare SCRI subgroups differed from the Medicare cohort HR trends, as the SCRI subgroup RIs consistently indicated a potential increased risk for GBS following COVID-19 diagnosis while the Medicare cohort subgroup HRs are largely around the null. Subgroup analyses in both analytic approaches were similar to the overall analysis results.

4.2.1.3. Sensitivity Analyses

Results of sensitivity analyses with expanded exclusion criteria in both the cohort and SCRI are summarized in Figure 7. In MarketScan, the cohort sample sizes were too small to estimate the HR for the sensitivity analysis. The Medicare cohort sensitivity analysis ($HR_{sensitivity}$ = 1.25; 95% CI, 0.78-2.00) was slightly elevated from but generally consistent with the overall cohort HR. Both the MarketScan and Medicare SCRI sensitivity analyses, (which account for event-dependent observation windows and adjust for seasonality) were consistent with the overall SCRI using the same model.

4.2.1.4. Alternative Risk Windows

Results of the analyses of alternative risk windows and time periods in the cohort (day 0 only, and all follow-up excluding day 0) and SCRI (the 7 days before COVID-19 diagnosis, day 0, the risk window excluding day 0, and the postexposure buffer period) are summarized in Figure 7.

In the MarketScan cohort analysis, the cohort sample sizes were too small to estimate the HR for day 0, alone, but the analysis excluding day 0 and starting follow-up on day 1 resulted in an HR estimate consistent with the overall cohort analysis ($HR_{alternative}$ = 9.57; 95% CI, 1.23-74.74). In the Medicare cohort analyses, analyses evaluating day 0 alone resulted in a reduced HR estimate ($HR_{day\ 0}$ = 0.45; 95% CI, 0.21-0.94), but in analyses excluding day 0 and starting follow-up on day 1, the estimate was increased above the overall cohort HR ($HR_{alternative}$ = 1.97; 95% CI, 1.04-3.74). This pattern suggested that a larger proportion of the comparator group had a GBS diagnosis on day 0, but a larger proportion of the COVID-19-diagnosed group had a diagnosis during follow-up (this can be observed on the cumulative incidence curve showing a large number of comparator cases on day 0, Figure 8-B).

In the SCRI analyses, both the MarketScan and Medicare analyses suggested substantially elevated RIs on day 0 (RIs > 73), with slightly attenuated RIs (compared with the extended, seasonality-adjusted overall model) in the analyses excluding day 0 and starting the risk period on day 1. This pattern suggests that among the COVID-19-diagnosed group, a large number of individuals had a diagnosis of both COVID-19 and GBS on the same day (i.e., Time 0).

Evaluation of the pre-exposure window and former buffer periods in the SCRI analyses (time periods outside of the expected risk period) resulted in RI estimates greater than 1, but with wide CIs, potentially suggesting some increased risk outside of the prespecified risk period.

4.2.1.5. Summary of Results

Findings from all data sources and analytical approaches demonstrated modest to strong associations between a COVID-19 diagnosis and the incidence of GBS, with overall cohort analysis HRs of 10.69 (95% CI, 1.38-82.74) in MarketScan and 1.06 (95% CI, 0.67-1.68) in Medicare, and SCRI RI (extended model, seasonality adjusted) estimates of 14.30 (95% CI, 2.34-87.19) for MarketScan and 11.65 (95% CI, 4.28-31.69) for Medicare. Among all

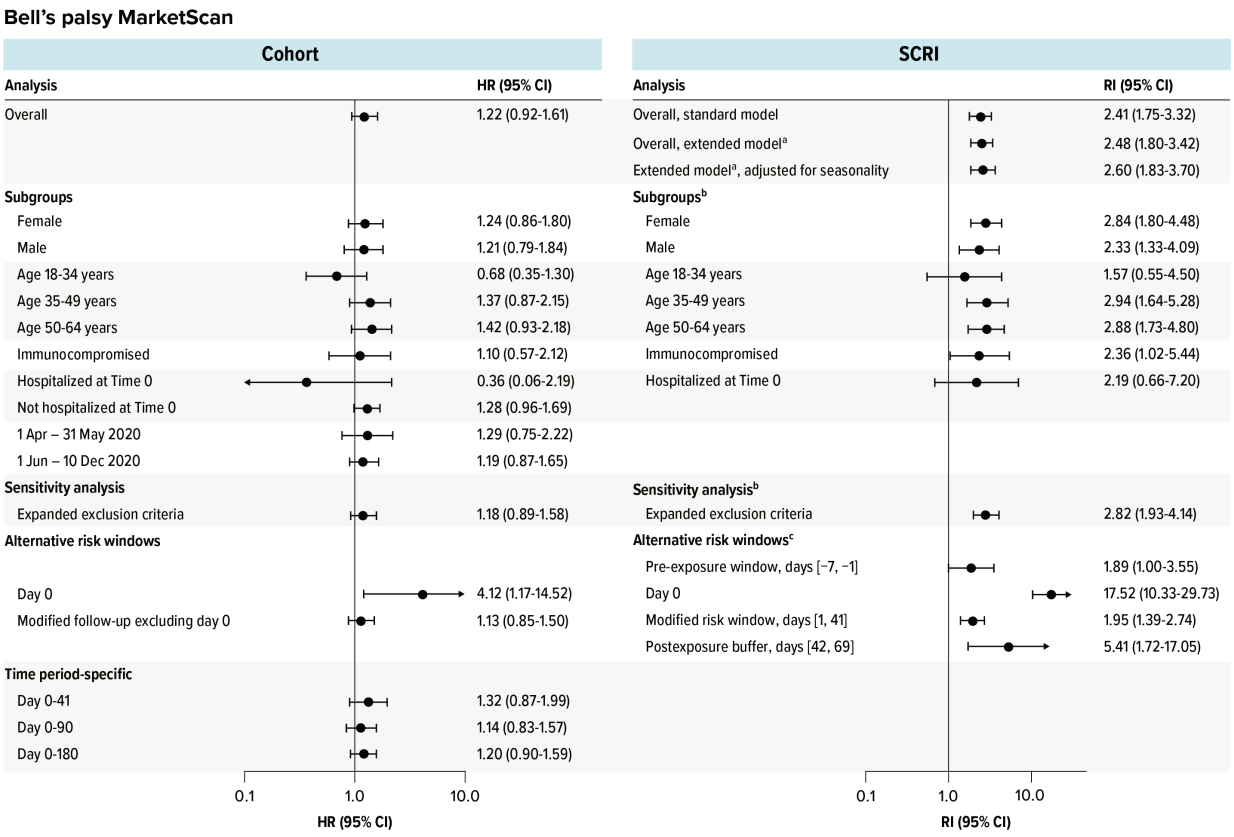
the overall analysis estimates, the Medicare cohort estimate was notable for being substantially closer to the null than the MarketScan estimates. However, in the alternative risk period analyses that excluded events occurring on day 0, the resulting Medicare cohort HR was closer in alignment with other estimates ($HR_{overall}$ = 1.06 [95% CI, 0.67-1.68], $HR_{alternative}$ = 1.97 [95% CI, 1.04-3.74]), as GBS events on day 0 were observed more than twice as frequently among comparators than those in the COVID-19—diagnosed group (Table B-5-Medicare.A).

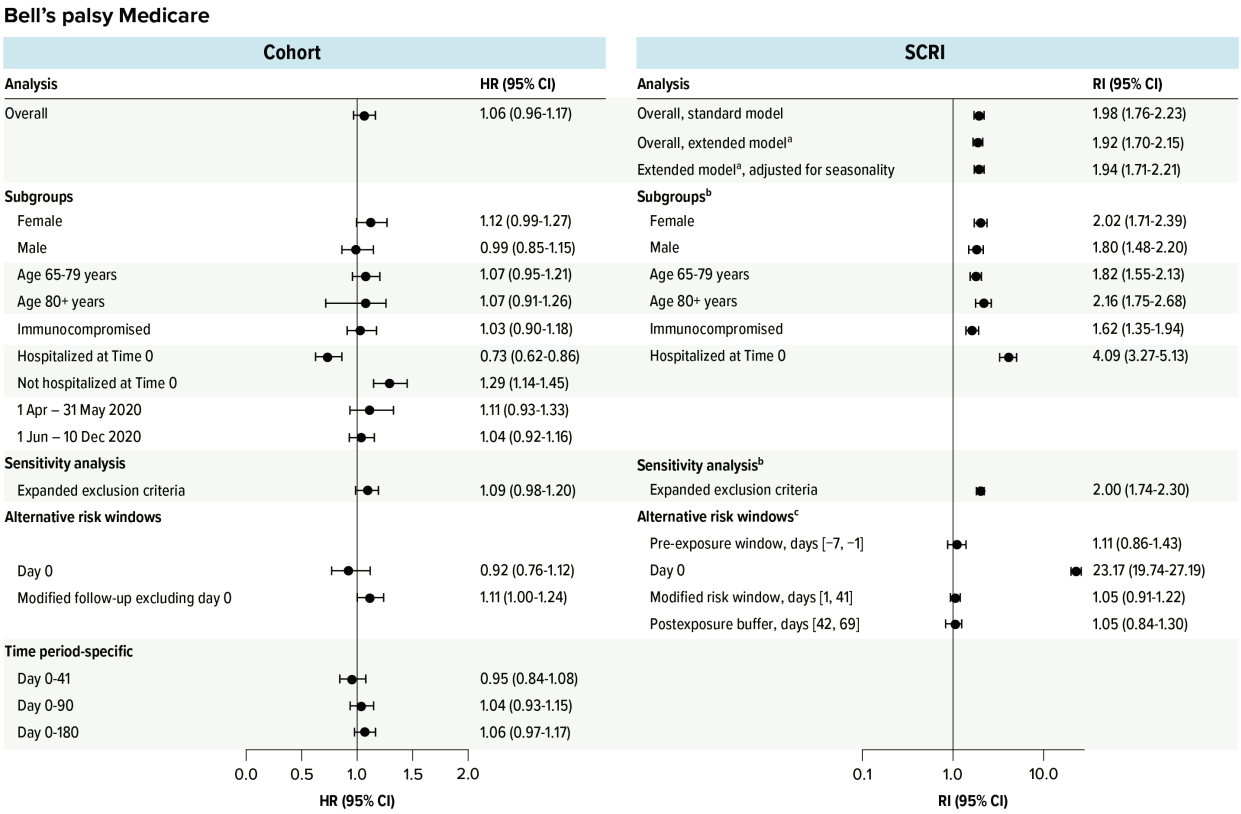
The magnitudes of the Medicare HR and RI estimates (extended, seasonality-adjusted model) were less than those in the younger MarketScan population for both the overall analysis (and alternative risk period analyses starting follow-up on day 1), likely driven by a higher observed incidence of GBS in Medicare (Table B-5-MarketScan.A, Table B-5-Medicare.A). However, the ability of comparing estimates across populations is hampered by limited precision of some estimates (e.g., in MarketScan, only 1 GBS case was identified among the comparator group).

4.2.2. Bell's Palsy

Bell's palsy was evaluated using both the cohort design and the SCRI design in both data sources. An overview of the results of all the outcome analyses is shown in Figure 9.

Figure 9. Estimated Association of a COVID-19 Diagnosis With Bell's Palsy, All Analyses and Data Sources





CI = confidence interval; HR = hazard ratio; RI = relative incidence; SCRI = self-controlled risk interval.

[a] Extended Poisson models accounting for event-dependent observation windows.

[b] Evaluated using the extended Poisson models accounting for event-dependent observation windows and adjustment for seasonality.

[c] Evaluated using modified extended Poisson models accounting for event-dependent observation windows to allow for 1-day intervals and adjustment for seasonality.

4.2.2.1. Overall Outcome Analyses

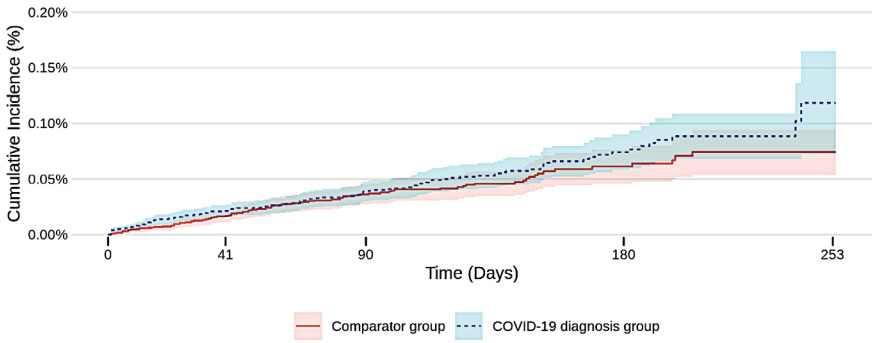
In the overall cohort analyses, the weighted cumulative incidence of Bell's palsy by COVID-19 exposure groups over follow-up is shown in Figure 10. The overall HR and RI estimates across all of follow-up and at prespecified time periods is shown in Figure 9 and Table B-5-MarketScan.B and Table B-5-Medicare.B.

The weighted cumulative incidence of Bell's palsy was generally low in both data sources across all of follow-up, but the cumulative incidence was approximately twice as high in Medicare than in MarketScan (Figure 10). In Medicare, a substantial number of Bell's palsy cases in both the COVID-19 and comparator groups were identified on day 0, concurrently with the COVID-19 diagnosis or matched index date.

For the cohort analyses, the overall HR in MarketScan was 1.22 (95% CI, 0.92-1.61) and in Medicare was 1.06 (95% CI, 0.96-1.17). In the SCRI analyses, overall RI estimates were generally modestly elevated and were consistent across the standard model, extended model, and extended model adjusted for seasonality (RIs during the risk period [days 0-41] ranged from 2.41 to 2.60 in MarketScan, 1.92 to 1.98 in Medicare). In the cohort analyses in both data sources, the time period–specific HRs were all consistent with their respective overall estimates.

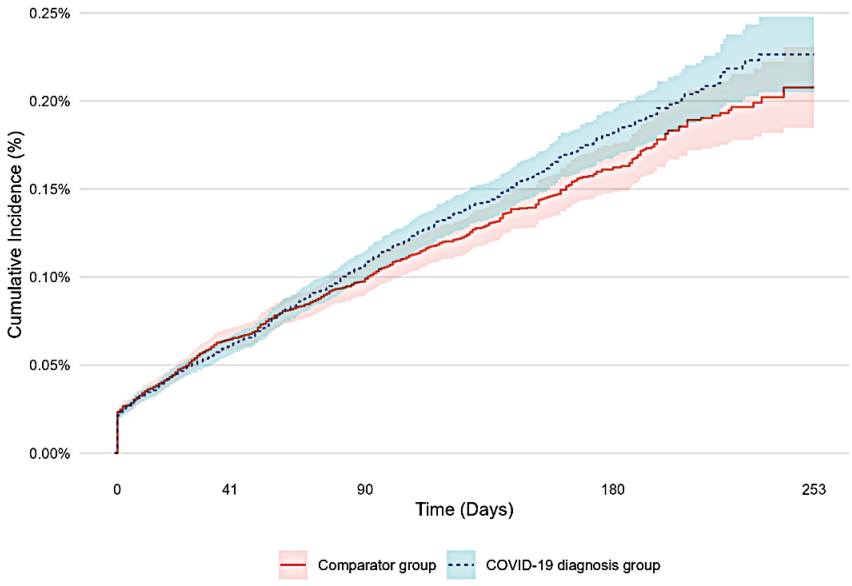
Figure 10. Weighted Cumulative Incidence of Bell's Palsy Among Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis

A. MarketScan



Comparator group					
At Risk	318573	187580	127909	36972	540
Censored	4485	132924	191701	281756	318476
Events	3	43	74	93	98
COVID-19 diagnosis group					
At Risk	319045	187314	127144	36325	527
Censored	4460	133667	192922	282840	318926
Events	13	57	84	112	119

B. Medicare



Comparator group					
At Risk	1014466	596499	408484	153402	1871
Censored	16194	423623	608520	861173	1013517
Events	237	561	730	909	949
COVID-19 diagnosis group					
At Risk	1014186	550138	372541	136139	1530
Censored	18217	469515	644023	878047	1013234
Events	218	520	724	917	952

COVID-19 = coronavirus disease 2019.
Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

4.2.2.2. Subgroup Analyses

The HRs and RIs for individual subgroups in both the cohort and SCRI analyses are shown in Figure 9. In both MarketScan and Medicare cohort subgroup analyses, the subgroup HR estimates were largely consistent with the overall estimate, except for the increased HR estimate in the Medicare subgroup of those not hospitalized at Time 0 (HR = 1.29; 95% CI, 1.14-1.45), and the decreased HR estimates below 1 in both the MarketScan and Medicare subgroups of those hospitalized on Time 0. In both MarketScan and Medicare SCRI subgroup analyses, the RI estimates were largely consistent with the overall RI, except for the amplified estimate in the Medicare subgroup of those hospitalized at Time 0 (RI = 4.09; 95% CI, 3.27-5.13).

4.2.2.3. Sensitivity Analyses

Results of sensitivity analyses with expanded exclusion criteria in both the cohort and SCRI are summarized in Figure 9. The sensitivity analysis estimates for all MarketScan and Medicare cohort and SCRI analyses remained consistent with their respective overall estimates.

4.2.2.4. Alternative Risk Windows

Results of the analyses of alternative risk windows in the cohort (day 0 and follow-up excluding day 0) and SCRI (the 7 days before COVID-19 diagnosis, day 0, the risk window excluding day 0, and the postexposure buffer period) are summarized in Figure 9.

In the cohort analyses evaluating day 0 alone, the MarketScan day 0 estimate (HR = 4.12; 95% CI, 1.17-14.52) was substantially elevated above the overall estimate (HR = 1.22; 95%CI, 0.92-1.61) (suggesting more Bell's palsy cases were concurrently diagnosed with COVID-19, Table B-5-MarketScan.B), while in Medicare, the opposite pattern was observed, with the day 0 estimate (HR = 0.92; 95%CI, 0.76-1.12) being reduced from the overall analysis (HR = 1.06, 95%CI, 0.96-1.17) (the result of more Bell's palsy cases in the comparator group diagnosed on day 0, Table B-5-Medicare.B). In the MarketScan cohort analysis, the HR estimates for the risk window excluding day 0 was slightly attenuated but remained generally consistent with the overall analysis. In Medicare, the HRs including and not including day 0 were very similar.

In the MarketScan and Medicare SCRI analyses, day 0 risk windows displayed RI estimates that were substantially increased in comparison to their respective overall SCRI analyses, suggesting substantial concurrent diagnoses of COVID-19 and Bell's palsy. The analyses of the modified risk periods excluding day 0 were attenuated from the overall in both data sources, substantially so in Medicare ($RI_{alternative}$ = 1.05; 95%, 0.91-1.22).

The MarketScan SCRI estimates for the pre-exposure window and postexposure buffer were both somewhat elevated above the null, suggesting potential risk in periods outside the prespecified risk period. However, the Medicare RI estimates for the pre-exposure window and postexposure buffer were very close to the null, consistent with no increased risk during these periods.

4.2.2.5. Summary of Results

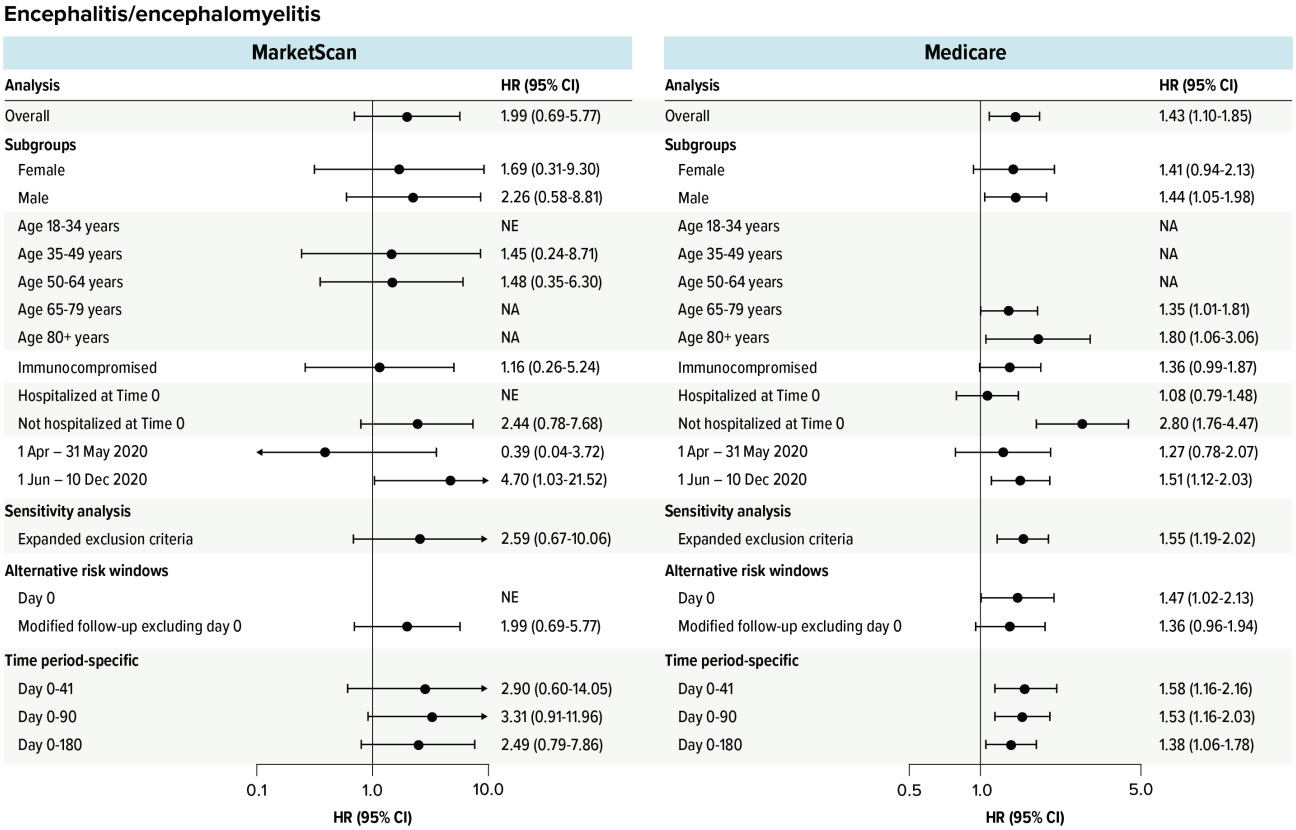
Estimates from the SCRI analyses in both data sources demonstrated inconsistent, modest associations between COVID-19 diagnosis and the incidence of Bell's palsy, particularly evidence with the SCRI analysis. The overall analysis RI estimates (extended, seasonality-adjusted model) were between 1.94 (95% CI, 1.71-2.21) and 2.60 (95% CI, 1.83-3.70) for Medicare and MarketScan, respectively. However, given the large Time 0 effects noted, the alternative risk period excluding day 0 and starting follow-up on day 1 may be more reliable; these analyses resulted in attenuated estimates also, of 1.95 (95% CI, 1.39-2.74) and 1.05 (95% CI, 0.91-1.22) in

MarketScan and Medicare, respectively. The overall HR estimates from the cohort analyses were also close to the null, Medicare 1.06 (95% CI, 0.96-1.17) and MarketScan 1.22 (95% CI,0.92-1.61), which were minimally changed after excluding day 0.

4.2.3. Encephalitis/Encephalomyelitis

Encephalitis/encephalomyelitis was evaluated only with the cohort design in both data sources, given the high mortality associated with the AE violated the assumptions of the SCRI. An overview of the results of all the outcome analyses for the cohort design in both data sources is shown in Figure 11.

Figure 11. Estimated Association of a COVID-19 Diagnosis With Encephalitis/Encephalomyelitis, All Analyses and Data Sources



CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; NA = not applicable; NE = not estimable.

4.2.3.1. Overall Outcome Analyses

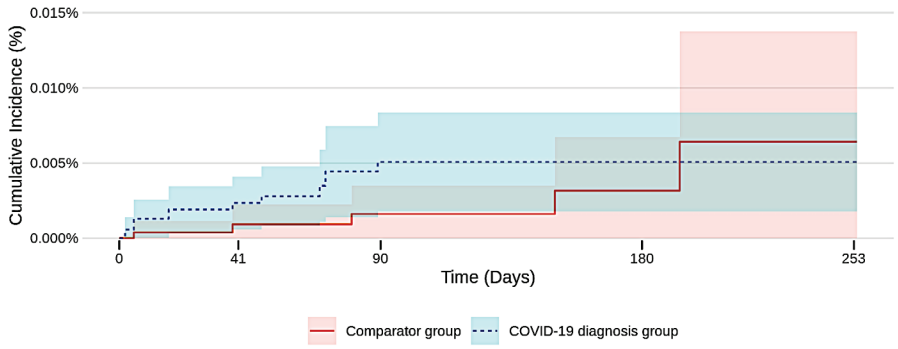
The cumulative incidence of encephalitis/encephalomyelitis was low in MarketScan, while incidence in Medicare was much larger (Figure 12). In Medicare, a substantial number of encephalitis or encephalomyelitis cases were identified on day 0, concurrently with COVID-19 diagnosis or the matched index date. In the COVID-19-diagnosed groups, all cases in MarketScan and most cases in Medicare occurred in the first 90 days of follow-up. The overall HR across all of follow-up and at prespecified time periods is shown in Figure 11 and Table B-5-MarketScan.C and Table B-5-Medicare.C.

For the cohort analyses, the overall HR in MarketScan was 1.99 (95% CI, 0.69-5.77) and in Medicare, it was 1.43 (95% CI, 1.10-1.85).

In both MarketScan and Medicare, the time period–specific HR estimates were generally consistent with each other and with the overall estimates.

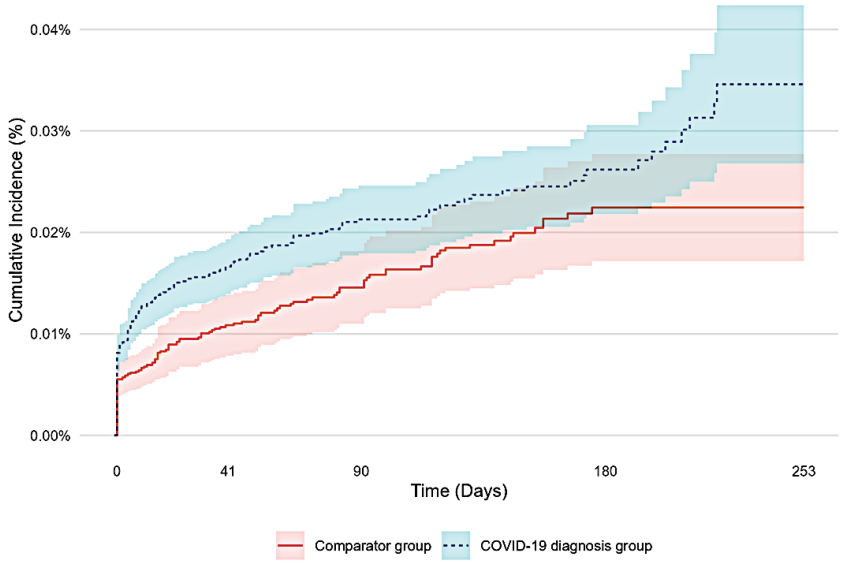
Figure 12. Weighted Cumulative Incidence of Encephalitis/Encephalomyelitis Among Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis

A. MarketScan



Comparator group					
At Risk	318553	187716	128033	37000	540
Censored	4472	132804	191627	281798	318548
Events	0	2	3	4	5
COVID-19 diagnosis group					
At Risk	319305	187342	127143	36306	528
Censored	4477	133951	193259	283222	319295
Events	0	6	10	10	10

B. Medicare



Comparator group					
At Risk	1015921	598063	409831	154179	1892
Censored	16188	423986	609236	862626	1015781
Events	56	98	117	140	140
COVID-19 diagnosis group					
At Risk	1016281	550894	372959	136078	1527
Censored	18313	471241	646243	880932	1016088
Events	83	153	174	186	192

COVID-19 = coronavirus disease 2019.
Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

4.2.3.2. Subgroup Analyses

The HRs for individual subgroups are shown in Figure 11. In MarketScan, sample sizes were too small to perform subgroup analyses in the 18-34 year age group and those hospitalized at Time 0. In both the MarketScan and Medicare cohort subgroup analyses, the HR estimates were largely consistent with the overall analysis in those subgroups which could be performed, except for the later study period (1 June-10 December 2020) in MarketScan, where it was elevated (HR = 4.70; 95% CI 1.03-21.52). In Medicare, the HRs were largely similar to the overall HR estimate, with the exception of the estimates among those not hospitalized at Time 0, which were elevated (HR = 2.80; 95% CI, 1.76-4.47).

4.2.3.3. Sensitivity Analyses

Results of sensitivity analyses with expanded exclusion criteria are summarized in Figure 11. The sensitivity analysis estimates obtained from the cohort and SCRI in both the MarketScan and Medicare cohorts remain consistent with their respective overall estimates.

4.2.3.4. Alternative Risk Windows

Results of the analyses of alternative risk windows (day 0 and follow-up excluding day 0) are summarized in Figure 11. In MarketScan, the sample sizes were too small to estimate the HR for the day 0 risk window, and the analysis of the risk period starting on day 0 was very similar to the overall because no cases occurred on day 0 (Table B-5-MarketScan-C). In Medicare, analyses of both the day 0 risk window ($HR_{day\ 0}$= 1.47; 95% CI, 1.02-2.13) and the risk period beginning on day 1 ($HR_{alternative}$ = 1.36; 95% CI, 0.96-1.94) were similar to the overall estimate; although a substantial number of cases occurred on day 0 (Table B-5-Medicare-C), the distribution of cases between exposure groups did not differ substantially on or after day 0.

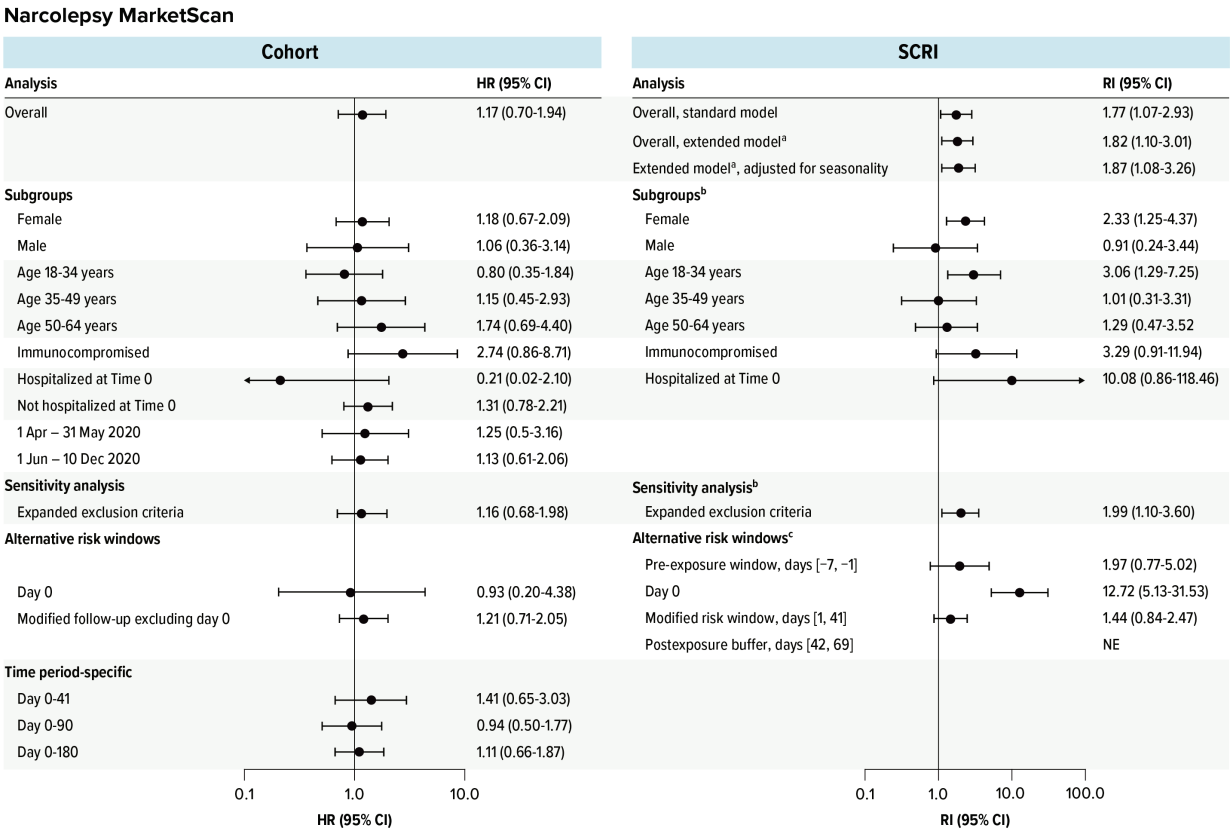
4.2.3.5. Summary of Results

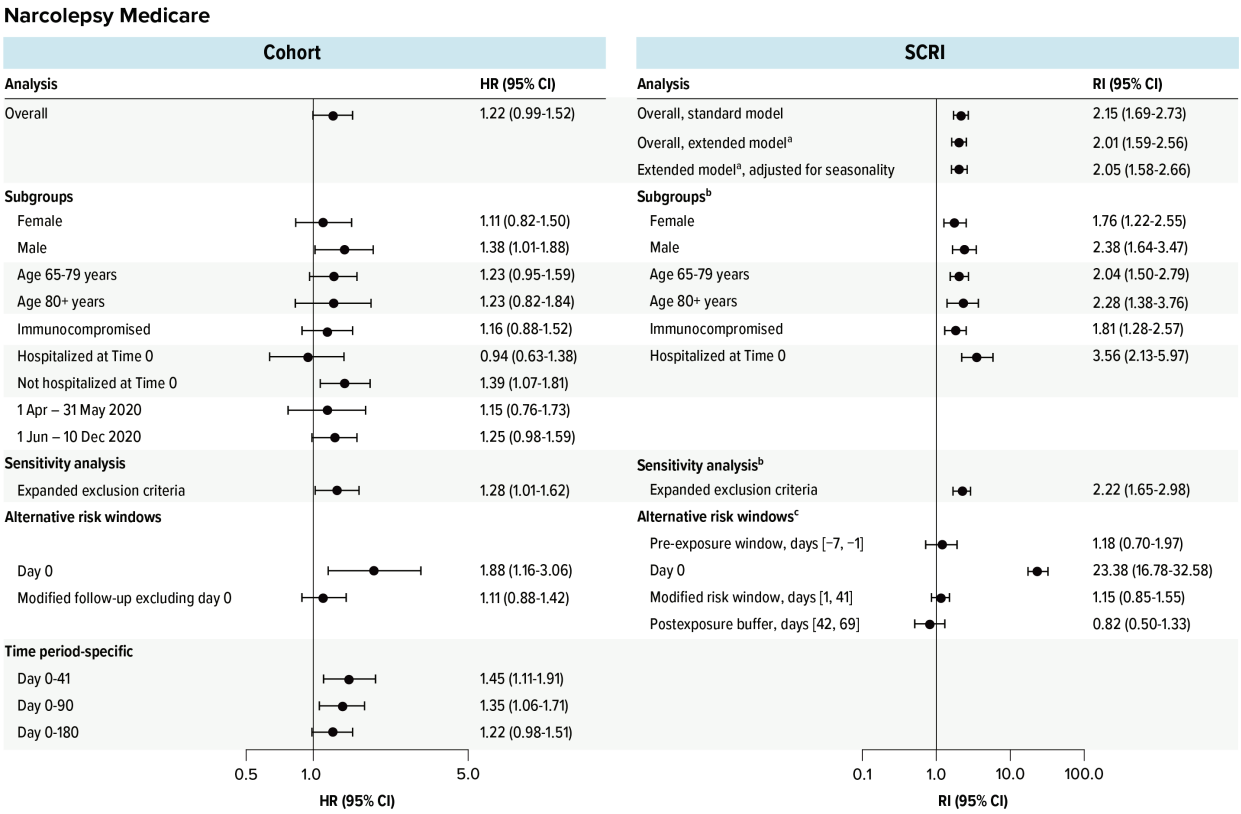
Estimates from all data sources and analytical approaches were consistent with a potential modest association between COVID-19 diagnosis and the incidence of encephalitis/encephalomyelitis, with overall HR estimates of 1.43 (95% CI, 1.10-1.85) and 1.99 (95% CI, 0.69-5.77) for Medicare and MarketScan, respectively. The results were generally consistent across all analyses, with some variation noted in some subgroup analyses. No Time 0 effects were observed with encephalitis/encephalomyelitis, and the alternative risk period analyses excluding day 0 had minimal or no impact. Analyses with SCRIs were not performed because the substantial risk of death after contracting encephalitis/encephalomyelitis violates the assumption of no event-dependent censoring (Table 1).

4.2.4. Narcolepsy

Narcolepsy was evaluated using both the cohort design and the SCRI design in both data sources. An overview of the results of all the outcome analyses for the cohort design and SCRI design in both data sources is shown in Figure 13.

Figure 13. Estimated Association of a COVID-19 Diagnosis With Narcolepsy, All Analyses and Data Sources





CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; NE = not estimable; RI = relative incidence; SCRI = self-controlled risk interval.

[a] Extended Poisson models accounting for event-dependent observation windows.

[b] Evaluated using the extended Poisson models accounting for event-dependent observation windows and adjustment for seasonality.

[c] Evaluated using modified extended Poisson models accounting for event-dependent observation windows to allow for 1-day intervals and adjustment for seasonality.

4.2.4.1. Overall Outcome Analyses

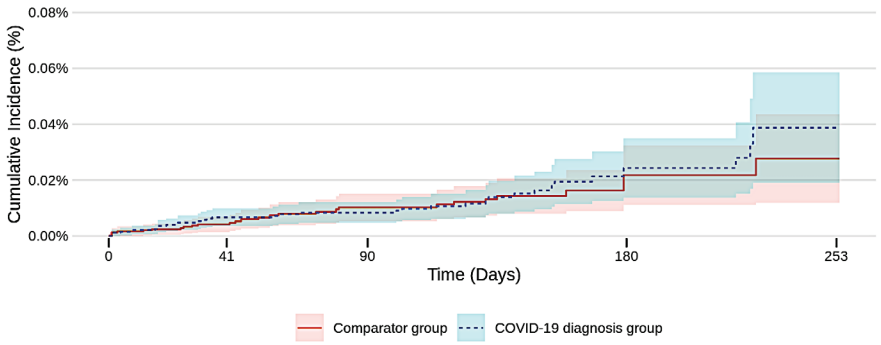
In the cohort analyses, the weighted cumulative incidence of narcolepsy by COVID-19-diagnosed and comparator group status over follow-up is shown in Figure 14. The cumulative incidence was low in both data sources, with the Medicare cumulative incidence being slightly higher than that of the MarketScan cohort. In MarketScan, the cumulative incidence was generally similar between the 2 exposure groups through most of follow-up, while in Medicare, the cumulative incidence in the COVID-19—diagnosed group was more consistently higher than the comparison group throughout the majority of follow-up. The overall HR and RI estimates across all of follow-up and at prespecified time periods are shown in Figure 13 and Table B-5-MarketScan.D and Table B-5-Medicare.D.

The overall analysis HR in MarketScan was 1.17 (95% CI, 0.70-1.94), while the Medicare cohort overall HR was 1.22 (95% CI, 0.99-1.52). The SCRI analyses (extended, seasonality-adjusted models) in both data sources resulted in RI estimates higher than the HR estimates from the cohort analyses: overall MarketScan RI = 1.87 (95% CI, 1.08-3.26); Medicare RI = 2.05 (95% CI, 1.58-2.66).

In the MarketScan cohort, the time period–specific HRs were all consistent with the overall estimate. In Medicare, the HR was highest in the day 0-41 estimate (HR = 1.45; 95% CI, 1.11-1.91) and was generally attenuated as the time period was extended.

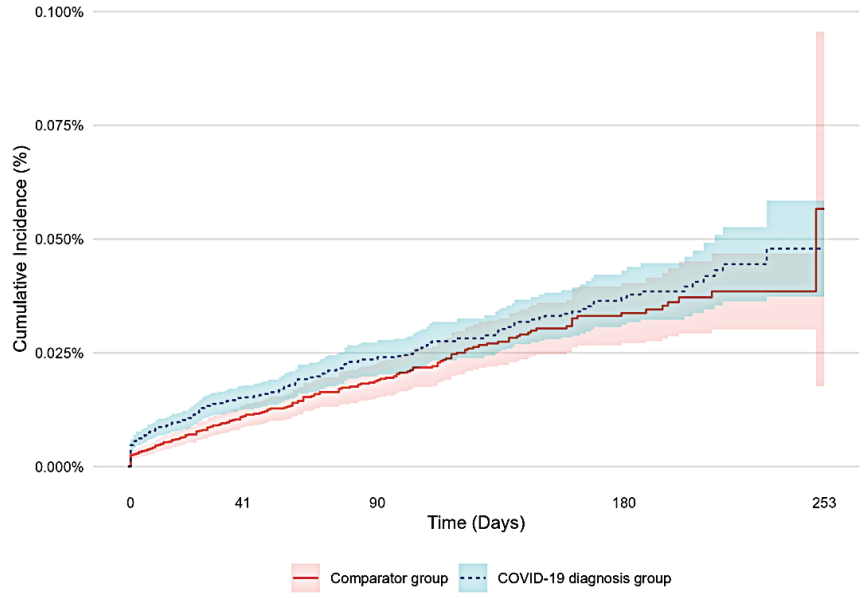
Figure 14. Weighted Cumulative Incidence of Narcolepsy Among Individuals With a COVID-19 Diagnosis and Comparators Without a COVID-19 Diagnosis

A. MarketScan



Comparator group					
At Risk	318512	187572	127914	36990	542
Censored	4484	132903	191681	281742	318482
Events	4	12	21	28	29
COVID-19 diagnosis group					
At Risk	318927	187338	127231	36399	529
Censored	4458	133561	192780	282731	318893
Events	4	17	20	31	34

B. Medicare



Comparator group					
At Risk	1015531	597486	409345	153850	1883
Censored	16203	424176	609326	862526	1015350
Events	25	92	131	174	181
COVID-19 diagnosis group					
At Risk	1015223	550877	373265	136529	1535
Censored	18271	470210	644890	879416	1015015
Events	48	129	168	201	209

COVID-19 = coronavirus disease 2019.

Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

4.2.4.2. Subgroup Analysis

The HRs and RIs for individual subgroups in both the cohort and SCRI analyses are shown in Figure 13. In both MarketScan and Medicare cohort subgroup analyses, the HR estimates were largely consistent with the overall HR, except for the subgroups hospitalized at Time 0 in MarketScan and Medicare where the HRs were decreased. In contrast, the SCRI analyses of both data sources demonstrated increased RI estimates in the hospitalized at Time 0 subgroup. Additionally, estimates in the male subgroup were generally lower in the MarketScan SCRI analysis.

4.2.4.3. Sensitivity Analyses

Results of sensitivity analyses with expanded exclusion criteria in both the cohort and SCRI are summarized in Figure 13. The estimates for the sensitivity analyses with expanded exclusion criteria in all cohort and SCRI analyses were consistent with their respective overall estimates.

4.2.4.4. Alternative Risk Windows

Results of the analyses of alternative risk windows in the cohort (day 0 and follow-up excluding day 0) and SCRI (the 7 days before COVID-19 diagnosis, day 0, the risk window excluding day 0, and the postexposure buffer period) are summarized in Figure 13, Table B-5-MarketScan.D, and Table B-5-Medicare.D.

In the MarketScan cohort analyses, HRs for the alternative risk window analyses of day 0 and those excluding day 0 were similar to each other and consistent with the overall HR estimate because there were few cases on day 0, and occurrence was similar in both groups (Table B-5-MarketScan.D). In the Medicare cohort, the day 0 estimate was elevated while the analysis starting follow-up on day 1 was attenuated. In both the MarketScan and Medicare SCRI analyses, the day 0 estimate was substantially elevated compared with the overall RI, while the RI for the modified period starting on day 1 was attenuated.

In both MarketScan and Medicare SCRI analyses, the pre-exposure windows were attenuated in comparison to the overall estimate, but estimates were still above 1. The postexposure buffer RI could not be estimated in MarketScan, but in Medicare, the RI was below 1.

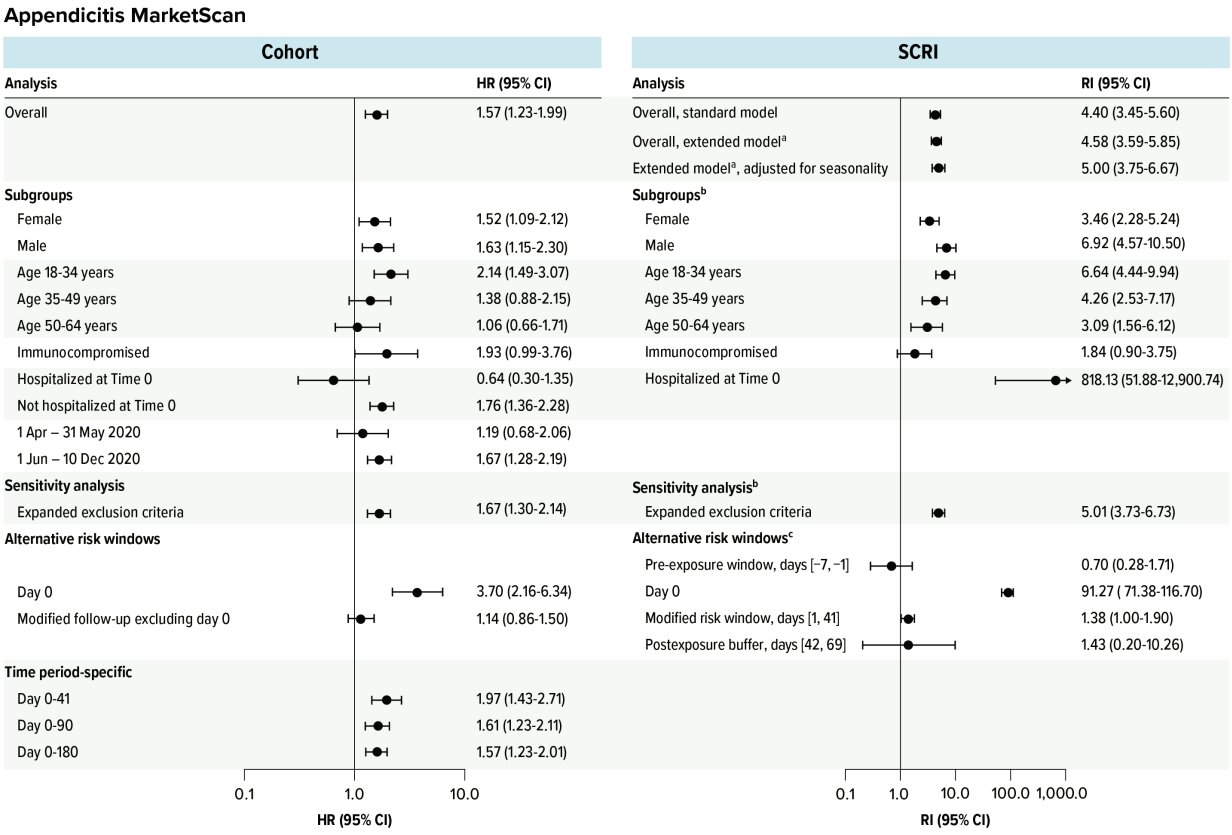
4.2.4.5. Summary of Results

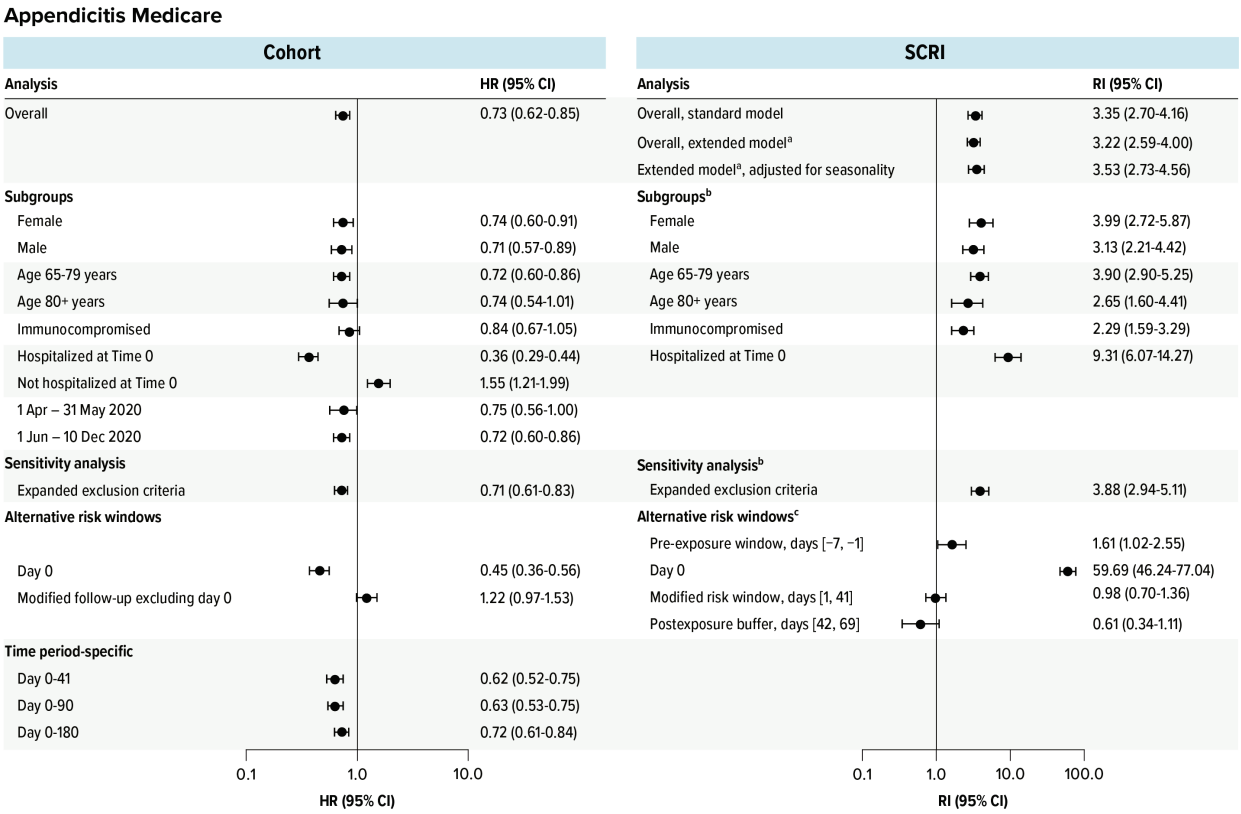
Estimates from all data sources and analytical approaches were inconsistent, and overall analyses generally demonstrated potential modest associations between COVID-19 diagnosis and the incidence of narcolepsy. The overall MarketScan cohort estimates were generally small and close to the null, but the Medicare cohort and the SCRI analyses in both data sources generally showed modestly increased risks. However, strong Time 0 effects were noted in both data sources, and analyses of alternative risk periods excluding day 0 generally resulted in attenuated HR and RI estimates.

4.2.5. Appendicitis

Appendicitis was evaluated with both the cohort design and the SCRI design in both data sources. An overview of the results of all the outcome analyses for the cohort design and SCRI design in both data sources is shown in Figure 15.

Figure 15. Estimated Association of a COVID-19 Diagnosis With Appendicitis, All Analyses and Data Sources





CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; RI = relative incidence; SCRI = self-controlled risk interval.

[a] Extended Poisson models accounting for event-dependent observation windows.

[b] Evaluated using the extended Poisson models accounting for event-dependent observation windows and adjustment for seasonality.

[c] Evaluated using modified extended Poisson models accounting for event-dependent observation windows to allow for 1-day intervals and adjustment for seasonality.

4.2.5.1. Overall Outcome Analyses

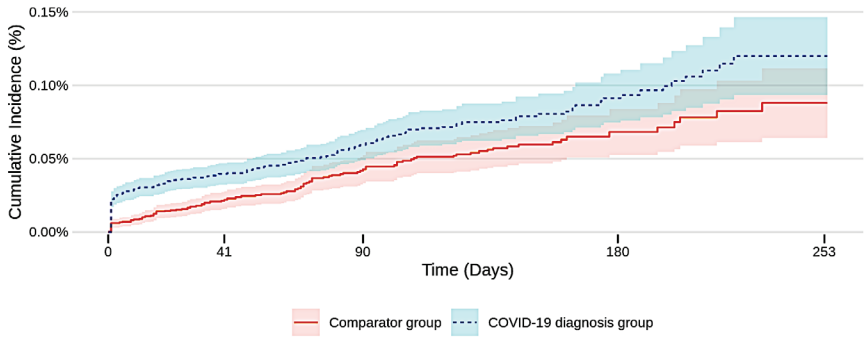
In the cohort analyses, the weighted cumulative incidence of appendicitis by COVID-19 exposure groups over follow-up is shown in Figure 16. In MarketScan, a relatively large number of COVID-19 cases were identified on day 0 (Table B-5-MarketScan.E), and the cumulative incidence was higher in the COVID-19-diagnosed group than the comparator group throughout follow-up. In Medicare, a relatively large proportion of appendicitis cases in both groups were identified on day 0 (Table B-5-Medicare.E), but the number of cases on day 0 was higher in the comparator group than the COVID-19-diagnosed group, resulting in the cumulative incidence being higher in the comparator group for much of follow-up, until they became more similar at approximately 180 days. The majority of the cases in all groups in both data sources occurred early in follow-up.

The overall HR and RI estimates across all of follow-up and at prespecified time periods is shown in Figure 15. In the overall MarketScan cohort analysis, those within the COVID-19 diagnosis group were more likely to experience appendicitis in comparison to the comparator group (HR = 1.57; 95% CI, 1.23-1.99). In contrast, the Medicare cohort analysis reported an HR below the null, HR = 0.73 (95% CI, 0.62-0.85), consistent with the pattern of cumulative incidence noted in Figure 16. The MarketScan SCRI analyses and Medicare SCRI analyses also suggested increased risk of appendicitis, with the standard, extended, and seasonality-adjusted SCRI models yielding fairly consistent RI estimates within each data source: MarketScan extended, seasonality-adjusted RI = 5.00 (95% CI, 3.75-6.67); Medicare RI = 3.53 (95% CI, 2.73-4.56).

In both the MarketScan and Medicare cohorts, the time period–specific HRs were all consistent with their respective overall estimate, with slight attenuation observed with increasing risk window length.

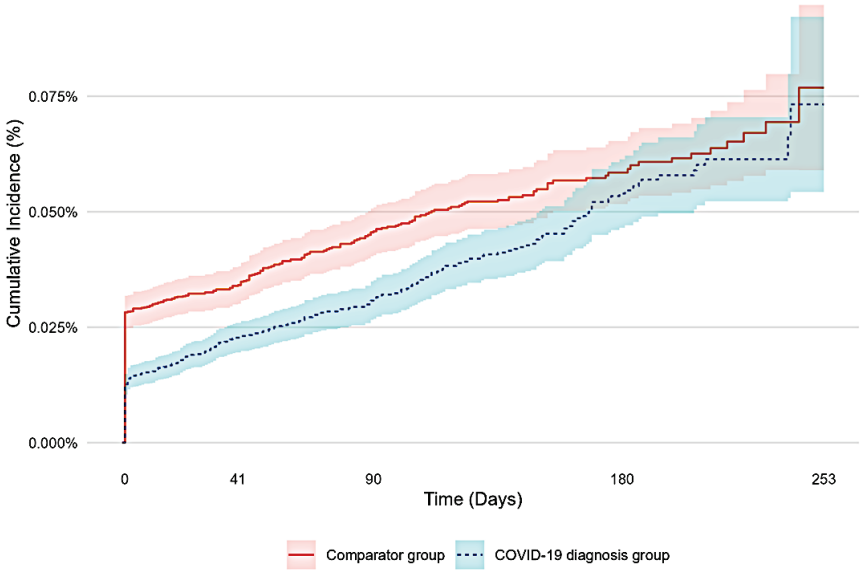
Figure 16. Weighted Cumulative Incidence of Appendicitis Among Individuals With a COVID-19 Diagnosis and Comparators Without a COVID-19 Diagnosis

A. MarketScan



Comparator group					
At Risk	317982	187344	127757	36949	539
Censored	4466	132546	191238	281171	317866
Events	19	60	92	111	116
COVID-19 diagnosis group					
At Risk	318684	186907	126850	36222	527
Censored	4462	133649	192793	282521	318503
Events	71	118	148	174	181

B. Medicare



Comparator group					
At Risk	1015094	597478	409443	153981	1890
Censored	16193	423505	608524	861705	1014655
Events	287	333	391	428	439
COVID-19 diagnosis group					
At Risk	1015412	550535	372933	136184	1519
Censored	18312	470680	645331	879847	1015105
Events	128	205	242	298	307

COVID-19 = coronavirus disease 2019.

Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

4.2.5.2. Subgroup Analyses

The HRs and RIs for individual subgroups in both the cohort and SCRI analyses are shown in Figure 15. In the MarketScan cohort, the HR estimates were largely consistent with the overall HR, except for ages 35-64 years, hospitalized at Time 0, and the earliest calendar period groups, which were attenuated. Similarly, in the Medicare cohort, most subgroup HRs were generally similar to the overall HR, except the HRs by hospitalization status at Time 0 were substantially different: the hospitalized at Time 0 subgroup (HR = 0.36; 95%CI, 0.29-0.44); nonhospitalized at Time 0 subgroup (HR = 1.55; 95%CI, 1.21-1.99). Conversely, the SCRI analyses in both data sources showed strongly increased RIs for the hospitalized at Time 0 subgroups.

4.2.5.3. Sensitivity Analyses

Results of sensitivity analyses with expanded exclusion criteria in both the cohort and SCRI are summarized in Figure 15. All cohort and SCRI sensitivity analyses estimates from both MarketScan and Medicare remained consistent with their respective overall estimates.

4.2.5.4. Alternative Risk Windows

Results of the analyses of alternative risk windows in the cohort (day 0 and follow-up excluding day 0) and SCRI (the 7 days before COVID-19 diagnosis, day 0, the risk window excluding day 0, and the postexposure buffer period) are summarized in Figure 15.

The HR estimate from MarketScan cohort analysis for day 0 was increased in comparison to the overall HR, and attenuated in the analysis removing day 0 from follow-up, consistent with the pattern observed in the cumulative incidence curves (Figure 16). Conversely, the RI estimate from the analysis of the Medicare cohort risk window for day 0 was decreased compared to the overall RI, while the analysis of the risk window excluding day 0 was increased compared to the overall ($HR_{alternative}$ = 1.22; 95% CI, 0.97-1.53).

Similar results were seen in both the MarketScan and Medicare SCRIs, with strongly increased RIs for day 0 alone (RIs > 59), and attenuated risks when day 0 was excluded and follow-up started on day 1, consistent with the large number of cases observed occurring on day 0. Similarly, in both the MarketScan and Medicare analysis, the estimates of the pre-exposure risk period and postexposure buffer risk window RIs were closer to or below the null compared to the overall in both data sources.

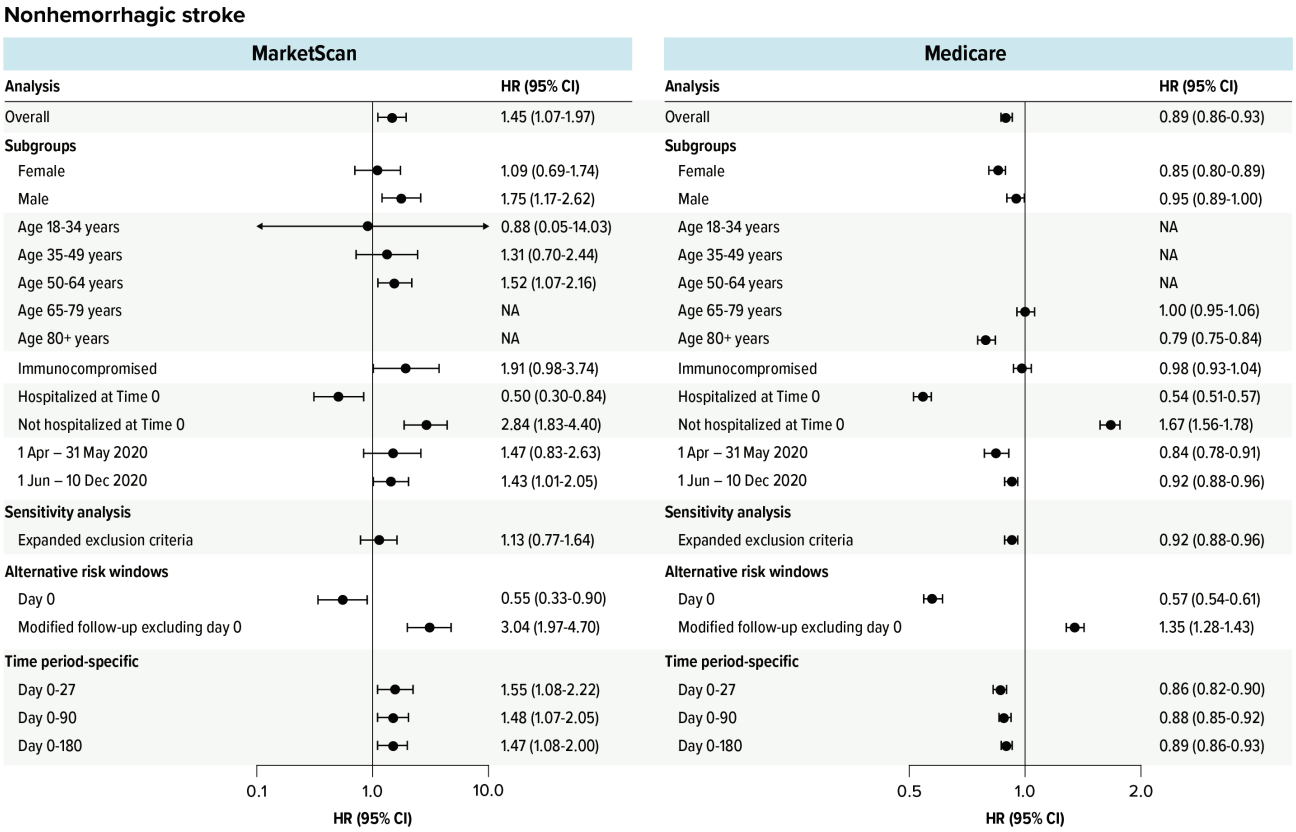
4.2.5.5. Summary of Results

The results of cohort overall analysis in MarketScan, and both data source–specific SCRI analyses, suggested an increased risk of appendicitis associated with a COVID-19 diagnosis, while the Medicare overall analyses suggested decreased risk. However, an alternative risk window analysis that excluded events occurring on day 0 shifted the Medicare HR upward across the null because events on day 0 were observed more than twice as frequently among comparators as COVID-19-diagnosed patients in both data sources (Table B-5-MarketScan.E, Table B-5-Medicare.E). Additionally, the SCRI analyses in Medicare were markedly attenuated in alternative risk window analyses (MarketScan $RI_{alternative}$ = 1.38 [95% CI, 1.00-1.90], Medicare $RI_{alternative}$ = 0.98 [95% CI, 0.70-1.36]). After considering the impact of concurrently diagnosed COVID-19 and appendicitis, the data suggest only a weak potentially increased risk of appendicitis after COVID-19 diagnosis.

4.2.6. Nonhemorrhagic Stroke

Nonhemorrhagic stroke was evaluated only with the cohort design in both data sources, given that the increased mortality associated with the AE violated the assumptions of the SCRI. An overview of the results of all the outcome analyses for the cohort design in both data sources is shown in Figure 17.

Figure 17. Estimated Association of a COVID-19 Diagnosis with Nonhemorrhagic Stroke, All Analyses and Data Sources



CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; NA = not applicable.

4.2.6.1. Overall Outcome Analyses

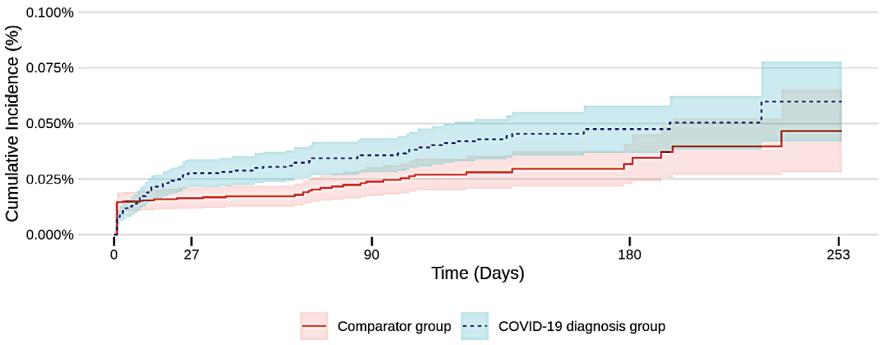
In the cohort analyses, the weighted cumulative incidence by COVID-19 exposure groups over follow-up is shown in Figure 18. In both data sources, a fairly large number of nonhemorrhagic stroke cases were identified on day 0, particularly among the comparator group (Table B-5-MarketScan.F, Table B-5-Medicare.F). In the COVID-19-diagnosed groups in both data sources, the majority of the nonhemorrhagic stroke cases occurred in first few weeks of follow-up. The overall HR estimates across all of follow-up and at prespecified time periods is shown in Figure 17.

In the overall MarketScan cohort analysis, those within the COVID-19 diagnosis group were found to be more likely to experience nonhemorrhagic stroke during the risk period compared to the comparator group (HR = 1.45; 95% CI, 1.07-1.97), while in the overall Medicare cohort analysis, those within the COVID-19 diagnosis group were found to be less likely to experience nonhemorrhagic stroke (HR = 0.89; 95% CI, 0.86-0.93). As seen in the cumulative incidence curves for Medicare, the lower incidence in the COVID-19-diagnosed groups was driven entirely by the nonhemorrhagic stroke cases in the comparator group on day 0.

In both cohorts, the time period–specific HRs were all consistent with their respective overall estimates, with slight attenuation with lengthening risk periods.

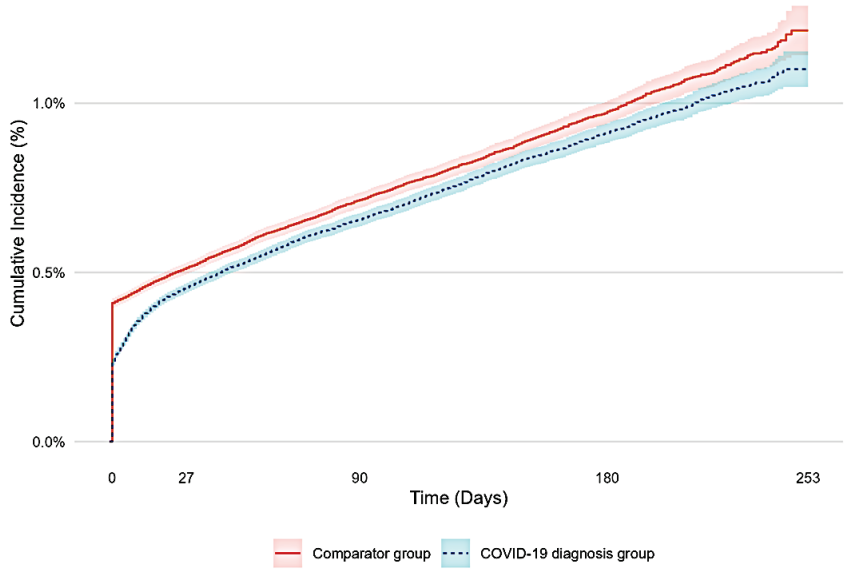
Figure 18. Weighted Cumulative Incidence of Nonhemorrhagic Stroke Among Individuals With a COVID-19 Diagnosis and Comparators Without a COVID-19 Diagnosis

A. MarketScan



Comparator group					
At Risk	317294	223841	127494	36790	534
Censored	4451	96787	190843	280680	317221
Events	46	51	62	70	73
COVID-19 diagnosis group					
At Risk	317828	223657	126311	35917	518
Censored	4449	97530	192529	282040	317723
Events	25	80	92	103	106

B. Medicare



Comparator group					
At Risk	928031	643872	371650	138713	1641
Censored	14523	289115	553733	783981	921630
Events	3802	4607	5576	6243	6401
COVID-19 diagnosis group					
At Risk	927951	604023	343271	125366	1414
Censored	16073	329557	582668	797970	922394
Events	2182	3918	4825	5437	5556

COVID-19 = coronavirus disease 2019.

Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

4.2.6.2. Subgroup Analyses

The HRs for individual subgroups are shown in Figure 17. In both cohorts, other than for hospitalized and nonhospitalized subgroups, the subgroup estimates that could be estimated were generally consistent with the overall estimates. In the MarketScan cohort, the HR estimates for the male, those ages 50-64 years, and the later calendar period subgroups were consistent with the overall estimate. In both data sources, the subgroups hospitalized at Time 0 showed greatly reduced HR estimates relative to the overall estimates, below the null, while the nonhospitalized subgroup showed strongly increased HRs above the null.

4.2.6.3. Sensitivity Analyses

Results of sensitivity analyses with expanded exclusion criteria are summarized in Figure 17. The MarketScan cohort sensitivity analysis HR was attenuated while the Medicare cohort sensitivity analysis HR estimate remained consistent with the overall estimate.

4.2.6.4. Alternative Risk Windows

Results of the analyses of alternative risk windows (day 0 and follow-up excluding day 0) are summarized in Figure 17.

Both MarketScan and Medicare identify similar trends in the HR estimates of the alternative risk windows. In both day 0 risk windows, the HR estimates were decreased in comparison to the overall estimates (HR estimates ≤ 0.57). In both risk windows that exclude day 0, the HR estimates were increased in comparison to the overall estimates, with both identifying an increased risk of nonhemorrhagic stroke in the COVID-19—diagnosed group. This potential increase in risk aligns with the MarketScan overall trend; however, the increase in risk diverges from the Medicare overall result. The results of these analyses are consistent with the observed trends in the cumulative incidence (Figure 18), where the differences between the groups are driven by an excess of comparator cases happening on day 0.

4.2.6.5. Summary of Results

Estimates from the MarketScan overall cohort analysis demonstrate a modest association between COVID-19 diagnosis and the incidence of nonhemorrhagic stroke. Analyses with SCRIs were not performed because the substantial risk of death after experiencing a nonhemorrhagic stroke violates the assumption of no event-dependent censoring (Table 1).

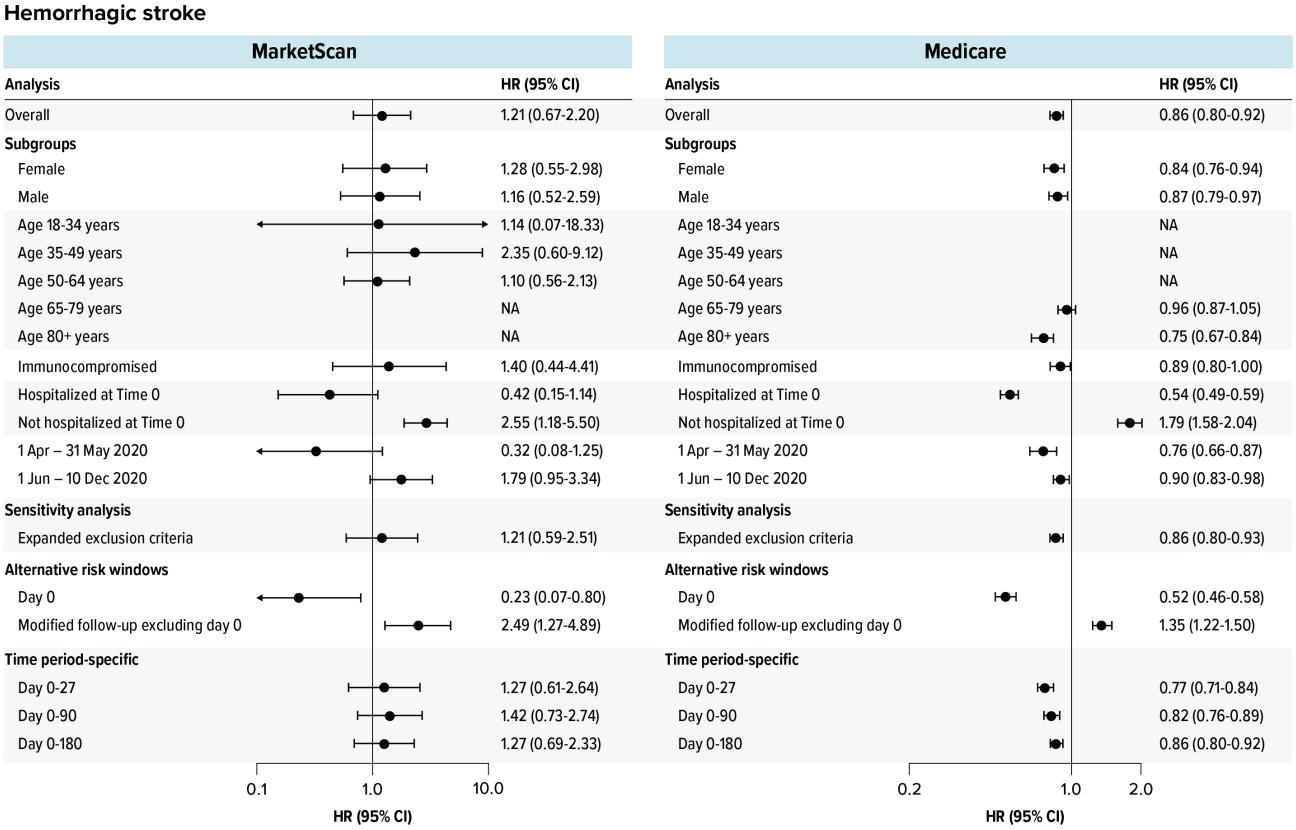
In the Medicare cohort, an HR estimate below 1.00 was observed in the overall cohort analysis, driven by cases in the comparator group on day 0 (Figure 18, Table B-5-Medicare.F). An analysis that excluded day 0 shifted the direction of effect, with HRs suggesting a positive association between COVID-19 diagnosis and nonhemorrhagic stroke in Medicare which was closer in alignment with the direction of effect in MarketScan (Medicare $HR_{overall}$ = 0.89 [95% CI, 0.86-0.93], $HR_{alternative}$ = 1.35 [95% CI, 1.28-1.43]; MarketScan $HR_{overall}$ = 1.45 [95% CI, 1.07-1.97], $HR_{alternative}$ = 3.04 [95% CI, 1.97-4.70]) because events on day 0 were observed more frequently among comparators than COVID-19-diagnosed patients in both data sources (Table B-5-MarketScan.F, Table B-5-Medicare.F).

Additionally, because a diagnosis of the nonhemorrhagic stroke outcome required an inpatient diagnosis (Table 1), many of the day 0 events in the comparator group may be due to matching on hospitalization, consequently increasing the probability of patients hospitalized for other, non-COVID—19 conditions (like stroke) on day 0. Therefore the subgroup analyses of patients hospitalized at Time 0 demonstrated a similar effect as the day 0 analyses.

4.2.7. Hemorrhagic Stroke

Hemorrhagic stroke was evaluated only using the cohort design in both data sources, given the increased mortality associated with the AE violated the assumptions of the SCRI. An overview of the results of all the outcome analyses for the cohort design in both data sources is shown in Figure 19.

Figure 19. Estimated Association of a COVID-19 Diagnosis With Hemorrhagic Stroke, All Analyses and Data Sources



CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; NA = not applicable; RI = relative incidence.

4.2.7.1. Overall Outcome Analyses

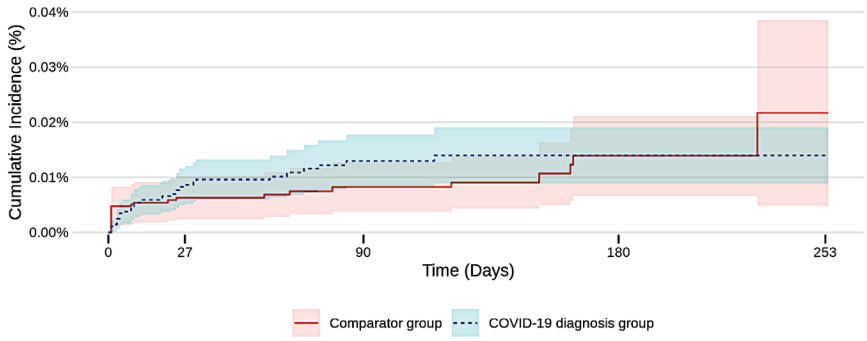
In the cohort analyses, the weighted cumulative incidence by COVID-19 exposure groups over follow-up is shown in Figure 20. In MarketScan, the cumulative incidence rates for hemorrhagic stroke per 100,000 person-years were 14.45 (95% CI, 9.30-19.60) for the COVID-19-diagnosed group and 21.65 (95% CI, 6.29-37.01) for the comparator (Table B-5-MarketScan.G) In Medicare the corresponding cumulative incidence was 313.04 (95% CI, 287.48-338.58) and 343.02 (95% CI, 300.53-385.49) (Table B-5-Medicare.G). Notably, a large number of hemorrhagic stroke cases in both data sources were identified on day 0, particularly among the comparator group (Table B-5-MarketScan.G, Table B-5-Medicare.G). In the COVID-19-diagnosed groups in both data sources, the majority of the AE cases occurred in first few weeks of follow-up. In MarketScan, the cumulative incidence was initially higher in the comparator group immediately after the start of follow-up, but the COVID-19-diagnosed group cumulative incidence quickly surpassed the comparator by day 27, and the incidence in the 2 groups became very similar by 180 days. In Medicare, the initial difference in hemorrhagic stroke incidence on day 0 persisted for the entirety of follow-up. The overall HR across all of follow-up and at prespecified time periods is shown in Figure 19.

In the MarketScan cohort analysis, the overall HR was 1.21 (95% CI, 0.67-2.20). In Medicare, the HR estimate was on the opposite side of the null (HR = 0.86; 95% CI, 0.80-0.92).

In both cohorts, the time period–specific HRs were all consistent with their respective overall estimates, with slight attenuation with longer follow-up seen in Medicare.

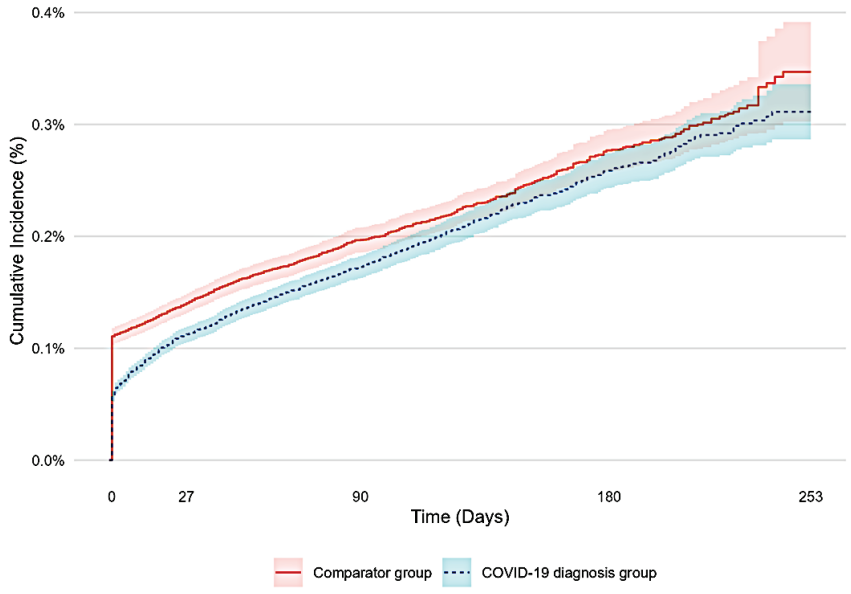
Figure 20. Weighted Cumulative Incidence of Hemorrhagic Stroke Among Individuals With a COVID-19 Diagnosis and Comparators Without a COVID-19 Diagnosis

A. MarketScan



Comparator group					
At Risk	318328	224608	127985	36978	536
Censored	4470	97092	191431	281575	318302
Events	15	19	22	26	27
COVID-19 diagnosis group					
At Risk	318970	224519	126864	36135	522
Censored	4473	97869	193183	283035	318937
Events	4	24	31	33	33

B. Medicare



Comparator group					
At Risk	1001720	696729	403422	151445	1854
Censored	15937	313923	599858	849420	999812
Events	1108	1354	1651	1864	1908
COVID-19 diagnosis group					
At Risk	1002779	649781	368648	134575	1509
Censored	17908	362267	635874	867565	1001198
Events	574	1036	1326	1544	1581

COVID-19 = coronavirus disease 2019.

Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

4.2.7.2. Subgroup Analyses

The HRs for individual subgroups are shown in Figure 19. In both MarketScan and Medicare, substantial differences in HR estimates were observed with hospitalization status at Time 0, with HR estimates below 1 in those hospitalized at Time 0, and HR estimates above 1 in those not hospitalized at Time 0).

4.2.7.3. Sensitivity Analyses

Results of sensitivity analyses with expanded exclusion criteria are summarized in Figure 19. The sensitivity analysis estimates for both MarketScan and Medicare cohort analyses remained consistent with their respective overall estimates.

4.2.7.4. Alternative Risk Windows

Results of the analyses of alternative risk windows (day 0 and follow-up excluding day 0) are summarized in Figure 19. In both MarketScan and Medicare analyses, the HR estimates for day 0 were decreased compared to the overall analyses, and the HR estimates excluding day 0 were increased. As seen in the cumulative incidence curves (Figure 20), there were more cases in the comparator group on day 0 in both data sources (Table B-5-MarketScan.G, Table B-5-Medicare.G), although that did not remain true for the entirety of follow-up.

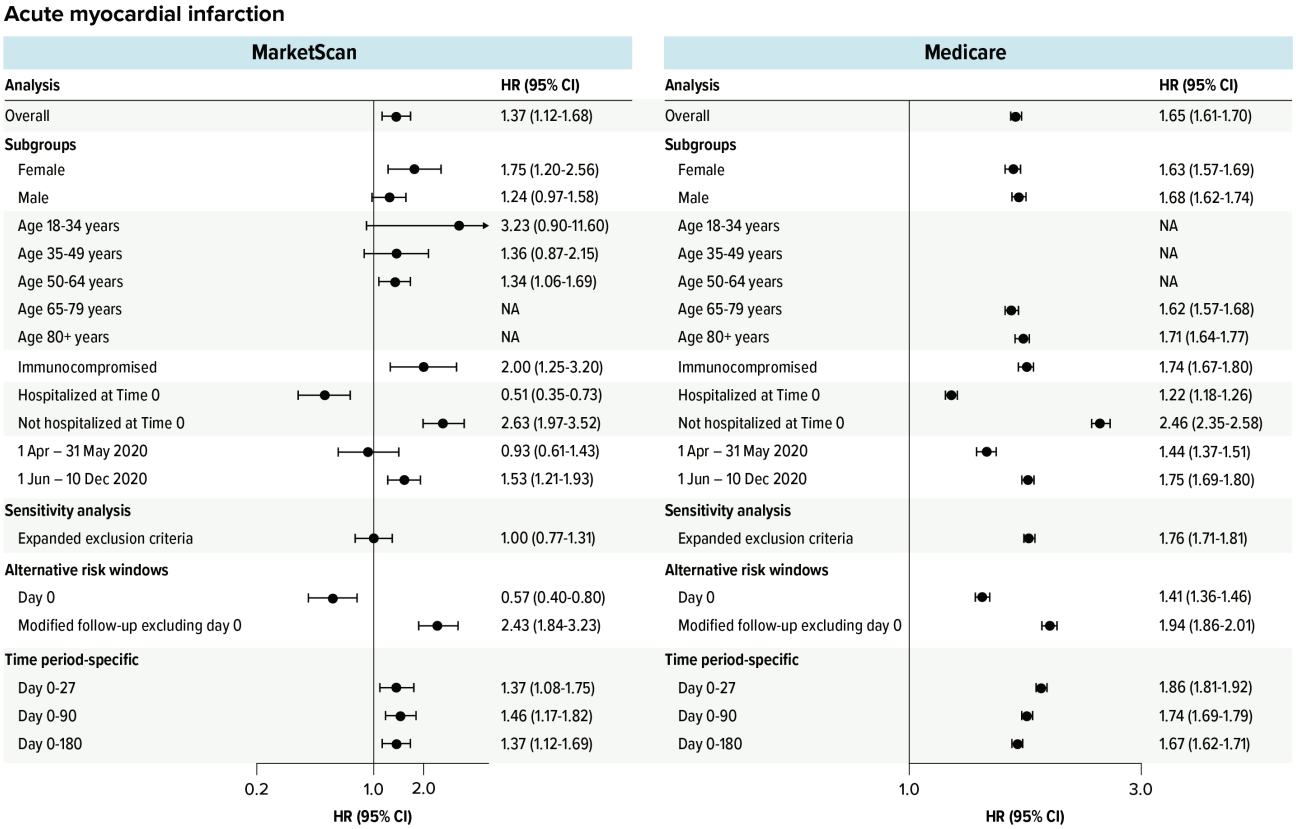
4.2.7.5. Summary of Results

Estimates from the overall cohort MarketScan analysis demonstrate a modestly increased risk of hemorrhagic stroke associated with a COVID-19 diagnosis. In the overall Medicare cohort analysis, a reduced HR estimate was observed (HR = 0.86; 95% CI, 0.80-0.92), but the effect measure estimate changed direction when day 0 was removed from follow-up ($HR_{alternative}$ = 1.35; 95% CI, 1.22-1.50) because events on day 0 were observed among comparators more often than COVID-19-diagnosed patients (Table B-5-MarketScan.G, Table B-5-Medicare.G). Similarly, because a diagnosis of the hemorrhagic stroke outcome required an inpatient diagnosis (Table 1), many of the day 0 events in the comparator group may be due to matching on hospitalization, thus, the subgroup analyses of patients hospitalized at Time 0 demonstrated a similar effect as the day 0 analyses.

4.2.8. Acute Myocardial Infarction

Acute myocardial infarction (AMI) was evaluated only with the cohort design in both data sources, given the increased mortality associated with the AE violated the assumptions of the SCRI. An overview of all AMI results for the cohort design in both data sources is shown in Figure 21.

Figure 21. Estimated Association of a COVID-19 Diagnosis With Acute Myocardial Infarction, All Analyses and Data Sources



CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; NA = not applicable.

4.2.8.1. Overall Outcome Analyses

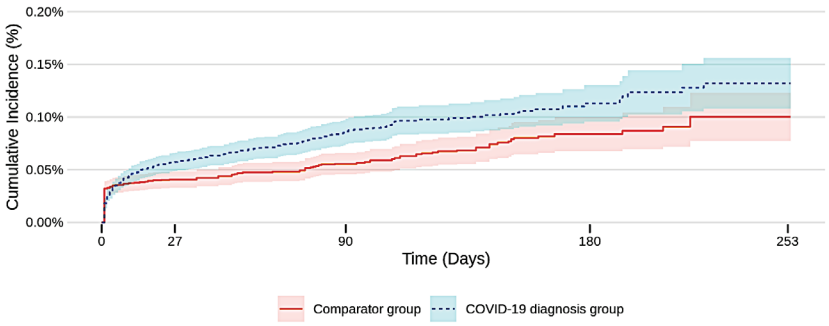
In the cohort analyses, the weighted cumulative incidence by COVID-19 exposure groups over follow-up is shown in Figure 22. In both data sources, a large number of patients were diagnosed with AMI on day 0. In MarketScan, more individuals in the comparator group had an AMI on day 0 than individuals in the COVID-19-diagnosed group (Table B-5-MarketScan.H), but the cumulative incidence in the COVID-19-diagnosed group quickly increased above that of the comparator group throughout the rest of follow-up. In Medicare, a large number of AMI cases in both groups were identified on day 0, but it was more common in the COVID-19-diagnosed group (Table B-5-Medicare.H), and the difference persisted across all of follow-up. In the COVID-19-diagnosed groups in both data sources, the majority of the AMI cases occurred in first few weeks of follow-up. Generally, the incidence of AMI was much higher in the older Medicare cohort than in MarketScan. The overall HR across all of follow-up and at prespecified time periods is shown in Figure 21.

The overall MarketScan and Medicare cohort analyses identified a moderate increase in the likelihood of AMI in those diagnosed with COVID-19 compared to the comparator group.

In the MarketScan cohort, the time period–specific HRs were consistent with the overall estimate. In Medicare, all time period–specific HRs were also consistent with the overall estimate, with attenuation observed in the longer follow-up periods.

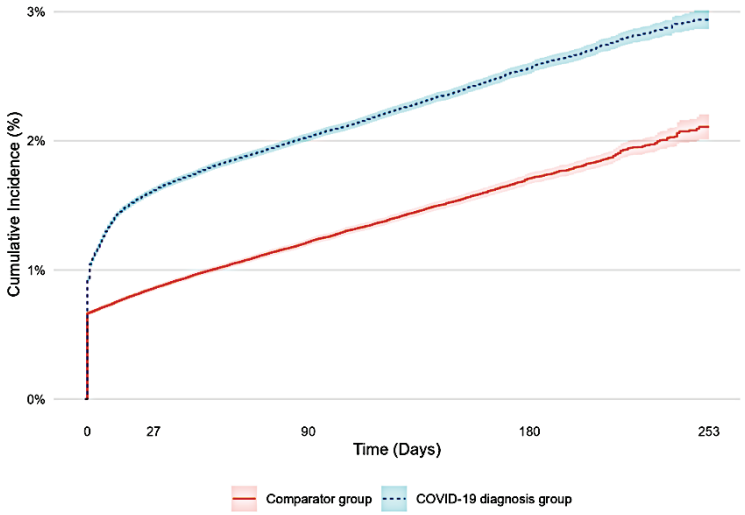
Figure 22. Weighted Cumulative Incidence of Acute Myocardial Infarction Among Individuals With a COVID-19 Diagnosis and Comparators Without a COVID-19 Diagnosis

A. MarketScan



Comparator group					
At Risk	317587	223997	127599	36832	533
Censored	4454	96849	190947	280827	317408
Events	102	126	150	174	178
COVID-19 diagnosis group					
At Risk	318220	223897	126456	35976	518
Censored	4454	97592	192649	282238	317976
Events	58	173	219	239	244

B. Medicare



Comparator group					
At Risk	974158	674827	390336	145793	1781
Censored	15221	301284	577050	818126	962676
Events	6493	8074	9885	11208	11482
COVID-19 diagnosis group					
At Risk	975114	628470	356950	129760	1425
Censored	17046	341699	604257	828018	956664
Events	9125	14894	16877	18194	18451

COVID-19 = coronavirus disease 2019.

Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

4.2.8.2. Subgroup Analyses

The HRs for individual subgroups are shown in Figure 21. In MarketScan, results from the subgroup analyses were generally aligned with the overall results, except for those hospitalized at Time 0, not hospitalized at Time 0, and the earlier time period. In Medicare, all subgroup analyses were precise and above the null, and similar to MarketScan, differences were seen for the hospitalized/nonhospitalized subgroup and the earlier calendar time period. In both data sources, the estimate in the hospitalized subgroup was far reduced from the overall estimate, while the estimate in the nonhospitalized subgroup was substantially increased from the overall estimate. Also in both data sources, the HRs in the earlier time period were attenuated compared with the overall estimate.

4.2.8.3. Sensitivity Analyses

Results of sensitivity analyses with expanded exclusion criteria are summarized in Figure 21. For sensitivity analyses, the HR was attenuated compared to the overall HR in MarketScan while in, Medicare, the estimate remained consistent with the overall HR.

4.2.8.4. Alternative Risk Windows

Results of the analyses of alternative risk windows (day 0 and follow-up excluding day 0) are summarized in Figure 21. In both MarketScan and Medicare analyses, the HR estimates for day 0 were decreased compared to the overall HR. In MarketScan,, there were more comparator cases on day 0 in the comparator group than the COVID-19-exposed group (resulting in an HR estimate < 1 on Time 0); in Medicare, though, there was a large number of AMI events on Time 0 in the comparator group, there was a larger number in the COVID-19-group, resulting in an HR estimate above 1, but still lower than the overall result, Figure 22). The HR estimates excluding day 0 and starting follow-up on day 1 were increased in both data sources.

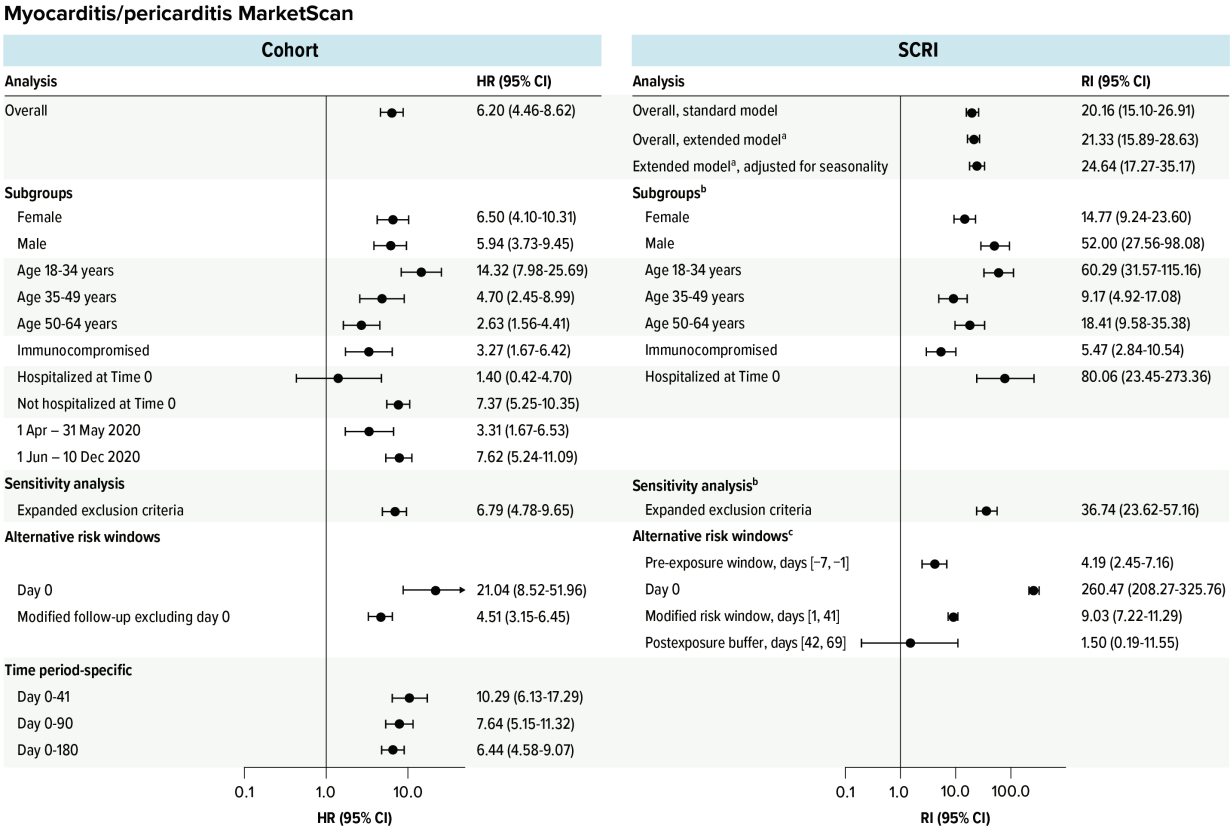
4.2.8.5. Summary of Results

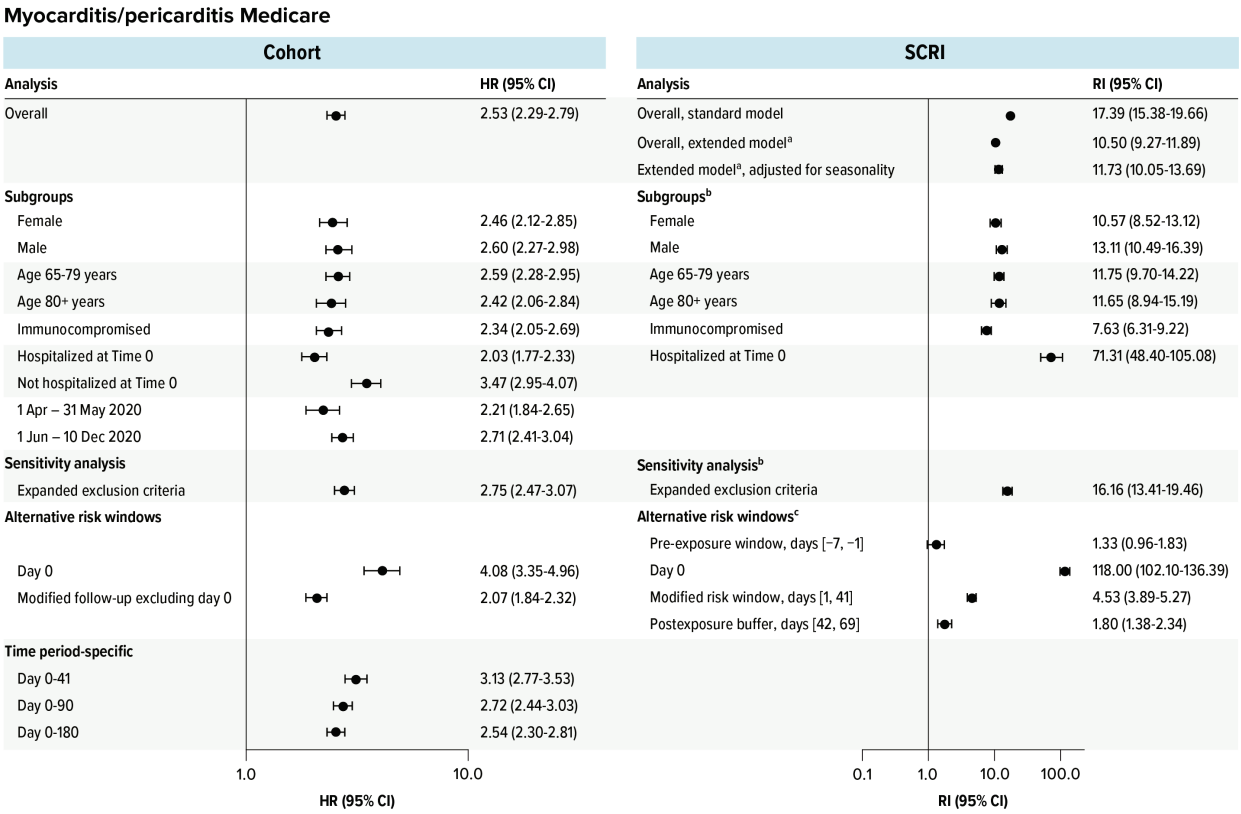
Estimates from all data sources demonstrated moderate to strong positive associations between COVID-19 diagnosis and the incidence of AMI. A large number of concurrent COVID-19 and AMI diagnoses were observed, and analyses excluding day 0 from follow-up generally found even stronger HR estimates. MarketScan and Medicare hazard estimates were generally similar for all analyses. Analyses with SCRIs were not performed because the substantial risk of death after experiencing an AMI violates the assumption of no event-dependent censoring (Table 1).

4.2.9. Myocarditis/Pericarditis

Myocarditis was evaluated with both the cohort design and the SCRI design in both data sources. An overview of all the myocarditis/pericarditis results for the cohort design and SCRI design in both data sources is shown in Figure 23.

Figure 23. Estimated Association of a COVID-19 Diagnosis With Myocarditis/Pericarditis, All Analyses





CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; RI = relative incidence; SCRI = self-controlled risk interval.

[a] Extended Poisson models accounting for event-dependent observation windows.

[b] Evaluated using the extended Poisson models accounting for event-dependent observation windows and adjustment for seasonality.

[c] Evaluated using a modified extended Poisson models accounting for event-dependent observation windows to allow for 1-day intervals and adjustment for seasonality.

4.2.9.1. Overall Outcome Analyses

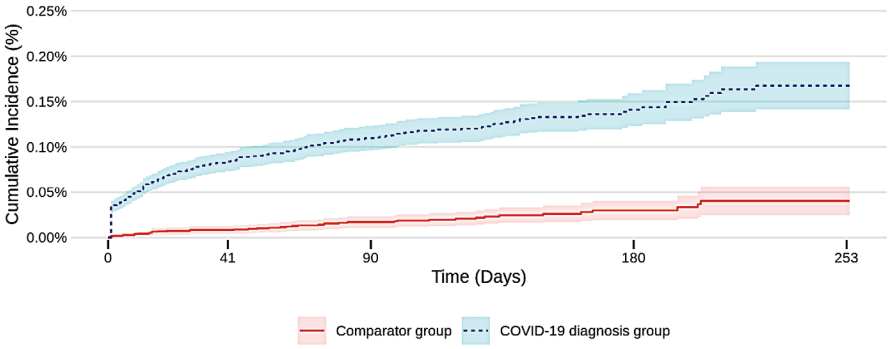
In the cohort analyses, the weighted cumulative incidence by COVID-19 exposure groups over follow-up is shown in Figure 24. In both data sources, a large number of myocarditis/pericarditis cases in the COVID-19-diagnosed group were identified concurrently with their COVID-19 diagnosis (Table B-5-MarketScan.I, Table B-5-Medicare.I). These initial differences on day 0 persisted across the rest of follow-up in both data sources. However, even after the events on day 0, the majority of the cases in the COVID-19-diagnosed groups in both data sources occurred in the first few weeks of follow-up. The cumulative incidence of myocarditis/pericarditis was approximately twice as high in the older Medicare cohort than the MarketScan cohort. The overall HR across all of follow-up and at prespecified time periods is shown in Figure 23.

The overall cohort analyses in both MarketScan and Medicare demonstrated strongly elevated HR estimates (MarketScan HR = 6.20; 95% CI, 4.46-8.62; Medicare HR = 2.53; 95% CI, 2.29-2.79). In the overall SCRI analyses, the RI estimates and 95% CI estimated with the standard, extended models accounting for event-dependent observation, and seasonality-adjusted Poisson models consistently demonstrated increased RI estimates (MarketScan extended seasonality-adjusted RI = 24.64; 95% CI, 17.27-35.17; Medicare RI = 11.73; 95% CI, 10.05-13.69).

In both cohorts, every time period–specific HR indicated an increased risk of myocarditis in the COVID-19-diagnosed group, consistent with the overall HR, with generally attenuated estimates in the longer follow-up periods.

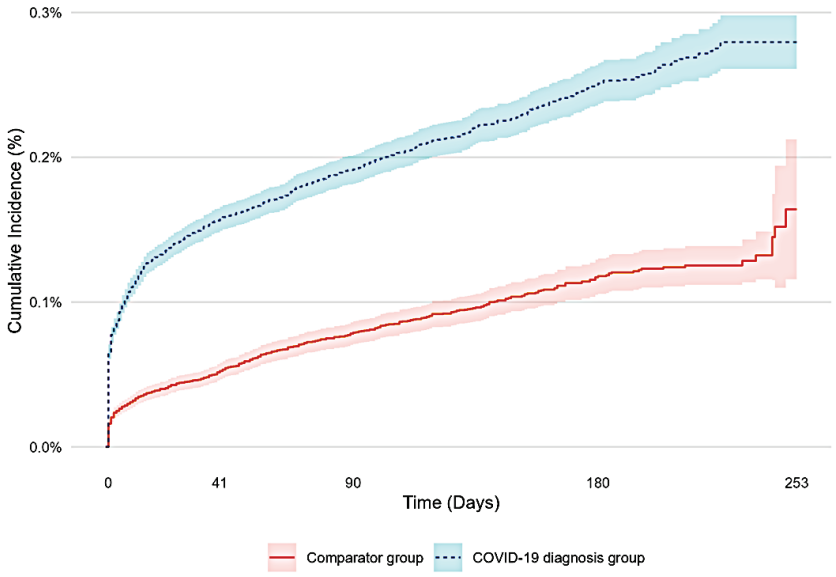
Figure 24. Weighted Cumulative Incidence of Myocarditis/Pericarditis Among Individuals With a COVID-19 Diagnosis and Comparators Without a COVID-19 Diagnosis

A. MarketScan



Comparator group					
At Risk	318407	187643	127973	36965	538
Censored	4471	132710	191508	281643	318356
Events	5	23	37	48	51
COVID-19 diagnosis group					
At Risk	319156	186973	126822	36131	523
Censored	4474	133937	193156	282952	318843
Events	109	241	281	306	314

B. Medicare



Comparator group					
At Risk	1014903	597318	409253	153828	1883
Censored	16189	423345	608317	861393	1014182
Events	164	466	599	706	721
COVID-19 diagnosis group					
At Risk	1015041	549840	372223	135813	1503
Censored	18286	469786	644319	878414	1013286
Events	668	1431	1584	1732	1755

COVID-19 = coronavirus disease 2019.

Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

4.2.9.2. Subgroup Analyses

The HRs and RIs for individual subgroups in both the cohort and SCRI analyses are shown in Figure 23. In MarketScan, subgroup HRs were generally consistent with the overall estimates, except for the estimate in individuals hospitalized at Time 0, which was substantially decreased compared with the overall. In the Medicare cohort analysis, all HR estimates were consistent with the overall HR.

In both the MarketScan and Medicare SCRI analysis, all RI estimates were consistent with the overall except for substantial increases noted in males in MarketScan, attenuated estimates for immunocompromised patients in MarketScan, and increased estimates in those hospitalized at Time 0 in both data sources.

4.2.9.3. Sensitivity Analyses

Results of sensitivity analyses with expanded exclusion criteria in both the cohort and SCRI are summarized in Figure 23. In both MarketScan and Medicare cohort sensitivity analyses, the HR for the expanded exclusion criteria remained consistent with the overall HR. Similar to the cohort design in MarketScan and Medicare, SCRI sensitivity analyses RIs were both increased compared to the overall extended model adjusted for seasonality.

4.2.9.4. Alternative Risk Windows

Results of the analyses of alternative risk windows in the cohort (day 0 and follow-up excluding day 0) and SCRI (the 7 days before COVID-19 diagnosis, day 0, the risk window excluding day 0, and the postexposure buffer period) are summarized in Figure 23.

In the MarketScan cohort analysis, the day 0 risk window HR estimate was substantially increased compared to the overall HR. Conversely, the HR for the risk window excluding day 0 showed a minor decrease. In the Medicare cohort, similar trends emerged within the risk windows; however, the differences between the overall estimate and the day 0 and non–day 0 risk windows were not as pronounced as observed in the MarketScan cohort. In both data sources, the analyses excluding day 0 and starting follow-up on day 1 were attenuated from the overall analyses, but still suggesting a potentially increased risk: MarketScan $HR_{alternative}$ = 4.51 (95% CI, 3.15-6.45); Medicare $HR_{alternative}$ = 2.07 (95% CI, 1.84-2.32).

In the SCRI analyses, both MarketScan and Medicare exhibited substantial increases in the day 0 risk window RIs compared to their respective overall estimates, because the COVID-19—diagnosed groups had an elevated number of cases on day 0 (Figure 24). The RI for the analyses of risk periods excluding day 0 from follow-up were substantially lower compared with the overall RIs.

For the SCRI alternative risk periods, the MarketScan pre-exposure risk window RI was elevated (RI = 4.19; 95% CI, 2.45-7.16), suggesting potentially increased risk before a formal COVID-19 diagnosis was recorded, but the same was not seen in Medicare.

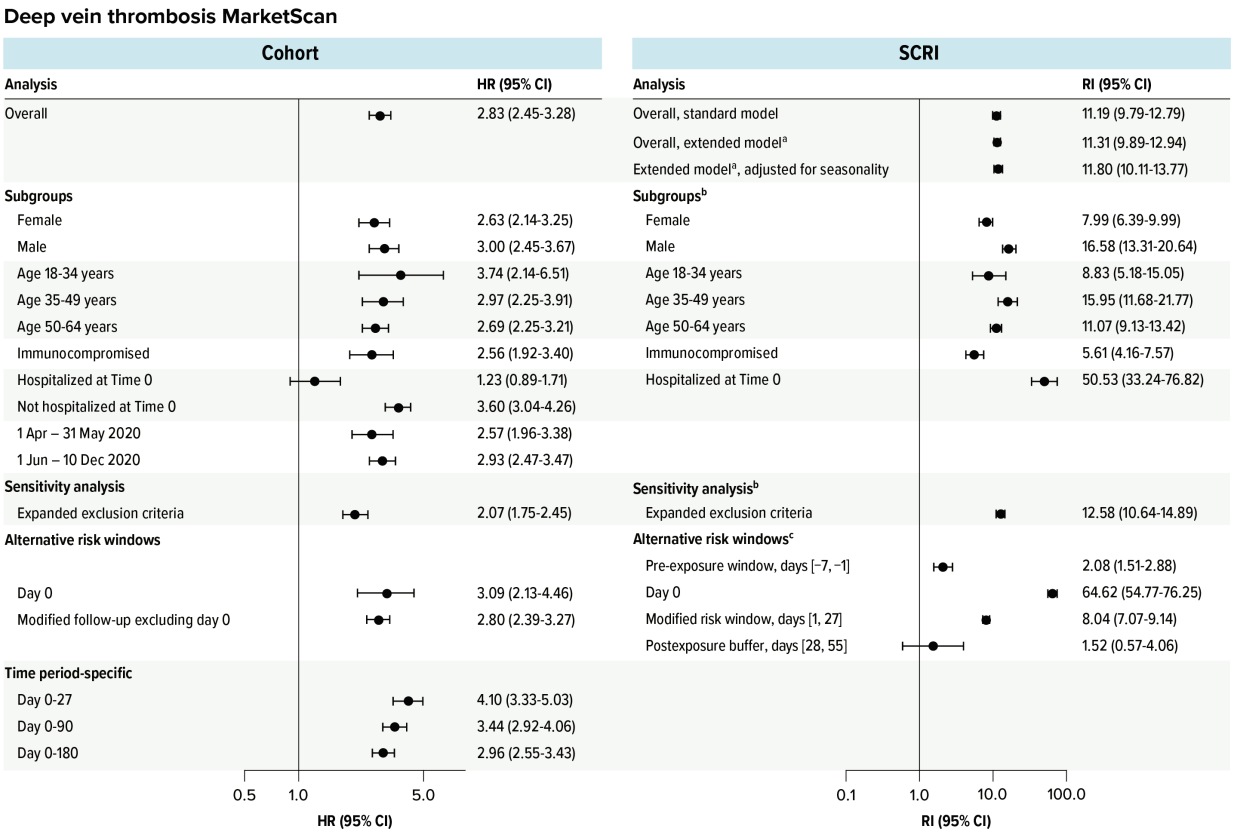
4.2.9.5. Summary of Results

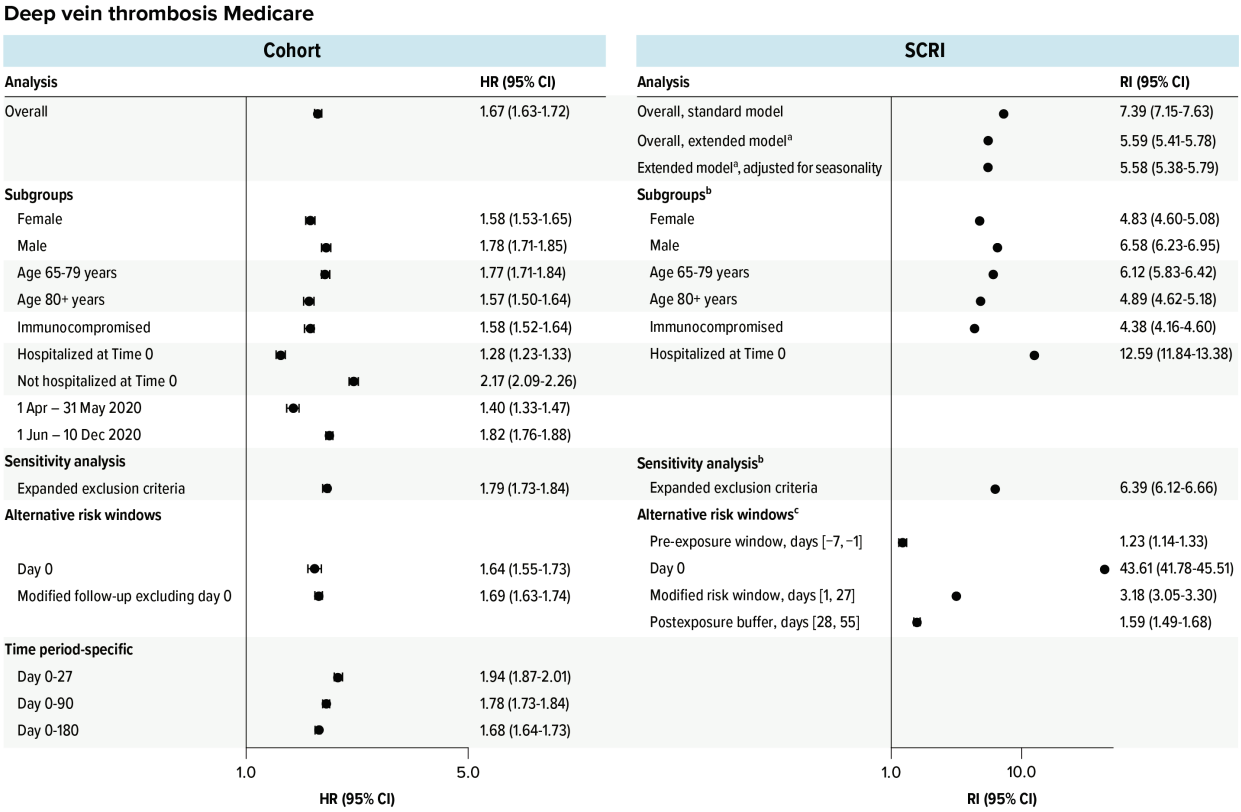
Estimates from all data sources and analytic approaches demonstrated consistent moderate to very strong associations between COVID-19 diagnosis and the incidence of myocarditis/pericarditis. SCRI estimates were generally much stronger than the cohort results in both data sources. A large number of patients in the COVID-19-diagnosed groups had myocarditis/pericarditis diagnoses on day 0. Some variation in effect measure magnitude was observed by hospitalization status, and alternative risk periods excluding day 0 were slightly attenuated, but still consistent with increased risk.

4.2.10. Deep Vein Thrombosis

Deep vein thrombosis (DVT) was evaluated with both the cohort design and the SCRI design in both data sources. An overview of the results of all the outcome analyses for the cohort design and SCRI design in both data sources is shown in Figure 25.

Figure 25. Estimated Association of a COVID-19 Diagnosis With Deep Vein Thrombosis, All Analyses





CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; RI = relative incidence; SCRI = self-controlled risk interval.

[a] Extended Poisson models accounting for event-dependent observation windows.

[b] Evaluated using the extended Poisson models accounting for event-dependent observation windows and adjustment for seasonality.

[c] Evaluated using a modified extended Poisson models accounting for event-dependent observation windows to allow for 1-day intervals and adjustment for seasonality.

4.2.10.1. Overall Outcome Analyses

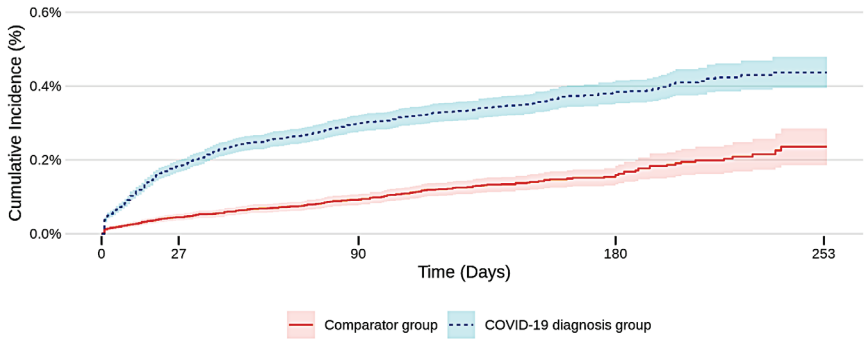
In the cohort analyses, the weighted cumulative incidence by COVID-19 exposure groups over follow-up is shown in Figure 26. In both data sources, the cumulative incidence of DVT was higher in the COVID-19-diagnosed group than the comparator group throughout follow-up. In Medicare, a large number of DVT cases were identified on day 0 (Table B-5-Medicare.J). The cumulative incidence of DVT was much higher in the older Medicare cohort. In both data sources, the majority of the AEs occurred in first 28 days of follow-up. The overall HR and RI estimates across all of follow-up and at prespecified time periods are shown in Figure 25.

For the overall analysis in both the MarketScan and Medicare cohort analyses, those within the COVID-19 diagnosis group were more likely to experience DVT than those in the comparator group (MarketScan HR = 2.83; 95% CI, 2.45-3.28; Medicare HR = 1.67; 95% CI, 1.63-1.72). Similarly, the overall SCRI analyses, the RI estimates from the standard Poisson models and the extended Poisson models accounting for event-dependent observation periods and seasonality all suggested increased risks of DVT associated with COVID-19 diagnosis (extended model adjusted for seasonality, MarketScan RI = 11.80; 95% CI, 10.11-13.77; Medicare RI = 5.58; 95% CI, 5.38-5.79).

In both cohort analyses, each time period–specific HR indicated an increased risk of DVT in the COVID-19-diagnosed group, consistent with the overall analysis, but attenuation was noted with longer follow-up.

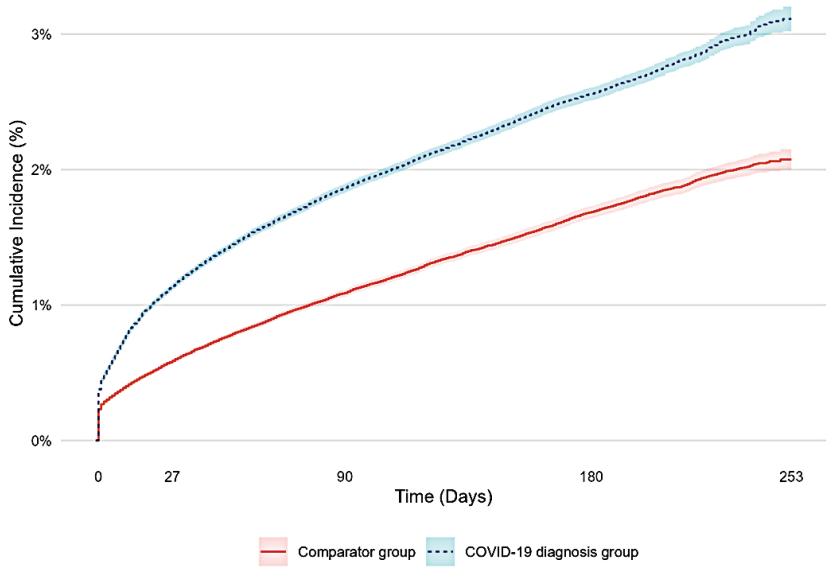
Figure 26. Weighted Cumulative Incidence of Deep Vein Thrombosis Among Individuals With a COVID-19 Diagnosis and Comparators Without a COVID-19 Diagnosis

A. MarketScan



Comparator group					
At Risk	317445	223867	127478	36780	529
Censored	4466	96831	190867	280643	317161
Events	39	128	210	267	284
COVID-19 diagnosis group					
At Risk	317812	223300	126005	35785	515
Censored	4451	97412	192186	281469	317011
Events	120	525	720	788	801

B. Medicare



Comparator group					
At Risk	981522	679935	392058	146088	1770
Censored	15584	306460	584765	826953	971748
Events	2270	5246	7835	9468	9774
COVID-19 diagnosis group					
At Risk	980365	630830	356024	128894	1434
Censored	17361	349664	613887	837165	964851
Events	3710	9953	13429	15171	15514

COVID-19 = coronavirus disease 2019.

Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

4.2.10.2. Subgroup Analyses

The HRs and RIs for individual subgroups in both the cohort and SCRI analyses are shown in Figure 25. In MarketScan and Medicare subgroup analyses, the HR estimates were generally consistent with the overall estimates, except for the cohort subgroups hospitalized at Time 0, which were attenuated (MarketScan HR = 1.23 [95% CI, 0.89-1.71]; Medicare HR = 1.28 [95% CI, 1.23-1.33]). Generally, the MarketScan and Medicare SCRI subgroup RIs were also consistent with the overall estimates, except for both data sources' hospitalized at Time 0 group, which were increased, and immunocompromised group, which was decreased.

4.2.10.3. Sensitivity Analyses

Results of sensitivity analyses with expanded exclusion criteria in both the cohort and SCRI are summarized in Figure 25. In the MarketScan and Medicare cohorts, both sensitivity analysis HRs were consistent with the overall HR. Although both data sources' SCRI sensitivity analysis RIs were also consistent with the trends of their respective overall estimates, the Medicare RI estimate was slightly decreased compared to the overall estimate.

4.2.10.4. Alternative Risk Windows

Results of the analyses of alternative risk windows in the cohort (day 0 and follow-up excluding day 0) and SCRI (the 7 days before COVID-19 diagnosis, day 0, the risk window excluding day 0, and the postexposure buffer period) are summarized in Figure 25.

In the MarketScan and Medicare cohort analyses, there was little difference between the analysis of day 0 alone and the analysis starting on day 1 because there was not a large difference in the proportion of cases identified on day 0 by exposure group (Table B-5-MarketScan.J, Table B-5-Medicare.J); both risk window HRs were consistent with the overall estimate.

Both SCRI analyses found substantially increased RIs for the day 0 risk windows and decreased RIs for modified risk windows. Across both data sources in the SCRI analyses, the RIs in the pre-exposure risk period and postexposure buffer were slightly above null, suggesting the potential for some risk in these periods outside the prespecified risk periods.

4.2.10.5. Summary of Results

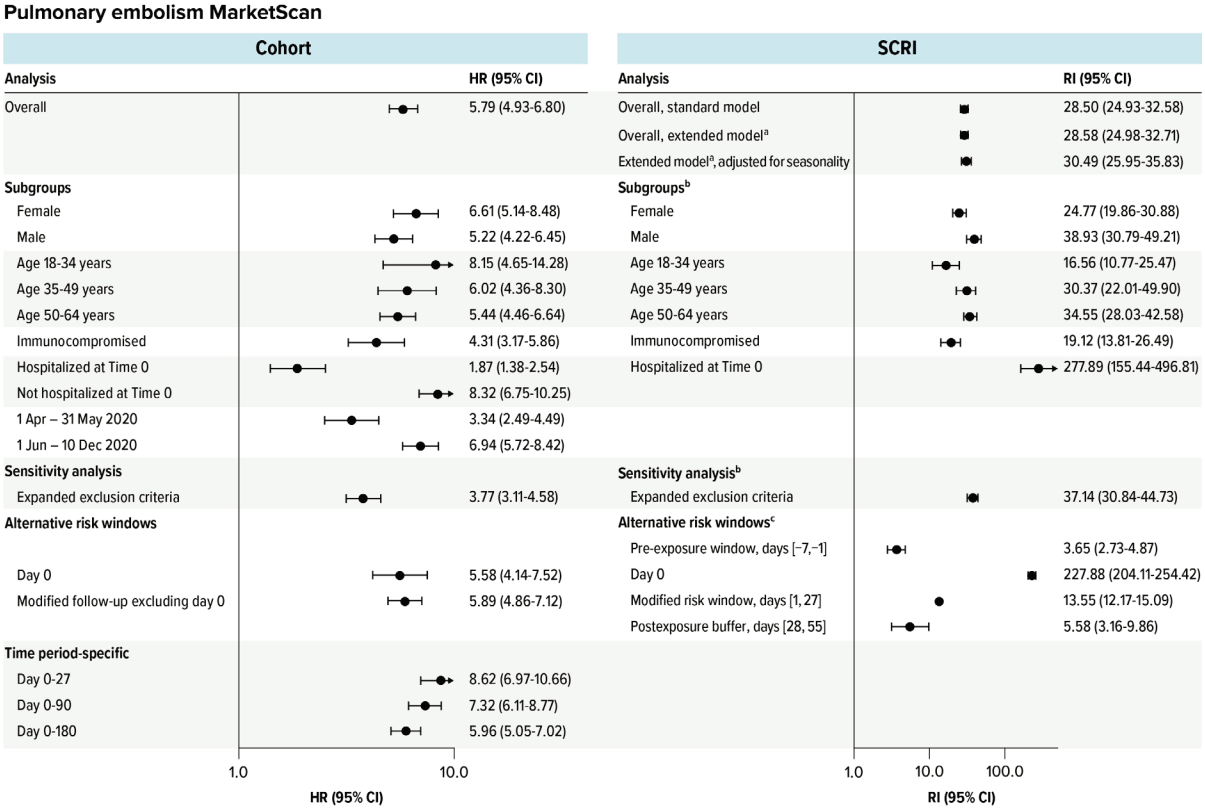
Estimates from all data sources and analytic approaches demonstrated moderate to very strong associations between COVID-19 diagnosis and the incidence of DVT. The magnitude of HR and RI estimates in Medicare were lower than MarketScan, likely the result of a much higher observed incidence of DVT in the Medicare cohort (Table B-5-MarketScan.J, Table B-5-Medicare.J). The cohort analysis saw little effect of removing day 0 from follow-up (suggesting little difference in the occurrence of day 0 events by treatment group), but the SCRI saw substantially increased RIs on day 0; among those who experienced DVT, a disproportionate number of them occurred on day 0 (i.e., concurrent with the COVID-19 diagnosis (Table B-14-MarketScan , Table B-14-Medicare).

4.2.11. Pulmonary Embolism

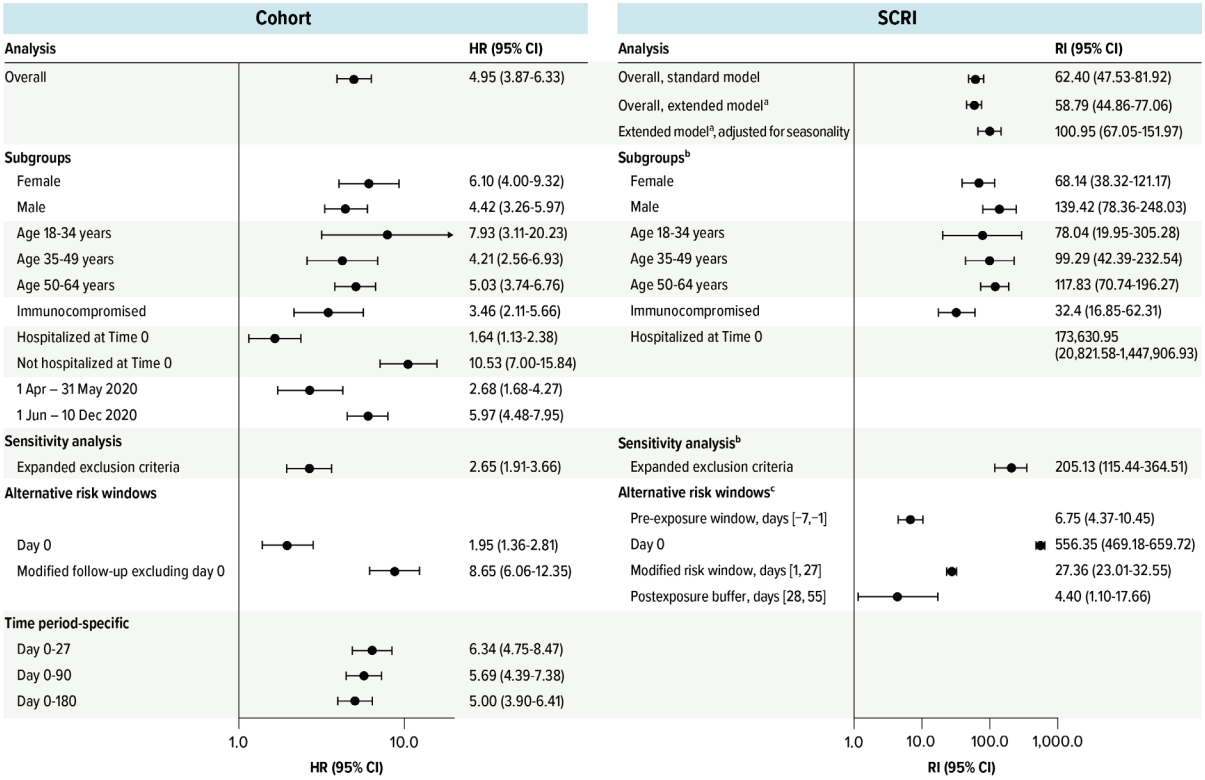
Pulmonary embolism was evaluated with both the cohort design and the SCRI design in MarketScan, but only with the cohort design in Medicare, given the increased risk of mortality associated with the AE in the older Medicare population. Additionally, pulmonary embolism was evaluated both in any medical care setting and

specifically in inpatient settings. An overview of the results of all the outcome analyses for the cohort design and SCRI design in both data sources and using both AE definitions is shown in Figure 27.

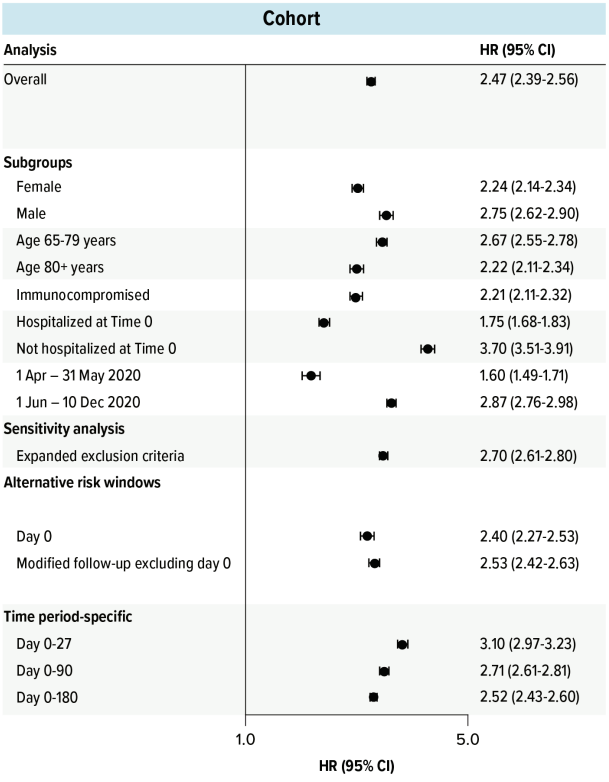
Figure 27. Estimated Association of a COVID-19 Diagnosis With Pulmonary Embolism, All Analyses

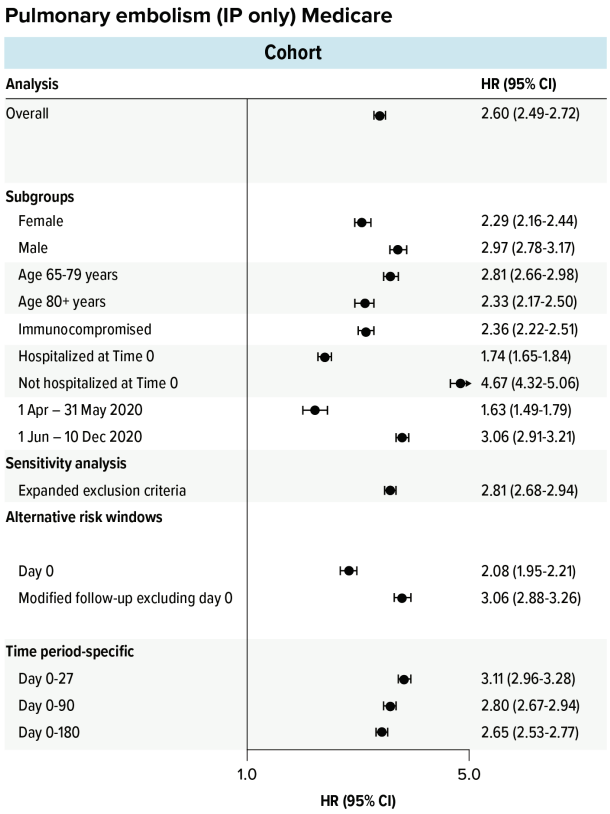


Pulmonary embolism (IP only) MarketScan



Pulmonary embolism Medicare





CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; IP = inpatient; RI = relative incidence; SCRI = self-controlled risk interval.

[a] Extended Poisson models accounting for event-dependent observation windows.

[b] Evaluated using the extended Poisson models accounting for event-dependent observation windows and adjustment for seasonality.

[c] Evaluated using a modified extended Poisson models accounting for event-dependent observation windows to allow for 1-day intervals and adjustment for seasonality.

4.2.11.1. Overall Outcome Analyses

In the cohort analyses, the weighted cumulative incidence by COVID-19 exposure groups over follow-up is shown for both pulmonary embolism definitions in Figure 28. Across both data sources, the cumulative incidence of pulmonary embolism (any setting) was higher than the cumulative incidence for inpatient pulmonary embolism, but the outcomes' cumulative incidences follow very similar patterns. A large number of PE cases (both in any setting and inpatient only) were identified on day 0 in both data sources, primarily among the COVID-19-diagnosed group (Table B-5-MarketScan.K, Table B-5-Medicare.K). Even after the events on day 0, the large majority of the cases in the COVID-19-diagnosed groups occurred very early in follow-up.

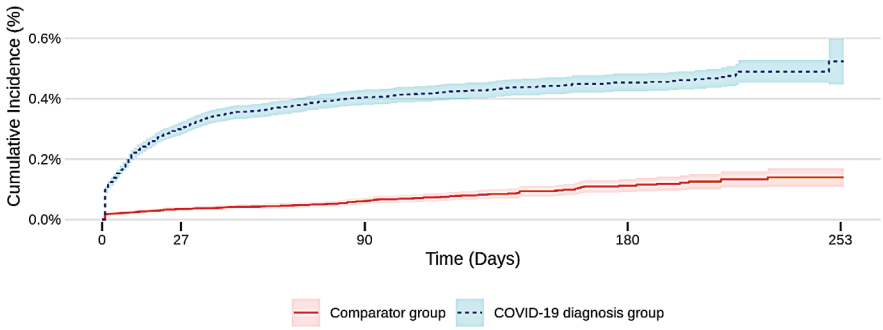
The overall HR and RI estimates across all of follow-up and at prespecified time periods is shown in Figure 27. In the overall MarketScan and Medicare cohort analyses, those diagnosed with COVID-19 were more likely to experience pulmonary embolism (any setting) and inpatient pulmonary embolism than those in the comparator group without a COVID-19 diagnosis, with consistently elevated HRs.

The SCRI analyses were not performed in Medicare because of violation of the event-dependent censoring criteria (Table 1), but for the overall MarketScan SCRI analysis, the extended regression model, which accounted for event-dependent observation windows and adjusted for seasonality, yielded consistently strongly elevated RI estimates for both outcome definitions, regardless of the Poisson model used.

In the pulmonary embolism MarketScan and Medicare cohort analyses for both pulmonary embolism outcomes, results for the time periods for day 0 to 27 and day 0 to 90 were increased compared to the overall HR, with day 0 to 27 displaying the greatest increase with attenuation in longer follow-up periods.

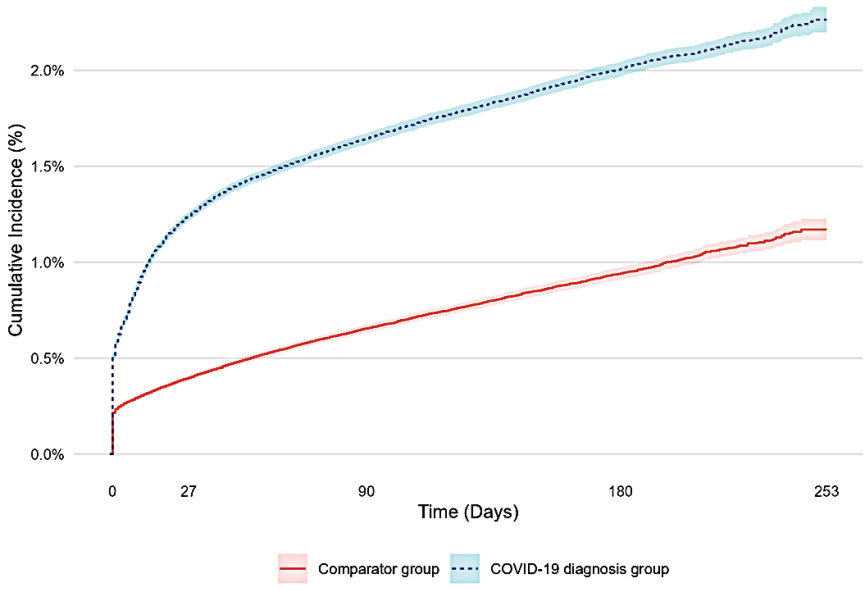
Figure 28. Weighted Cumulative Incidence of Pulmonary Embolism Among Individuals With a COVID-19 Diagnosis and Comparators Without a COVID-19 Diagnosis

A. MarketScan, Any Setting



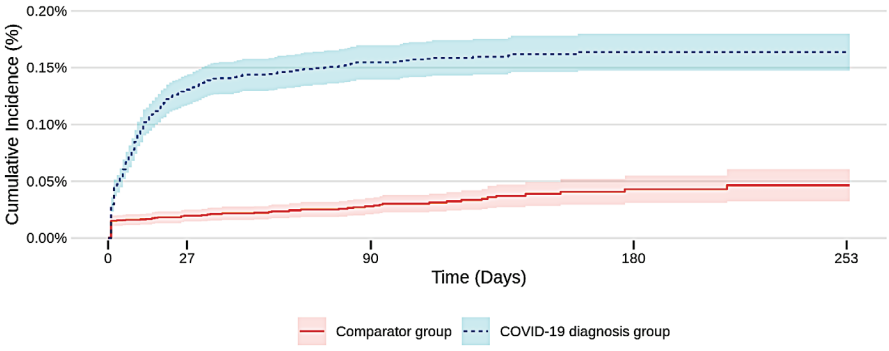
Comparator group					
At Risk	317841	224139	127677	36850	534
Censored	4467	96980	191126	281051	317647
Events	56	104	146	186	194
COVID-19 diagnosis group					
At Risk	318107	223272	126041	35856	515
Censored	4451	97377	192101	281375	316990
Events	315	893	1066	1108	1118

B. Medicare, Any Setting



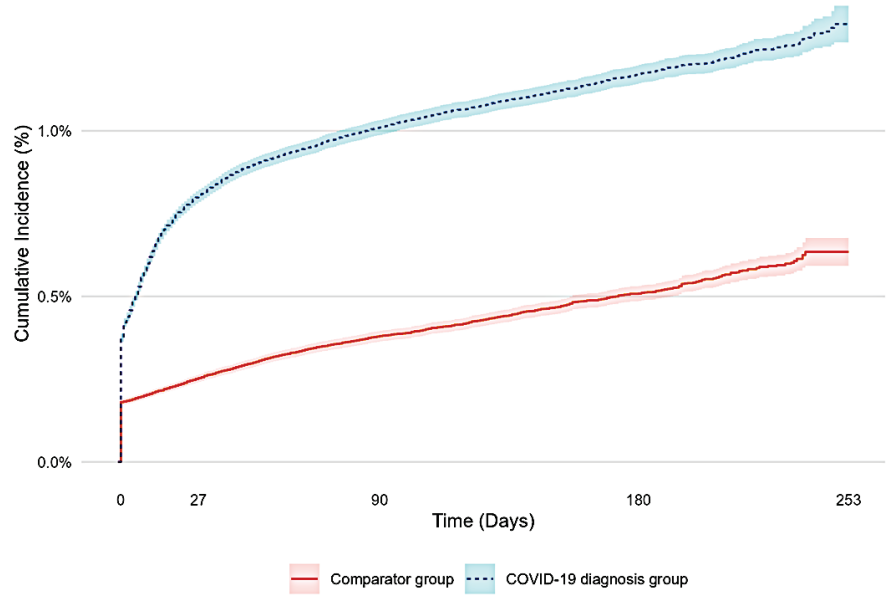
Comparator group					
At Risk	996510	691789	400267	150011	1817
Censored	15827	311251	594371	841654	990479
Events	2149	3702	5053	5853	6031
COVID-19 diagnosis group					
At Risk	996236	640054	362875	132106	1464
Censored	17735	355084	623144	850838	981903
Events	5138	11253	13245	14176	14333

C. MarketScan, Inpatient Only



Comparator group					
At Risk	317841	224177	127726	36880	534
Censored	4467	96986	191148	281121	317753
Events	48	60	74	86	87
COVID-19 diagnosis group					
At Risk	318107	223656	126365	35992	518
Censored	4455	97503	192422	281916	317675
Events	94	382	423	432	432

D. Medicare, Inpatient Only



Comparator group					
At Risk	996510	692667	401257	150599	1829
Censored	15841	311674	595373	843499	992990
Events	1803	2396	3068	3423	3520
COVID-19 diagnosis group					
At Risk	996236	642364	364610	132935	1479
Censored	17768	356701	626285	855403	987371
Events	3739	7348	8376	8786	8865

COVID-19 = coronavirus disease 2019.

Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

4.2.11.2. Subgroup Analyses

The HRs and RIs for individual subgroups in both the cohort and SCRI analyses are shown in Figure 27. In the MarketScan and Medicare cohort analyses, the any-setting and inpatient-only pulmonary embolism subgroup HRs were consistent with the trends of the overall estimates. In all cohort analyses for both outcomes, the HR estimate in the subgroup hospitalized at Time 0 subgroup was still elevated, but it had lower HR estimates than the overall analysis, while the nonhospitalized subgroup had higher estimates; the magnitude of the difference between the hospitalized and nonhospitalized subgroups varied by data source and outcome definition. HRs by calendar time also varied substantially in the cohort analyses of both data sources, with elevated HRs for PE (any setting and IP only) observed during the later time period (1 June 2020 to 10 December 2020). In the Medicare cohort's inpatient pulmonary embolism analyses, the HR for those in the earlier time period was also attenuated compared to the overall and the HR for those in the later time period was increased. In the any-setting and inpatient-only pulmonary embolism MarketScan SCRI analyses, all subgroup RIs were generally aligned with the trends of the overall estimates, except the RIs for those hospitalized at Time 0, which were substantially increased in both analyses.

4.2.11.3. Sensitivity Analyses

Results of sensitivity analyses with expanded exclusion criteria in both the cohort and SCRI are summarized in Figure 27. Across all MarketScan and Medicare cohorts, the sensitivity analysis HRs for the any-setting and inpatient-only pulmonary embolism outcomes were relatively consistent with the overall trend and identified an increased risk of pulmonary embolism in the COVID-19—diagnosed group. Although consistent with the overall trend, both MarketScan sensitivity HRs were decreased compared to the overall estimate, and the Medicare HRs were increased. In the any-setting and inpatient-only pulmonary embolism MarketScan SCRI analysis, the RIs for the expanded exclusion criteria were also consistent with the overall direction; however, both estimates were increased compared to the overall estimate.

4.2.11.4. Alternative Risk Windows

Results of the analyses of alternative risk windows in the cohort (day 0 and follow-up excluding day 0) and SCRI (the 7 days before COVID-19 diagnosis, day 0, the risk window excluding day 0, and the postexposure buffer period) are summarized in Figure 27.

In the any-setting pulmonary embolism cohort analyses in MarketScan and Medicare, there was little difference between the analyses of day 0 alone and follow-up excluding day 0. For the inpatient pulmonary embolism cohort analyses, however, the day 0 estimate tended to be reduced compared to the overall analysis, and the HR when starting follow-up on day 1 was increased. In the MarketScan SCRI analyses, the day 0 RI estimates were profoundly increased, consistent with the large numbers of patients (particularly in the exposure group) with events on day 0 (Table B-14-MarketScan).

In the any-setting and inpatient-only pulmonary embolism MarketScan SCRI analyses, the pre-exposure and postexposure buffer risk window RIs were all slightly increased, representing potential increased risk outside the prespecified risk period.

4.2.11.5. Summary of Results

Estimates from all data sources demonstrated moderate to strong associations between COVID-19 diagnosis and the incidence of pulmonary embolism. Analyses with SCRIs were not performed in the Medicare sample

because the substantial risk of death after experiencing a pulmonary embolism in the older population violates the assumption of no event-dependent censoring (Table 1). SCRI analyses were performed in MarketScan.

The magnitude of the effects seen in the Medicare cohort were less than those seen in the MarketScan cohort, likely the result of a much higher observed incidence of pulmonary embolism in the Medicare cohort (Table B-5-MarketScan.K, Table B-5-Medicare.K). Estimates from the self-controlled risk analysis in MarketScan suggested a very strong association between COVID-19 diagnosis and pulmonary embolism. In Medicare the numbers of events were larger and the 95% CIs were narrower for both study designs, but generally the direction of association was the same across both data sources and study designs, suggesting increased risk.

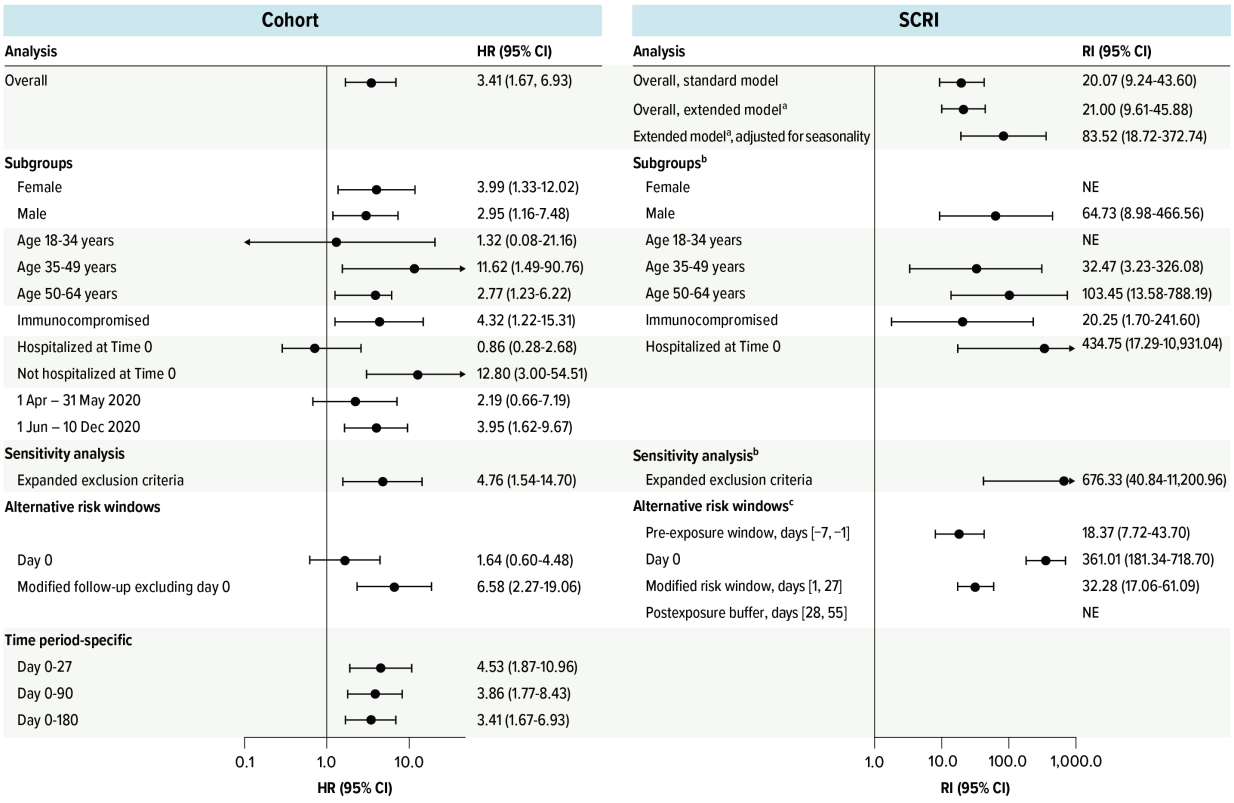
In an analysis restricted to patients hospitalized on Time 0, results were similar for the cohort analyses of both data sources, while the estimate from the SCRI in MarketScan was 3 times as large as the overall pulmonary embolism analysis. Although a large number of patients had events on day 0, the effect measure estimates remained elevated in all analyses, even after removing day 0 from follow-up.

4.2.12. Disseminated Intravascular Coagulation

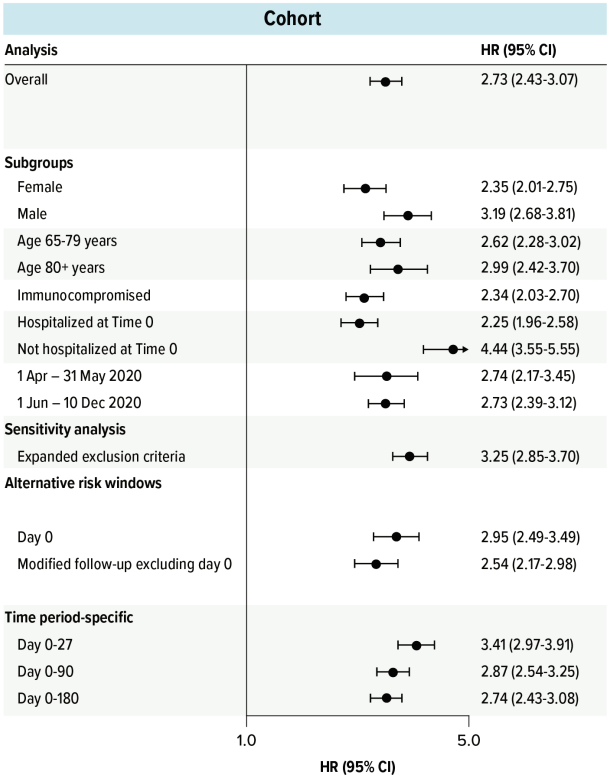
Disseminated intravascular coagulation was evaluated with both the cohort design and the SCRI design in MarketScan, but only with the cohort design in Medicare, given the increased risk of mortality associated with the outcome in the older Medicare population. An overview of the results of all the outcome analyses for the cohort design and SCRI design in both data sources is shown in Figure 29.

Figure 29. Estimated Association of a COVID-19 Diagnosis With Disseminated Intravascular Coagulation

Disseminated intravascular coagulation MarketScan



Disseminated intravascular coagulation Medicare



CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; NE = not estimable; RI = relative incidence; SCRI = self-controlled risk interval.

[a] Extended Poisson models accounting for event-dependent observation windows.

[b] Evaluated using the extended Poisson models accounting for event-dependent observation windows and adjustment for seasonality.

[c] Evaluated using a modified extended Poisson models accounting for event-dependent observation windows to allow for 1-day intervals and adjustment for seasonality.

4.2.12.1. Overall Outcome Analyses

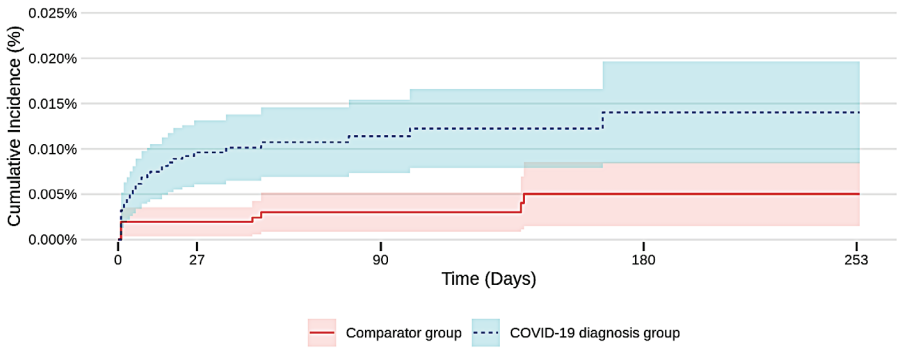
In the cohort analyses, the weighted cumulative incidence by COVID-19 exposure groups over follow-up is shown in Figure 30. The cumulative incidence of DIC was higher in the COVID-19-diagnosed group than the comparator group across all of follow-up in both data sources. However, the majority of cases in the COVID-19-diagnosed groups in both data sources occurred in the first few weeks of follow-up. The cumulative incidence in both groups was much higher in the Medicare cohort than in MarketScan. In both data sources, a relatively large number of DIC cases were identified on day 0. The overall HR and MarketScan RI estimates across all of follow-up and at prespecified time periods is shown in Figure 29 and Table B-5-MarketScan.L and Table B-5-Medicare.L.

For the overall cohort analysis in both MarketScan and Medicare cohort analyses, those diagnosed with COVID-19 were more likely to experience DIC than those in the comparator group (MarketScan HR = 3.41; 95% CI 1.67-6.93; Medicare HR = 2.73; 95% CI 2.43-3.07). In the MarketScan SCRI analyses (SCRI analyses were not performed in Medicare), the RI estimates and 95% CI estimated with the standard and extended Poisson models accounting for event-dependent observation periods and seasonality are summarized in Figure 29, but all models showed substantially elevated RI estimates (RI > 20). For the overall MarketScan SCRI analysis the extended regression model, which accounted for event-dependent observation windows and adjusted for seasonality, estimated the RI of DIC after being diagnosed with COVID-19 as 83.52 (95% CI, 18.72-372.74).

In the cohort time period–specific analyses for both data sources, the largest HRs were observed for the shorter time intervals (the prespecified risk period), with the HR attenuating as the follow-up increased.

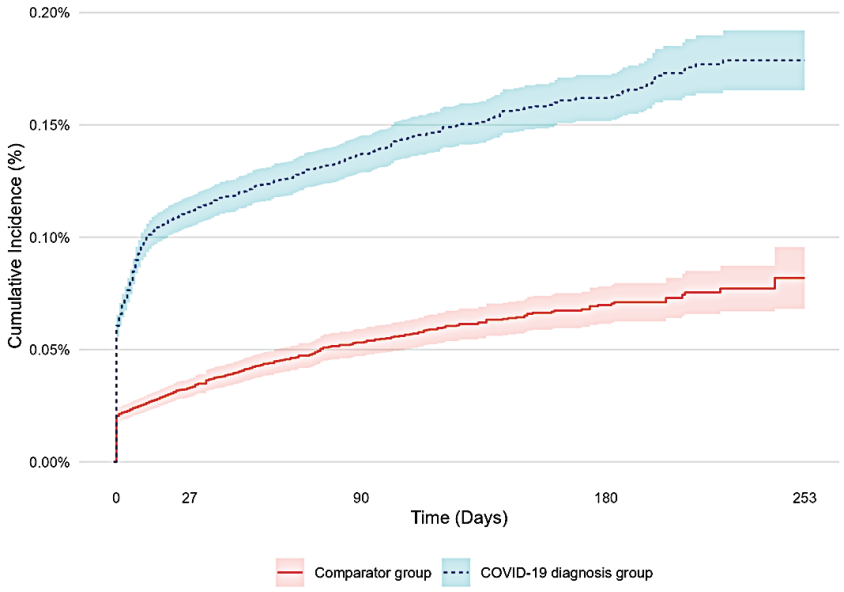
Figure 30. Weighted Cumulative Incidence of Disseminated Intravascular Coagulation Among Individuals With a COVID-19 Diagnosis and Comparators Without a COVID-19 Diagnosis

A. MarketScan



Comparator group					
At Risk	318650	224821	128086	37017	539
Censored	4472	97219	191667	281872	318640
Events	6	6	8	10	10
COVID-19 diagnosis group					
At Risk	319108	224664	127052	36266	525
Censored	4472	97857	193133	283042	319074
Events	10	28	31	33	33

B. Medicare



Comparator group					
At Risk	1015784	706948	409846	154196	1891
Censored	16202	318950	608773	862140	1015303
Events	209	316	424	473	481
COVID-19 diagnosis group					
At Risk	1016029	657368	372891	136048	1520
Censored	18301	368014	645047	879636	1014753
Events	615	1066	1191	1261	1277

COVID-19 = coronavirus disease 2019.

Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

4.2.12.2. Subgroup Analyses

The HRs and RIs for individual subgroups in both the cohort and SCRI analyses are shown in Figure 29. In MarketScan, the subgroup HR estimates closely paralleled the overall analyses, except for those aged 18-34 years and those hospitalized at Time 0, which were attenuated. In the Medicare cohort analysis, the subgroup HR estimates were generally consistent with the overall analysis, except in the nonhospitalized at Time 0, which had a substantially increased HR estimate for DIC.

In the MarketScan SCRI analysis, limited sample sizes precluded the analysis of subgroup estimates for women and those aged 18 to 34 years. In the subgroups that could be evaluated, the subgroup RIs were generally increased; however, the consistently larger CIs for each subgroup overlapped with the overall RI estimate.

4.2.12.3. Sensitivity Analyses

Results of sensitivity analyses with expanded exclusion criteria in both the cohort and SCRI are summarized in Figure 29. In both MarketScan and Medicare cohort analyses, the sensitivity analysis HRs remained consistent with the overall estimates. In the MarketScan SCRI sensitivity analysis, the RI for the expanded exclusion criteria was substantially increased compared to the overall RI, although the estimate was very imprecise.

4.2.12.4. Alternative Risk Windows

Results of the analyses of alternative risk windows in the cohort (day 0 and follow-up excluding day 0) and SCRI (the 7 days before COVID-19 diagnosis, day 0, the risk window excluding day 0, and the postexposure buffer period) are summarized in Figure 29.

In the MarketScan cohort, the HR for the analysis of day 0 alone was somewhat attenuated toward the null, compared with the overall analyses, while the analysis of the risk period starting on day 1 was slightly higher. In the Medicare cohort, however, the HR considering only day 0 was slightly increased (consistent with the larger proportion of day 0 cases in the COVID-19—diagnosed group in Medicare, Figure 30). In the MarketScan SCRI analysis, the day 0 RI estimate was substantially increased (RI = 361.01; 95% CI 181.34-718.70), because a large proportion of the total observed cases during the prespecified risk period (12/33 cases) occurred on day 0 (Table B-14-MarketScan).

In the MarketScan SCRI analysis, the pre-exposure (RI = 18.37 [95% CI, 7.72-43.70]) and modified risk window (RI = 32.28 [95% CI, 17.06-61.09]) RIs were largely consistent with the overall; however, the day 0 risk window RI was greatly increased compared to the overall estimate.

In the MarketScan SCRI, the analysis of the pre-exposure window showed an elevated RI before the COVID-19 diagnosis. The postexposure buffer period could not be analyzed.

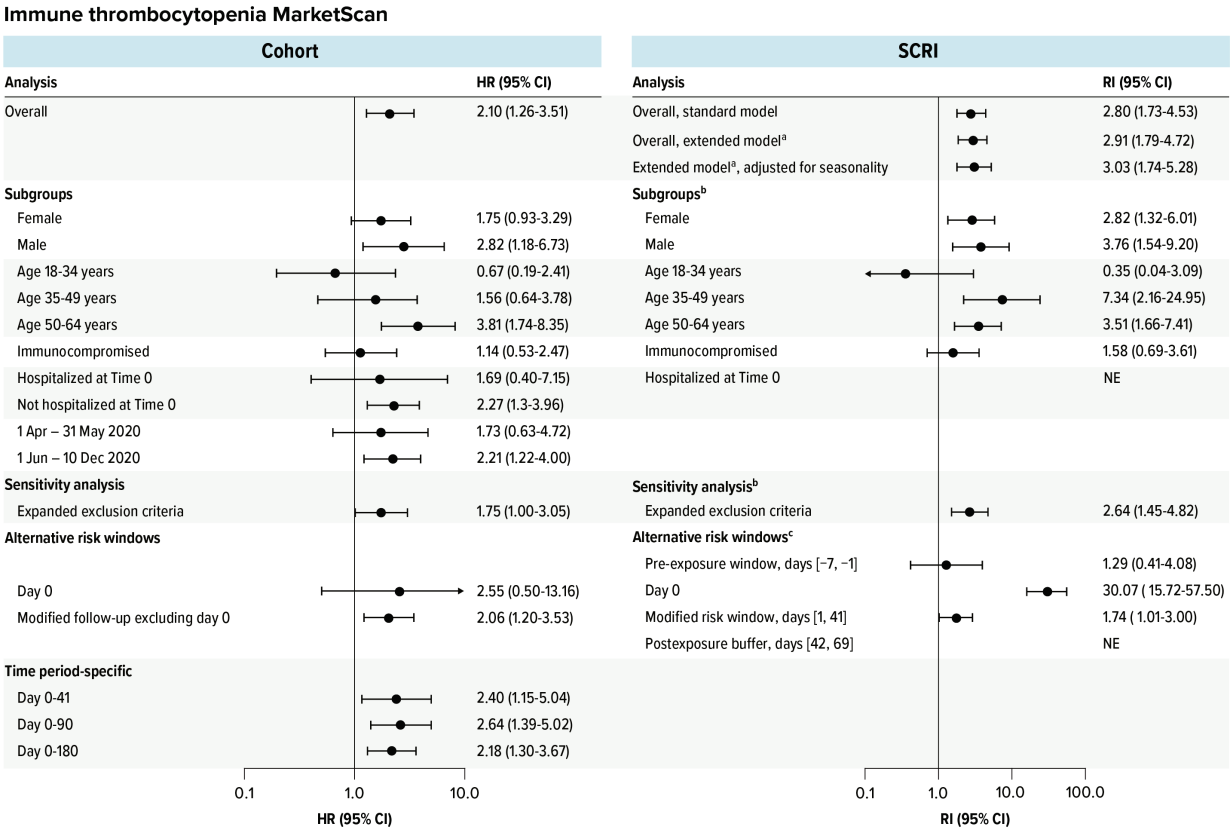
4.2.12.5. Summary of Results

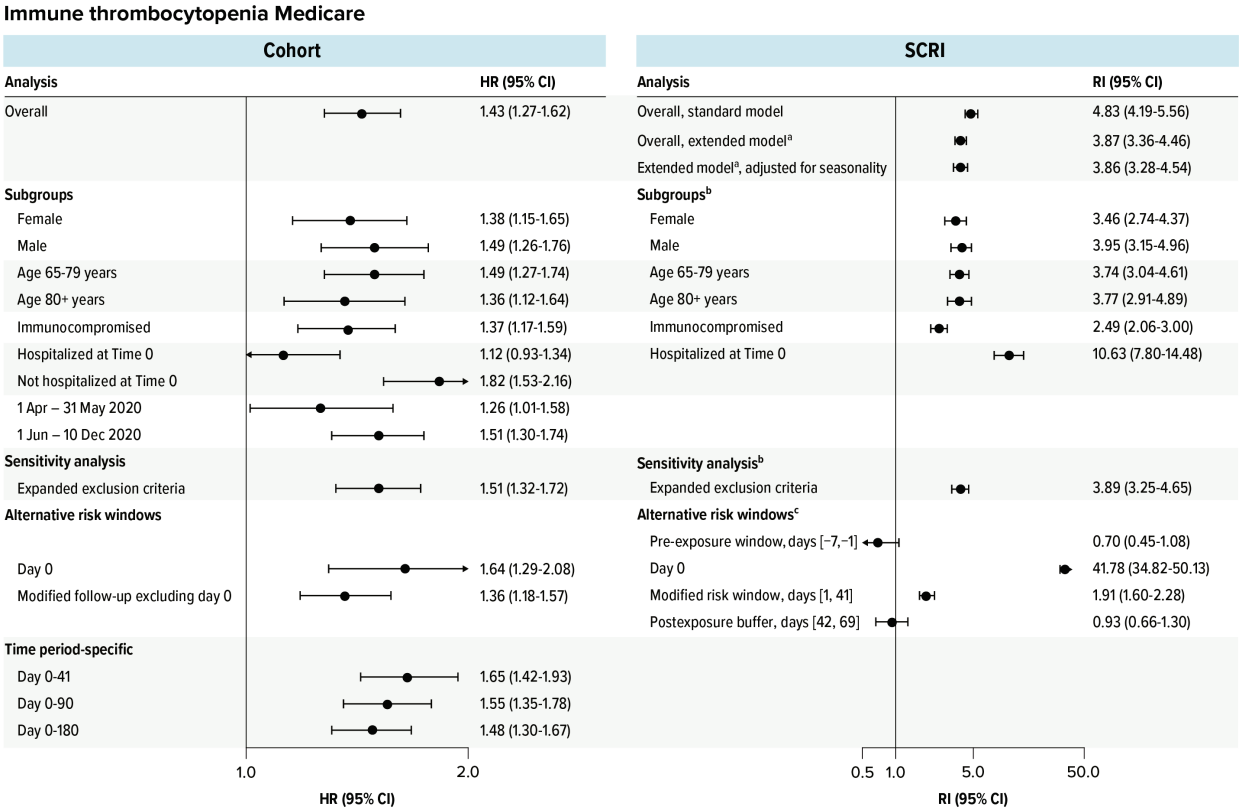
Estimates from all data sources and study designs demonstrated moderate to strong associations of COVID-19 diagnosis with DIC. The magnitude of the Medicare HR estimates was lower than in MarketScan, likely the result of a much higher observed incidence of DIC in the Medicare cohort (Table B-5-MarketScan.L, Table B-5-Medicare.L). The relatively large number of cases on day 0 resulted in a markedly increased day 0 RI in the SCRI, but the cumulative incidence curves and cohort analyses of the risk period without day 0 suggest that the increased risk in the COVID-19-diagnosed group continued throughout follow-up.

4.2.13. Immune Thrombocytopenia

Immune thrombocytopenia was evaluated with both the cohort design and the SCRI design in both data sources. An overview of the results of all the outcome analyses for the cohort design and SCRI design in both data sources is shown in Figure 31.

Figure 31. Estimated Association of a COVID-19 Diagnosis With Immune Thrombocytopenia, All Analyses





CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; NE = not estimable; RI = relative incidence.

[a] Extended Poisson models accounting for event-dependent observation windows.

[b] Evaluated using the extended Poisson models accounting for event-dependent observation windows and adjustment for seasonality.

[c] Evaluated using a modified extended Poisson models accounting for event-dependent observation windows to allow for 1-day intervals and adjustment for seasonality.

4.2.13.1. Overall Outcome Analyses

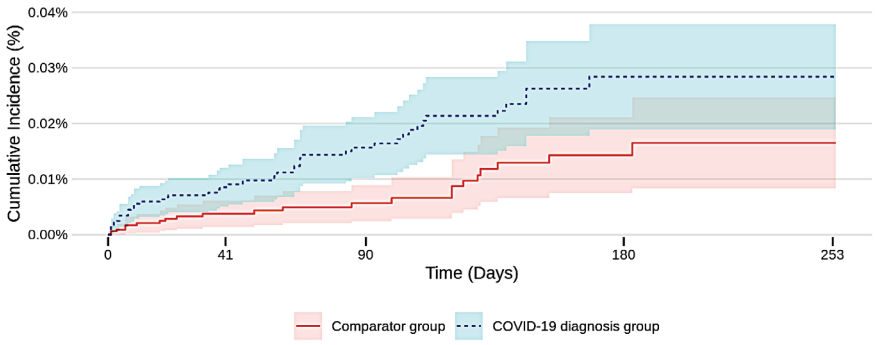
In the cohort analyses, the weighted cumulative incidence by COVID-19 exposure groups throughout follow-up is shown in Figure 32 and Table B-5-MarketScan.M and Table B-5-Medicare.M. In both data sources, the cumulative incidence of ITP was higher in the COVID-19 diagnosis group throughout all of follow-up. In Medicare, a large number of ITP cases were identified on day 0, but in MarketScan, there were relatively few cases identified on day 0. In both the COVID-19 and comparator groups, the incidence was higher in Medicare than in MarketScan (< 0.03% in MarketScan, > 0.1% in Medicare).

The overall HR and RI estimates across all of follow-up and at prespecified time periods is shown in Figure 31. For the overall cohort analysis in both MarketScan and Medicare, the HR estimates were modestly elevated and reasonably precise (MarketScan HR = 2.10; 95% CI, 1.26-3.51; Medicare HR = 1.43; 95% CI, 1.27-1.62). The RI estimates from the SCRI analyses were also consistently elevated regardless of the model used. The RI estimates from the extended model for event-dependent assessment periods and adjusted for seasonality were 3.03 (95% CI, 1.74-5.28) in MarketScan, and 3.86 (95% CI, 3.28-4.54) in Medicare.

In both data sources' cohort analyses, all 3 time period–specific HRs were consistent with the overall estimates, with slight attenuation of the results seen with the longest follow-up times compared with shorter follow-up times in Medicare.

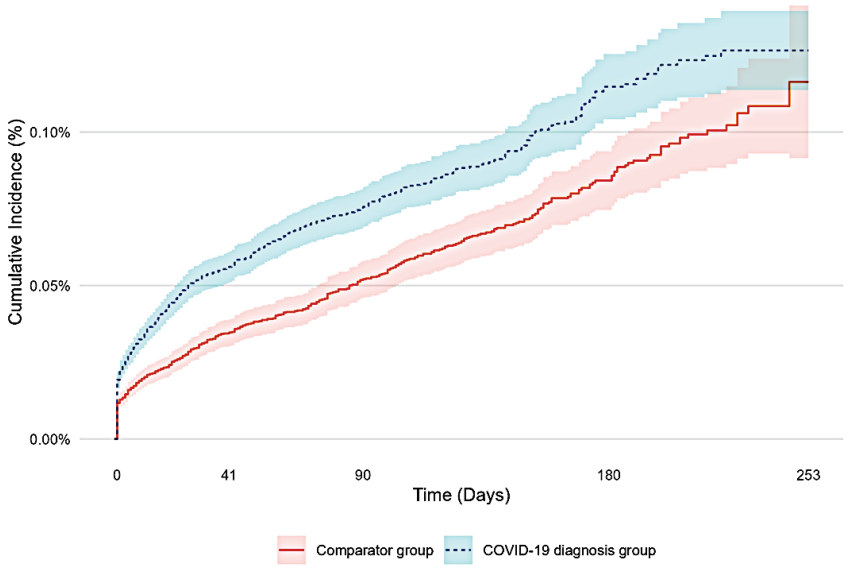
Figure 32. Weighted Cumulative Incidence of Immune Thrombocytopenia Among Individuals With a COVID-19 Diagnosis and Comparators Without a COVID-19 Diagnosis

A. MarketScan



Comparator group					
At Risk	318367	187594	127946	36959	539
Censored	4465	132731	191518	281636	318345
Events	2	10	13	21	22
COVID-19 diagnosis group					
At Risk	319082	187175	127015	36255	528
Censored	4469	133878	193139	283014	319035
Events	5	25	35	46	46

B. Medicare



Comparator group					
At Risk	1013898	596927	409113	153865	1894
Censored	16167	422879	607656	860576	1013396
Events	119	304	388	477	502
COVID-19 diagnosis group					
At Risk	1013882	549428	372060	135772	1523
Censored	18268	469956	644335	878354	1013199
Events	195	491	580	672	683

COVID-19 = coronavirus disease 2019.

Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

4.2.13.2. Subgroup Analyses

The HRs and RIs for individual subgroups in both the cohort and SCRI analyses are shown in Figure 31. In the MarketScan SCRI analysis, sample sizes were too small to estimate subgroups for those hospitalized at Time 0. In the MarketScan cohort and SCRI analyses, there was considerable heterogeneity by age group, with HR and RI estimates below 1 for the 18-34 years age group and higher estimates for the older age groups. In the older Medicare population, no heterogeneity by age group was observed. In the Medicare cohort analysis, the HR was much lower in the hospitalized at Time 0 subgroup and higher in the nonhospitalized subgroup; in MarketScan, the differences between the hospitalized and nonhospitalized subgroups were not as extreme.

4.2.13.3. Sensitivity Analyses

Results of sensitivity analyses with expanded exclusion criteria in both the cohort and SCRI are summarized in Figure 31. In both data sources and analyses, the results of the sensitivity analyses with expanded exclusion criteria were very consistent with the overall analysis.

4.2.13.4. Alternative Risk Windows

Results of the analyses of alternative risk windows in the cohort (day 0 and follow-up excluding day 0) and SCRI (the 7 days before COVID-19 diagnosis, day 0, the risk window excluding day 0, and the postexposure buffer period) are summarized in Figure 31.

In the MarketScan and Medicare cohort analysis, the HR estimates for the day 0 risk window were slightly higher than the overall HR, and the HRs for the risk windows excluding day 0 generally remained consistent with the overall HR. In contrast, the SCRI analysis in both MarketScan and Medicare found very large RIs for day 0 alone and substantially attenuated RIs for the modified risk window excluding day 0.

In both the MarketScan and Medicare SCRI analyses of the pre-exposure period, the RI estimates were at or slightly below the null. The analysis of the MarketScan postexposure buffer could not be performed because of sample size, but the RI estimate in the Medicare postexposure buffer period was null, suggesting no increased risks outside of the prespecified risk period.

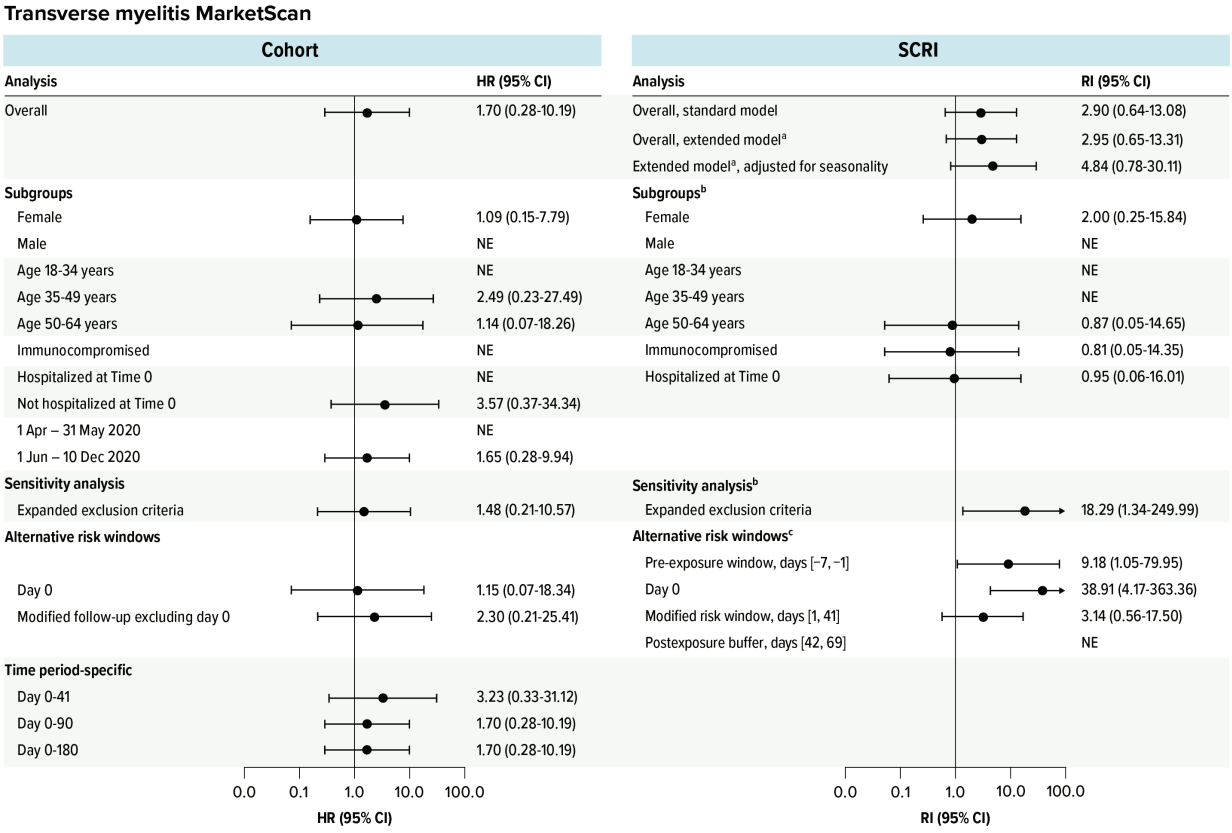
4.2.13.5. Summary of Results

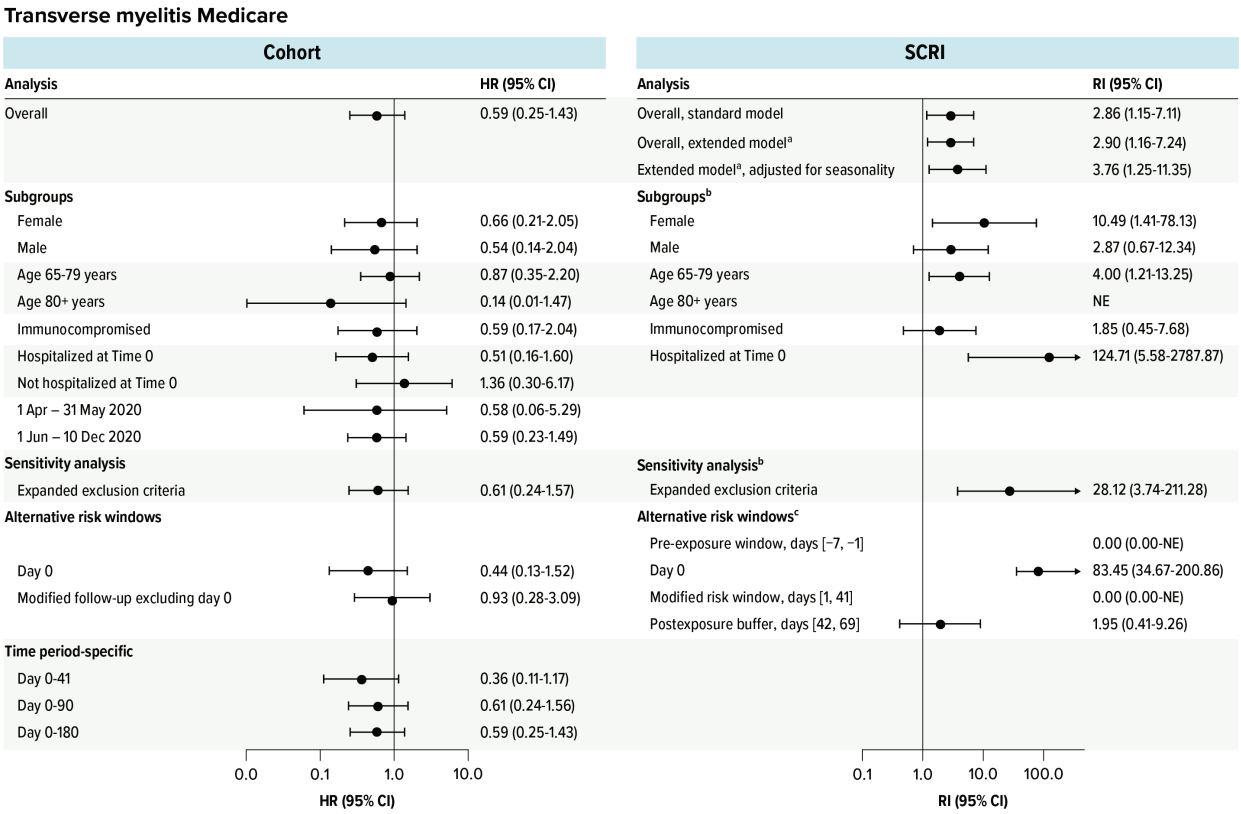
Estimates from all data sources and analytical approaches demonstrated moderate associations between COVID-19 diagnosis and the incidence of ITP. MarketScan and Medicare HR and RI estimates were similar (MarketScan HR= 2.10 [95% CI, 1.26-3.51], RI = 3.03 [95% CI, 1.74-5.28]; Medicare HR = 1.43 [95% CI, 1.27-1.62], RI = 3.86 [95% CI, 3.28-4.54]) including in alternative risk period analyses excluding day 0, although the SCRI alternative risk period estimates were more attenuated (MarketScan $HR_{alternative}$ = 2.06 [95% CI, 1.20-3.53], $RI_{alternative}$ = 1.74 [95% CI, 1.01-3.00]; Medicare $HR_{alternative}$ = 1.36 [95% CI, 1.18-1.57], $RI_{alternative}$ = 1.91 [95% CI, 1.60-2.28]).

4.2.14. Transverse Myelitis

Transverse myelitis was evaluated with both the cohort design and the SCRI design in both data sources. An overview of the results of all the outcome analyses for the cohort design and SCRI design in both data sources is shown in Figure 33.

Figure 33. Estimated Association of a COVID-19 Diagnosis With Transverse Myelitis, All Analyses





CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; NE = not estimable; RI = relative incidence.

[a] Extended Poisson models accounting for event-dependent observation windows.

[b] Evaluated using the extended Poisson models accounting for event-dependent observation windows and adjustment for seasonality.

[c] Evaluated using a modified extended Poisson models accounting for event-dependent observation windows to allow for 1-day intervals and adjustment for seasonality.

4.2.14.1. Overall Outcome Analyses

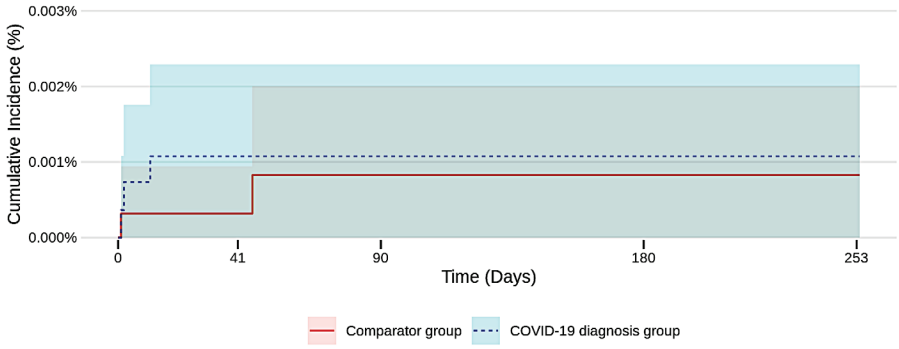
In the cohort analyses, the weighted cumulative incidence by COVID-19 exposure groups over follow-up is shown in Figure 34. In MarketScan, there were very few cases in either exposure group throughout all of follow-up (Table B-5-MarketScan.N). In Medicare, a large proportion of cases in both groups were identified on day 0 (Table B-5-Medicare.N), but the number of cases identified on day 0 was higher in the comparator group than the COVID-19-diagnosed group (counts suppressed), resulting in the cumulative incidence being higher in the comparator group for all of follow-up.

The overall HR and RI estimates across all of follow-up and at prespecified time periods is shown in Figure 33. In the overall MarketScan cohort analyses, estimates were imprecise given the small numbers of cases, but the estimated HR was 1.70 (95% CI, 0.28-1.19). In contrast, the Medicare cohort analysis reported a HR below the null, HR = 0.59 (95% CI, 0.25-1.43), consistent with the pattern of cumulative incidence shown in Figure 34. The MarketScan SCRI analyses and Medicare SCRI analyses also suggested increased risk of transverse myelitis, with the standard, extended, and seasonality-adjusted SCRI models yielding fairly consistent RI estimates within each data source: MarketScan extended, seasonality-adjusted RI = 4.84 (95% CI, 0.78-30.11); Medicare extended, seasonality-adjusted RI = 3.76 (95% CI, 1.25-11.35).

In both the MarketScan and Medicare cohorts, the time period–specific HRs were all consistent with their respective overall estimate, with slight attenuation toward the null observed with increasing risk window length.

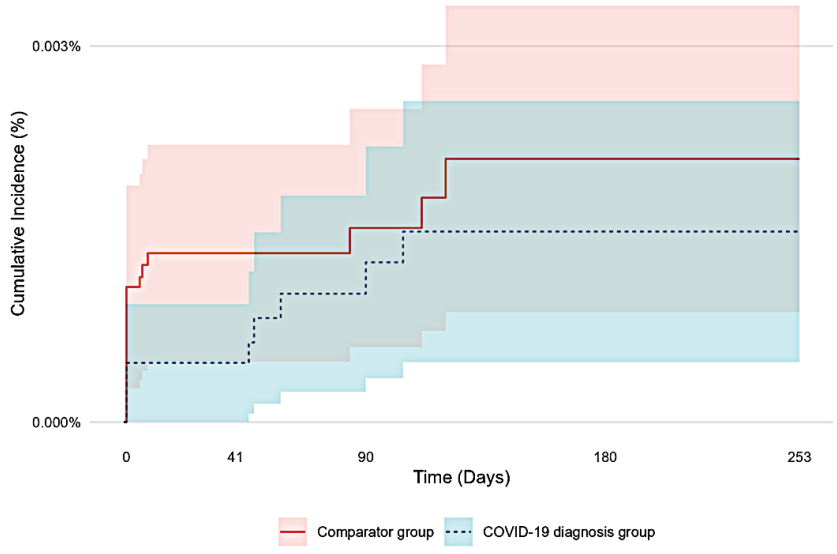
Figure 34. Weighted Cumulative Incidence of Transverse Myelitis Among Individuals With a COVID-19 Diagnosis and Comparators Without a COVID-19 Diagnosis

A. MarketScan



Comparator group					
At Risk	318524	187708	128029	37002	539
Censored	4470	132784	191604	281770	318522
Events	1	1	2	2	2
COVID-19 diagnosis group					
At Risk	319305	187299	127085	36253	527
Censored	4477	134000	193325	283282	319302
Events	1	3	3	3	3

B. Medicare



Comparator group					
At Risk	1016168	598179	409864	154174	1891
Censored	16209	424205	609558	863003	1016152
Events	11	13	14	16	16
COVID-19 diagnosis group					
At Risk	1016479	551104	373073	136158	1527
Censored	18316	471391	646495	881231	1016470
Events	< 11	< 11	< 11	< 11	< 11

COVID-19 = coronavirus disease 2019.

Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

4.2.14.2. Subgroup Analysis

The HRs and RIs for individual subgroups in both the cohort and SCRI analyses are shown in Figure 33. In the MarketScan cohort, the sample sizes were too small to estimate subgroups in males, those aged 18 to 34 years, the immunocompromised, those hospitalized at Time 0, and those in the earliest time period. In the subgroups that could be performed, estimates were generally imprecise as transverse myelitis was rare. No meaningful differences were observed for subgroups in MarketScan in either study design. In the Medicare SCRI analysis, estimates were elevated in females (RI = 10.49; 95% CI, 1.41-78.13) and in those hospitalized at Time 0 (RI = 124; 95% CI, 5.58-2787.87).

4.2.14.3. Sensitivity Analyses

Results of sensitivity analyses with expanded exclusion criteria in both the cohort and SCRI are summarized in Figure 33. In both data sources, the sensitivity analysis for the SCRI resulted in a greatly elevated RI estimate compared to the overall estimate, but the estimate was very imprecise, with very wide CIs (MarketScan: $RI_{sensitivity}$ = 18.29; 95% CI, 1.34-249.99; Medicare: $RI_{sensitivity}$ = 28.12; 95% CI, 3.74-211.28).

4.2.14.4. Alternative Risk Windows

Results of the analyses of alternative risk windows in the cohort (day 0 and follow-up excluding day 0) and SCRI (the 7 days before COVID-19 diagnosis, day 0, the risk window excluding day 0, and the postexposure buffer period) are summarized in Figure 33.

The MarketScan cohort analysis for day 0 was decreased in comparison to the overall and elevated in the analysis removing day 0 from follow-up. A similar pattern was seen in the Medicare cohort, where the analysis for day 0 was decreased in comparison to the overall estimate and elevated in the analysis removing day 0 from follow-up (though still not above the null with HR = 0.93; 95% CI, 0.28-3.09). In contrast, the SCRI from MarketScan showed greatly elevated RI on day 0 (RI > 38), with an attenuated estimate in the analysis that removed day 0. In the Medicare SCRI analysis, all events in the prespecified risk period occurred on day 0, resulting in a elevated RI on day 0 (RI > 83), thus precluding the estimation of the alternative risk window excluding these day 0 events.

In the MarketScan SCRI analysis, the pre-exposure buffer window showed an elevated RI (RI > 9), but the lack of events in the postexposure buffer window precluded estimation of the alternative risk window for the postexposure buffer period. In the Medicare SCRI analysis, a lack of events in the pre-exposure window and modified risk window precluded estimation of RIs, and the small number of cases in the postexposure buffer period resulted in an imprecise RI estimate.

In the MarketScan cohort analysis, the time-specific HRs were comparable to the overall estimate, except for day 0-41 where they were elevated, consistent with the cumulative incidence curve. In the Medicare cohort analysis, the time-specific HRs were clustered around the overall estimate, with the lowest estimate for the day 0-41 period.

4.2.14.5. Summary of Results

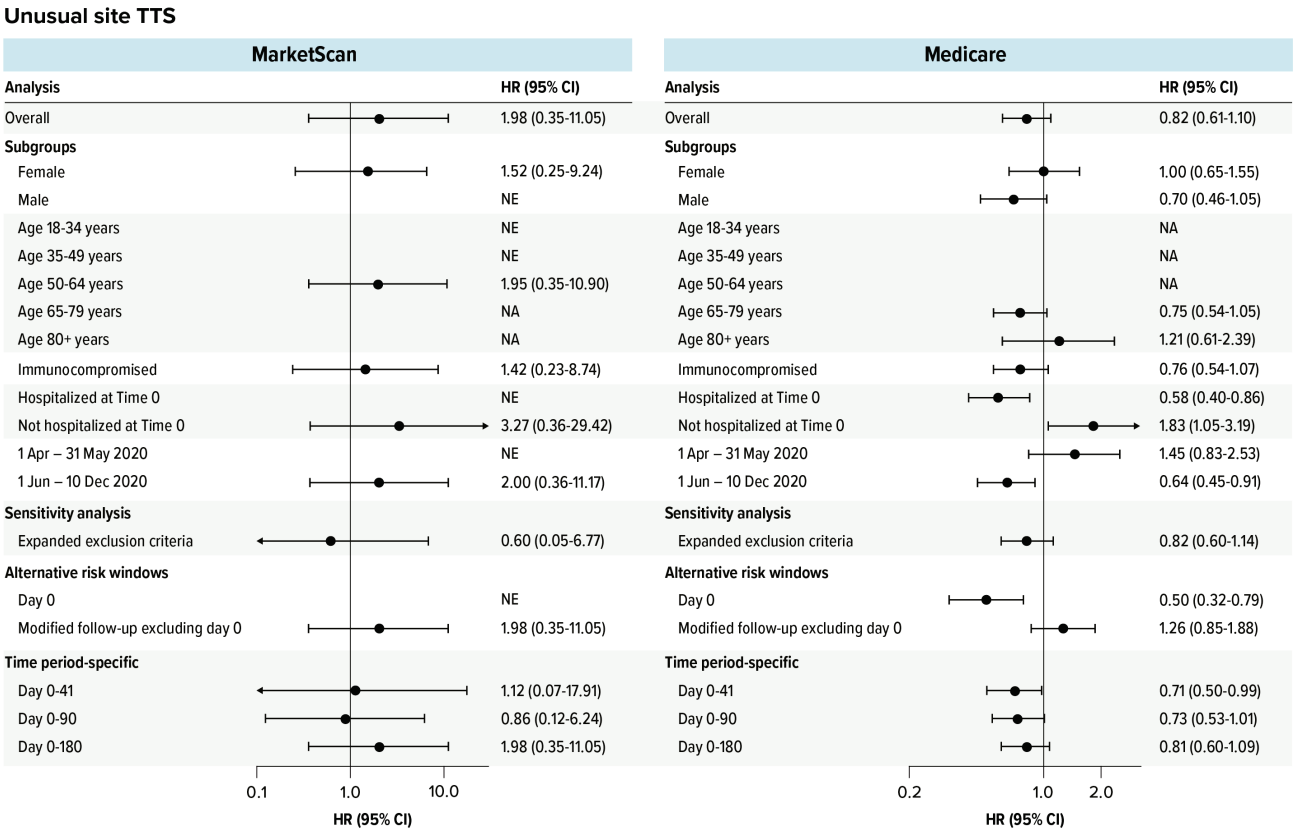
The results from both data sources and study designs were generally imprecise and inconsistent. In MarketScan and Medicare, the SCRI analyses suggested a potentially increased risk of transverse myelitis associated with a COVID-19 diagnosis (RI = 4.84 [95% CI, 0.78-30.11]; RI = 3.76 [95% CI, 1.25-11.35], respectively), while the MarketScan overall cohort HR was closer to the null (HR = 1.70 [95% CI, 0.28-10.19]) and Medicare overall cohort HR was below the null (HR = 0.59 [95% CI, 0.25-1.43). However, strong Time 0

effects were noted in the SCRI analyses, and the alternative risk period analyses that excluded day 0 shifted the Medicare HR upward and toward the null because events on day 0 were much more common among the comparator group than in the COVID-19 patients (Table B-5-Medicare.N). After considering the impact of concurrently diagnosed COVID-19 and transverse myelitis, the data are somewhat inconclusive due to the imprecision of estimates, but a potentially moderate increase in risk of transverse myelitis after COVID-19 diagnosis cannot be ruled out.

4.2.15. Unusual Site Thrombosis With Thrombocytopenia Syndrome

Unusual site thrombosis with thrombocytopenia syndrome (TTS) was evaluated only with the cohort design in both data sources, given the increased mortality associated with the AE violated the assumptions of the SCRI. An overview of the results of all the outcome analyses for the cohort design in both data sources is shown in Figure 35.

Figure 35. Estimated Association of a COVID-19 Diagnosis With Unusual Site TTS, All Analyses



CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; NA = not applicable; NE = not estimable; TTS = thrombosis with thrombocytopenia syndrome.

4.2.15.1. Overall Outcome Analyses

In the cohort analyses, the weighted cumulative incidence of unusual site TTS by COVID-19 exposure groups over follow-up is shown in Figure 36. In MarketScan, no cases were identified at day 0 in either the COVID-19 or the comparator group, and events over the follow-up period were similar resulting in similar cumulative incidence curves throughout most of follow-up (Table B-5-MarketScan.O). In contrast, in Medicare more than twice as many unusual site TTS cases were identified on day 0 were in the comparator group compared to the

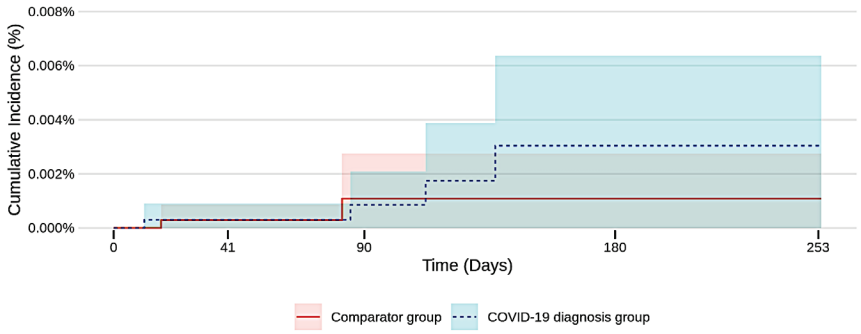
COVID-19-diagnosed group, which comprised a large proportion of the total events in the comparator group over the follow-up period (Table B-5-Medicare.O).

The overall HR across all of follow-up and at prespecified time periods is shown in Figure 35. In the overall MarketScan cohort analysis, those within the COVID-19 diagnosis group were found to be more likely to experience unusual site TTS during the risk period in comparison to the comparator group (HR = 1.98; 95% CI, 0.35-11.05); however, estimates were imprecise. In contrast, the overall Medicare cohort analysis reported a HR below the null HR=0.82 (95% CI, 0.61-1.10), consistent with the pattern of the cumulative incidence noted in Figure 36.

In the MarketScan and Medicare cohorts, the day-180 time period–specific HR estimates were identical or very close to the overall estimate because all cases in MarketScan and most of the cases in Medicare had accumulated by that point (Figure 36).

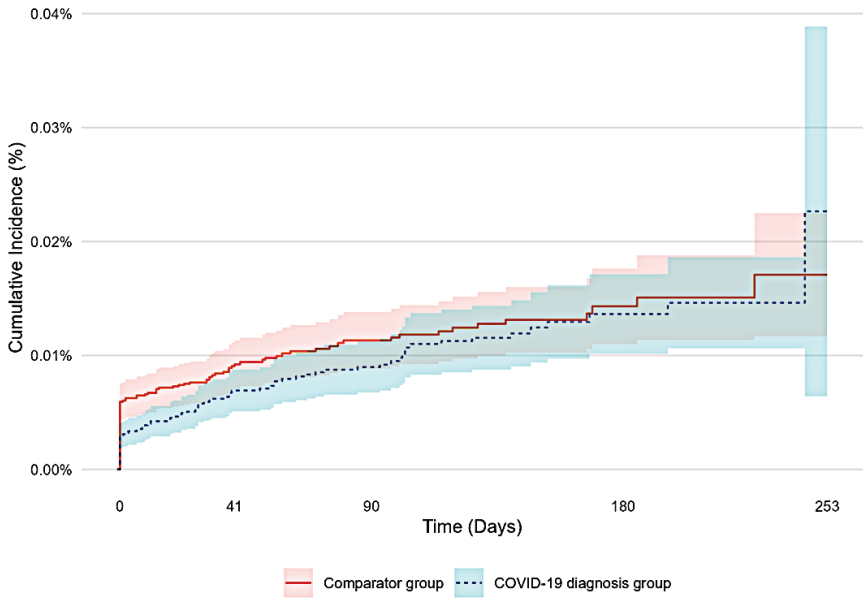
Figure 36. Weighted Cumulative Incidence of Unusual Site TTS Among Individuals With a COVID-19 Diagnosis and Comparators Without a COVID-19 Diagnosis

A. MarketScan



Comparator group					
At Risk	318569	187758	128082	37009	540
Censored	4472	132779	191597	281807	318567
Events	0	1	2	2	2
COVID-19 diagnosis group					
At Risk	319183	187200	126982	36180	523
Censored	4472	133979	193306	283232	319179
Events	0	1	2	4	4

B. Medicare



Comparator group					
At Risk	1015888	598128	409941	154214	1888
Censored	16216	423893	609115	862595	1015782
Events	60	85	95	104	106
COVID-19 diagnosis group					
At Risk	1016282	551081	373080	136141	1519
Censored	18324	471159	646236	880978	1016199
Events	30	59	68	81	83

COVID-19 = coronavirus disease 2019; TTS = thrombosis with thrombocytopenia syndrome.

Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

4.2.15.2. Subgroup Analyses

The HRs for individual subgroups in both cohort analyses are shown in Figure 35. In the MarketScan cohort, the HR estimates were largely consistent with the overall estimates; however, sample sizes were too small to estimate subgroups in the male, aged 18-49 years, hospitalized at Time 0, and earliest time period groups. In the Medicare cohort, the subgroup HR estimates were generally similar to the overall estimates, except for elevated estimates in the nonhospitalized at Time 0 and earlier calendar time period groups, which showed HRs above 1 and the increased estimate in the nonhospitalized at Time 0 group.

4.2.15.3. Sensitivity Analyses

Results of sensitivity analyses with expanded exclusion criteria for the cohort analyses are summarized in Figure 35. The sensitivity analysis estimates for the MarketScan cohort analysis showed an HR estimate was below the null, unlike the overall estimate, though the sensitivity analysis was imprecise. In Medicare, the sensitivity analysis HR estimate was identical to the overall estimate (HR = 0.82).

4.2.15.4. Alternative Risk Windows

Results of the analyses of alternative risk windows (day 0 and follow-up excluding day 0) are summarized in Figure 35. The MarketScan cohort analysis for day 0 identified 0 events in either group, resulting in identical estimates for the alternative risk window excluding day 0 (HR = 1.98; 95% CI, 0.35-11.05). In Medicare, the number of events in the comparator group at day 0 was much larger than in the COVID-19—diagnosed group; excluding day 0 events resulted in an HR estimate above the null (HR = 1.26; 95% CI, 0.85-1.88).

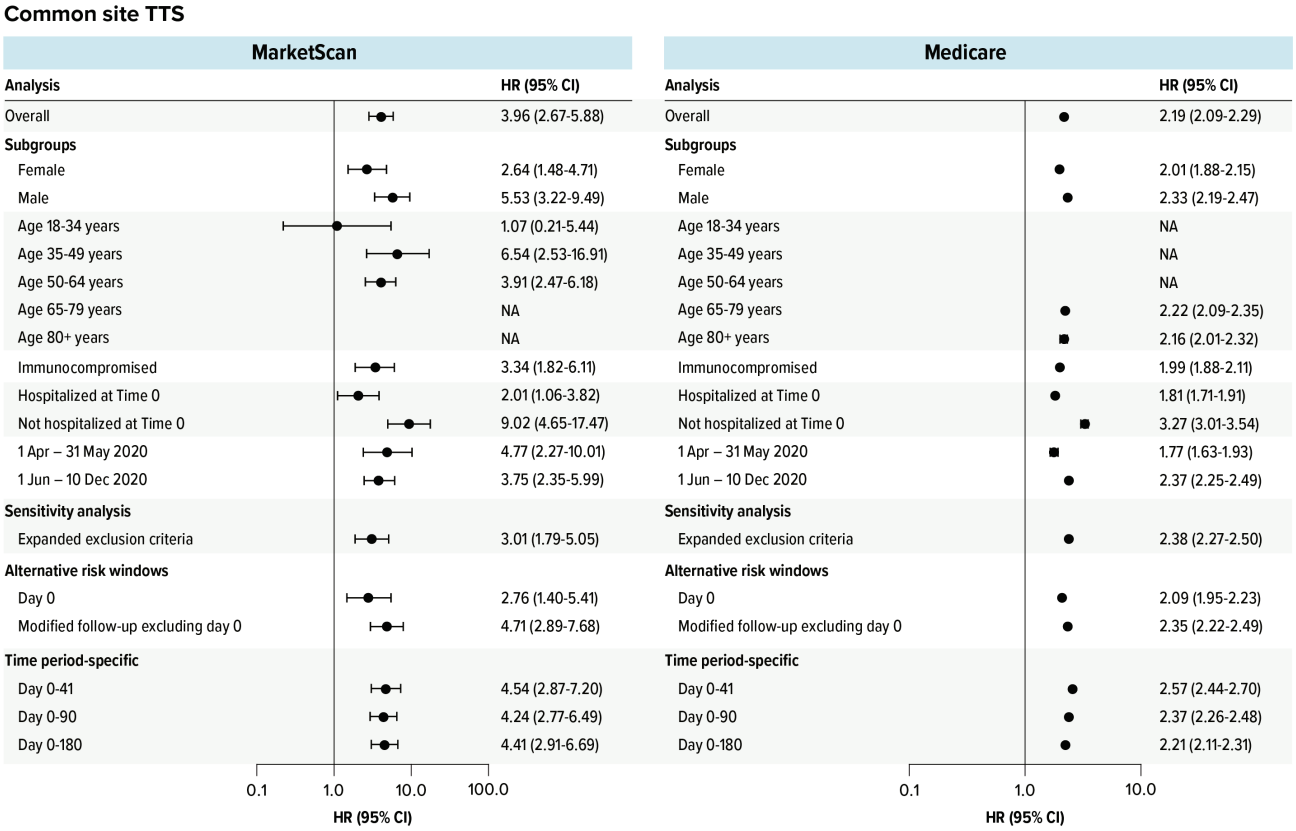
4.2.15.5. Summary of Results

The overall cohort analysis in MarketScan could not rule out an increased risk of unusual site TTS associated with a COVID-19 diagnosis, as the HR estimates were generally increased, but all were imprecise. The results of the Medicare overall analyses were below the null. However, an alternative risk window analysis in Medicare which excluded events occurring on day 0 shifted the Medicare HR upward across the null because events on day 0 were observed more than twice as frequently among comparators than COVID-19-diagnosed patients in both data sources. Analyses with SCRIs were not performed because the substantial risk of death after experiencing an unusual site TTS violates the assumption of no event-dependent censoring (Table 1). After considering the impact of concurrently diagnosed COVID-19 and unusual site TTS, the data suggest a slight potentially increased risk of unusual site TTS after COVID-19 diagnosis.

4.2.16. Common Site TTS

Common site TTS was evaluated only with the cohort design in both data sources, given that the increased mortality associated with the AE violated the assumptions of the SCRI. An overview of the results of all the outcome analyses for the cohort design in both data sources is shown in Figure 37.

Figure 37. Estimated Association of a COVID-19 Diagnosis With Common Site TTS, All Analyses



CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; NA = not applicable; TTS = thrombosis with thrombocytopenia syndrome.

4.2.16.1. Overall Outcome Analyses

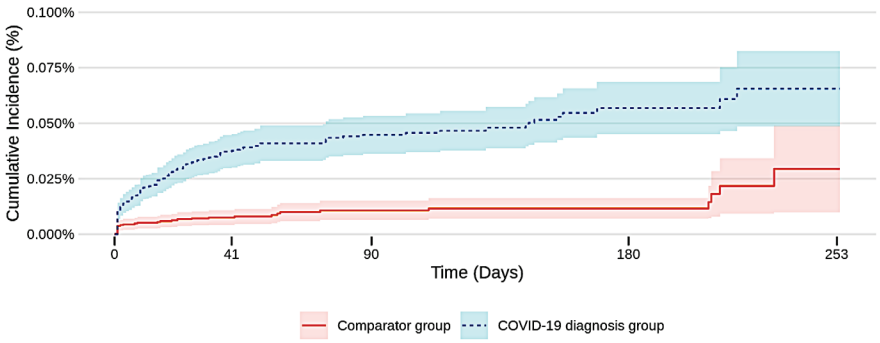
In the cohort analyses, the weighted cumulative incidence by COVID-19 exposure groups over follow-up is shown in Figure 38. In MarketScan and Medicare, more than twice as many common site TTS cases in the COVID-19-diagnosed group were identified on day 0 compared with the comparator group, and the cumulative incidence curve was higher in the COVID-19-diagnosed group than the comparator group throughout the follow-up (Table B-5-MarketScan.P, Table B-5-Medicare.P). In both data sources, the majority of cases in the COVID-19-diagnosed groups occurred very early in follow-up (Figure 38).

The overall HR across all of follow-up and at prespecified time periods is shown in Figure 37. In the overall MarketScan and Medicare cohort analyses, those diagnosed with COVID-19 were more likely to experience common TTS than the comparator group; MarketScan HR = 3.96 (95% CI, 2.67-5.88), Medicare HR = 2.19 (95% CI, 2.09-2.29). Analyses with SCRIs were not performed because the substantial risk of death after experiencing an unusual site TTS violates the assumption of no event-dependent censoring.

In both MarketScan and Medicare cohorts, the time period–specific HRs were all consistent with their respective overall estimate, with a slight attenuation observed in Medicare with increasing risk window length.

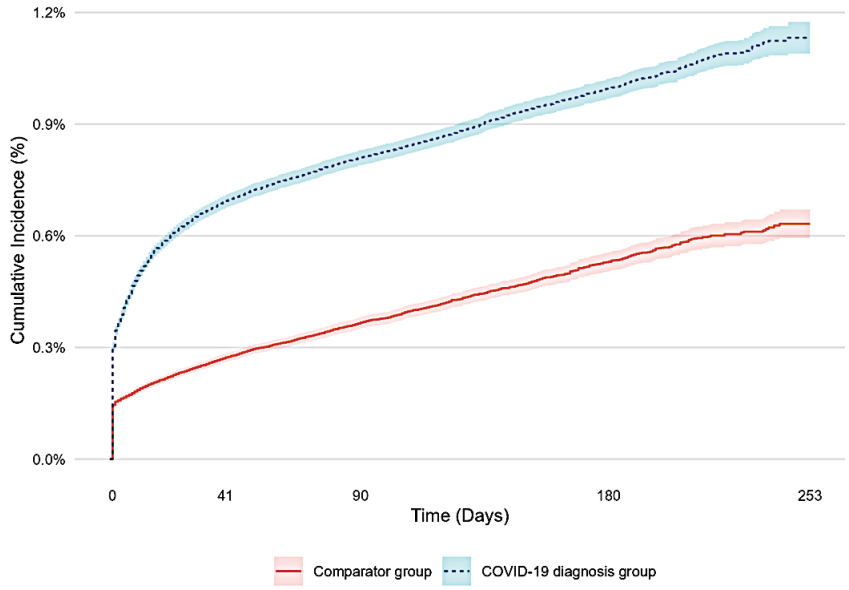
Figure 38. Weighted Cumulative Incidence of Common TTS Among Individuals With a COVID-19 Diagnosis and Comparators Without a COVID-19 Diagnosis

A. MarketScan



Comparator group					
At Risk	318474	187687	128031	36991	537
Censored	4472	132732	191526	281703	318442
Events	12	23	27	28	32
COVID-19 diagnosis group					
At Risk	319051	187034	126862	36125	519
Censored	4471	133910	193181	283035	318925
Events	33	104	116	124	126

B. Medicare



Comparator group					
At Risk	1004591	590725	404657	151902	1860
Censored	15984	417551	600246	850318	1001119
Events	1461	2476	2931	3382	3472
COVID-19 diagnosis group					
At Risk	1005959	544536	368789	134407	1488
Censored	17946	461108	633455	865208	998615
Events	3050	6252	6778	7247	7343

COVID-19 = coronavirus disease 2019; TTS = thrombosis with thrombocytopenia syndrome .

Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

4.2.16.2. Subgroup Analyses

The cohort HRs for individual subgroups are shown in Figure 37. In the MarketScan cohort, the HR estimates for subgroups remained largely consistent with the overall estimates, except for the estimate for those aged 18 to 34, where the point estimate was attenuated, though the wide confidence intervals remained consistent with the overall and other subgroup estimates. In the older Medicare cohort, all HR subgroup estimates were consistent with the overall except for the estimate among those not hospitalized at Time 0, where the HR was elevated. Across both data sources, the majority of the subgroup HRs identified an increased risk of common site TTS in their respective COVID-19—diagnosed groups.

4.2.16.3. Sensitivity Analyses

Results of sensitivity analyses with expanded exclusion criteria in the cohort analyses are summarized in Figure 37. All MarketScan and Medicare cohort analyses estimates remained consistent with their respective overall estimates.

4.2.16.4. Alternative Risk Windows

Results of the analyses of alternative risk windows (day 0 and follow-up excluding day 0) are summarized in Figure 37. In the MarketScan and Medicare cohort analyses, the day 0 HRs were slightly attenuated compared with the overall estimate, while the modified approach excluding day 0 was slightly higher. But generally, the relative effect of concurrent events on day 0 was less than seen with some other AEs, despite the larger number of events occurring on day 0 (Figure 38).

4.2.16.5. Summary of Results

The overall cohort analysis in MarketScan and Medicare both suggested an increased risk of common site TTS associated with COVID-19 diagnosis. Sensitivity analyses and alternative risk window analyses were similar or slightly elevated compared to the overall estimates. Analyses with SCRIs were not performed because the substantial risk of death after experiencing a common site TTS violates the assumption of no event-dependent censoring (Table 1). After considering the impact of concurrently diagnosed COVID-19 and common site TTS, the data suggest a moderate to strongly increased risk of common site TTS after COVID-19 diagnosis.

4.3. Additional Analyses

4.3.1. Cohort Negative Control Outcome Analyses

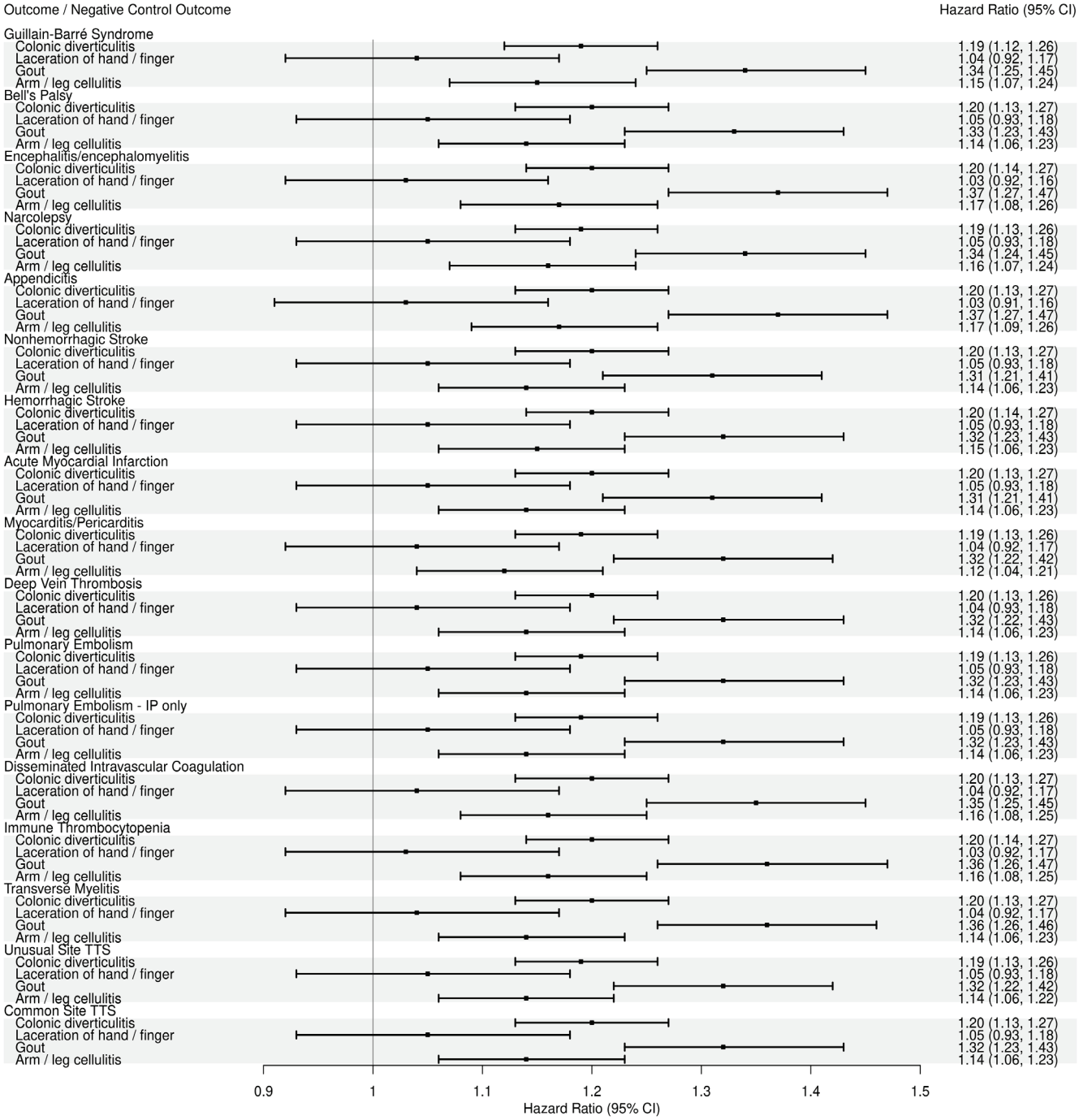
The distributions of histories of negative control outcomes before the index date in each AE-specific analysis set are described in Table B-6-MarketScan and Table B-6-Medicare, and the occurrence of negative control outcomes on the same day as AE cases in each analysis set is shown in Table B-7-MarketScan and Table B-7-Medicare. Few negative control outcomes occurred on the same day as the AE in each analysis set (generally the percentage of negative control outcomes and AEs on the same day was < 0.01%), with the exception of the following, which were elevated in both data sources: colonic diverticulitis and appendicitis (MarketScan, 0.25%; Medicare, 0.17%); arm/leg cellulitis and deep vein thrombosis (MarketScan, 0.47%; Medicare, 1.20%); and gout and pulmonary embolism (MarketScan, 0.35%; Medicare, 0.67%). Additional negative control outcome—AE pairs were elevated only in Medicare (Table B-7-Medicare).

The estimated associations of a COVID-19 diagnosis with the negative control outcomes in each AE-specific analysis set are described in Table B-8-MarketScan and Table B-8-Medicare; a summary of all negative control analysis results is given in Figure 39. HR estimates for laceration of hand and finger were similar in both data sources and were generally null (HRs ranging from 1.03 to 1.07) across all AE-specific analysis sets in both data sources. In MarketScan, the HR estimates for arm/leg cellulitis were slightly increased above the null, but in

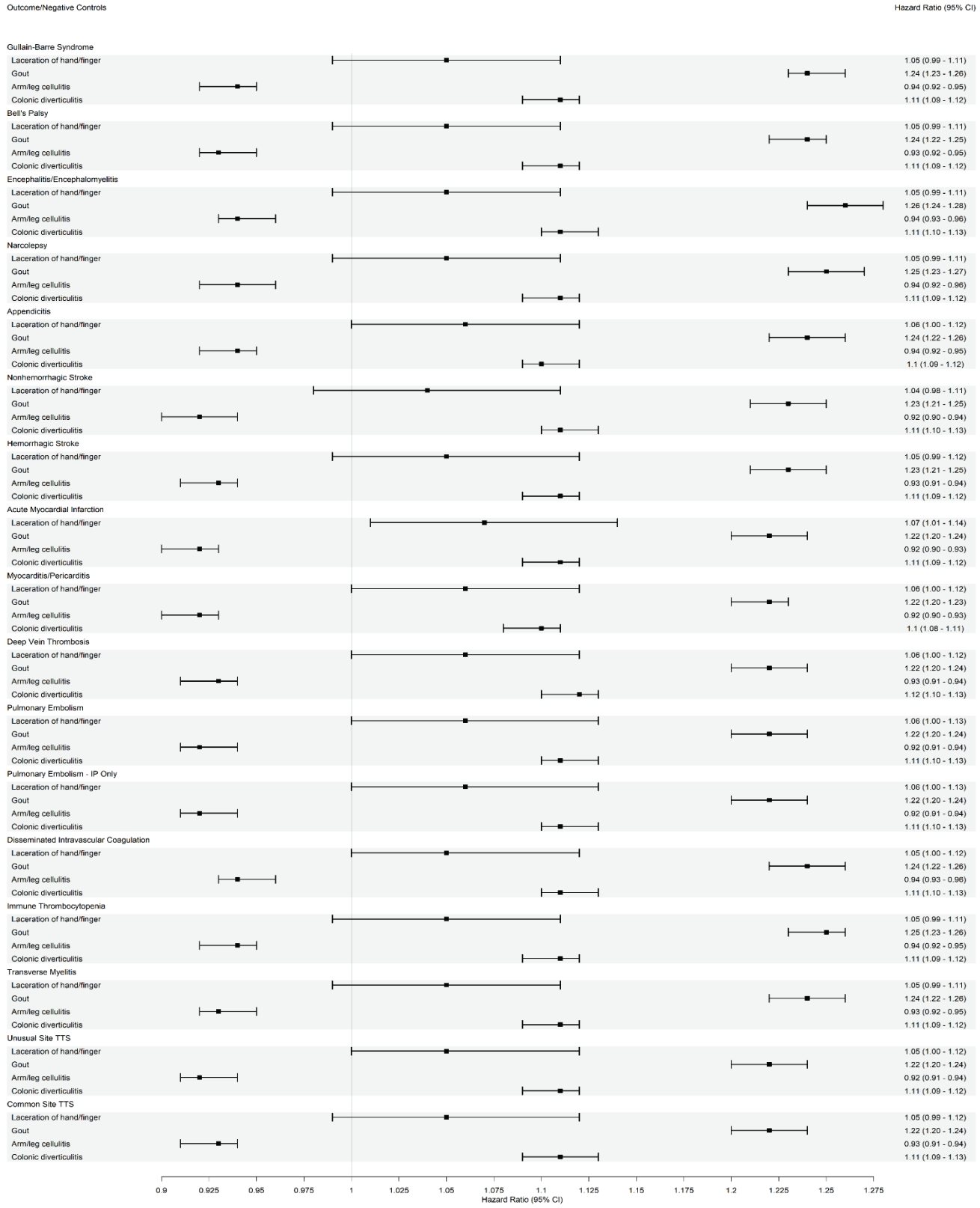
Medicare, the arm/leg cellulitis estimates were below the null. Although the magnitude of the estimates varied slightly by data source, the estimates were very consistent across AE-specific analysis sets. The strongest associations were observed with gout in MarketScan (AE analysis set-specific HRs of approximately 1.35) and Medicare (HRs of approximately 1.23).

Figure 39. Association of a COVID-19 Diagnosis with Negative Control Outcomes Within Outcome-Specific Analysis Sets

A. MarketScan



B. Medicare



CI = confidence interval; COVID-19 = coronavirus disease 2019; IP = inpatient; TTS = thrombosis with thrombocytopenia syndrome.

4.3.2. Ad Hoc Analyses of Hospitalized and Nonhospitalized Subgroups

For the main analyses of each AE, subgroup analyses were performed by hospitalization status at Time 0. In the cohort analyses in both data sources, effect estimate heterogeneity was observed, where the estimate was lower in the subgroup of those hospitalized at Time 0, and higher in those not hospitalized at Time 0. Although the magnitude of the difference varied by AE, this pattern was observed for the cohort analyses for all AEs, when the subgroup analyses could be estimated (of note, the opposite pattern tended to be observed in the SCRI analyses, with higher RI estimates in the hospitalized subgroups). To further investigate the potential explanation for this observed heterogeneity in the cohort analyses, ad hoc descriptive and outcome analyses were performed for the cohort analyses of 3 selected AEs: AMI, pulmonary embolism (any setting), and nonhemorrhagic stroke. The characteristics of individuals were described by exposure group in the hospitalized and nonhospitalized subgroups (in MarketScan, characteristics were reported in each of the 3 AE-specific analysis sets; in Medicare, the characteristics were described in the overall descriptive cohort before restriction to specific analysis sets).

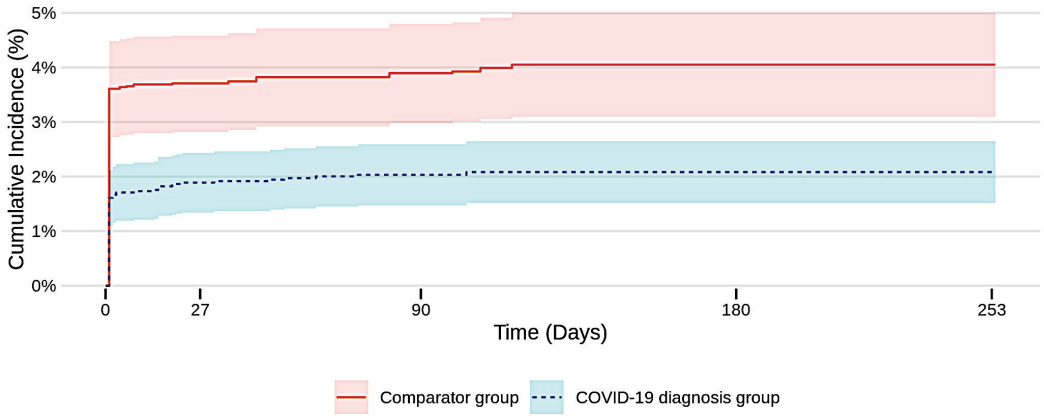
In MarketScan in all 3 AE-specific analysis sets, a higher proportion of individuals in both exposure groups in the hospitalized at Time 0 subgroup had a history of comorbidities. However, within the hospitalized subgroups, the matched comparator group had higher distributions of comorbidities like cancer, chronic liver disease, dementia, heart conditions, inpatient surgery, and trauma in the prior year that the COVID-19—diagnosed group; individuals in the COVID-19-diagnosed group were more likely to have diabetes or were obese/severely obese (Table B-9-MarketScan). In Medicare, the hospitalized subgroup generally had more comorbidities than the nonhospitalized subgroup in both exposure groups. Among the hospitalized subgroup, a higher proportion of individuals in comparator group had a history of comorbidities such as cancer, chronic kidney or renal disease, chronic liver disease, heart conditions, surgery, nutritional deficiency, sepsis, smoking/nicotine dependency, stroke/cerebral vascular disease, and trauma (Table B-9-Medicare). In the hospitalized subgroups of both data sources, the comparator groups also had higher healthcare utilization in the 365 days before the matched index date.

The cumulative incidence of AEs was also plotted by exposure group for the hospitalized and nonhospitalized at Time 0 subgroups (Figure 40 displays the cumulative incidence curves for acute myocardial infarction as an example; Figure 41 displays the cumulative incidence for pulmonary embolism [any setting]). In both data sources, cumulative incidence among the hospitalized subgroups was generally higher compared to the nonhospitalized subgroups. The outcome definitions for some AEs (e.g., AMI and nonhemorrhagic stroke) required a hospitalized diagnosis (Table 1). However, the largest differences between the groups were the occurrence of AEs on day 0. AEs were observed to be very common on day 0 in the hospitalized subgroup in both exposure groups; in the COVID-19-diagnosed group, this may be influenced by COVID-19 testing and subsequent diagnosis secondary to seeking care for the severe AE. In the comparator group, this may be influenced by matching on hospitalization status, where hospital-based comparators without COVID-19 may be hospitalized for other, severe reasons such as occurrence of the AEs being investigated. For example, in MarketScan, among patients who experienced a pulmonary embolism, 96% (54/56 cases) of day 0 cases were hospitalized in the comparator group, compared to 38% (122/324 cases) in the COVID-19—diagnosed group. Other AEs had a similar proportion of day 0 events among COVID-19 and comparator patients, for example 100% of COVID-19 (57/57 cases) and comparator (101/101) cases who experienced an AMI on day 0 were hospitalized patients. However, a larger proportion of the total events in the risk period occurred on day 0 in the comparator group (comparator, 101/176 cases; COVID-19—diagnosed group, 57/252 cases), contributing to a paradoxically reduced effect measure estimates. In Medicare, patterns were similar; 100% of day 0 events

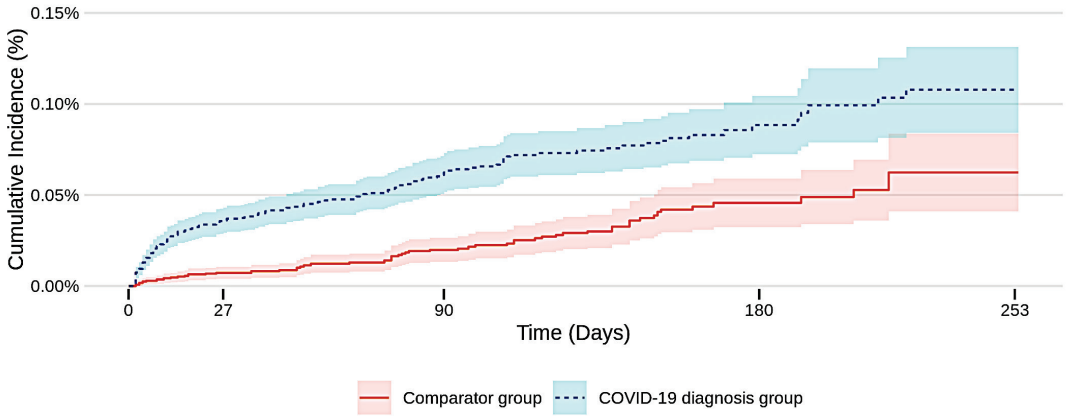
in the COVID-19-diagnosed group (9,219/9,219 cases) and their matched comparators (6,396/6,396 cases) occurred in the hospitalization subgroup (because the AE definition required a hospitalized AMI diagnosis).

Figure 40. Weighted Cumulative Incidence of Acute Myocardial Infarction Among Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis, by Hospitalization at Time 0 and Data Source

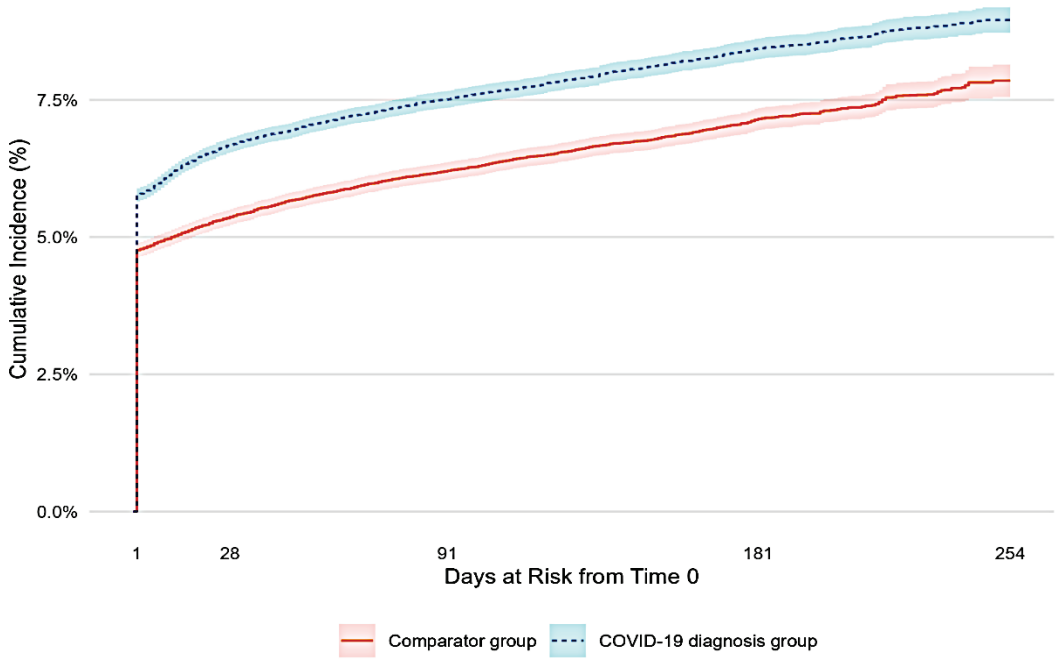
A. Hospitalized at Time 0, MarketScan



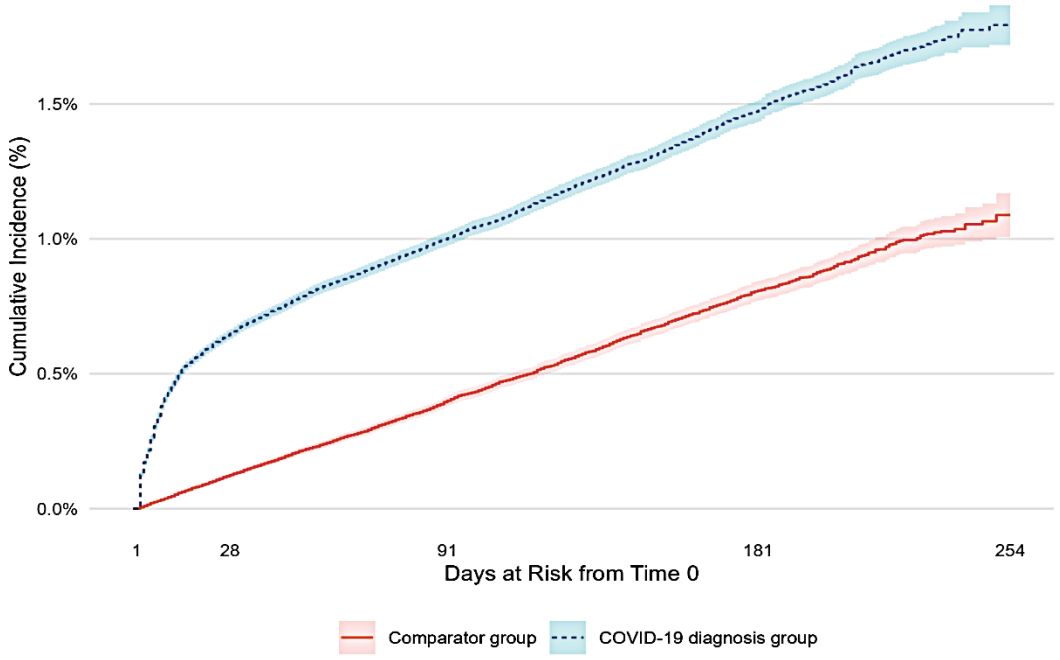
B. Nonhospitalized at Time 0, MarketScan



C. Hospitalized at Time 0, Medicare



D. Nonhospitalized at Time 0, Medicare

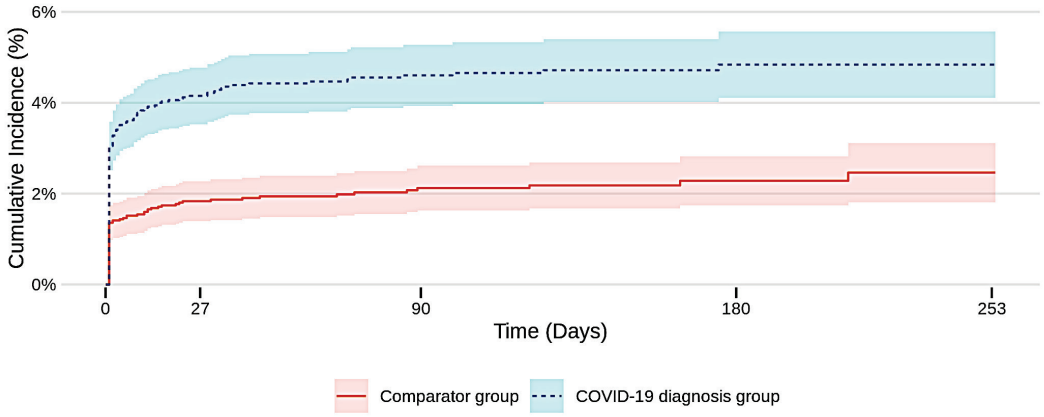


COVID-19 = coronavirus disease 2019.

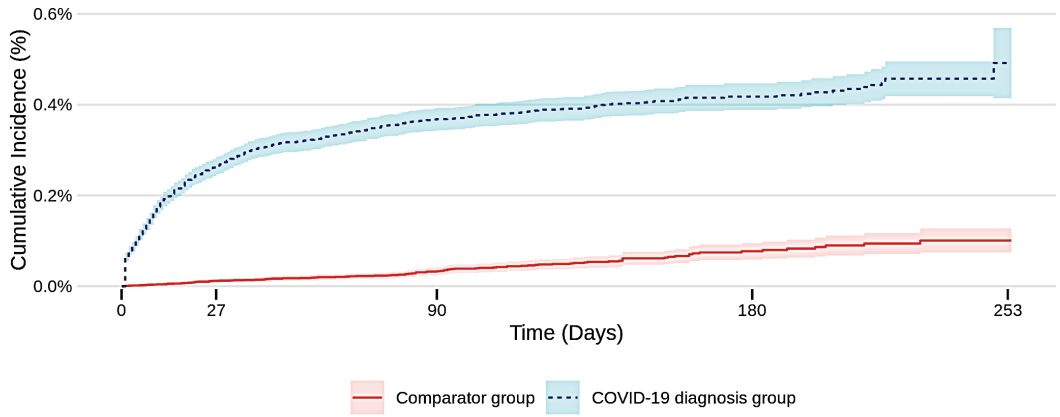
Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots. In the MarketScan plots, this is labelled as day 0; in the Medicare plots, this is labelled as day 1 at risk.

Figure 41. Weighted Cumulative Incidence of Pulmonary Embolism Among Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis, by Hospitalization at Time 0 and Data Source

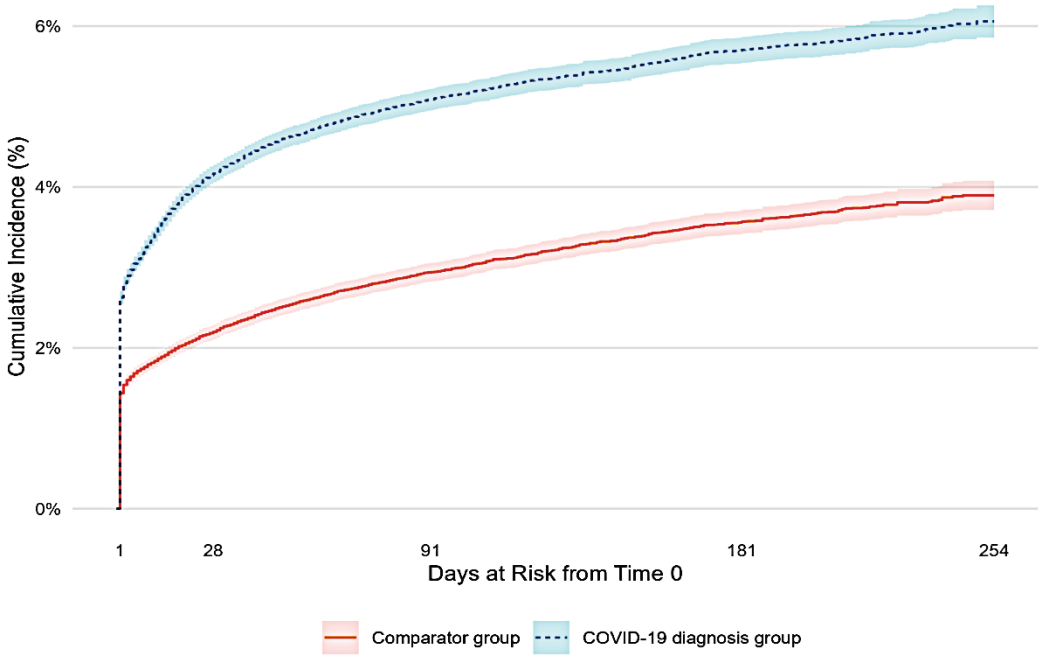
A. Hospitalized at Time 0, MarketScan



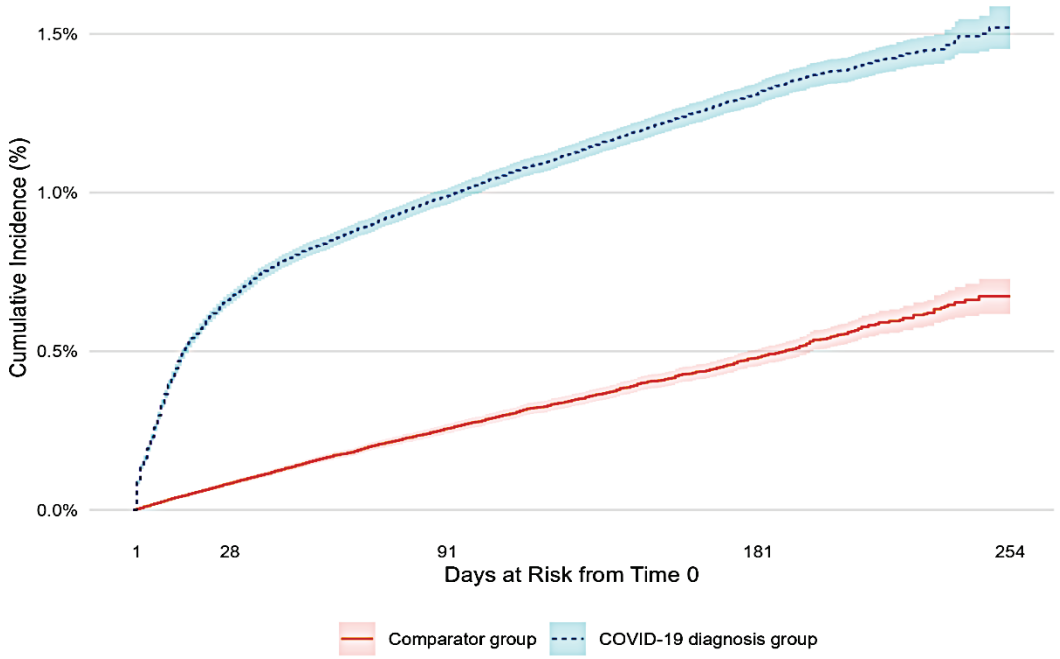
B. Nonhospitalized at Time 0, MarketScan



C. Hospitalized at Time 0, Medicare



D. Nonhospitalized at Time 0, Medicare



COVID-19 = coronavirus disease 2019.

Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots. In the MarketScan plots, this is labelled as day 0; in the Medicare plots, this is labelled as day 1 at risk.

4.3.3. Attributable Risk Analyses

The cohort and SCRI analyses both estimated relative measures of risk (HRs and RIs). To provide additional context for any increases in relative risk observed, the SCRI analyses were used to estimate attributable risks, estimating the number of excess cases of the AEs resulting from COVID-19 diagnosis (Table 5). In MarketScan, although elevated RI estimates of some extent were seen for most AEs, the highest attributable risk estimates were for the thrombotic events, including DVT and pulmonary embolism. Pulmonary embolism was not evaluated using the SCRI approach in Medicare because of the increased risk of mortality in older individuals, but strongly increased attributable risk estimates were seen for DVT and myocarditis/pericarditis.

Table 5. Estimated Attributable Risk of Adverse Events Associated With COVID-19 Diagnosis

Adverse event	MarketScan Extended model adjusted for seasonality [a] RI (95% CI)	MarketScan AR per 100,000 COVID-19 cases	Medicare Extended model adjusted for seasonality [a] RI (95% CI)	Medicare AR per 100,000 COVID-19 cases
Guillain-Barré syndrome	14.3 (2.34-87.19)	1.97	11.65 (4.28-31.69)	3.10
Bell's palsy	2.6 (1.83-3.7)	11.53	1.94 (1.71-2.21)	25.56
Narcolepsy	1.87 (1.08-3.26)	3.09	2.05 (1.58-2.66)	6.75
Appendicitis	5 (3.75-6.67)	33.86	3.53 (2.73-4.56)	13.67
Myocarditis/pericarditis	24.64 (17.27-35.17)	79.47	11.73 (10.05-13.69)	125.81
Deep vein thrombosis	11.8 (10.11-13.77)	173.48	5.58 (5.38-5.79)	870.48
Pulmonary embolism – any setting	30.49 (25.95-35.83)	332.15	NA	NA
Pulmonary embolism – inpatient only	100.95 (67.05-151.97)	147.56	NA	NA
Disseminated intravascular coagulation	83.52 (18.72-372.74)	9.86	NA	NA
Immune thrombocytopenia	3.03 (1.74-5.28)	5.87	3.86 (3.28-4.54)	39.07
Transverse myelitis	4.84 (0.78-30.11)	0.72	3.76 (1.25-11.35)	0.77

AR = attributable risk; CI = confidence interval; COVID-19 = coronavirus disease 2019; NA = not applicable; RI = relative incidence.

[a] Attributable risk estimates derived from the self-controlled risk interval analyses with the extended model accounting for event-dependent observation windows and adjusted for seasonality.

5. Discussion

5.1. Overview of Results

The associations between diagnosis with COVID-19 and 16 AEs (and 4 additional negative control outcomes) were performed in 2 databases using 2 study designs and a variety of secondary, subgroup, and sensitivity analyses. The primary, overall analyses generally suggested some association of a COVID-19 diagnosis with most AEs, although the strength of the estimates and consistency across outcomes varied widely across study designs, analyses, and data sources (Table 6). Although the overall cohort analyses suggested null or paradoxically reduced associations for some AEs, additional subgroup analyses or analyses with alternative risk periods addressed some identified bias (e.g., conditioning on hospitalization which inflated AE rates in hospitalized comparators, Section 5.1.1.2).

Table 6. Overall Analysis Results From Cohort and SCRI Analyses for All Adverse Events and Data Sources

Adverse event	MarketScan cohort, sIPT-weighted HR (95% CI)	MarketScan SCRI, extended model adjusted for seasonality [a] RI (95% CI)	Medicare cohort, sIPT-weighted HR (95% CI)	Medicare SCRI, extended model adjusted for seasonality [a] RI (95% CI)
Overall analyses (day 0 included in follow-up)				
Guillain-Barré syndrome	10.69 (1.38-82.74)	14.30 (2.34, 87.19)	1.06 (0.67-1.68)	11.65 (4.28-31.69)
Bell's palsy	1.22 (0.92-1.61)	2.60 (1.83-3.70)	1.06 (0.96-1.17)	1.94 (1.71-2.21)
Encephalitis/ encephalomyelitis	1.99 (0.69-5.77)	NA	1.43 (1.1-1.85)	NA
Narcolepsy	1.17 (0.70-1.94)	1.87 (1.08-3.26)	1.22 (0.99-1.52)	2.05 (1.58-2.66)
Appendicitis	1.57 (1.23-1.99)	5.00 (3.75-6.67)	0.73 (0.62-0.85)	3.53 (2.73-4.56)
Nonhemorrhagic stroke	1.45 (1.07-1.97)	NA	0.89 (0.86-0.93)	NA
Hemorrhagic stroke	1.21 (0.67-2.20)	NA	0.86 (0.8-0.92)	NA
Acute myocardial infarction	1.37 (1.12-1.68)	NA	1.65 (1.61-1.7)	NA
Myocarditis/pericarditis	6.20 (4.46-8.62)	24.64 (17.27-35.17)	2.53 (2.29-2.79)	11.73 (10.05-13.69)
Deep vein thrombosis	2.83 (2.45-3.28)	11.80 (10.11-13.77)	1.67 (1.63-1.72)	5.58 (5.38-5.79)
Pulmonary embolism – any setting	5.79 (4.93-6.80)	30.49 (25.95-35.83)	2.47 (2.39-2.56)	NA
Pulmonary embolism - inpatient only	4.95 (3.87-6.33)	100.95 (67.05-151.97)	2.60 (2.49-2.72)	NA
Disseminated intravascular coagulation	3.41 (1.67-6.93)	83.52 (18.72-372.74)	2.73 (2.43-3.07)	NA
Immune thrombocytopenia	2.10 (1.26-3.51)	3.03 (1.74-5.28)	1.43 (1.27-1.62)	3.86 (3.28, 4.54)
Transverse myelitis	1.70 (0.28-10.19)	4.84 (0.78-30.11)	0.59 (0.25-1.43)	3.76 (1.25-11.35)
Unusual site TTS	1.98 (0.35-11.05)	NA	0.82 (0.61-1.10)	NA
Common site TTS	3.96 (2.67-5.88)	NA	2.19 (2.09-2.29)	NA
Alternative risk period analyses (day 0 not included in follow-up)				
Guillain-Barré syndrome	9.57 (1.23-74.74)	8.53 (2.45-29.65)	1.97 (1.04-3.74)	4.63 (1.78-12.01)
Bell's palsy	1.13 (0.85-1.50)	1.95 (1.39-2.74)	1.11 (1.00-1.24)	1.05 (0.91-1.22)
Encephalitis/ encephalomyelitis	1.99 (0.69-5.77)	NA	1.36 (0.96-1.94)	NA
Narcolepsy	1.21 (0.71-2.05)	1.44 (0.84-2.47)	1.11 (0.88-1.42)	1.15 (0.85-1.55)
Appendicitis	1.14 (0.86-1.50)	1.38 (1.00-1.90)	1.22 (0.97-1.53)	0.98 (0.70-1.36)
Nonhemorrhagic stroke	3.04 (1.97-4.70)	NA	1.35 (1.28-1.43)	NA
Hemorrhagic stroke	2.49 (1.27-4.89)	NA	1.35 (1.22-1.50)	NA
Acute myocardial infarction	2.43 (1.84-3.23)	NA	1.94 (1.86-2.01)	NA
Myocarditis/pericarditis	4.51 (3.15-6.45)	9.03 (7.22-11.29)	2.07 (1.84-2.32)	4.53 (3.89-5.27)

Adverse event	MarketScan cohort, sIPT-weighted HR (95% CI)	MarketScan SCRI, extended model adjusted for seasonality [a] RI (95% CI)	Medicare cohort, sIPT-weighted HR (95% CI)	Medicare SCRI, extended model adjusted for seasonality [a] RI (95% CI)
Deep vein thrombosis	2.80 (2.39-3.27)	8.04 (7.07-9.14)	1.69 (1.63-1.74)	3.18 (3.05-3.30)
Pulmonary embolism – any setting	5.89 (4.86-7.12)	13.55 (12.17-15.09)	2.53 (2.42-2.63)	NA
Pulmonary embolism – inpatient only	8.65 (6.06-12.35)	27.36 (23.01-32.55)	3.06 (2.88-3.26)	NA
Disseminated intravascular coagulation	6.58 (2.27-19.06)	32.28 (17.06-61.09)	2.54 (2.17-2.98)	NA
Immune thrombocytopenia	2.06 (1.20-3.53)	1.74 (1.01-3.00)	1.36 (1.18-1.57)	1.91 (1.60-2.28)
Transverse myelitis	2.30 (0.21-25.41)	3.14 (0.56-17.50)	0.93 (0.28-3.09)	0 (0-NE)
Unusual site TTS	1.98 (0.35-11.05)	NA	1.26 (0.85-1.88)	NA
Common site TTS	4.71 (2.89-7.68)	NA	2.35 (2.22-2.49)	NA

CI = confidence interval; HR = hazard ratio; IP = inpatient; NA = not applicable; RI = relative incidence; SCRI = self-controlled risk interval; sIPT = stabilized inverse probability of treatment; TTS = thrombosis with thrombocytopenia syndrome.

[a] Conditional Poisson model accounting for event-dependent observation windows and adjusted for seasonality as calendar month groupings.

The strongest overall effect estimates were observed in the cardiac/thrombotic AEs, including stroke, acute myocardial infarction, pulmonary embolism, myocarditis/pericarditis, DVT, common site TTS, and DIC. Neurologic or immune-mediated AE estimates showed weaker associations with COVID-19 diagnosis, including appendicitis, encephalitis, GBS, and transverse myelitis. Central nervous system AEs were less strongly associated, with smaller estimates and modest associations observed for Bell's palsy and narcolepsy.

HRs from MarketScan were generally larger than those from Medicare, potentially reflecting the higher incidence of these AEs in the comparator group of the Medicare-insured population (Table B-5-MarketScan, Table B-5-Medicare). Self-controlled risk analyses demonstrated a similar trend toward larger estimates in MarketScan than in Medicare (Table B-12-MarketScan, Table B-12-Medicare). Estimates from the self-controlled risk analysis were generally of higher magnitude than those from the cohort because they estimate different parameters, have different entry criteria, and have different observation periods. The cohort design followed all eligible patients for all of follow-up (potentially > 250 days), compared to the shorter duration in the SCRI prespecified risk window (28 or 42 days depending on the AE) and reference window used in the SCRI. However, time period–specific HRs were estimated using the same risk period in the cohort analysis as for the SCRI, and even when the same risk period after COVID-19 diagnosis was used, the SCRI generally resulted in larger estimates, although it is acknowledged that the cohort-derived HRs and the SCRI-derived RIs estimate different parameters and are not directly comparable.

Given the wide range of incidence of some of the AEs, ranging from very rare to quite common, the relative measurements of association (i.e., HR and RI) could translate into different absolute population burdens (Section 4.3.3, Table 5). For example, in Medicare, the RIs from the overall SCRI for GBS (RI = 11.65; 95% CI, 4.28-31.69) and myocarditis/pericarditis (RI = 11.73; 95% CI, 10.05-13.69) were relatively similar, but they translated into vastly different attributable risks for the AE (3.10 GBS cases/100,000 COVID-19 cases; 125.81 myocarditis/pericarditis cases/100,000 COVID-19 cases). The attributable risk estimates for Medicare tended to be higher than the MarketScan estimates for most AEs (other than appendicitis and transverse myelitis),

given the higher observed incidence of most AEs in the older Medicare population. Generally, attributable risk estimates were highest for the cardiac/thrombotic estimates in both data sources.

Some potential methodological issues regarding including Time 0 in the risk period/follow-up, the placement of risk periods, and matching on hospitalization resulted in occasional anomalies in the study results, affecting multiple AEs, data sources, and study designs. These issues may have affected different analyses differently (e.g., depending on the severity of the AE, whether the AE required hospitalization). These global issues are discussed separately in the following sections.

5.1.1. Results Excluding Day 0 and Starting Follow-Up on Day 1

For many AEs, the direction of the HR and RI estimates from similar analyses from the cohort and SCRI study designs was the same, providing some reassurance to the validity of the findings as the two designs are complementary. However, in the instances where the results of the 2 study designs disagree, the inclusion of day 0 in the follow-up period of risk period may influence the study designs in different directions. The overall cohort and SCRI analyses included day 0 in the follow-up period, but alternative risk period analyses excluding day 0 and starting follow-up on day 1 were also performed for both study designs. HR and RI estimates for these alternative risk period analyses are shown in Table 6.

5.1.1.1. Concurrent COVID-19 and AE Diagnoses

For many AEs analyzed, a substantial number of patients experienced an AE on the same day that they were diagnosed with COVID-19, or on the day they were matched to a patient with COVID-19. Early in the pandemic, COVID-19 testing for all hospitalized patients (regardless of presenting symptoms) may have been more routine. This observation identifies a potential source of bias; patients who experience an AE that requires hospitalization or other interaction with medical professionals are more likely to be tested for and diagnosed with COVID-19. In the cohort analysis, this may increase the probability of AEs among the COVID-19-diagnosed group relative to the comparison group, increasing the HR estimate for some AEs. An alternative risk window analysis was performed that excluded patients who experienced an AE on day 0 of follow-up, and for some AEs in the cohort analyses, this resulted in reduced HR estimates (e.g., for myocarditis/pericarditis) (Table B-5-MarketScan, Table B-5-Medicare). Note that for other AEs in the cohort analysis, excluding day 0 increased the HR estimate due to other Time 0 effects in the comparator group—these are discussed in subsequent sections. In the SCRI, however, these concurrent AEs and COVID-19 diagnoses increased likelihood of the AE occurring during the risk window when day 0 was included in the risk window, and thus most alternative risk period analyses excluding day 0 resulted in decreased RI estimates, as has been noted in other studies[17,45] (Table 6, Table B-14-MarketScan, Table B-14-Medicare).

5.1.1.2. Conditioning on Hospitalization at Time 0

A number of AE estimates showed paradoxical HR effect measure estimates below 1.00 associated with COVID-19 diagnosis in the cohort analyses among patients who were hospitalized on Time 0. In the hospitalized at Time 0 subgroup analyses in MarketScan, HRs estimates below 1.00 were observed for Bell's palsy, narcolepsy, appendicitis, hemorrhagic and nonhemorrhagic stroke, AMI, and DIC; in the hospitalized subgroup analyses in Medicare, HRs estimates below 1.00 were observed for GBS, Bell's palsy, narcolepsy, appendicitis, hemorrhagic and nonhemorrhagic stroke, and transverse myelitis. Because estimates among nonhospitalized patients were consistently above the null, these paradoxical subgroup estimates are likely a result of bias induced by matching on hospitalization status at Time 0. Conditioning on a clinical characteristic (i.e., hospitalization) that is associated with the common causes of an exposure (receiving a COVID-19

diagnosis) or outcome (experiencing an AE) can induce bias through collider-stratification.[60] More intuitively, during the early phase of COVID-19 pandemic there were unprecedented challenges to the healthcare system which altered patients' care-seeking patterns; healthcare utilization was low during this stage of the pandemic so that most hospitalizations were related to severe COVID-19 or other severe conditions or events. While this time period was not included in the SCRI study period, it was included in the cohort analyses. Thus, if a patient was hospitalized, they were either very sick with COVID-19 or very sick with something else, such as 1 of the severe AEs in this study. In this hospitalized group, patients who were not diagnosed with COVID-19 in both data sources had more recent inpatient admissions, ED visits, inpatient surgeries, and more pre-existing comorbidities such as cancer, liver disease, and heart disease (Table B-9-MarketScan, Table B-9-Medicare). In the cohort alternative risk period analyses where day 0 (i.e., Time 0, the day of COVID-19 diagnosis or matched comparator date) was excluded and follow-up began on day 1, the HR estimates for most AEs from MarketScan and Medicare increased compared to the analyses including day 0, which may be explained by this bias begin concentrated on Time 0.

5.1.2. Pre-Exposure and Postexposure Buffer Periods: Self-Controlled Risk Analysis

In the overall SCRI analysis, pre- and postexposure buffer periods were employed during which events were not counted toward RI estimates. SCRI analyses are frequently used to evaluate acute, clearly defined exposures like vaccination; however, while COVID-19 diagnoses are received on a specific day, the timing of the underlying infection and severity is unknown. The use of these buffers, outside of the prespecified risk period, acknowledged the uncertainty of the biologically relevant risk period relative to the COVID-19 diagnosis. Two consequences of this approach were considered. First, patients who were diagnosed with COVID-19 on a given date may have been at risk for COVID-19-associated AEs in the days prior to diagnosis; because these events were excluded in the overall analysis, the overall RI estimates may underestimate the true effect. Many alternative risk period analyses in MarketScan and Medicare showed RIs greater than 1 for the 7-day pre-exposure period, suggesting that the start of the true biologically relevant risk period may precede the COVID-19 diagnosis (Time 0) in many cases. Second, the duration of the COVID-19 infection may continue after the date of the diagnosis, and the duration of the biologically plausible risk period for experiencing an AE after COVID-19 infection may not be well defined. Thus, COVID-19-associated AEs may occur after the prespecified risk period, and not considering events that occur after the AE-specific risk period may also result in underestimation of the effect estimate. Many alternative risk period analyses found slightly elevated RI estimates in the postexposure buffer period, and most AEs had at least 1 event in the pre- and postexposure buffer periods (Table B-14-MarketScan, Table B-14-Medicare).

5.1.3. Negative Control Findings

Negative control outcome analyses were conducted in the cohort study to evaluate the potential for unmeasured confounding and other biases remaining after matching and weighting. In this study, negative control estimates suggested modest associations between COVID-19 diagnosis and increased risk for colonic diverticulitis and gout. In MarketScan, COVID-19 was associated with a slight increased risk of arm/leg cellulitis, while in Medicare, it was associated with a slight decreased risk. In both data sources, estimates for laceration of hand/finger were within the expected range of association for a negative control outcome. These non-null findings for some negative control outcomes are suggestive of potential residual bias in the overall cohort estimates. Many of the same global issues discussed previously in relation to the AEs (i.e., events on day 0) are applicable to the negative control outcomes, also, and may explain some of the observed findings (reverse causality, where seeking care for the negative control outcome increased the probability of receiving a concurrent COVID-19 diagnosis; matching on hospitalization increases the probability of selecting comparators

with arm/leg cellulitis). These potential biases may be addressed in the alternative risk period analyses not including day 0 in follow-up, but additional bias from unmeasured confounding cannot be ruled out.

Negative control outcomes must meet key assumptions about the relationship between the exposure, confounders, and negative control outcome. These assumptions may be difficult or impossible to empirically test. Additionally, negative control outcomes may be subject to their own biases (e.g., misclassification). Additionally, some recent emerging evidence may be suggestive of potential associations between COVID-19 and the a priori selected negative control outcomes, violating key assumptions of the negative control analysis. Some evidence suggests that gastrointestinal disruption, which may include colonic diverticulitis, may be associated with immune-dysregulation secondary to COVID-19.[61,62] Gout flares have been associated with COVID-19 vaccination,[63] recent research suggests that patients with gout are more susceptible to COVID-19 infection, hospitalization, and severe outcomes,[64] and gout diagnoses have been observed more commonly after a COVID-19 diagnosis.[15] Thus there may be a potential association between COVID-19 and gout, violating a key assumption of the negative control analyses.

Additionally, some of the selected negative control outcomes may share similar presentations with the AEs, as demonstrated by the concurrent diagnoses of both (Section 4.3.1). For example, appendicitis and colonic diverticulitis symptoms may be similar (e.g., febrile, lower quadrant pain), and DVT and arm/leg cellulitis may initially be confused for each other. Initial presenting diagnoses or rule-out diagnoses for a negative control outcome when a true AE was present may explain some of the observed associations.

5.2. Contextualizing Literature

Ongoing research continues to unveil the multifaceted, adverse impacts of COVID-19 on the human body, both in the immediate period following infection and in the long term. Although initially understood as solely a respiratory illness, every organ system can be negatively affected by infection.[65,66] Growing evidence links the direct and indirect damage caused by COVID-19 with postinfection AEs involving the respiratory, cardiac, immune, and peripheral/central nervous systems.[67-73]

5.2.1. Neurologic or Immune-Mediated Events

5.2.1.1. Guillain-Barré Syndrome

Systematic reviews examining the relationship between COVID-19 and GBS collected and analyzed case reports, case series, observational studies, and cohort studies. These cases and cohorts originated in a variety of countries in Europe, Asia, and the Americas.[74,75] These analyses identified consistent trends regarding the development of GBS following a recent COVID-19 infection,[73,74,76-78] consistent with the results we observed in this study. Additionally, persistent trends across published studies identified older, male patients as the most common group afflicted with post-COVID-19-related GBS. Few systemic reviews provided an analysis of the strength of the association between COVID-19 and GBS because of the heterogenous definitions of GBS and COVID-19, difficulty identifying asymptomatic infections, lack of uniform case report data, and inability to establish the temporality of events.[73,74,76-78] Although some epidemiological studies have cast doubt on the association between the 2 conditions, a large proportion of systematic reviews identify or suggest a potential relationship between COVID-19 infection and the onset of GBS.[79] Our study also suggested a reasonably strong association between COVID-19 and GBS.

5.2.1.2. Bell's Palsy

The findings of this report indicated a modest, yet inconsistent, potential relationship between COVID-19 diagnosis and development of Bell's palsy. Within the identified systematic reviews, researchers collected case reports, case series, and retrospective analyses examining the relationship between COVID-19 and Bell's palsy in a wide range of countries. A systematic review of Bell's palsy case reports suggested a potential association between the 2 conditions because the majority of Bell's palsy cases developed after the onset of COVID-19 symptoms.[19] A European self-controlled study also reported increased risk of Bell's palsy after COVID-19 infection.[13] Additionally, development of Bell's palsy has commonly been associated with postviral infection inflammation caused by Lyme disease, HIV, and herpes simplex virus 1 and 2.[80,81] Researchers across multiple reviews noted the limitations of a short follow-up period—neurologic conditions may take time to develop, the potential for concurrent viral infections, the higher likelihood of case reports for severe manifestations of COVID-19, and the lack of data regarding new COVID-19 variants.[19,75,82,83]

5.2.1.3. Transverse Myelitis

Transverse myelitis is commonly triggered by postinfection inflammation (HIV, herpes simplex, Epstein-Barr, etc.), autoimmune diseases, and demyelination of nerve fibers.[84,85] Given the rarity of the condition, limited evidence exists regarding the connection between COVID-19 and transverse myelitis. Similarly, in our analyses, the resulting HR and RI estimates were inconsistent across analyses and data sources, driven in many instances by very small numbers of cases. However, existing case reports and systematic analyses observed development of transverse myelitis after COVID-19 diagnosis, suggesting a potential association between COVID-19 and subsequent onset of transverse myelitis.[86-88] These hypotheses are highly speculative because of the difficulties of establishing temporality within case reports and the heterogeneity of reporting. Cases within these reports and systematic reviews originated in European, North American, Middle Eastern, African, and East Asian countries.[86-88]

5.2.1.4. Encephalitis/Encephalomyelitis

Although the pathophysiology of encephalomyelitis is not well understood, the association between viral pathogens and the symptoms of encephalomyelitis are well documented.[89] The following systematic and meta-analyses collected a variety of case reports, case series, and cross-sectional studies in the reviews, with studies and cases originating largely in North American and European populations. A meta-analysis by Siow et al. estimated incidence of post-COVID-19 encephalitis in hospitalized patients of 0.215%, with the incidence in severe COVID-19 patients (i.e., requiring intensive care unit or high-dependence unit care) increasing substantially (6.7%).[90] These trends within the literature mirror the overall cohort findings of this report, which indicate a modest, but somewhat inconsistent, association between COVID-19 and encephalitis/encephalomyelitis. In addition to an overall relationship, trends across reviews identified older individuals and those with more severe COVID-19 cases to be at greater risk of developing encephalitis following COVID-19 infection.[90-92] The strengths of the analyses were limited by the lack of established chronology between onset of COVID-19 and encephalitis symptoms, the overlap between COVID-19 and encephalitis symptomatology, and the publication bias associated with case reports.[93]

5.2.1.5. Narcolepsy

Case reports and mechanistic studies in this review have hypothesized an association between the autoimmune dysregulation caused by COVID-19 infection and the onset of narcolepsy. The hypothesized association between the 2 conditions stems from case reports of post-COVID-19 development of narcolepsy

and mechanistic studies, which establish the ability of COVID-19 to cause inflammatory and olfactory dysfunction.[94] The hypothesis surrounding post-COVID-19 development of narcolepsy also stems from the long history of links between infectious agents (H1N1, Epstein-Barr virus, etc.) and the postviral onset of narcolepsy.[95] Although not well documented in the surrounding literature, within this report, the association between COVID-19 and narcolepsy was moderately strong but rather inconsistent.

5.2.1.6. Immune Thrombocytopenia

Analyses of post-COVID-19 ITP utilized case reports and case series from multiple countries. Across reviews, elderly and severely ill COVID-19 patients displayed consistent increased risks of ITP.[96-98] Although little evidence exists regarding a causal relationship between COVID-19 and ITP, these studies frequently identified a latency period of 18 to 21 days between COVID-19 diagnosis and the development of ITP. Additionally, because of mounting evidence of the importance of platelet levels in COVID-19 disease severity, ITP is now considered a potential prognostic factor for the severity of COVID-19 infection.[99] The association between COVID-19 and immune thrombocytopenia was consistently moderate to strong in all analyses.

5.2.1.7. Appendicitis

Although limited literature currently exists regarding the association of appendicitis and COVID-19, case studies of COVID-19 patients with subsequent appendicitis have been reported, and mechanistic evidence has shown that SARS-CoV-2 virus can infect gastrointestinal tissues.[100] Additionally, case studies of COVID-19 patients with subsequent appendicitis events also support this potential relationship. However, analyzing the relationship between COVID-19 and appendicitis is complicated by the changing care-seeking behavior of patients during the pandemic. The incidence of complicated appendicitis has increased since the pandemic's onset, driven by worsening patient conditions because of delays in patients seeking medical care for minor appendicitis symptoms.[101] These difficulties in assessing temporality and confounding factors were also present in this report's findings. Although a potential weak increase in risk of appendicitis following COVID-19 diagnosis cannot be ruled out in these data, the overall results were inconsistent across study designs and data sources, attenuated in the sensitivity analyses, and changed markedly following the exclusion of day 0 events.

5.2.2. Cardiac/Thrombotic Events

5.2.2.1. Myocarditis/Pericarditis

Overall, this report identified a moderate to strong association between COVID-19 diagnosis and the development of myocarditis/pericarditis. The relationship between COVID-19 and myocarditis/pericarditis has been well documented in case reports and large observational studies. Studies and reviews (including our study) consistently identified strong associations between COVID-19 infection and subsequent onset of myocarditis[8,9,15,102,103] and pericarditis.[8] Studies also frequently found youths, elderly populations, and males to be at particular risk for myocarditis following COVID-19 infection. Notably, Boehmer et al. identified the potential bias inherent between comparator groups because physicians were more likely to diagnose myocarditis in COVID-19 patients than those without COVID-19.[9]

5.2.2.2. Thrombosis With Thrombocytopenia Syndrome

The novel combination of having both concurrent thrombosis with thrombocytopenia (thrombosis occurring at either an unusual or a common site) was observed after adenovirus-based COVID-19 vaccination.[104] Although few studies have evaluated TTS after COVID-19 infection (rather than vaccination), COVID-19 infection has been associated separately with both thrombosis and thrombocytopenia.[104] Thrombocytopenia findings largely originated from large retrospective cohort studies using Chinese national healthcare data and systematic

reviews using a variety of global healthcare data. During the initial phase of the pandemic, a large retrospective cohort study found 36.2% of admitted COVID-19 patients to have thrombocytopenia.[105] Although thrombocytopenia is generally a rare condition in the general population, it remains strongly associated with disease severity and mortality.[106,107] The risks of both thrombosis and thrombocytopenia have been shown to be higher with COVID-19 infection than COVID-19 vaccination.[104] In this report's findings in the cohort analyses, the association between COVID-19 diagnosis and TTS was strong, especially at common sites.

5.2.2.3. Acute Myocardial Infarction

Some robust studies have analyzed the relationship between COVID-19 and onset of AMI.[8,10,12,15,16,18,108] Del Prete et al found that roughly 25% of COVID-19 patients developed myocardial injury after infection, regardless of family history.[108] Barda et al found an RR greater than 3.0 for the association between SARS-CoV-2 infection and AMI in Israel.[8] In a meta-analysis of observational studies, COVID-19 patients were found to be at an increased risk of developing AMI (HR = 1.93; 95% CI, 1.65–2.26, I^2 = 83.5%), consistent with the results of this study.[109] Additionally, the meta-analysis reported that older age groups and men were at higher risk of AMI among patients with COVID-19. Although the analysis identified an increased risk of AMI in patients with COVID-19, potential biases may have been introduced by the lack of information on vaccination status and the difficulty of identifying asymptomatic and moderate COVID-19 cases.[109]

5.2.2.4. Pulmonary Embolism

Studies of COVID-19 and pulmonary embolism, including systematic reviews and meta-analyses comprised case reports, observational studies, and randomized controlled trials from mostly European and East Asian populations. Within population-based, real-world studies, those diagnosed with COVID-19 were found to have an increased risk of pulmonary embolism.[8,12,14,15,18,110] The pooled incidence for pulmonary embolism in patients with COVID-19 ranged from 15% to 20%, consistently identifying higher frequencies of pulmonary embolism in males and patients in intensive care units versus other care settings.[111-116] A large self-controlled analysis of Swedish data also identified a strongly increased risk of pulmonary embolism associated with COVID-19.[14] The analyses described in this report also identified strong, consistent associations with pulmonary embolism, both in the any-setting and inpatient-only analyses.

5.2.2.5. Deep Vein Thrombosis

Population-based studies, systematic review, and meta-analyses regarding DVT originated from prospective, retrospective, and cross-sectional studies, mostly conducted in Europe, North America, and Asia. The risk and prevalence of DVT in COVID-19 patients varied widely between studies and severity of disease, but COVID-19 was generally demonstrated to be associated with increased risk of DVT.[8,12,14,18,113,117-120] However, across analyses, ICU and critically ill patients were found to be at higher risk and to have a higher prevalence of DVT compared to asymptomatic and hospitalized populations. Although studies in this review varied greatly regarding the strength of the association between DVT and COVID-19, the cohort and SCRI analyses in this report identified consistent, moderate to strong associations between COVID-19 diagnosis and the diagnosis of DVT. Our study showed consistently strong associations between COVID-19 and deep vein thrombosis, consistent with other, recent large population studies.[14]

5.2.2.6. Disseminated Intravascular Coagulation

Data regarding DIC in patients with COVID-19—as described in systematic reviews and meta-analyses, case reports, case series, and observational cohorts—were collected from a wide range of countries. Growing evidence that the reactionary immune response to COVID-19 infection can result in unregulated inflammation

has led researchers to hypothesize that COVID-19 infection is a trigger for the development of DIC.[121,122] However, researchers found difficulty capturing the strength of the association between the 2 conditions because fatality rates were high in COVID-19 patients who developed DIC, and fatal cases of DIC may be identified more readily.[123,124] Within the general population, DIC remains a rare condition, but within cohorts of patients with COVID-19, analyses estimated that roughly 2% to 7% of individuals with COVID-19 will develop DIC.[123,124] The DIC Medicare analyses in this report were unable to utilize a SCRI design because the substantial risk of death following DIC violated the assumptions of no event-dependent censoring. However, the cohort and MarketScan SCRI analyses that could be employed indicated consistent, moderate to strong associations between COVID-19 diagnosis and the development of DIC.

5.2.2.7. Stroke

Numerous large population-based studies have noted associations between COVID-19 and stroke, including nonhemorrhagic and hemorrhagic stroke.[8,10,12,16-18] Systematic and meta-analyses collated a variety of observational cohorts and case reports, largely originating in North American and European populations. Across multiple meta-analyses, patients infected with COVID-19 were found to be at increased odds of ischemic stroke compared to those without COVID-19 (OR = 3.58; 95% CI = 1.43–8.92, I^2 = 43%) and (OR: 2.41; 95% CI, 1.08–5.38), respectively.[71,125] Katsanos et al. also identified an increased odds of cryptogenic stroke in those diagnosed with COVID-19 (OR = 3.98; 95% CI = 1.62–9.77, I^2 = 0%).[71] Compared to those infected with influenza, COVID-19 patients also displayed a higher likelihood of ischemic stroke (OR = 7.6; 95% CI, 2.3-25.2).[126] Stroke events in COVID-19 patients were associated with older age, comorbidities, and COVID-19 severity.[125,127] Researchers noted that the strength of their findings was potentially confounded by the inability to consistently establish temporality in some patients because medical records often do not differentiate between patients who were seeking care for stroke-related symptoms or COVID-19 symptoms or if patients were infected with COVID-19 before or after hospital admission.[71] These nuances of the timing and temporality of stroke and COVID-19 occurrence were also present in this report; nonhemorrhagic stroke required an inpatient diagnosis and day 0 stroke events for both stroke types were more common in the comparator group. When analyses of nonhemorrhagic and hemorrhagic stroke starting follow-up the day after day 0, the Medicare and MarketScan analyses aligned with the evidence mentioned above and identified an elevated risk of stroke in the COVID-19-diagnosed group.

5.3. Strengths and Limitations

5.3.1. Strengths

The study used 2 separate designs and a variety of analytic approaches in 2 large data sources to estimate the association between a COVID-19 diagnosis and various AEs. This large population-based study allowed us to obtain robust estimates, particularly for rare AEs. The cohort approach allowed for estimation of incidence, changing incidence over time, and was not subject to the potentially restrictive assumptions of self-controlled designs. Matching methods identified individuals without COVID-19 diagnoses who were similar to those with COVID-19 diagnoses in terms of geography, calendar date, and personal characteristics: additional adjustment with propensity score-based weights further balanced the COVID-19-diagnosed group and comparator groups. The SCRI did not require the identification of a comparator group, as the counterfactual for a COVID-19 diagnosis could be difficult to identify in observational data. Additionally, the SCRI design was not subject to confounding between the COVID-19 and comparator groups by time-invariant confounding factors. Using 2 complementary approaches and a variety of sensitivity, secondary, and subgroup analyses allowed evaluation

of the associations while accounting for multiple potential issues that may be unique to a time period of COVID-19-related healthcare disruptions.

5.3.2. Limitations

This study was subject to several limitations common to observational studies in existing healthcare databases. Insurance billing claims are generated for reimbursement purposes rather than clinical care or research. Thus, not all relevant medical conditions or events would be recorded in claims data, and recorded concepts may be subject to misclassification. Diagnoses are recorded in insurance billing claims when they result in reimbursable healthcare interactions. A recorded medical diagnosis of COVID-19 may not align with the onset of infection, onset of symptoms, or peak severity. In administrative claims data, the onset and resolution of COVID-19 infection are unknown. Additionally, laboratory test results are not recorded in claims. Thus, this study evaluated recorded COVID-19 diagnoses from providers rather than laboratory-confirmed COVID-19 infection. Although COVID-19 diagnoses have been shown to have reasonably high validity in claims data, the validity may have varied over calendar time[27,29,128] after the introduction of the COVID-19 ICD-10-CM code and changes in diagnostic technology and capacity.

Similarly, identification of the AEs was dependent on claims-based algorithms, and outcome misclassification is possible. Validation studies of postvaccination AEs in vaccination surveillance studies have demonstrated low positive predictive values for some AEs, particularly for some algorithms, including for ITP and Bell's palsy.[129]

The populations contained in the 2 data sources contributing to this study differed by age and associated comorbidity status, and eligibility for inclusion in the data sources varied (i.e., commercial employer-based insurance or Medicare status). These key differences in patient characteristics and data structure (e.g., granularity of timing of inpatient diagnoses during a hospitalization) may also result in heterogeneity of the exposure effect estimates between data sources. Although the results generally agree between data sources, there are differences in the magnitude of the estimates and the impacts of certain subgroup or alternative risk period analyses. Thus, the results of the 2 data sources are presented separately without pooling or meta-analysis. While both data sources are large, case counts were still small for some AEs, resulting in imprecise HR or RI estimates.

Limitations specific to each study design are described in the following sections.

5.3.2.1. Cohort Design

Observational research based in administrative healthcare claims is subject to limitations, such as the potential for misclassification of COVID-19 exposure (i.e., underreporting of COVID-19 diagnoses), differential misclassification of outcomes by COVID-19 status, and unmeasured confounding between exposure groups. In this study, many potential biases have been addressed by the study design, but the potential for residual bias remained. The cohort design may be subject to bias from confounding between groups with and without COVID-19 diagnoses resulting from differences in characteristics between the groups, including risk factors for COVID-19 and AEs, healthcare-seeking behavior, or access to healthcare. In this study, only relatively small differences between exposure groups were noted for clinical characteristics, although differences in healthcare utilization were larger between the unweighted groups. Confounding by measured covariates was addressed through matching and weighting approaches with prespecified covariates, and all characteristics were well-balanced after weighting, but the potential for confounding by unmeasured characteristics remained. Additionally, other key variables (e.g., covariates and matching criteria such as immunocompromised status) were identified using diagnosis codes. These characteristics were identified with

binary indicators which may not account for the severity of the condition; thus, a lack of adjustment for severity of disease status may remain, even after matching and weighting. Additionally, the potential for exposure (COVID-19 diagnosis) misclassification cannot be ruled out, and the extent of exposure misclassification cannot be quantified because many COVID-19 infections did not result in a medically attended diagnosis. The cohort design may have been subjected to differential exposure misclassification of the comparator group without a COVID-19 diagnosis. Thus, this study could only evaluate COVID-19 diagnoses rather than COVID-19 infections. Sensitivity analyses considering additional exclusion criteria to assess the effect of potentially misclassified COVID-19 cases by excluding those with related respiratory diagnoses did not show substantial differences from the overall analyses, but some truly COVID-19-infected individuals may be in the comparator group.

To restrict the cohort to a healthcare-seeking population and better align the exposure and comparator groups, the cohort design inclusion criteria required individuals to have at least 1 healthcare encounter in the year before Time 0; fewer were dropped in Medicare because most individuals have at least 1 encounter. However, this requirement may have limited the generalizability of the results to populations without routine healthcare encounters, and the study population for the cohort design differed from the study population for the SCRI design.

As discussed earlier (Section 5.1.1, Section 5.1.1.2), the results of the cohort analyses were sensitive to the inclusion or exclusion of day 0 in the follow-up. The effect of removing day 0 from follow-up varied depending on the severity and setting of the AE, ranging from reducing an elevated HR (e.g., myocarditis/pericarditis), having no meaningful effect (e.g., encephalitis/encephalomyelitis), to switching the direction of the effect (e.g., hemorrhagic stroke). Many of these effects seemed related to matching on hospitalization status, where the recording of hospital diagnosed on the admission date obscured the true temporal ordering of some diagnoses and frequently resulted in an increased number of severe diagnoses on day 0, often disproportionately affecting the matched comparator group. Day 0 was originally included in the follow-up period to ensure capture of all COVID-19-associated AEs, and matching on hospitalization was included to account for disease severity and surveillance bias, but these decisions inadvertently may have introduced various other biases like reverse causality and collider stratification bias. Similarly, including hospitalization status on Time 0 as an exact matching factor resulted in the exclusion of a large number of hospitalized COVID-19 cases in Medicare due to failure to find a match, further reducing the generalizability of our findings to hospitalized COVID-19 cases. Excluding day 0 from follow-up seemed to reduce the effects of these biases (and many of the conclusions drawn by these reports rely on the alternative risk period analyses without day 0), but the result may be reduced generalizability to hospitalized cases and exclusion of true COVID-19—associated AE cases.

5.3.2.2. Self-Controlled Risk Interval Design

The SCRI design is subject to the following key assumptions:[49,50]

- There is a well-defined and transient risk interval after exposure.
- The occurrence of the outcome does not alter probability of exposure.
- The occurrence of an outcome does not affect the duration of the risk or reference observation windows (e.g., by increasing mortality risk).
- Event rates are constant within each window.
- Outcome events are independently recurrent or rare.

Bias may be introduced if these assumptions are violated. The SCRI is highly sensitive to the correct placement and duration of the risk and reference windows in relation to exposure. The primary limitation of the SCRI

design is that the biologically relevant time period for AEs relative to COVID-19 diagnosis was unknown. COVID-19 may not qualify as a transient exposure because the duration of COVID-19 infection is highly variable and, in some cases, can be prolonged. Because COVID-19 infection is highly variable in length, the assignment of risk and reference windows relative to a recorded diagnosis may not result in appropriate placement of the risk and control windows relevant to biologically meaningful time periods within individuals (Section 5.1.2). In addition, the true length of a risk window for the study outcomes was unknown; nor did we determine whether the risk changed or remained constant during the true risk window or whether the risk of AEs reverted to that from the pre-exposure period (i.e., before COVID-19 infection) after COVID-19 resolution; therefore, comparing the risk window with a postexposure reference period may not have reflected the full extent of increased risk of a COVID-19 infection relative to pre-exposure levels. Misspecification of the risk and reference windows may have biased the results; thus, periods both before and after the risk window were evaluated separately in sensitivity analyses.

Additionally, some assumptions of the SCRI designs may have been violated in this setting. Many AEs increase the risk of mortality, and COVID-19 itself increases this risk as well; thus, the duration of risk and reference windows may be affected by both AEs and exposure (i.e., COVID-19 diagnosis).

Similar to the Time 0 effects seen in the cohort, the SCRI analyses were sensitive to the inclusion of day 0 in the risk period. For almost all AEs where the SCRI was performed, the alternative risk period analyses starting on day 1 resulted in attenuated RI estimates compared with the overall estimates. Additionally, the RI estimates for day 0 alone were almost all very high, suggesting the potential for reverse causality.[45] The conclusions of this report are generally drawn from the alternative risk period analyses starting the risk period on day 1, which seem to reduce the impact of reverse causality, but they may exclude true COVID-19-associated AEs.

The SCRI design intrinsically addresses confounding by time-invariant factors, but it is sensitive to time-varying factors, such as changing risk of AEs over time because of seasonality or age. We adjusted for seasonality, and given the relatively short study period, limited time-varying confounding because of age was expected.

The SCRI occasionally resulted in notably elevated RI estimates for rare events, where low incidences in the risk period were divided by very low incidences in the comparator periods.[54]

6. Conclusions

Having a COVID-19 diagnosis was associated with multiple AEs. The strengths of the observed associations varied somewhat by data source, study design, and analytic approach, but increases in relative and absolute risk were consistently observed with many AEs. Among the cardiovascular AEs, the strongest associations were observed for myocarditis/pericarditis, disseminated intravascular coagulation, and pulmonary embolism. Weaker, but still consistently elevated associations were observed for other cardiovascular AEs such as nonhemorrhagic stroke, hemorrhagic stroke, acute myocardial infarction, deep vein thrombosis, and common site TTS, which also translated into larger absolute risks. For the neurologic/immune-mediated AEs, a particularly strong association was seen for GBS, and a weaker but still consistent association was also seen for ITP. The remaining AEs were generally rare and results were imprecise or inconsistent across data sources and designs (e.g., Bell's palsy, encephalitis/encephalomyelitis, narcolepsy, appendicitis, transverse myelitis, and common site TTS), but modestly increased risks of these AEs associated with COVID-19 cannot be ruled out. These results applied only to the time period before the introduction of COVID-19 vaccines, and subsequent changes in predominant circulating viral variants, COVID-19 vaccinations, and healthcare utilization patterns may reduce the generalizability of these results to more recent time periods. However, these results suggest

that COVID-19 diagnoses contributed to potentially large numbers of serious AEs in the US population before the introduction of COVID-19 vaccines.

7. References

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Appendices

Appendix A. Additional Clarifying Information

Table A-1. Deviations or Modifications From or Clarifications to Study Protocol

Protocol section(s)	Change	Rationale
5.2.2.2	The cohort matching procedure in Medicare was updated to matching on county or adjoining county of residence, instead of just county of residence.	Matching with the original matching criterion of county of residence resulted in a matching rate of just less than 90%; as described in the protocol, modifications of the matching criteria were evaluated, and expanding the matching criteria to include adjoining counties improved the matching rate while maintaining matching on a granular measure of geography.
5.3.1.3	Clarified that Table Shell B-3 was to display the sIPT weights after truncation, rather than before.	To avoid ambiguity in the protocol.
5.3.1.5	An additional sensitivity analysis was added to the cohort analyses removing day 0 from follow-up and adding it to the baseline period.	Negative control analyses suggested a large co-occurrence of negative control outcomes and COVID-19 diagnoses on day 0, potentially because of reverse causality or confounding by healthcare utilization on day 0.
6.3.1.3	An additional SCRI analysis was added to the overall analyses adjusting for seasonality by calendar month.	The protocol stated that adjustment for seasonality may be considered if feasible. The seasonality-adjusted estimates were minimally different from the main analyses but were less precise, so the seasonality-adjusted analyses were presented separately.
6.3.1.3, 6.3.1.4	The subgroup and sensitivity analyses were performed using the extended conditional Poisson model adjusting for seasonality by calendar month.	To ensure adequate control of potential time-varying confounding and event-dependent censoring (both of which may vary by adverse event), it was determined to be most conservative to apply the updated models to the analyses of all adverse events.
6.3.1.4	The alternative risk period analyses for the SCRI were performed with extended Poisson models for event-dependent observation windows and adjusted for seasonality which were modified to account for 1-day observation periods.	The standard macros for SCRI analyses with event-dependent observation periods were unable to accommodate a 1-day period which was needed for the analysis of day 0 alone, thus the interval boundaries of the macro were modified.

sIPT = stabilized inverse probability of treatment; SCRI = self-controlled risk interval.

Table A-2. Covariates for AE-Specific Propensity Score Models

Covariate	Model form	Guillain-Barré syndrome	Bell's palsy	ENC	Narcolepsy	Appendicitis	Nonhemorrhagic stroke	Hemorrhagic stroke	AMI	Myo-/pericarditis	Deep vein thrombosis	Pulmonary embolism[a]	DIC	ITP	Transverse myelitis	Unusual site TTS	Common site TTS
Age[b]	Age, age^2, age^3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sex[b]	Binary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
County/MSA and state of residence[b]	Categorical, indicator for each level	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Race/ethnicity[c]	Categorical, indicator for each level	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dual Medicare/Medicaid eligibility[c]	Binary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Reason for entering Medicare[c]	Categorical, indicator for each level	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalization status on Time 0[b]	Binary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SNF/LTC residence on Time 0[b, c]	Binary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Animal exposure/bites or rabies	Binary			X						X				X			
Antiphospholipid syndrome	Binary													X	X	X	X
Autoimmune disorders	Binary	X	X	X			X	X	X	X	X	X	X	X	X	X	X
Brain lesions related to secondary narcolepsy	Binary				X												
Cancer	Binary		X				X	X	X	X	X	X	X	X		X	X
Chronic lymphocytic leukemia	Binary													X			
Chronic kidney disease/renal disease	Binary						X	X	X	X	X	X	X			X	X
End-stage renal disease[c]	Binary					X	X	X	X	X	X	X	X			X	X
Chronic liver disease	Binary						X	X	X	X	X	X	X				
Chronic lung disease	Binary						X	X	X						X	X	X

Covariate	Model form	Guillain-Barré syndrome	Bell's palsy	ENC	Narcolepsy	Appendicitis	Nonhemorrhagic stroke	Hemorrhagic stroke	AMI	Myo-/pericarditis	Deep vein thrombosis	Pulmonary embolism[a]	DIC	ITP	Transverse myelitis	Unusual site TTS	Common site TTS
Dementia/neurologic conditions	Binary	X	X	X	X		X	X			X	X	X		X	X	X
Diabetes mellitus, type 1 or 2	Binary		X				X	X	X	X	X	X			X	X	X
Disseminated intravascular coagulation	Binary															X	X
Heart conditions	Binary						X	X	X	X	X	X				X	X
Hemiplegia/paraplegia	Binary	X					X	X			X	X			X	X	X
Herpes simplex virus infection	Binary	X	X	X						X				X			
Hypertension	Binary						X	X	X	X							
Immunocompromised state[b]	Binary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Infection associated with GBS	Binary	X															
Infection associated with ITP	Binary													X			
Infection associated with myocarditis/pericarditis	Binary									X							
Inpatient surgery	Binary	X									X	X	X			X	X
Lipid abnormality	Binary						X		X		X	X				X	X
Mental health conditions	Binary		X		X			X	X								
Nutritional deficiencies	Binary									X					X		
Obesity	Binary	X	X		X		X		X	X	X	X				X	X
Peripheral vascular disease	Binary						X	X	X	X	X	X				X	X
Pneumonia or lower respiratory tract infection	Binary	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy[d]	Binary		X				X	X	X		X	X	X			X	X
Sepsis	Binary									X			X	X			
Sickle cell disease/thalassemia	Binary						X	X	X		X	X					X
Smoking/nicotine dependency	Binary						X	X	X		X	X	X			X	X
Stroke/cerebrovascular disease	Binary				X		X	X	X		X	X					X
Thromboembolism	Binary										X	X	X			X	X
Thrombophilia	Binary						X		X		X	X	X			X	X
Trauma	Binary	X					X	X		X	X	X	X				X

Covariate	Model form	Guillain-Barré syndrome	Bell's palsy	ENC	Narcolepsy	Appendicitis	Nonhemorrhagic stroke	Hemorrhagic stroke	AMI	Myo-/pericarditis	Deep vein thrombosis	Pulmonary embolism[a]	DIC	ITP	Transverse myelitis	Unusual site TTS	Common site TTS
Tuberculosis	Binary									X	X			X		X	X
Inpatient hospital stays before Time 0	Categorical, indicator for each level	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ED visits	Categorical, indicator for each level	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Outpatient visits	Categorical, indicator for each level	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SNF/LTC stay[e]	Binary	X		X			X	X	X		X	X	X	X	X	X	X
Influenza vaccination in previous year	Binary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; AMI = acute myocardial infarction; DIC = disseminated intravascular coagulation; DVT = deep vein thrombosis; ED = emergency department; GBS = Guillain-Barré syndrome; ITP = immune thrombocytopenia; LTC = long-term care; MSA = metropolitan statistical area; SNF = skilled nursing facility; TTS = thrombosis with thrombocytopenia syndrome.

[a] Evaluated both as inpatient-only, and in any setting. Both outcomes used the same propensity score model in the same analysis set.

[b] Matching variables were included in all propensity score models.

[c] Only included in Medicare.

[d] Only included in MarketScan.

[e] SNF and LTC both included in Medicare; only SNF included in MarketScan.

Sources: National Institute of Neurologic Disorders and Stroke[85,130-133]; National Institute of Diabetes and Digestive and Kidney Diseases[134]; National Heart, Lung, and Blood Institute.[135,136]

Appendix B. Complete Analytic Tables and Figures

Note about Table numbering: tables are numbered similarly across data sources, thus Table B-1-MarketScan and Table B-2-Medicare report the results of the same analysis.

B.1. MarketScan

B.1.1. Cohort Analyses

Table B-1-MarketScan. Selection of Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis for the Cohort Study, MarketScan

Characteristic	Value
Overall study cohort	
Individuals with COVID-19 diagnosis during the study period	569,754
Excluded for being aged outside age range, N (%)	53,723 (9.43)
Excluded for lacking 365 days of continuous data base enrollment before Time 0, N (%)	142,532 (25.02)
Excluded for lacking ≥ 1 healthcare claim during 365 days before Time 0, N (%)	51,066 (8.96)
Excluded for having a COVID-19 diagnosis before Time 0, N (%)	7,002 (1.23)
Excluded for having a select respiratory infection before Time 0, N (%)	382 (0.07)
Eligible adults with new-onset COVID-19	358,306
Excluded for failing to match, N (%)	39,006 (10.89)
Matched individuals with COVID-19	319,300
Matched comparator observations[a] (unique individuals)	319,300 (312,282)
Total study cohort	638,600
Adverse event-specific analysis sets[b]	
Excluded for having previous Guillain-Barré syndrome	97 (0.02)
Guillain-Barré syndrome analysis set	638,503
Excluded for having previous Bell's palsy	501 (0.08)
Bell's palsy analysis set	638,099
Excluded for having previous encephalitis/encephalomyelitis	72 (0.01)
Encephalitis/encephalomyelitis analysis set	638,528
Excluded for having previous narcolepsy	698 (0.11)
Narcolepsy analysis set	637,902
Excluded for having previous appendicitis	1,295 (0.20)
Appendicitis analysis set	637,305
Excluded for having previous nonhemorrhagic stroke	2,697 (0.42)
Nonhemorrhagic stroke analysis set	635,903
Excluded for having previous hemorrhagic stroke	539 (0.08)
Hemorrhagic stroke analysis set	638,061
Excluded for having previous acute myocardial infarction	2,010 (0.31)
Acute myocardial infarction analysis set	636,590
Excluded for having previous myocarditis pericarditis	341 (0.05)
Myocarditis/pericarditis analysis set	638,259
Excluded for having previous deep vein thrombosis	2,558 (0.40)
Deep vein thrombosis analysis set	636,042

Characteristic	Value
Excluded for having previous pulmonary embolism	1,869 (0.29)
Pulmonary embolism analysis set[c]	636,731
Excluded for having previous disseminated intravascular coagulation	57 (0.01)
Disseminated intravascular coagulation analysis set	638,543
Excluded for having previous immune thrombocytopenia	467 (0.07)
Immune thrombocytopenia analysis set	638,133
Excluded for having previous transverse myelitis	106 (0.02)
Transverse myelitis analysis set	638,494
Excluded for having previous unusual site thrombosis with thrombocytopenia	47 (0.01)
Unusual site thrombosis with thrombocytopenia analysis set	638,553
Excluded for having previous common site thrombosis with thrombocytopenia	281 (0.04)
Common site thrombosis with thrombocytopenia analysis set	638,319

COVID-19 = coronavirus disease 2019.

[a] A unique individual may be included multiple times because of matching with replacement, and an individual may be included in both the exposure and comparator groups. This table counts each instance of an individual's entry separately as distinct observations; the number of unique individuals is reported separately.

[b] Denominators for all adverse event-specific exclusions are the total study cohort; exclusions are noncumulative across analysis sets.

[c] Both pulmonary embolism outcomes (i.e., inpatient-only, and in any setting) were evaluated in the same analysis set.

Table B-2-MarketScan. Characteristics of Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis Included in the Cohort Study, MarketScan

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group	ASD
Total selected observations [a] (unique individuals)	319,300 (319,300)	319,300 (312,282)	
Demographic characteristics			
Age, years			
Mean (SD)	41.8 (13.6)	41.8 (13.6)	0.00
Median (Q1, Q3)	43 (30, 53)	43 (30, 53)	
Age groups, n (%)			
18-34 years	105,842 (33.15)	105,842 (33.15)	
35-49 years	101,071 (31.65)	101,071 (31.65)	
50-64 years	112,387 (35.20)	112,387 (35.20)	
Sex, n (%)			0.00
Female	178,975 (56.05)	178,975 (56.05)	
Male	140,325 (43.95)	140,325 (43.95)	
US geographic region, n (%)			0.00
Northeast	62,215 (19.48)	62,224 (19.49)	
North Central	71,170 (22.29)	71,149 (22.28)	
South	149,868 (46.94)	149,880 (46.94)	
West	36,037 (11.29)	36,037 (11.29)	
Unknown	10 (0.00)	10 (0.00)	
Hospitalized on Time 0, n (%)	4,046 (1.27)	4,046 (1.27)	0.00
Comorbidities, n (%)			
Animal exposure/bites or rabies	976 (0.31)	1,017 (0.32)	0.00
Antiphospholipid syndrome	160 (0.05)	142 (0.04)	0.00
Autoimmune disorders	12,677 (3.97)	12,973 (4.06)	0.00
Brain lesions related to secondary narcolepsy	30 (0.01)	22 (0.01)	0.00
Cancer	13,421 (4.20)	14,271 (4.47)	0.01
Chronic lymphocytic leukemia	213 (0.07)	175 (0.05)	0.00
Chronic kidney disease or renal disease (other than end-stage renal disease)	6,052 (1.90)	5,101 (1.60)	0.02
Chronic liver disease	10,763 (3.37)	8,968 (2.81)	0.03
Chronic lung diseases	32,616 (10.21)	25,419 (7.96)	0.08
Dementia or other neurologic condition	19,722 (6.18)	16,421 (5.14)	0.04
Diabetes, Type 1 or 2	33,117 (10.37)	25,491 (7.98)	0.08
Disseminated intravascular coagulation [b]	24 (0.01)	15 (0.00)	0.00
Heart conditions	37,470 (11.74)	31,315 (9.81)	0.06
Hemiplegia or paraplegia	857 (0.27)	815 (0.26)	0.00
Herpes simplex infection	6,082 (1.90)	4,738 (1.48)	0.03
Hypertension	78,717 (24.65)	69,065 (21.63)	0.07
Immunocompromised state	37,672 (11.80)	37,672 (11.80)	0.00
Infection associated with GBS	17,961 (5.63)	13,575 (4.25)	0.06
Viral infection associated with ITP	1,290 (0.40)	1,115 (0.35)	0.01
Infection associated with myocarditis/pericarditis	16,753 (5.25)	13,462 (4.22)	0.05

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group	ASD
Inpatient surgery	1,985 (0.62)	2,925 (0.92)	0.03
Lipid abnormality	73,480 (23.01)	66,630 (20.87)	0.05
Mental health conditions	73,913 (23.15)	69,877 (21.88)	0.03
Nutritional deficiency	2,088 (0.65)	2,095 (0.66)	0.00
Obese or severely obese	63,585 (19.91)	49,693 (15.56)	0.11
Peripheral vascular disease	4,393 (1.38)	3,712 (1.16)	0.02
Pneumonia or lower respiratory tract infection	41,355 (12.95)	28,356 (8.88)	0.13
Pregnancy	2,616 (0.82)	2,288 (0.72)	0.01
Sepsis	1,277 (0.40)	942 (0.30)	0.02
Sickle cell disease or thalassemia	750 (0.23)	637 (0.20)	0.01
Smoking/nicotine dependency	11,536 (3.61)	14,735 (4.61)	0.05
Stroke or cerebrovascular disease	4,730 (1.48)	4,021 (1.26)	0.02
Thromboembolism	3,531 (1.11)	2,885 (0.90)	0.02
Thrombophilia	1,096 (0.34)	906 (0.28)	0.01
Trauma	204 (0.06)	259 (0.08)	0.01
Tuberculosis	138 (0.04)	115 (0.04)	0.00
Healthcare utilization, n (%)			
Inpatient stays in previous 365 days			0.05
0	305,018 (95.53)	303,556 (95.07)	
1-2	13,162 (4.12)	14,411 (4.51)	
≥ 3	1,120 (0.35)	1,333 (0.42)	
ED visits in previous 365 days			0.13
0	255,758 (80.10)	271,663 (85.08)	
1-2	54,798 (17.16)	42,181 (13.21)	
≥ 3	8,744 (2.74)	5,456 (1.71)	
Outpatient provider visits [c] in previous 365 days			0.19
0	2,076 (0.65)	2,815 (0.88)	
1-2	56,880 (17.81)	78,501 (24.59)	
3-5	76,244 (23.88)	80,629 (25.25)	
6-10	76,772 (24.04)	68,388 (21.42)	
≥ 11	107,328 (33.61)	88,967 (27.86)	
SNF/LTC stay [d]	341 (0.11)	158 (0.05)	0.02
Influenza vaccination in previous year	90,018 (28.19)	95,167 (29.80)	0.04

AE = adverse event; ASD = absolute standardized difference; COVID-19 = coronavirus disease 2019; ED = emergency department; GBS = Guillain-Barré syndrome; ITP = immune thrombocytopenia; LTC = long-term care; Q1 = first quartile, Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] A unique individual may be included multiple times because of matching with replacement, and an individual may be included in both the exposure and comparator groups. This table counts each instance of an individual's entry separately as distinct observations; the number of unique individuals is reported separately.

[b] This serves as an AE-specific exclusion criterion when the condition is evaluated as an outcome, but history of the condition serves as a covariate for analyses of other AEs.

[c] Unique days on which an outpatient visit occurred.

[d] SNF and LTC both identified in Medicare; SNF identified in MarketScan.

Table B-3-MarketScan. Characteristics of Individuals With a COVID-19 Diagnosis Included in the Cohort Study and Those Excluded for Failing to Match, MarketScan

Characteristic	COVID-19 diagnosis (exposure) group retained by matching	Individuals with a COVID-19 diagnosis who failed to match
Total unique individuals	319,300	39,006
Demographic characteristics		
Age, years		
Mean (SD)	41.8 (13.6)	44.1 (13.6)
Median (Q1, Q3)	43 (30, 53)	47 (33, 56)
Age groups, n (%)		
18-34 years	105,842 (33.15)	10,485 (26.88)
35-49 years	101,071 (31.65)	12,060 (30.92)
50-64 years	112,387 (35.20)	16,461 (42.20)
Sex, n (%)		
Female	178,975 (56.05)	22,793 (58.43)
Male	140,325 (43.95)	16,213 (41.57)
US geographic region, n (%)		
Northeast	62,215 (19.48)	949 (2.43)
North central	71,170 (22.29)	1,788 (4.58)
South	149,868 (46.94)	26,883 (68.92)
West	36,037 (11.29)	9,057 (23.22)
Unknown	10 (0.00)	329 (0.84)
Hospitalized on Time 0, n (%)	4,046 (1.27)	8,738 (22.40)
Comorbidities, n (%)		
Animal exposure/bites or rabies	976 (0.31)	124 (0.32)
Antiphospholipid syndrome	160 (0.05)	28 (0.07)
Autoimmune disorders	12,677 (3.97)	1,759 (4.51)
Brain lesions related to secondary narcolepsy	30 (0.01)	2 (0.01)
Cancer	13,421 (4.20)	1,987 (5.09)
Chronic lymphocytic leukemia	213 (0.07)	41 (0.11)
Chronic kidney disease or renal disease (other than end-stage renal disease)	6,052 (1.90)	1,495 (3.83)
Chronic liver disease	10,763 (3.37)	1,566 (4.01)
Chronic lung diseases	32,616 (10.21)	4,285 (10.99)
Dementia or other neurologic condition	19,722 (6.18)	2,551 (6.54)
Diabetes, Type 1 or 2	33,117 (10.37)	6,374 (16.34)
Disseminated intravascular coagulation[a]	24 (0.01)	9 (0.02)
Heart conditions	37,470 (11.74)	5,494 (14.09)
Hemiplegia or paraplegia	857 (0.27)	202 (0.52)
Herpes simplex infection	6,082 (1.90)	709 (1.82)
Hypertension	78,717 (24.65)	13,371 (34.28)
Immunocompromised state	37,672 (11.80)	5,422 (13.90)
Infection associated with GBS	17,961 (5.63)	2,091 (5.36)
Viral infection associated with ITP	1,290 (0.40)	209 (0.54)

Characteristic	COVID-19 diagnosis (exposure) group retained by matching	Individuals with a COVID-19 diagnosis who failed to match
Infection associated with myocarditis/pericarditis	16,753 (5.25)	2,322 (5.95)
Inpatient surgery	1,985 (0.62)	379 (0.97)
Lipid abnormality	73,480 (23.01)	10,908 (27.96)
Mental health conditions	73,913 (23.15)	10,422 (26.72)
Nutritional deficiency	2,088 (0.65)	374 (0.96)
Obese or severely obese	63,585 (19.91)	9,775 (25.06)
Peripheral vascular disease	4,393 (1.38)	733 (1.88)
Pneumonia or lower respiratory tract infection	41,355 (12.95)	5,598 (14.35)
Pregnancy	2,616 (0.82)	266 (0.68)
Sepsis	1,277 (0.40)	340 (0.87)
Sickle cell disease or thalassemia	750 (0.23)	112 (0.29)
Smoking/nicotine dependency	11,536 (3.61)	1,391 (3.57)
Stroke or cerebrovascular disease	4,730 (1.48)	715 (1.83)
Thromboembolism	3,531 (1.11)	642 (1.65)
Thrombophilia	1,096 (0.34)	137 (0.35)
Trauma	204 (0.06)	38 (0.10)
Tuberculosis	138 (0.04)	21 (0.05)
Healthcare utilization, n (%)		
Inpatient stays in previous 365 days		
0	305,018 (95.53)	36,528 (93.65)
1-2	13,162 (4.12)	2,138 (5.48)
≥ 3	1,120 (0.35)	340 (0.87)
ED visits in previous 365 days		
0	255,758 (80.10)	30,760 (78.86)
1-2	54,798 (17.16)	7,022 (18.00)
≥ 3	8,744 (2.74)	1,224 (3.14)
Outpatient provider visits[b] in previous 365 days		
0	2,076 (0.65)	248 (0.64)
1-2	56,880 (17.81)	5,749 (14.74)
3-5	76,244 (23.88)	7,326 (18.78)
6-10	76,772 (24.04)	8,223 (21.08)
≥ 11	107,328 (33.61)	17,460 (44.76)
SNF/LTC stay[c]	341 (0.11)	104 (0.27)
Influenza vaccination in previous year	90,018 (28.19)	12,166 (31.19)

AE = adverse event; COVID-19 = coronavirus disease 2019; ED = emergency department; GBS = Guillain-Barré syndrome; ITP = immune thrombocytopenia; LTC = long-term care; Q1 = first quartile, Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] This serves as an AE-specific exclusion criterion when the condition is evaluated as an outcome, but history of the condition serves as a covariate for analyses of other AEs.

[b] Unique days on which an outpatient visit occurred.

[c] SNF and LTC both identified in Medicare; SNF identified in MarketScan.

Table B-4-MarketScan. Distribution of Stabilized Inverse Probability of Treatment Weights in Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis Included in the Cohort Study, MarketScan

A. Guillain-Barré Syndrome

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	319,254	319,249
Total weighted sample size (sum of all sIPT weights)	319,279	318,556
Distribution of sIPT weights		
Mean (SD)	1.00 (0.14)	1.00 (0.14)
Median (Q1, Q3)	0.99 (0.90, 1.08)	0.97 (0.89, 1.07)
Minimum	0.74	0.74
Maximum	1.42	1.42

B. Bell's Palsy

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	319,031	319,068
Total weighted sample size (sum of all sIPT weights)	319,045	318,573
Distribution of sIPT weights		
Mean (SD)	1.00 (0.13)	1.00 (0.14)
Median (Q1, Q3)	0.98 (0.90, 1.08)	0.98 (0.89, 1.08)
Minimum	0.76	0.76
Maximum	1.39	1.39

C. Encephalitis/Encephalomyelitis

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	319,264	319,264
Total weighted sample size (sum of all sIPT weights)	319,305	318,553
Distribution of sIPT weights		
Mean (SD)	1.00 (0.13)	1.00 (0.14)
Median (Q1, Q3)	0.99 (0.91, 1.08)	0.98 (0.89, 1.07)
Minimum	0.75	0.75
Maximum	1.39	1.39

D. Narcolepsy

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	318,932	318,970
Total weighted sample size (sum of all sIPT weights)	318,927	318,512
Distribution of sIPT weights		
Mean (SD)	1.00 (0.13)	1.00 (0.13)
Median (Q1, Q3)	0.98 (0.91, 1.08)	0.98 (0.89, 1.08)
Minimum	0.76	0.76
Maximum	1.38	1.38

E. Appendicitis

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	318,640	318,665
Total weighted sample size (sum of all sIPT weights)	318,684	317,982
Distribution of sIPT weights		
Mean (SD)	1.00 (0.13)	1.00 (0.13)
Median (Q1, Q3)	0.99 (0.91, 1.08)	0.98 (0.89, 1.07)
Minimum	0.75	0.75
Maximum	1.38	1.38

F. Nonhemorrhagic Stroke

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	317,884	318,019
Total weighted sample size (sum of all sIPT weights)	317,828	317,294
Distribution of sIPT weights		
Mean (SD)	1.00 (0.15)	1.00 (0.15)
Median (Q1, Q3)	0.99 (0.90, 1.09)	0.97 (0.88, 1.07)
Minimum	0.73	0.73
Maximum	1.46	1.46

G. Hemorrhagic Stroke

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	319,035	319,026
Total weighted sample size (sum of all sIPT weights)	318,970	318,328
Distribution of sIPT weights		
Mean (SD)	1.00 (0.14)	1.00 (0.15)
Median (Q1, Q3)	0.99 (0.90, 1.09)	0.98 (0.88, 1.07)
Minimum	0.73	0.73
Maximum	1.45	1.45

H. Acute Myocardial Infarction

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	318,271	318,319
Total weighted sample size (sum of all sIPT weights)	318,220	317,587
Distribution of sIPT weights		
Mean (SD)	1.00 (0.15)	1.00 (0.15)
Median (Q1, Q3)	0.99 (0.89, 1.09)	0.97 (0.88, 1.07)
Minimum	0.73	0.73
Maximum	1.47	1.47

I. Myocarditis/Pericarditis

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	319,096	319,163
Total weighted sample size (sum of all sIPT weights)	319,156	318,407
Distribution of sIPT weights		
Mean (SD)	1.00 (0.14)	1.00 (0.14)
Median (Q1, Q3)	0.99 (0.90, 1.09)	0.97 (0.88, 1.07)
Minimum	0.74	0.74
Maximum	1.43	1.43

J. Deep Vein Thrombosis

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	317,909	318,133
Total weighted sample size (sum of all sIPT weights)	317,812	317,445
Distribution of sIPT weights		
Mean (SD)	1.00 (0.15)	1.00 (0.15)
Median (Q1, Q3)	0.99 (0.90, 1.09)	0.97 (0.88, 1.07)
Minimum	0.73	0.73
Maximum	1.47	1.47

K. Pulmonary Embolism (Overall and Inpatient Only)

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	318,207	318,524
Total weighted sample size (sum of all sIPT weights)	318,107	317,841
Distribution of sIPT weights		
Mean (SD)	1.00 (0.15)	1.00 (0.15)
Median (Q1, Q3)	0.99 (0.90, 1.09)	0.97 (0.88, 1.08)
Minimum	0.73	0.73
Maximum	1.46	1.46

L. Disseminated Intravascular Coagulation

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	319,264	319,279
Total weighted sample size (sum of all sIPT weights)	319,108	318,650
Distribution of sIPT weights		
Mean (SD)	1.00 (0.14)	1.00 (0.14)
Median (Q1, Q3)	0.98 (0.90, 1.08)	0.98 (0.88, 1.08)
Minimum	0.74	0.74
Maximum	1.43	1.43

M. Immune Thrombocytopenia

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	319,058	319,075
Total weighted sample size (sum of all sIPT weights)	319,082	318,367
Distribution of sIPT weights		
Mean (SD)	1.00 (0.13)	1.00 (0.14)
Median (Q1, Q3)	0.99 (0.91, 1.08)	0.98 (0.88, 1.07)
Minimum	0.75	0.75
Maximum	1.39	1.39

N. Transverse Myelitis

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	319,250	319,244
Total weighted sample size (sum of all sIPT weights)	319,305	318,524
Distribution of sIPT weights		
Mean (SD)	1.00 (0.14)	1.00 (0.14)
Median (Q1, Q3)	0.99 (0.90, 1.08)	0.98 (0.89, 1.07)
Minimum	0.75	0.75
Maximum	1.41	1.41

O. Unusual Site Thrombosis With Thrombocytopenia Syndrome

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	319,276	319,277
Total weighted sample size (sum of all sIPT weights)	319,183	318,569
Distribution of sIPT weights		
Mean (SD)	1.00 (0.15)	1.00 (0.15)
Median (Q1, Q3)	0.99 (0.89, 1.09)	0.97 (0.88, 1.07)
Minimum	0.73	0.73
Maximum	1.47	1.47

P. Common Site Thrombosis With Thrombocytopenia Syndrome

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	319,147	319,172
Total weighted sample size (sum of all sIPT weights)	319,051	318,474
Distribution of sIPT weights		
Mean (SD)	1.00 (0.15)	1.00 (0.15)
Median (Q1, Q3)	0.99 (0.89, 1.09)	0.97 (0.88, 1.08)
Minimum	0.73	0.73
Maximum	1.47	1.47

COVID-19 = coronavirus disease 2019; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; sIPT = stabilized inverse probability of treatment.

[a] A unique individual may be included multiple times because of matching with replacement, and an individual may be included in both the exposure and comparator groups. This table counts each instance of an individual's entry separately as distinct observations.

Table B-5-MarketScan. Association of a COVID-19 Diagnosis With Adverse Events, Cohort Design, MarketScan

A. Guillain-Barré Syndrome

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	11	26,740,944	5.44 (2.07-8.80)	10.99 (1.42-85.10)	10.69 (1.38-82.74)
All of follow-up (day 0 – end)	Comparator	1	26,735,597	1.48 (0.00-4.37)	—	—
Day 0	COVID-19	1	319,254	0.31 (0.00-0.93)	NE	NE
Day 0	Comparator	0	319,249	0.00 (0.00-0.00)	—	—
Day 0-41	COVID-19	6	10,376,982	2.17 (0.43-3.91)	NE	NE
Day 0-41	Comparator	0	10,362,270	0.00 (0.00-0.00)	—	—
Day 0-90	COVID-19	11	17,882,686	5.44 (2.07-8.80)	NE	NE
Day 0-90	Comparator	0	17,864,738	0.00 (0.00-0.00)	—	—
Day 0-180	COVID-19	11	25,263,900	5.44 (2.07-8.80)	10.99 (1.42-85.10)	10.69 (1.38-82.74)
Day 0-180	Comparator	1	25,260,391	1.48 (0.00-4.37)	—	—
Alternative risk windows						
All of follow-up (day 1 – end)	COVID-19	10	26,740,943	5.12 (1.82-8.43)	9.99 (1.28-78.02)	9.57 (1.23-74.74)
All of follow-up (day 1 – end)	Comparator	1	26,735,597	1.48 (0.00-4.37)	—	—
Day 1-41	COVID-19	5	10,376,981	1.86 (0.22-3.49)	NE	NE
Day 1-41	Comparator	0	10,362,270	0.00 (0.00-0.00)	—	—
Day 1-90	COVID-19	10	17,882,685	5.12 (1.82-8.43)	NE	NE
Day 1-90	Comparator	0	17,864,738	0.00 (0.00-0.00)	—	—
Day 1-180	COVID-19	10	25,263,899	5.12 (1.82-8.43)	9.99 (1.28-78.02)	9.57 (1.23-74.74)
Day 1-180	Comparator	1	25,260,391	1.48 (0.00-4.37)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; GBS = Guillain-Barré syndrome; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; NE = not estimable; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

— denotes the reference group.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, hospitalization status on Time 0, autoimmune disorders, dementia/neurologic conditions, hemiplegia/paraplegia, herpes simplex virus infection, immunocompromised state, infection associated with GBS, inpatient surgery, obesity, pneumonia or lower respiratory tract infection, trauma, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

B. Bell's Palsy

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	122	26,710,504	116.84 (76.12-157.53)	1.31 (1.00-1.73)	1.22 (0.92-1.61)
All of follow-up (day 0 – end)	Comparator	93	26,715,069	70.60 (51.68-89.51)	—	—
Day 0	COVID-19	13	319,031	4.07 (1.86-6.29)	4.33 (1.24-15.21)	4.12 (1.17-14.52)
Day 0	Comparator	3	319,068	0.94 (0.00-2.00)	—	—
Day 0-41	COVID-19	58	10,368,518	21.82 (16.13-27.50)	1.41 (0.94-2.12)	1.32 (0.87-1.99)
Day 0-41	Comparator	41	10,355,838	16.47 (11.26-21.67)	—	—
Day 0-90	COVID-19	86	17,866,015	40.40 (31.44-49.36)	1.21 (0.88-1.66)	1.14 (0.83-1.57)
Day 0-90	Comparator	71	17,852,585	35.65 (26.99-44.30)	—	—
Day 0-180	COVID-19	115	25,236,371	77.03 (60.22-93.83)	1.29 (0.97-1.71)	1.20 (0.90-1.59)
Day 0-180	Comparator	89	25,241,296	57.76 (43.68-71.83)	—	—
Alternative risk windows						
All of follow-up (day 1 – end)	COVID-19	109	26,710,491	112.77 (72.11-153.41)	1.21 (0.91-1.61)	1.13 (0.85-1.50)
All of follow-up (day 1 – end)	Comparator	90	26,715,066	69.66 (50.80-88.51)	—	—
Day 1-41	COVID-19	45	10,368,505	17.74 (12.51-22.98)	1.18 (0.77-1.82)	1.10 (0.71-1.71)
Day 1-41	Comparator	38	10,355,835	15.53 (10.53-20.53)	—	—
Day 1-90	COVID-19	73	17,866,002	36.33 (27.64-45.01)	1.07 (0.77-1.49)	1.01 (0.73-1.41)
Day 1-90	Comparator	68	17,852,582	34.71 (26.18-43.23)	—	—
Day 1-180	COVID-19	102	25,236,358	72.95 (56.30-89.61)	1.19 (0.89-1.59)	1.10 (0.82-1.47)
Day 1-180	Comparator	86	25,241,293	56.82 (42.81-70.82)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, hospitalization status on Time 0, autoimmune disorders, cancer, dementia/neurologic conditions, diabetes mellitus, type 1 or 2, herpes simplex virus infection, immunocompromised state, mental health conditions, obesity, pregnancy, inpatient hospital stays before Time 0, ED visits, outpatient visits, influenza vaccination in previous year.

C. Encephalitis/Encephalomyelitis

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	11	26,738,915	5.28 (1.99-8.58)	2.20 (0.76-6.33)	1.99 (0.69-5.77)
All of follow-up (day 0 – end)	Comparator	5	26,737,424	6.17 (0.00-13.19)	—	—
Day 0	COVID-19	0	319,264	0.00 (0.00-0.00)	NE	NE
Day 0	Comparator	0	319,264	0.00 (0.00-0.00)	—	—
Day 0-41	COVID-19	7	10,377,062	2.59 (0.64-4.53)	3.50 (0.73-16.83)	2.90 (0.60-14.05)
Day 0-41	Comparator	2	10,362,727	0.85 (0.00-2.06)	—	—
Day 0-90	COVID-19	11	17,882,298	5.28 (1.99-8.58)	3.66 (1.02-13.13)	3.31 (0.91-11.96)
Day 0-90	Comparator	3	17,865,652	1.58 (0.00-3.45)	—	—
Day 0-180	COVID-19	11	25,262,136	5.28 (1.99-8.58)	2.75 (0.88-8.63)	2.49 (0.79-7.86)
Day 0-180	Comparator	4	25,262,074	3.05 (0.00-6.50)	—	—
Alternative risk windows						
All of follow-up (day 1 – end)	COVID-19	11	26,738,915	5.28 (1.99-8.58)	2.20 (0.76-6.33)	1.99 (0.69-5.77)
All of follow-up (day 1 – end)	Comparator	5	26,737,424	6.17 (0.00-13.19)	—	—
Day 1-41	COVID-19	7	10,377,062	2.59 (0.64-4.53)	3.50 (0.73-16.83)	2.90 (0.60-14.05)
Day 1-41	Comparator	2	10,362,727	0.85 (0.00-2.06)	—	—
Day 1-90	COVID-19	11	17,882,298	5.28 (1.99-8.58)	3.66 (1.02-13.13)	3.31 (0.91-11.96)
Day 1-90	Comparator	3	17,865,652	1.58 (0.00-3.45)	—	—
Day 1-180	COVID-19	11	25,262,136	5.28 (1.99-8.58)	2.75 (0.88-8.63)	2.49 (0.79-7.86)
Day 1-180	Comparator	4	25,262,074	3.05 (0.00-6.50)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; NE = not estimable; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, hospitalization status on Time 0, animal exposure/bites or rabies, autoimmune disorders, dementia/neurologic conditions, herpes simplex virus infection, immunocompromised state, pneumonia or lower respiratory tract infection, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

D. Narcolepsy

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	36	26,713,511	40.71 (20.30-61.12)	1.29 (0.78-2.13)	1.17 (0.70-1.94)
All of follow-up (day 0 – end)	Comparator	28	26,712,922	26.57 (11.61-41.53)	—	—
Day 0	COVID-19	4	318,932	1.25 (0.03-2.48)	1.00 (0.21-4.71)	0.93 (0.20-4.38)
Day 0	Comparator	4	318,970	1.25 (0.00-2.76)	—	—
Day 0-41	COVID-19	18	10,366,487	6.96 (3.71-10.22)	1.50 (0.70-3.22)	1.41 (0.65-3.03)
Day 0-41	Comparator	12	10,353,453	4.64 (1.83-7.45)	—	—
Day 0-90	COVID-19	21	17,864,785	8.85 (4.96-12.74)	1.05 (0.56-1.97)	0.94 (0.50-1.77)
Day 0-90	Comparator	20	17,849,489	9.69 (5.19-14.19)	—	—
Day 0-180	COVID-19	33	25,238,153	25.42 (14.66-36.19)	1.22 (0.73-2.05)	1.11 (0.66-1.87)
Day 0-180	Comparator	27	25,239,075	20.98 (10.80-31.15)	—	—
Alternative risk windows						
All of follow-up (day 1 – end)	COVID-19	32	26,713,507	39.46 (19.08-59.83)	1.33 (0.79-2.26)	1.21 (0.71-2.05)
All of follow-up (day 1 – end)	Comparator	24	26,712,918	25.32 (10.44-40.20)	—	—
Day 1-41	COVID-19	14	10,366,483	5.71 (2.69-8.73)	1.75 (0.73-4.17)	1.65 (0.69-3.94)
Day 1-41	Comparator	8	10,353,449	3.39 (1.01-5.76)	—	—
Day 1-90	COVID-19	17	17,864,781	7.60 (3.90-11.29)	1.06 (0.54-2.10)	0.95 (0.48-1.88)
Day 1-90	Comparator	16	17,849,485	8.43 (4.19-12.67)	—	—
Day 1-180	COVID-19	29	25,238,149	24.17 (13.47-34.87)	1.26 (0.73-2.18)	1.14 (0.66-1.98)
Day 1-180	Comparator	23	25,239,071	19.72 (9.66-29.79)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, hospitalization status on Time 0, brain lesions related to secondary narcolepsy, dementia/neurologic conditions, immunocompromised state, mental health conditions, obesity, stroke/cerebrovascular disease, inpatient hospital stays before Time 0, ED visits, outpatient visits, influenza vaccination in previous year.

E. Appendicitis

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	182	26,675,934	120.80 (94.34-147.24)	1.60 (1.26-2.03)	1.57 (1.23-1.99)
All of follow-up (day 0 – end)	Comparator	114	26,681,952	88.23 (63.46-112.99)	—	—
Day 0	COVID-19	70	318,640	21.97 (16.82-27.11)	3.68 (2.17-6.24)	3.70 (2.16-6.34)
Day 0	Comparator	19	318,665	5.96 (3.14-8.78)	—	—
Day 0-41	COVID-19	118	10,353,256	40.34 (32.98-47.70)	2.00 (1.46-2.74)	1.97 (1.43-2.71)
Day 0-41	Comparator	59	10,342,167	22.58 (16.66-28.51)	—	—
Day 0-90	COVID-19	149	17,840,910	61.27 (50.83-71.71)	1.65 (1.27-2.16)	1.61 (1.23-2.11)
Day 0-90	Comparator	90	17,828,761	43.63 (33.89-53.37)	—	—
Day 0-180	COVID-19	175	25,203,030	94.41 (76.94-111.87)	1.61 (1.26-2.05)	1.57 (1.23-2.01)
Day 0-180	Comparator	109	25,209,311	66.85 (51.83-81.87)	—	—
Alternative risk windows						
All of follow-up (day 1 – end)	COVID-19	112	26,675,864	98.85 (72.90-124.80)	1.18 (0.89-1.55)	1.14 (0.86-1.50)
All of follow-up (day 1 – end)	Comparator	95	26,681,933	82.27 (57.66-106.88)	—	—
Day 1-41	COVID-19	48	10,353,186	18.37 (13.11-23.63)	1.20 (0.79-1.82)	1.14 (0.75-1.75)
Day 1-41	Comparator	40	10,342,148	16.62 (11.41-21.83)	—	—
Day 1-90	COVID-19	79	17,840,840	39.31 (30.22-48.40)	1.11 (0.81-1.54)	1.06 (0.77-1.47)
Day 1-90	Comparator	71	17,828,742	37.67 (28.34-46.99)	—	—
Day 1-180	COVID-19	105	25,202,960	72.45 (55.76-89.14)	1.17 (0.88-1.55)	1.12 (0.84-1.49)
Day 1-180	Comparator	90	25,209,292	60.89 (46.14-75.64)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, hospitalization status on Time 0, immunocompromised state, pneumonia or lower respiratory tract infection, inpatient hospital stays before Time 0, ED visits, outpatient visits, influenza vaccination in previous year.

F. Nonhemorrhagic Stroke

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	106	26,599,730	62.28 (42.00-82.55)	1.41 (1.05-1.90)	1.45 (1.07-1.97)
All of follow-up (day 0 – end)	Comparator	75	26,621,239	49.47 (28.95-69.99)	—	—
Day 0	COVID-19	25	317,884	7.86 (4.78-10.95)	0.53 (0.33-0.87)	0.55 (0.33-0.90)
Day 0	Comparator	47	318,019	14.78 (10.47-19.09)	—	—
Day 0-27	COVID-19	79	7,500,505	27.42 (21.34-33.49)	1.52 (1.07-2.16)	1.55 (1.08-2.22)
Day 0-27	Comparator	52	7,494,929	16.59 (11.99-21.19)	—	—
Day 0-90	COVID-19	92	17,796,405	35.63 (28.07-43.19)	1.44 (1.04-1.98)	1.48 (1.07-2.05)
Day 0-90	Comparator	64	17,792,229	24.55 (18.09-31.01)	—	—
Day 0-180	COVID-19	103	25,133,875	47.41 (36.92-57.89)	1.43 (1.06-1.94)	1.47 (1.08-2.00)
Day 0-180	Comparator	72	25,154,286	35.50 (24.68-46.31)	—	—
Alternative risk windows						
All of follow-up (day 1 – end)	COVID-19	81	26,599,705	54.42 (34.38-74.46)	2.89 (1.88-4.45)	3.04 (1.97-4.70)
All of follow-up (day 1 – end)	Comparator	28	26,621,192	34.70 (14.63-54.76)	—	—
Day 1-27	COVID-19	54	7,500,480	19.55 (14.32-24.79)	10.79 (4.32-26.98)	10.87 (4.24-27.87)
Day 1-27	Comparator	5	7,494,882	1.81 (0.22-3.41)	—	—
Day 1-90	COVID-19	67	17,796,380	27.77 (20.86-34.67)	3.94 (2.31-6.71)	4.15 (2.42-7.12)
Day 1-90	Comparator	17	17,792,182	9.77 (4.96-14.58)	—	—
Day 1-180	COVID-19	78	25,133,850	39.55 (29.52-49.57)	3.12 (1.99-4.90)	3.26 (2.06-5.14)
Day 1-180	Comparator	25	25,154,239	20.72 (10.80-30.64)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, hospitalization status on Time 0, autoimmune disorders, cancer, chronic kidney disease/renal disease, chronic liver disease, chronic lung disease, dementia/neurologic conditions, diabetes mellitus, type 1 or 2, heart conditions, hemiplegia/paraplegia, hypertension, immunocompromised state, lipid abnormality, obesity, peripheral vascular disease, pneumonia or lower respiratory tract infection, pregnancy, sickle cell disease/thalassemia, smoking/nicotine dependency, stroke/cerebrovascular disease, thrombophilia, trauma, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

G. Hemorrhagic Stroke

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	34	26,716,900	14.45 (9.30-19.60)	1.21 (0.67-2.21)	1.21 (0.67-2.20)
All of follow-up (day 0 – end)	Comparator	28	26,715,092	21.65 (6.29-37.01)	—	—
Day 0	COVID-19	4	319,035	1.25 (0.03-2.48)	0.25 (0.07-0.86)	0.23 (0.07-0.80)
Day 0	Comparator	16	319,026	5.02 (1.23-8.80)	—	—
Day 0-27	COVID-19	26	7,528,957	9.21 (5.65-12.78)	1.30 (0.62-2.73)	1.27 (0.61-2.64)
Day 0-27	Comparator	20	7,519,275	6.53 (2.46-10.60)	—	—
Day 0-90	COVID-19	33	17,868,284	13.50 (8.70-18.30)	1.43 (0.74-2.79)	1.42 (0.73-2.74)
Day 0-90	Comparator	23	17,851,757	8.50 (3.86-13.14)	—	—
Day 0-180	COVID-19	34	25,241,673	14.45 (9.30-19.60)	1.26 (0.68-2.31)	1.27 (0.69-2.33)
Day 0-180	Comparator	27	25,241,583	14.96 (6.96-22.97)	—	—
Alternative risk windows						
All of follow-up (day 1 – end)	COVID-19	30	26,716,896	13.19 (8.19-18.19)	2.50 (1.28-4.87)	2.49 (1.27-4.89)
All of follow-up (day 1 – end)	Comparator	12	26,715,076	16.64 (1.75-31.52)	—	—
Day 1-27	COVID-19	22	7,528,953	7.96 (4.61-11.30)	5.49 (1.89-15.93)	5.18 (1.78-15.10)
Day 1-27	Comparator	4	7,519,259	1.52 (0.02-3.01)	—	—
Day 1-90	COVID-19	29	17,868,280	12.25 (7.60-16.89)	4.14 (1.81-9.45)	4.01 (1.75-9.18)
Day 1-90	Comparator	7	17,851,741	3.49 (0.80-6.17)	—	—
Day 1-180	COVID-19	30	25,241,669	13.19 (8.19-18.19)	2.73 (1.37-5.44)	2.77 (1.38-5.55)
Day 1-180	Comparator	11	25,241,567	9.95 (2.90-17.00)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, hospitalization status on Time 0, autoimmune disorders, cancer, chronic kidney disease/renal disease, chronic liver disease, chronic lung disease, dementia/neurologic conditions, diabetes mellitus, type 1 or 2, heart conditions, hemiplegia/paraplegia, hypertension, immunocompromised state, mental health conditions, peripheral vascular disease, pneumonia or lower respiratory tract infection, pregnancy, sickle cell disease/thalassemia, smoking/nicotine dependency, stroke/cerebrovascular disease, trauma, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

H. Acute Myocardial Infarction

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	252	26,634,779	135.08 (110.99-159.17)	1.43 (1.17-1.75)	1.37 (1.12-1.68)
All of follow-up (day 0 – end)	Comparator	176	26,639,458	98.98 (76.29-121.66)	—	—
Day 0	COVID-19	57	318,271	17.91 (13.26-22.56)	0.56 (0.40-0.79)	0.57 (0.40-0.80)
Day 0	Comparator	101	318,319	31.73 (25.01-38.44)	—	—
Day 0-27	COVID-19	177	7,508,331	59.91 (51.04-68.77)	1.43 (1.12-1.81)	1.37 (1.08-1.75)
Day 0-27	Comparator	124	7,500,148	39.86 (32.36-47.36)	—	—
Day 0-90	COVID-19	225	17,816,297	90.06 (77.68-102.42)	1.53 (1.23-1.90)	1.46 (1.17-1.82)
Day 0-90	Comparator	147	17,805,329	54.34 (44.67-64.02)	—	—
Day 0-180	COVID-19	247	25,165,498	116.22 (99.12-133.32)	1.44 (1.17-1.76)	1.37 (1.12-1.69)
Day 0-180	Comparator	172	25,172,228	83.12 (66.75-99.50)	—	—
Alternative risk windows						
All of follow-up (day 1 – end)	COVID-19	195	26,634,722	117.20 (93.55-140.84)	2.60 (1.96-3.45)	2.43 (1.84-3.23)
All of follow-up (day 1 – end)	Comparator	75	26,639,357	67.27 (45.59-88.95)	—	—
Day 1-27	COVID-19	120	7,508,274	42.00 (34.45-49.55)	5.21 (3.34-8.14)	4.73 (3.01-7.44)
Day 1-27	Comparator	23	7,500,047	8.14 (4.80-11.48)	—	—
Day 1-90	COVID-19	168	17,816,240	72.16 (60.69-83.63)	3.65 (2.62-5.09)	3.32 (2.37-4.66)
Day 1-90	Comparator	46	17,805,228	22.62 (15.65-29.59)	—	—
Day 1-180	COVID-19	190	25,165,441	98.33 (81.87-114.79)	2.68 (2.00-3.58)	2.50 (1.87-3.34)
Day 1-180	Comparator	71	25,172,127	51.41 (36.47-66.35)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, hospitalization status on Time 0, autoimmune disorders, cancer, chronic kidney disease/renal disease, chronic liver disease, chronic lung disease, diabetes mellitus, type 1 or 2, heart conditions, hypertension, immunocompromised state, lipid abnormality, mental health conditions, obesity, peripheral vascular disease, pneumonia or lower respiratory tract infection, pregnancy, sickle cell disease/thalassemia, smoking/nicotine dependency, stroke/cerebrovascular disease, thrombophilia, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

I. Myocarditis/Pericarditis

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	326	26,700,852	176.28 (148.46-204.10)	6.94 (5.03-9.58)	6.20 (4.46-8.62)
All of follow-up (day 0 – end)	Comparator	47	26,724,695	38.19 (23.04-53.35)	—	—
Day 0	COVID-19	111	319,096	34.79 (28.32-41.26)	22.20 (9.06-54.40)	21.04 (8.52-51.96)
Day 0	Comparator	5	319,163	1.57 (0.19-2.94)	—	—
Day 0-41	COVID-19	248	10,364,863	87.02 (76.07-97.96)	11.81 (7.16-19.48)	10.29 (6.13-17.29)
Day 0-41	Comparator	21	10,358,982	7.50 (3.80-11.20)	—	—
Day 0-90	COVID-19	290	17,858,664	113.96 (100.29-127.62)	8.53 (5.82-12.50)	7.64 (5.15-11.32)
Day 0-90	Comparator	34	17,858,515	15.87 (9.99-21.75)	—	—
Day 0-180	COVID-19	318	25,227,482	147.72 (128.57-166.86)	7.23 (5.18-10.09)	6.44 (4.58-9.07)
Day 0-180	Comparator	44	25,250,642	28.08 (18.15-38.02)	—	—
Alternative risk windows						
All of follow-up (day 1 – end)	COVID-19	215	26,700,741	141.54 (114.47-168.61)	5.12 (3.61-7.26)	4.51 (3.15-6.45)
All of follow-up (day 1 – end)	Comparator	42	26,724,690	36.63 (21.53-51.72)	—	—
Day 1-41	COVID-19	137	10,364,752	52.25 (43.42-61.08)	8.56 (4.70-15.57)	7.22 (3.89-13.42)
Day 1-41	Comparator	16	10,358,977	5.93 (2.50-9.37)	—	—
Day 1-90	COVID-19	179	17,858,553	79.20 (67.15-91.24)	6.17 (4.03-9.44)	5.43 (3.50-8.43)
Day 1-90	Comparator	29	17,858,510	14.30 (8.59-20.02)	—	—
Day 1-180	COVID-19	207	25,227,371	112.97 (94.94-131.00)	5.31 (3.69-7.63)	4.66 (3.21-6.77)
Day 1-180	Comparator	39	25,250,637	26.52 (16.68-36.36)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, hospitalization status on Time 0, animal exposure/bites or rabies, autoimmune disorders, cancer, chronic kidney disease/renal disease, chronic liver disease, diabetes mellitus, type 1 or 2, heart conditions, herpes simplex virus infection, hypertension, immunocompromised state, infection associated with myocarditis/pericarditis, nutritional deficiencies, obesity, peripheral vascular disease, pneumonia or lower respiratory tract infection, sepsis, trauma, tuberculosis, inpatient hospital stays before Time 0, ED visits, outpatient visits, influenza vaccination in previous year.

J. Deep Vein Thrombosis

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	835	26,547,327	459.22 (414.09-504.34)	3.06 (2.65-3.54)	2.83 (2.45-3.28)
All of follow-up (day 0 – end)	Comparator	273	26,617,237	226.72 (178.80-274.62)	—	—
Day 0	COVID-19	123	317,909	38.69 (31.85-45.53)	3.24 (2.25-4.66)	3.09 (2.13-4.46)
Day 0	Comparator	38	318,133	11.94 (8.15-15.74)	—	—
Day 0-27	COVID-19	545	7,493,934	192.94 (176.67-209.20)	4.51 (3.68-5.52)	4.10 (3.33-5.03)
Day 0-27	Comparator	121	7,496,083	42.35 (34.49-50.20)	—	—
Day 0-90	COVID-19	748	17,770,409	311.48 (288.29-334.65)	3.72 (3.16-4.39)	3.44 (2.92-4.06)
Day 0-90	Comparator	201	17,793,014	90.68 (75.99-105.37)	—	—
Day 0-180	COVID-19	820	25,087,815	399.57 (367.76-431.38)	3.20 (2.76-3.70)	2.96 (2.55-3.43)
Day 0-180	Comparator	257	25,151,882	156.79 (132.07-181.50)	—	—
Alternative risk windows						
All of follow-up (day 1 – end)	COVID-19	712	26,547,204	420.69 (376.06-465.31)	3.03 (2.59-3.55)	2.80 (2.39-3.27)
All of follow-up (day 1 – end)	Comparator	235	26,617,199	214.80 (167.02-262.56)	—	—
Day 1-27	COVID-19	422	7,493,811	154.31 (139.53-169.08)	5.08 (3.98-6.49)	4.54 (3.54-5.83)
Day 1-27	Comparator	83	7,496,045	30.41 (23.53-37.28)	—	—
Day 1-90	COVID-19	625	17,770,286	272.89 (250.73-295.05)	3.84 (3.19-4.61)	3.53 (2.94-4.24)
Day 1-90	Comparator	163	17,792,976	78.75 (64.56-92.94)	—	—
Day 1-180	COVID-19	697	25,087,692	361.02 (329.93-392.10)	3.19 (2.71-3.74)	2.94 (2.50-3.46)
Day 1-180	Comparator	219	25,151,844	144.86 (120.43-169.28)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, hospitalization status on Time 0, autoimmune disorders, cancer, chronic kidney disease/renal disease, chronic liver disease, dementia/neurologic conditions, diabetes mellitus, type 1 or 2, heart conditions, hemiplegia/paraplegia, immunocompromised state, inpatient surgery, lipid abnormality, obesity, peripheral vascular disease, pneumonia or lower respiratory tract infection, pregnancy, sickle cell disease/thalassemia, smoking/nicotine dependency, stroke/cerebrovascular disease, thromboembolism, thrombophilia, trauma, tuberculosis, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

K. Pulmonary Embolism

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis, any setting						
All of follow-up (day 0 – end)	COVID-19	1167	26,554,692	546.90 (471.49-622.26)	6.25 (5.33-7.32)	5.79 (4.93-6.80)
All of follow-up (day 0 – end)	Comparator	187	26,657,127	133.19 (104.84-161.53)	—	—
Day 0	COVID-19	324	318,207	101.82 (90.74-112.90)	5.79 (4.30-7.78)	5.58 (4.14-7.52)
Day 0	Comparator	56	318,524	17.58 (12.74-22.43)	—	—
Day 0-27	COVID-19	926	7,494,045	317.55 (297.02-338.07)	9.00 (7.29-11.11)	8.62 (6.97-10.66)
Day 0-27	Comparator	103	7,505,396	35.08 (28.03-42.12)	—	—
Day 0-90	COVID-19	1110	17,769,645	422.24 (396.64-447.84)	7.78 (6.50-9.29)	7.32 (6.11-8.77)
Day 0-90	Comparator	143	17,816,392	60.73 (50.03-71.42)	—	—
Day 0-180	COVID-19	1156	25,092,063	475.22 (444.93-505.49)	6.43 (5.47-7.56)	5.96 (5.05-7.02)
Day 0-180	Comparator	180	25,188,321	106.14 (86.95-125.33)	—	—
Alternative risk windows, any setting						
All of follow-up (day 1 – end)	COVID-19	843	26,554,368	445.54 (370.86-520.15)	6.45 (5.35-7.77)	5.89 (4.86-7.12)
All of follow-up (day 1 – end)	Comparator	131	26,657,071	115.63 (87.71-143.55)	—	—
Day 1-27	COVID-19	602	7,493,721	215.95 (198.64-233.25)	12.83 (9.53-17.26)	12.27 (9.08-16.59)
Day 1-27	Comparator	47	7,505,340	17.50 (12.47-22.52)	—	—
Day 1-90	COVID-19	786	17,769,321	320.75 (297.63-343.87)	9.05 (7.25-11.30)	8.44 (6.74-10.57)
Day 1-90	Comparator	87	17,816,336	43.15 (33.66-52.64)	—	—
Day 1-180	COVID-19	832	25,091,739	373.78 (345.55-402.00)	6.73 (5.55-8.14)	6.13 (5.04-7.46)
Day 1-180	Comparator	124	25,188,265	88.58 (70.02-107.12)	—	—
Overall analysis, inpatient only						
All of follow-up (day 0 – end)	COVID-19	442	26,616,138	168.13 (151.50-184.76)	5.14 (4.04-6.55)	4.95 (3.87-6.33)
All of follow-up (day 0 – end)	Comparator	86	26,665,160	45.75 (31.96-59.53)	—	—
Day 0	COVID-19	93	318,207	29.23 (23.29-35.17)	1.94 (1.35-2.79)	1.95 (1.36-2.81)
Day 0	Comparator	48	318,524	15.07 (10.55-19.59)	—	—
Day 0-27	COVID-19	391	7,503,329	134.42 (121.05-147.79)	6.52 (4.89-8.68)	6.34 (4.75-8.47)
Day 0-27	Comparator	60	7,506,109	19.61 (14.32-24.91)	—	—
Day 0-90	COVID-19	433	17,802,413	158.42 (143.16-173.69)	5.85 (4.52-7.57)	5.69 (4.39-7.38)
Day 0-90	Comparator	74	17,819,471	28.42 (21.36-35.49)	—	—
Day 0-180	COVID-19	442	25,147,026	168.13 (151.50-184.76)	5.20 (4.08-6.64)	5.00 (3.90-6.41)
Day 0-180	Comparator	85	25,195,098	41.67 (30.43-52.91)	—	—
Alternative risk windows, inpatient only						
All of follow-up (day 1 – end)	COVID-19	349	26,616,045	138.94 (123.40-154.48)	9.19 (6.53-12.95)	8.65 (6.06-12.35)
All of follow-up (day 1 – end)	Comparator	38	26,665,112	30.68 (17.69-43.67)	—	—
Day 1-27	COVID-19	298	7,503,236	105.23 (93.24-117.21)	24.85 (13.95-44.25)	24.04 (13.37-43.20)

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Day 1-27	Comparator	12	7,506,061	4.54 (1.96-7.13)	—	—
Day 1-90	COVID-19	340	17,802,320	129.24 (115.16-143.30)	13.08 (8.78-19.49)	12.59 (8.40-18.87)
Day 1-90	Comparator	26	17,819,423	13.36 (8.01-18.70)	—	—
Day 1-180	COVID-19	349	25,146,933	138.94 (123.40-154.48)	9.44 (6.67-13.36)	8.85 (6.18-12.69)
Day 1-180	Comparator	37	25,195,050	26.61 (16.35-36.86)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, hospitalization status on Time 0, autoimmune disorders, cancer, chronic kidney disease/renal disease, chronic liver disease, dementia/neurologic conditions, diabetes mellitus, type 1 or 2, heart conditions, hemiplegia/paraplegia, immunocompromised state, inpatient surgery, lipid abnormality, obesity, peripheral vascular disease, pneumonia or lower respiratory tract infection, pregnancy, sickle cell disease/thalassemia, smoking/nicotine dependency, stroke/cerebrovascular disease, thromboembolism, thrombophilia, trauma, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

L. Disseminated Intravascular Coagulation

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	35	26,739,450	14.87 (8.79-20.95)	3.50 (1.73-7.07)	3.41 (1.67-6.93)
All of follow-up (day 0 – end)	Comparator	10	26,738,875	5.45 (1.43-9.47)	—	—
Day 0	COVID-19	11	319,264	3.45 (1.41-5.48)	1.83 (0.68-4.96)	1.64 (0.60-4.48)
Day 0	Comparator	6	319,279	1.88 (0.38-3.38)	—	—
Day 0-27	COVID-19	30	7,534,333	10.15 (6.50-13.80)	5.00 (2.08-12.00)	4.53 (1.87-10.96)
Day 0-27	Comparator	6	7,525,421	1.88 (0.38-3.38)	—	—
Day 0-90	COVID-19	33	17,881,869	11.95 (7.76-16.13)	4.12 (1.90-8.93)	3.86 (1.77-8.43)
Day 0-90	Comparator	8	17,866,711	3.00 (0.84-5.17)	—	—
Day 0-180	COVID-19	35	25,262,382	14.87 (8.79-20.95)	3.50 (1.73-7.07)	3.41 (1.67-6.93)
Day 0-180	Comparator	10	25,263,408	5.45 (1.43-9.47)	—	—
Alternative risk windows						
All of follow-up (day 1 – end)	COVID-19	24	26,739,439	11.43 (5.69-17.16)	5.99 (2.08-17.26)	6.58 (2.27-19.06)
All of follow-up (day 1 – end)	Comparator	4	26,738,869	3.57 (0.00-7.30)	—	—
Day 1-41	COVID-19	19	7,534,322	6.71 (3.68-9.74)	NE	NE
Day 1-41	Comparator	0	7,525,415	0.00 (0.00-0.00)	—	—
Day 1-90	COVID-19	22	17,881,858	8.50 (4.84-12.16)	10.99 (2.58-46.73)	11.42 (2.66-49.00)
Day 1-90	Comparator	2	17,866,705	1.12 (0.00-2.68)	—	—
Day 1-180	COVID-19	24	25,262,371	11.43 (5.69-17.16)	5.99 (2.08-17.26)	6.58 (2.27-19.06)
Day 1-180	Comparator	4	25,263,402	3.57 (0.00-7.30)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; NE = not estimable; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, hospitalization status on Time 0, autoimmune disorders, cancer, chronic kidney disease/renal disease, chronic liver disease, dementia/neurologic conditions, immunocompromised state, inpatient surgery, pneumonia or lower respiratory tract infection, pregnancy, sepsis, smoking/nicotine dependency, thromboembolism, thrombophilia, trauma, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

M. Immune Thrombocytopenia

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	47	26,717,161	29.14 (19.46-38.83)	2.14 (1.29-3.54)	2.10 (1.26-3.51)
All of follow-up (day 0 – end)	Comparator	22	26,720,033	17.17 (8.34-26.00)	—	—
Day 0	COVID-19	5	319,058	1.57 (0.19-2.94)	2.50 (0.48-12.87)	2.55 (0.50-13.16)
Day 0	Comparator	2	319,075	0.63 (0.00-1.50)	—	—
Day 0-41	COVID-19	25	10,369,709	9.16 (5.51-12.82)	2.50 (1.20-5.20)	2.40 (1.15-5.04)
Day 0-41	Comparator	10	10,356,449	3.67 (1.37-5.97)	—	—
Day 0-90	COVID-19	35	17,869,046	15.75 (10.26-21.24)	2.69 (1.42-5.09)	2.64 (1.39-5.02)
Day 0-90	Comparator	13	17,854,642	5.63 (2.43-8.84)	—	—
Day 0-180	COVID-19	47	25,242,076	29.14 (19.46-38.83)	2.24 (1.34-3.74)	2.18 (1.30-3.67)
Day 0-180	Comparator	21	25,245,932	14.41 (7.44-21.37)	—	—
Alternative risk windows						
All of follow-up (day 1 – end)	COVID-19	42	26,717,156	27.58 (17.99-37.16)	2.10 (1.23-3.58)	2.06 (1.20-3.53)
All of follow-up (day 1 – end)	Comparator	20	26,720,031	16.54 (7.76-25.33)	—	—
Day 1-41	COVID-19	20	10,369,704	7.59 (4.21-10.98)	2.50 (1.10-5.66)	2.37 (1.03-5.42)
Day 1-41	Comparator	8	10,356,447	3.04 (0.92-5.17)	—	—
Day 1-90	COVID-19	30	17,869,041	14.18 (8.87-19.49)	2.73 (1.37-5.44)	2.66 (1.32-5.34)
Day 1-90	Comparator	11	17,854,640	5.01 (1.92-8.09)	—	—
Day 1-180	COVID-19	42	25,242,071	27.58 (17.99-37.16)	2.21 (1.29-3.80)	2.15 (1.24-3.71)
Day 1-180	Comparator	19	25,245,930	13.78 (6.86-20.69)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; ITP = immune thrombocytopenia; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, hospitalization status on Time 0, animal exposure/bites or rabies, antiphospholipid syndrome, autoimmune disorders, cancer, chronic lymphocytic leukemia, herpes simplex virus infection, immunocompromised state, infection associated with ITP, pneumonia or lower respiratory tract infection, sepsis, tuberculosis, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

N. Transverse Myelitis

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	3	26,740,061	0.99 (0.00-2.11)	1.50 (0.25-8.97)	1.70 (0.28-10.19)
All of follow-up (day 0 – end)	Comparator	2	26,737,142	0.87 (0.00-2.12)	—	—
Day 0	COVID-19	1	319,250	0.31 (0.00-0.93)	1.00 (0.06-15.99)	1.15 (0.07-18.34)
Day 0	Comparator	1	319,244	0.31 (0.00-0.93)	—	—
Day 0-41	COVID-19	3	10,376,835	0.99 (0.00-2.11)	3.00 (0.31-28.82)	3.23 (0.33-31.12)
Day 0-41	Comparator	1	10,362,334	0.31 (0.00-0.93)	—	—
Day 0-90	COVID-19	3	17,882,293	0.99 (0.00-2.11)	1.50 (0.25-8.97)	1.70 (0.28-10.19)
Day 0-90	Comparator	2	17,865,167	0.87 (0.00-2.12)	—	—
Day 0-180	COVID-19	3	25,263,068	0.99 (0.00-2.11)	1.50 (0.25-8.97)	1.70 (0.28-10.19)
Day 0-180	Comparator	2	25,261,534	0.87 (0.00-2.12)	—	—
Alternative risk windows						
All of follow-up (day 1 – end)	COVID-19	2	26,740,060	0.68 (0.00-1.62)	2.00 (0.18-22.04)	2.30 (0.21-25.41)
All of follow-up (day 1 – end)	Comparator	1	26,737,141	0.56 (0.00-1.64)	—	—
Day 1-41	COVID-19	2	10,376,834	0.68 (0.00-1.62)	NE	NE
Day 1-41	Comparator	0	10,362,333	0.00 (0.00-0.00)	—	—
Day 1-90	COVID-19	2	17,882,292	0.68 (0.00-1.62)	2.00 (0.18-22.04)	2.30 (0.21-25.41)
Day 1-90	Comparator	1	17,865,166	0.56 (0.00-1.64)	—	—
Day 1-180	COVID-19	2	25,263,067	0.68 (0.00-1.62)	2.00 (0.18-22.04)	2.30 (0.21-25.41)
Day 1-180	Comparator	1	25,261,533	0.56 (0.00-1.64)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; NE = not estimable; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, hospitalization status on Time 0, antiphospholipid syndrome, autoimmune disorders, chronic lung disease, dementia/neurologic conditions, diabetes mellitus, type 1 or 2, hemiplegia/paraplegia, immunocompromised state, nutritional deficiencies, pneumonia or lower respiratory tract infection, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

O. Unusual Site Thrombosis With Thrombocytopenia Syndrome

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	4	26,742,577	3.23 (0.00-6.61)	2.00 (0.37-10.93)	1.98 (0.35-11.05)
All of follow-up (day 0 – end)	Comparator	2	26,739,280	1.12 (0.00-2.75)	—	—
Day 0	COVID-19	0	319,276	0.00 (0.00-0.00)	NE	NE
Day 0	Comparator	0	319,277	0.00 (0.00-0.00)	—	—
Day 0-41	COVID-19	1	10,377,780	0.36 (0.00-1.06)	1.00 (0.06-15.97)	1.12 (0.07-17.91)
Day 0-41	Comparator	1	10,363,299	0.38 (0.00-1.14)	—	—
Day 0-90	COVID-19	2	17,884,030	1.11 (0.00-2.74)	1.00 (0.14-7.10)	0.86 (0.12-6.24)
Day 0-90	Comparator	2	17,866,772	1.12 (0.00-2.75)	—	—
Day 0-180	COVID-19	4	25,265,479	3.23 (0.00-6.61)	2.00 (0.37-10.93)	1.98 (0.35-11.05)
Day 0-180	Comparator	2	25,263,670	1.12 (0.00-2.75)	—	—
Alternative risk windows						
All of follow-up (day 1 – end)	COVID-19	4	26,742,577	3.23 (0.00-6.61)	2.00 (0.37-10.93)	1.98 (0.35-11.05)
All of follow-up (day 1 – end)	Comparator	2	26,739,280	1.12 (0.00-2.75)	—	—
Day 1-41	COVID-19	1	10,377,780	0.36 (0.00-1.06)	1.00 (0.06-15.97)	1.12 (0.07-17.91)
Day 1-41	Comparator	1	10,363,299	0.38 (0.00-1.14)	—	—
Day 1-90	COVID-19	2	17,884,030	1.11 (0.00-2.74)	1.00 (0.14-7.10)	0.86 (0.12-6.24)
Day 1-90	Comparator	2	17,866,772	1.12 (0.00-2.75)	—	—
Day 1-180	COVID-19	4	25,265,479	3.23 (0.00-6.61)	2.00 (0.37-10.93)	1.98 (0.35-11.05)
Day 1-180	Comparator	2	25,263,670	1.12 (0.00-2.75)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; NE = not estimable; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, hospitalization status on Time 0, antiphospholipid syndrome, autoimmune disorders, cancer, chronic kidney disease/renal disease, chronic lung disease, dementia/neurologic conditions, diabetes mellitus, type 1 or 2, disseminated intravascular coagulation, heart conditions, hemiplegia/paraplegia, immunocompromised state, inpatient surgery, lipid abnormality, obesity, peripheral vascular disease, pneumonia or lower respiratory tract infection, pregnancy, smoking/nicotine dependency, thromboembolism, thrombophilia, tuberculosis, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

P. Common Site Thrombosis With Thrombocytopenia Syndrome

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	126	26,718,714	65.89 (48.92-82.86)	3.94 (2.67-5.80)	3.96 (2.67-5.88)
All of follow-up (day 0 – end)	Comparator	32	26,727,825	30.18 (10.67-49.69)	—	—
Day 0	COVID-19	32	319,147	10.03 (6.55-13.50)	2.67 (1.37-5.18)	2.76 (1.40-5.41)
Day 0	Comparator	12	319,172	3.76 (1.63-5.89)	—	—
Day 0-41	COVID-19	103	10,370,382	37.09 (29.84-44.33)	4.48 (2.85-7.03)	4.54 (2.87-7.20)
Day 0-41	Comparator	23	10,359,221	8.10 (4.74-11.46)	—	—
Day 0-90	COVID-19	115	17,869,897	44.72 (36.27-53.18)	4.26 (2.80-6.47)	4.24 (2.77-6.49)
Day 0-90	Comparator	27	17,859,436	10.61 (6.45-14.78)	—	—
Day 0-180	COVID-19	124	25,243,789	57.24 (45.25-69.22)	4.43 (2.94-6.67)	4.41 (2.91-6.69)
Day 0-180	Comparator	28	25,253,167	11.52 (6.99-16.06)	—	—
Alternative risk windows						
All of follow-up (day 1 – end)	COVID-19	94	26,718,682	55.87 (39.25-72.48)	4.70 (2.90-7.61)	4.71 (2.89-7.68)
All of follow-up (day 1 – end)	Comparator	20	26,727,813	26.42 (7.02-45.82)	—	—
Day 1-41	COVID-19	71	10,370,350	27.06 (20.70-33.42)	6.44 (3.42-12.15)	6.54 (3.42-12.51)
Day 1-41	Comparator	11	10,359,209	4.34 (1.74-6.95)	—	—
Day 1-90	COVID-19	83	17,869,865	34.70 (26.99-42.41)	5.53 (3.19-9.58)	5.43 (3.10-9.49)
Day 1-90	Comparator	15	17,859,424	6.85 (3.27-10.44)	—	—
Day 1-180	COVID-19	92	25,243,757	47.22 (35.74-58.69)	5.74 (3.38-9.77)	5.66 (3.30-9.71)
Day 1-180	Comparator	16	25,253,155	7.76 (3.76-11.77)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, hospitalization status on Time 0, antiphospholipid syndrome, autoimmune disorders, cancer, chronic kidney disease/renal disease, chronic lung disease, dementia/neurologic conditions, diabetes mellitus, type 1 or 2, disseminated intravascular coagulation, heart conditions, hemiplegia/paraplegia, immunocompromised state, inpatient surgery, lipid abnormality, obesity, peripheral vascular disease, pneumonia or lower respiratory tract infection, pregnancy, sickle cell disease/thalassemia, smoking/nicotine dependency, stroke/cerebrovascular disease, thromboembolism, thrombophilia, trauma, tuberculosis, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

Table B-6-MarketScan. Negative Control Outcomes Occurring Before Time 0 in Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis Included in the Cohort Study, sIPT-Weighted Exposure Groups, MarketScan

Analysis set	Negative control outcome	COVID-19 diagnosis (exposure) group, N (%)	Comparator group, N (%)	ASD
Guillain-Barré syndrome	Colonic diverticulitis	8,159 (2.56)	7,899 (2.47)	0.00
	Laceration of hand/finger	2,429 (0.76)	2,589 (0.81)	0.01
	Gout	4,201 (1.32)	3,929 (1.23)	0.01
	Arm/leg cellulitis	5,940 (1.86)	5,488 (1.72)	0.01
Bell's palsy	Colonic diverticulitis	8,172 (2.56)	7,906 (2.48)	0.01
	Laceration of hand/finger	2,420 (0.76)	2,596 (0.81)	0.01
	Gout	4,178 (1.31)	3,963 (1.24)	0.01
	Arm/leg cellulitis	5,923 (1.86)	5,520 (1.73)	0.01
Encephalitis/encephalomyelitis	Colonic diverticulitis	8,210 (2.57)	7,844 (2.46)	0.01
	Laceration of hand/finger	2,428 (0.76)	2,591 (0.81)	0.01
	Gout	4,239 (1.33)	3,887 (1.22)	0.01
	Arm/leg cellulitis	5,979 (1.87)	5,451 (1.71)	0.01
Narcolepsy	Colonic diverticulitis	8,150 (2.56)	7,913 (2.48)	0.00
	Laceration of hand/finger	2,413 (0.76)	2,597 (0.81)	0.01
	Gout	4,192 (1.31)	3,948 (1.24)	0.01
	Arm/leg cellulitis	5,948 (1.86)	5,475 (1.72)	0.01
Appendicitis	Colonic diverticulitis	8,146 (2.56)	7,795 (2.45)	0.01
	Laceration of hand/finger	2,415 (0.76)	2,595 (0.81)	0.01
	Gout	4,234 (1.33)	3,886 (1.22)	0.01
	Arm/leg cellulitis	5,975 (1.88)	5,450 (1.71)	0.01
Nonhemorrhagic stroke	Colonic diverticulitis	8,077 (2.54)	7,788 (2.45)	0.01
	Laceration of hand/finger	2,437 (0.77)	2,567 (0.81)	0.00
	Gout	4,107 (1.29)	3,918 (1.23)	0.01
	Arm/leg cellulitis	5,850 (1.84)	5,454 (1.71)	0.01
Hemorrhagic stroke	Colonic diverticulitis	8,187 (2.57)	7,852 (2.46)	0.01
	Laceration of hand/finger	2,438 (0.76)	2,575 (0.81)	0.01
	Gout	4,165 (1.31)	3,939 (1.23)	0.01
	Arm/leg cellulitis	5,925 (1.86)	5,483 (1.72)	0.01
Acute myocardial infarction	Colonic diverticulitis	8,109 (2.55)	7,823 (2.46)	0.01
	Laceration of hand/finger	2,432 (0.76)	2,574 (0.81)	0.01
	Gout	4,113 (1.29)	3,914 (1.23)	0.01
	Arm/leg cellulitis	5,855 (1.84)	5,475 (1.72)	0.01
Myocarditis/pericarditis	Colonic diverticulitis	8,155 (2.56)	7,895 (2.47)	0.00
	Laceration of hand/finger	2,442 (0.77)	2,570 (0.81)	0.00
	Gout	4,165 (1.31)	3,963 (1.24)	0.01
	Arm/leg cellulitis	5,892 (1.85)	5,550 (1.74)	0.01
Deep vein thrombosis	Colonic diverticulitis	8,078 (2.54)	7,796 (2.45)	0.01
	Laceration of hand/finger	2,434 (0.77)	2,574 (0.81)	0.01
	Gout	4,124 (1.30)	3,915 (1.23)	0.01
	Arm/leg cellulitis	5,806 (1.83)	5,411 (1.70)	0.01

Analysis set	Negative control outcome	COVID-19 diagnosis (exposure) group, N (%)	Comparator group, N (%)	ASD
Pulmonary embolism	Colonic diverticulitis	8,106 (2.55)	7,824 (2.46)	0.01
	Laceration of hand/finger	2,436 (0.77)	2,567 (0.81)	0.00
	Gout	4,132 (1.30)	3,928 (1.23)	0.01
	Arm/leg cellulitis	5,851 (1.84)	5,465 (1.72)	0.01
Disseminated intravascular coagulation	Colonic diverticulitis	8,196 (2.57)	7,859 (2.46)	0.01
	Laceration of hand/finger	2,430 (0.76)	2,594 (0.81)	0.01
	Gout	4,212 (1.32)	3,904 (1.22)	0.01
	Arm/leg cellulitis	5,961 (1.87)	5,471 (1.71)	0.01
Immune thrombocytopenia	Colonic diverticulitis	8,192 (2.57)	7,837 (2.46)	0.01
	Laceration of hand/finger	2,423 (0.76)	2,588 (0.81)	0.01
	Gout	4,232 (1.33)	3,892 (1.22)	0.01
	Arm/leg cellulitis	5,958 (1.87)	5,462 (1.71)	0.01
Transverse myelitis	Colonic diverticulitis	8,212 (2.57)	7,851 (2.46)	0.01
	Laceration of hand/finger	2,429 (0.76)	2,586 (0.81)	0.01
	Gout	4,221 (1.32)	3,906 (1.22)	0.01
	Arm/leg cellulitis	5,932 (1.86)	5,495 (1.72)	0.01
Unusual site TTS	Colonic diverticulitis	8,186 (2.56)	7,877 (2.47)	0.01
	Laceration of hand/finger	2,445 (0.77)	2,576 (0.81)	0.00
	Gout	4,170 (1.31)	3,955 (1.24)	0.01
	Arm/leg cellulitis	5,915 (1.85)	5,510 (1.73)	0.01
Common site TTS	Colonic diverticulitis	8,174 (2.56)	7,861 (2.46)	0.01
	Laceration of hand/finger	2,445 (0.77)	2,576 (0.81)	0.00
	Gout	4,162 (1.30)	3,948 (1.24)	0.01
	Arm/leg cellulitis	5,902 (1.85)	5,505 (1.72)	0.01

ASD = absolute standardized difference; COVID-19 = coronavirus disease 2019; sIPT = stabilized inverse probability of treatment; TTS = thrombosis with thrombocytopenia syndrome.

Table B-7-MarketScan. Negative Control Outcomes and Study Outcomes Occurring on the Same Day in Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis Included in the Cohort Study, MarketScan

Analysis set	Negative control outcome	Outcome cases, N	Negative control outcome case, N	Cases occurring on same day, %[a]
Guillain-Barré syndrome	Colonic diverticulitis	12	5,162	0.00
	Laceration of hand/finger	12	1,117	0.00
	Gout	12	2,922	0.00
	Arm/leg cellulitis	12	3,054	0.00
Bell's palsy	Colonic diverticulitis	215	5,157	0.00
	Laceration of hand/finger	215	1,117	0.00
	Gout	215	2,921	0.07
	Arm/leg cellulitis	215	3,055	0.00
Encephalitis/encephalomyelitis	Colonic diverticulitis	16	5,160	0.00
	Laceration of hand/finger	16	1,117	0.00
	Gout	16	2,923	0.00
	Arm/leg cellulitis	16	3,056	0.00
Narcolepsy	Colonic diverticulitis	64	5,157	0.00
	Laceration of hand/finger	64	1,115	0.00
	Gout	64	2,920	0.00
	Arm/leg cellulitis	64	3,056	0.00
Appendicitis	Colonic diverticulitis	296	5,143	0.25
	Laceration of hand/finger	296	1,112	0.00
	Gout	296	2,921	0.00
	Arm/leg cellulitis	296	3,055	0.00
Nonhemorrhagic stroke	Colonic diverticulitis	181	5,098	0.02
	Laceration of hand/finger	181	1,111	0.00
	Gout	181	2,883	0.14
	Arm/leg cellulitis	181	3,013	0.00
Hemorrhagic stroke	Colonic diverticulitis	62	5,151	0.04
	Laceration of hand/finger	62	1,117	0.00
	Gout	62	2,914	0.03
	Arm/leg cellulitis	62	3,051	0.00
Acute myocardial infarction	Colonic diverticulitis	428	5,112	0.00
	Laceration of hand/finger	428	1,114	0.00
	Gout	428	2,886	0.14
	Arm/leg cellulitis	428	3,018	0.00
Myocarditis/pericarditis	Colonic diverticulitis	373	5,156	0.00
	Laceration of hand/finger	373	1,117	0.00
	Gout	373	2,922	0.07
	Arm/leg cellulitis	373	3,056	0.00
Deep vein thrombosis	Colonic diverticulitis	1,108	5,098	0.12
	Laceration of hand/finger	1,108	1,113	0.00
	Gout	1,108	2,892	0.24
	Arm/leg cellulitis	1,108	2,994	0.47
Pulmonary embolism	Colonic diverticulitis	1,354	5,116	0.22

Analysis set	Negative control outcome	Outcome cases, N	Negative control outcome case, N	Cases occurring on same day, %[a]
	Laceration of hand/finger	1,354	1,113	0.00
	Gout	1,354	2,887	0.35
	Arm/leg cellulitis	1,354	3,027	0.13
Disseminated intravascular coagulation	Colonic diverticulitis	45	5,159	0.00
	Laceration of hand/finger	45	1,117	0.00
	Gout	45	2,924	0.00
	Arm/leg cellulitis	45	3,058	0.03
Immune thrombocytopenia	Colonic diverticulitis	69	5,156	0.00
	Laceration of hand/finger	69	1,113	0.00
	Gout	69	2,921	0.00
	Arm/leg cellulitis	69	3,051	0.03
Transverse myelitis	Colonic diverticulitis	5	5,162	0.00
	Laceration of hand/finger	5	1,116	0.00
	Gout	5	2,923	0.00
	Arm/leg cellulitis	5	3,058	0.00
Unusual site TTS	Colonic diverticulitis	6	5,161	0.00
	Laceration of hand/finger	6	1,117	0.00
	Gout	6	2,922	0.00
	Arm/leg cellulitis	6	3,059	0.00
Common site TTS	Colonic diverticulitis	158	5,151	0.00
	Laceration of hand/finger	158	1,116	0.00
	Gout	158	2,917	0.07
	Arm/leg cellulitis	158	3,049	0.00

COVID-19 = coronavirus disease 2019; TTS = thrombosis with thrombocytopenia syndrome.

[a] Percentages calculated as the proportion of identified negative control outcome cases occurring on the same day as an adverse event.

Table B-8-MarketScan. Association of a COVID-19 Diagnosis With Select Negative Control Outcomes, MarketScan

A. Guillain-Barré Syndrome

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	2,893	26,522,703	1.28 (1.21-1.35)	1.19 (1.12-1.26)
	Comparator	2,269	26,574,738	—	—
Laceration of hand or finger	COVID-19	583	26,695,104	1.09 (0.97-1.23)	1.04 (0.92-1.17)
	Comparator	534	26,694,949	—	—
Gout	COVID-19	1,737	26,604,333	1.47 (1.36-1.58)	1.34 (1.25-1.45)
	Comparator	1,185	26,643,637	—	—
Arm/leg cellulitis	COVID-19	1,694	26,604,592	1.25 (1.16-1.34)	1.15 (1.07-1.24)
	Comparator	1,360	26,629,680	—	—

B. Bell's Palsy

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	2,890	26,500,832	1.28 (1.21-1.35)	1.20 (1.13-1.27)
	Comparator	2,267	26,561,287	—	—
Laceration of hand or finger	COVID-19	583	26,672,960	1.09 (0.97-1.23)	1.05 (0.93-1.18)
	Comparator	534	26,681,208	—	—
Gout	COVID-19	1,735	26,582,239	1.46 (1.36-1.58)	1.33 (1.23-1.43)
	Comparator	1,186	26,629,668	—	—
Arm/leg cellulitis	COVID-19	1,694	26,582,439	1.25 (1.16-1.34)	1.14 (1.06-1.23)
	Comparator	1,361	26,615,708	—	—

C. Encephalitis/Encephalomyelitis

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	2,893	26,521,493	1.28 (1.21-1.35)	1.20 (1.14-1.27)
	Comparator	2,267	26,576,972	—	—
Laceration of hand or finger	COVID-19	583	26,693,894	1.09 (0.97-1.23)	1.03 (0.92-1.16)
	Comparator	534	26,697,057	—	—
Gout	COVID-19	1,736	26,603,162	1.46 (1.36-1.58)	1.37 (1.27-1.47)
	Comparator	1,187	26,645,510	—	—
Arm/leg cellulitis	COVID-19	1,695	26,603,360	1.25 (1.16-1.34)	1.17 (1.08-1.26)
	Comparator	1,361	26,631,637	—	—

D. Narcolepsy

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	2,891	26,497,462	1.28 (1.21-1.35)	1.19 (1.13-1.26)
	Comparator	2,266	26,554,395	—	—
Laceration of hand or finger	COVID-19	582	26,669,531	1.09 (0.97-1.23)	1.05 (0.93-1.18)
	Comparator	533	26,674,329	—	—
Gout	COVID-19	1,736	26,578,668	1.47 (1.36-1.58)	1.34 (1.24-1.45)
	Comparator	1,184	26,622,978	—	—
Arm/leg cellulitis	COVID-19	1,695	26,578,854	1.25 (1.16-1.34)	1.16 (1.07-1.24)
	Comparator	1,361	26,608,826	—	—

E. Appendicitis

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	2,882	26,470,808	1.28 (1.21-1.35)	1.20 (1.13-1.27)
	Comparator	2,261	26,530,106	—	—
Laceration of hand or finger	COVID-19	579	26,642,375	1.09 (0.97-1.22)	1.03 (0.91-1.16)
	Comparator	533	26,650,015	—	—
Gout	COVID-19	1,735	26,551,258	1.46 (1.36-1.58)	1.37 (1.27-1.47)
	Comparator	1,186	26,598,458	—	—
Arm/leg cellulitis	COVID-19	1,696	26,551,427	1.25 (1.16-1.34)	1.17 (1.09-1.26)
	Comparator	1,359	26,584,609	—	—

F. Nonhemorrhagic Stroke

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	2,859	26,392,589	1.28 (1.21-1.35)	1.20 (1.13-1.27)
	Comparator	2,239	26,468,653	—	—
Laceration of hand or finger	COVID-19	579	26,562,062	1.09 (0.97-1.23)	1.05 (0.93-1.18)
	Comparator	532	26,587,017	—	—
Gout	COVID-19	1,710	26,472,921	1.46 (1.36-1.57)	1.31 (1.21-1.41)
	Comparator	1,173	26,536,599	—	—
Arm/leg cellulitis	COVID-19	1,673	26,473,224	1.25 (1.16-1.35)	1.14 (1.06-1.23)
	Comparator	1,340	26,523,407	—	—

G. Hemorrhagic Stroke

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	2,890	26,500,629	1.28 (1.21-1.35)	1.20 (1.14-1.27)
	Comparator	2,261	26,557,717	—	—
Laceration of hand or finger	COVID-19	583	26,672,773	1.09 (0.97-1.23)	1.05 (0.93-1.18)
	Comparator	534	26,677,448	—	—
Gout	COVID-19	1,731	26,582,593	1.46 (1.36-1.58)	1.32 (1.23-1.43)
	Comparator	1,183	26,626,091	—	—
Arm/leg cellulitis	COVID-19	1,692	26,582,434	1.25 (1.16-1.34)	1.15 (1.06-1.23)
	Comparator	1,359	26,612,036	—	—

H. Acute Myocardial Infarction

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	2,869	26,434,651	1.28 (1.21-1.36)	1.20 (1.13-1.27)
	Comparator	2,243	26,496,134	—	—
Laceration of hand or finger	COVID-19	581	26,605,423	1.09 (0.97-1.23)	1.05 (0.93-1.18)
	Comparator	533	26,614,523	—	—
Gout	COVID-19	1,715	26,516,482	1.47 (1.36-1.58)	1.31 (1.21-1.41)
	Comparator	1,171	26,564,554	—	—
Arm/leg cellulitis	COVID-19	1,677	26,515,756	1.25 (1.16-1.35)	1.14 (1.06-1.23)
	Comparator	1,341	26,550,736	—	—

I. Myocarditis/Pericarditis

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	2,890	26,507,823	1.28 (1.21-1.35)	1.19 (1.13-1.26)
	Comparator	2,266	26,567,831	—	—
Laceration of hand or finger	COVID-19	583	26,679,817	1.09 (0.97-1.23)	1.04 (0.92-1.17)
	Comparator	534	26,687,812	—	—
Gout	COVID-19	1,735	26,589,187	1.46 (1.36-1.58)	1.32 (1.22-1.42)
	Comparator	1,187	26,636,265	—	—
Arm/leg cellulitis	COVID-19	1,695	26,589,374	1.25 (1.16-1.34)	1.12 (1.04-1.21)
	Comparator	1,361	26,622,530	—	—

J. Deep Vein Thrombosis

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	2,857	26,404,536	1.28 (1.21-1.35)	1.20 (1.13-1.26)
	Comparator	2,241	26,481,363	—	—
Laceration of hand or finger	COVID-19	580	26,574,649	1.09 (0.97-1.23)	1.04 (0.93-1.18)
	Comparator	533	26,599,393	—	—
Gout	COVID-19	1,719	26,485,214	1.47 (1.36-1.58)	1.32 (1.22-1.43)
	Comparator	1,173	26,548,758	—	—
Arm/leg cellulitis	COVID-19	1,663	26,486,769	1.25 (1.16-1.35)	1.14 (1.06-1.23)
	Comparator	1,331	26,536,023	—	—

K. Pulmonary Embolism

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	2,864	26,435,543	1.28 (1.21-1.35)	1.19 (1.13-1.26)
	Comparator	2,252	26,513,896	—	—
Laceration of hand or finger	COVID-19	581	26,605,787	1.09 (0.97-1.23)	1.05 (0.93-1.18)
	Comparator	532	26,633,031	—	—
Gout	COVID-19	1,715	26,516,943	1.47 (1.36-1.58)	1.32 (1.23-1.43)
	Comparator	1,172	26,582,223	—	—
Arm/leg cellulitis	COVID-19	1,678	26,516,063	1.25 (1.16-1.34)	1.14 (1.06-1.23)
	Comparator	1,349	26,568,170	—	—

L. Disseminated Intravascular Coagulation

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	2,891	26,523,090	1.28 (1.21-1.35)	1.20 (1.13-1.27)
	Comparator	2,268	26,579,118	—	—
Laceration of hand or finger	COVID-19	583	26,695,353	1.09 (0.97-1.23)	1.04 (0.92-1.17)
	Comparator	534	26,699,181	—	—
Gout	COVID-19	1,737	26,604,582	1.46 (1.36-1.58)	1.35 (1.25-1.45)
	Comparator	1,187	26,647,634	—	—
Arm/leg cellulitis	COVID-19	1,695	26,604,853	1.24 (1.16-1.34)	1.16 (1.08-1.25)
	Comparator	1,363	26,633,501	—	—

M. Immune Thrombocytopenia

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	2,890	26,502,380	1.28 (1.21-1.35)	1.20 (1.14-1.27)
	Comparator	2,266	26,560,956	—	—
Laceration of hand or finger	COVID-19	581	26,674,494	1.09 (0.97-1.23)	1.03 (0.92-1.17)
	Comparator	532	26,681,080	—	—
Gout	COVID-19	1,735	26,583,723	1.46 (1.36-1.58)	1.36 (1.26-1.47)
	Comparator	1,186	26,629,535	—	—
Arm/leg cellulitis	COVID-19	1,691	26,583,970	1.24 (1.16-1.34)	1.16 (1.08-1.25)
	Comparator	1,360	26,615,500	—	—

N. Transverse Myelitis

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	2,893	26,521,594	1.28 (1.21-1.35)	1.20 (1.13-1.27)
	Comparator	2,269	26,576,457	—	—
Laceration of hand or finger	COVID-19	583	26,693,995	1.09 (0.97-1.23)	1.04 (0.92-1.17)
	Comparator	533	26,696,775	—	—
Gout	COVID-19	1,737	26,603,224	1.47 (1.36-1.58)	1.36 (1.26-1.46)
	Comparator	1,186	26,645,147	—	—
Arm/leg cellulitis	COVID-19	1,695	26,603,505	1.24 (1.16-1.34)	1.14 (1.06-1.23)
	Comparator	1,363	26,630,988	—	—

O. Unusual Site Thrombosis With Thrombocytopenia Syndrome

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	2,892	26,524,240	1.28 (1.21-1.35)	1.19 (1.13-1.26)
	Comparator	2,269	26,578,476	—	—
Laceration of hand or finger	COVID-19	583	26,696,408	1.09 (0.97-1.23)	1.05 (0.93-1.18)
	Comparator	534	26,698,687	—	—
Gout	COVID-19	1,735	26,605,998	1.46 (1.36-1.58)	1.32 (1.22-1.42)
	Comparator	1,187	26,647,140	—	—
Arm/leg cellulitis	COVID-19	1,696	26,605,809	1.25 (1.16-1.34)	1.14 (1.06-1.22)
	Comparator	1,363	26,633,007	—	—

P. Common Site Thrombosis With Thrombocytopenia Syndrome

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	2,888	26,511,782	1.28 (1.21-1.35)	1.20 (1.13-1.27)
	Comparator	2,263	26,569,855	—	—
Laceration of hand or finger	COVID-19	582	26,683,792	1.09 (0.97-1.23)	1.05 (0.93-1.18)
	Comparator	534	26,689,766	—	—
Gout	COVID-19	1,734	26,593,502	1.47 (1.36-1.58)	1.32 (1.23-1.43)
	Comparator	1,183	26,638,535	—	—
Arm/leg cellulitis	COVID-19	1,691	26,593,408	1.25 (1.16-1.34)	1.14 (1.06-1.23)
	Comparator	1,358	26,624,355	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighted.

— denotes the reference group.

Table B-9-MarketScan. Characteristics of Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis, by Hospitalization at Time 0, MarketScan

A. Acute Myocardial Infarction Analysis Set

Characteristic	Hospitalized on Time 0, COVID-19 diagnosis (exposure) group	Hospitalized on Time 0, Comparator group	Hospitalized on Time 0, ASD	Nonhospitalized on Time 0, COVID-19 diagnosis (exposure) group	Nonhospitalized on Time 0, Comparator group	Nonhospitalized on Time 0, ASD
Total selected individuals[a] (unique individuals)	3,996 (3,996)	3,901 (3,564)		314,275 (314,275)	314,418 (307,884)	
Demographic characteristics						
Age, years						
Mean (SD)	48.8 (12.5)	48.5 (12.5)	0.02	41.7 (13.6)	41.7 (13.6)	0.00
Median (Q1, Q3)	53 (40, 59)	52 (39, 59)		43 (30, 53)	43 (30, 53)	
Age groups, n (%)						
18-34 years	710 (17.77)	711 (18.23)		105,100 (33.44)	105,102 (33.43)	
35-49 years	943 (23.60)	937 (24.02)		99,916 (31.79)	99,957 (31.79)	
50-64 years	2,343 (58.63)	2,253 (57.75)		109,259 (34.77)	109,359 (34.78)	
Sex, n (%)			0.01			0.00
Female	2,015 (50.43)	1,991 (51.04)		176,589 (56.19)	176,671 (56.19)	
Male	1,981 (49.57)	1,910 (48.96)		137,686 (43.81)	137,747 (43.81)	
US geographic region, n (%)			0.00			0.00
Northeast	679 (16.99)	660 (16.92)		61,306 (19.51)	61,362 (19.52)	
North central	756 (18.92)	740 (18.97)		70,176 (22.33)	70,175 (22.32)	
South	2,074 (51.90)	2,032 (52.09)		147,323 (46.88)	147,400 (46.88)	
West	487 (12.19)	469 (12.02)		35,460 (11.28)	35,471 (11.28)	
Unknown				10 (0.00)	10 (0.00)	
Hospitalized on Time 0, n (%)	3,996 (100.0)	3,901 (100.0)	0.00	0 (0.00)	0 (0.00)	0.00
Comorbidities, n (%)						
Autoimmune disorders	163 (4.08)	128 (3.28)	0.04	12,436 (3.96)	12,776 (4.06)	0.01
Cancer	237 (5.93)	383 (9.82)	0.14	13,094 (4.17)	13,799 (4.39)	0.01

Characteristic	Hospitalized on Time 0, COVID-19 diagnosis (exposure) group	Hospitalized on Time 0, Comparator group	Hospitalized on Time 0, ASD	Nonhospitalized on Time 0, COVID-19 diagnosis (exposure) group	Nonhospitalized on Time 0, Comparator group	Nonhospitalized on Time 0, ASD
Chronic kidney disease or renal disease (other than end-stage renal disease)	324 (8.11)	392 (10.05)	0.07	5,453 (1.74)	4,473 (1.42)	0.03
Chronic liver disease	247 (6.18)	435 (11.15)	0.18	10,389 (3.31)	8,435 (2.68)	0.04
Chronic lung diseases	653 (16.34)	644 (16.51)	0.00	31,696 (10.09)	24,580 (7.82)	0.08
Diabetes, Type 1 or 2	1,134 (28.38)	784 (20.10)	0.19	31,579 (10.05)	24,358 (7.75)	0.08
Heart conditions	837 (20.95)	1,195 (30.63)	0.22	35,604 (11.33)	29,139 (9.27)	0.07
Hypertension	1,861 (46.57)	1,820 (46.65)	0.00	76,013 (24.19)	66,464 (21.14)	0.07
Immunocompromised state	581 (14.54)	564 (14.46)	0.00	36,775 (11.70)	36,839 (11.72)	0.00
Lipid abnormality	1,477 (36.96)	1,369 (35.09)	0.04	71,213 (22.66)	64,504 (20.52)	0.05
Mental health conditions	828 (20.72)	1,557 (39.91)	0.43	72,759 (23.15)	68,009 (21.63)	0.04
Obese or severely obese	1,340 (33.53)	1,067 (27.35)	0.13	61,801 (19.66)	48,271 (15.35)	0.11
Peripheral vascular disease	165 (4.13)	234 (6.00)	0.09	4,058 (1.29)	3,310 (1.05)	0.02
Pneumonia or lower respiratory tract infection	756 (18.92)	629 (16.12)	0.07	40,321 (12.83)	27,518 (8.75)	0.13
Pregnancy	41 (1.03)	16 (0.41)	0.07	2,575 (0.82)	2,272 (0.72)	0.01
Sickle cell disease or thalassemia	17 (0.43)	17 (0.44)	0.00	727 (0.23)	614 (0.20)	0.01
Smoking/nicotine dependency	192 (4.80)	647 (16.59)	0.39	11,172 (3.55)	13,853 (4.41)	0.04
Stroke or cerebrovascular disease	154 (3.85)	290 (7.43)	0.16	4,418 (1.41)	3,539 (1.13)	0.03
Thrombophilia	16 (0.40)	46 (1.18)	0.09	1,057 (0.34)	839 (0.27)	0.01
Healthcare utilization, n (%)						
Inpatient stays in previous 365 days			0.79			0.00
0	3,520 (88.09)	2,127 (54.52)		301,056 (95.79)	301,061 (95.75)	
1-2	392 (9.81)	1,293 (33.15)		12,295 (3.91)	12,603 (4.01)	
≥ 3	84 (2.10)	481 (12.33)		924 (0.29)	754 (0.24)	
ED visits in previous 365 days			0.22			0.13
0	2,786 (69.72)	2,392 (61.32)		252,478 (80.34)	268,693 (85.46)	
1-2	979 (24.50)	1,111 (28.48)		53,443 (17.01)	40,797 (12.98)	

Characteristic	Hospitalized on Time 0, COVID-19 diagnosis (exposure) group	Hospitalized on Time 0, Comparator group	Hospitalized on Time 0, ASD	Nonhospitalized on Time 0, COVID-19 diagnosis (exposure) group	Nonhospitalized on Time 0, Comparator group	Nonhospitalized on Time 0, ASD
≥ 3	231 (5.78)	398 (10.20)		8,354 (2.66)	4,928 (1.57)	
Outpatient provider visits[b] in previous 365 days			0.40			0.19
0	32 (0.80)	58 (1.49)		2,041 (0.65)	2,755 (0.88)	
1-2	492 (12.31)	248 (6.36)		56,369 (17.94)	78,223 (24.88)	
3-5	770 (19.27)	416 (10.66)		75,402 (23.99)	80,126 (25.48)	
6-10	914 (22.87)	722 (18.51)		75,703 (24.09)	67,484 (21.46)	
≥ 11	1,788 (44.74)	2,457 (62.98)		104,760 (33.33)	85,830 (27.30)	
SNF/LTC stay[c]	29 (0.73)	37 (0.95)	0.02	269 (0.09)	102 (0.03)	0.02
Influenza vaccination in previous year	1,174 (29.38)	1,268 (32.50)	0.07	88,488 (28.16)	93,555 (29.75)	0.04

ASD = absolute standardized difference; COVID-19 = coronavirus disease 2019; ED = emergency department; LTC = long-term care; Q1 = first quartile, Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] A unique individual may be included multiple times because of matching with replacement, and an individual may be included in both the exposure and comparator groups. This table counts each instance of an individual's entry separately as distinct observations; the number of unique individuals is reported separately.

[b] Unique days on which an outpatient visit occurred.

[c] SNF and LTC both identified in Medicare; SNF identified in MarketScan.

B. Pulmonary Embolism Analysis Set

Characteristic	Hospitalized on Time 0, COVID-19 diagnosis (exposure) group	Hospitalized on Time 0, Comparator group	Hospitalized on Time 0, ASD	Nonhospitalized on Time 0, COVID-19 diagnosis (exposure) group	Nonhospitalized on Time 0, Comparator group	Nonhospitalized on Time 0, ASD
Total selected individuals[a] (unique individuals)	3,999 (3,999)	3,974 (3,624)		314,208 (314,208)	314,550 (308,006)	
Demographic characteristics						
Age, years						
Mean (SD)	48.9 (12.5)	48.7 (12.5)	0.01	41.7 (13.6)	41.7 (13.6)	0.00
Median (Q1, Q3)	53 (40, 59)	53 (40, 59)		43 (30, 53)	43 (30, 53)	
Age groups, n (%)						
18-34 years	705 (17.63)	708 (17.82)		104,998 (33.42)	105,044 (33.40)	
35-49 years	937 (23.43)	934 (23.50)		99,784 (31.76)	99,910 (31.76)	
50-64 years	2,357 (58.94)	2,332 (58.68)		109,426 (34.83)	109,596 (34.84)	
Sex, n (%)			0.00			0.00
Female	2,007 (50.19)	1,999 (50.30)		176,387 (56.14)	176,551 (56.13)	
Male	1,992 (49.81)	1,975 (49.70)		137,821 (43.86)	137,999 (43.87)	
US geographic region, n (%)			0.00			0.00
Northeast	686 (17.15)	676 (17.01)		61,303 (19.51)	61,382 (19.51)	
North central	762 (19.05)	755 (19.00)		70,154 (22.33)	70,222 (22.32)	
South	2,073 (51.84)	2,057 (51.76)		147,298 (46.88)	147,461 (46.88)	
West	478 (11.95)	486 (12.23)		35,443 (11.28)	35,475 (11.28)	
Unknown				10 (0.00)	10 (0.00)	
Hospitalized on Time 0, n (%)	3,999 (100.0)	3,974 (100.0)	0.00	0 (0.00)	0 (0.00)	0.00
Comorbidities, n (%)						
Autoimmune disorders	163 (4.08)	131 (3.30)	0.04	12,391 (3.94)	12,759 (4.06)	0.01
Cancer	235 (5.88)	382 (9.61)	0.14	13,007 (4.14)	13,746 (4.37)	0.01
Chronic kidney disease or renal disease (other than end-stage renal disease)	337 (8.43)	436 (10.97)	0.09	5,571 (1.77)	4,557 (1.45)	0.03
Chronic liver disease	247 (6.18)	437 (11.00)	0.17	10,360 (3.30)	8,416 (2.68)	0.04

Characteristic	Hospitalized on Time 0, COVID-19 diagnosis (exposure) group	Hospitalized on Time 0, Comparator group	Hospitalized on Time 0, ASD	Nonhospitalized on Time 0, COVID-19 diagnosis (exposure) group	Nonhospitalized on Time 0, Comparator group	Nonhospitalized on Time 0, ASD
Dementia or other neurologic condition	283 (7.08)	455 (11.45)	0.15	19,294 (6.14)	15,877 (5.05)	0.05
Diabetes, Type 1 or 2	1,145 (28.63)	827 (20.81)	0.18	31,721 (10.10)	24,504 (7.79)	0.08
Heart conditions	850 (21.26)	1,286 (32.36)	0.25	35,996 (11.46)	29,598 (9.41)	0.07
Hemiplegia or paraplegia	48 (1.20)	107 (2.69)	0.11	776 (0.25)	677 (0.22)	0.01
Immunocompromised state	587 (14.68)	578 (14.54)	0.00	36,715 (11.68)	36,830 (11.71)	0.00
Inpatient surgery	94 (2.35)	453 (11.40)	0.36	1,819 (0.58)	2,417 (0.77)	0.02
Lipid abnormality	1,496 (37.41)	1,436 (36.13)	0.03	71,517 (22.76)	64,880 (20.63)	0.05
Obese or severely obese	1,340 (33.51)	1,092 (27.48)	0.13	61,726 (19.64)	48,298 (15.35)	0.11
Peripheral vascular disease	171 (4.28)	253 (6.37)	0.09	4,103 (1.31)	3,364 (1.07)	0.02
Pneumonia or lower respiratory tract infection	749 (18.73)	646 (16.26)	0.07	40,272 (12.82)	27,505 (8.74)	0.13
Pregnancy	40 (1.00)	16 (0.40)	0.07	2,562 (0.82)	2,271 (0.72)	0.01
Sickle cell disease or thalassemia	17 (0.43)	15 (0.38)	0.01	717 (0.23)	606 (0.19)	0.01
Smoking/nicotine dependency	193 (4.83)	667 (16.78)	0.39	11,246 (3.58)	13,973 (4.44)	0.04
Stroke or cerebrovascular disease	157 (3.93)	329 (8.28)	0.18	4,480 (1.43)	3,623 (1.15)	0.02
Thromboembolism	84 (2.10)	179 (4.50)	0.13	2,354 (0.75)	1,930 (0.61)	0.02
Thrombophilia	13 (0.33)	44 (1.11)	0.09	921 (0.29)	753 (0.24)	0.01
Trauma	12 (0.30)	76 (1.91)	0.15	186 (0.06)	171 (0.05)	0.00
Healthcare utilization, n (%)						
Inpatient stays in previous 365 days			0.81			0.00
0	3,514 (87.87)	2,132 (53.65)		300,841 (95.75)	300,967 (95.68)	
1-2	395 (9.88)	1,352 (34.02)		12,420 (3.95)	12,835 (4.08)	
≥ 3	90 (2.25)	490 (12.33)		947 (0.30)	748 (0.24)	
ED visits in previous 365 days			0.25			0.13
0	2,793 (69.84)	2,439 (61.37)		252,472 (80.35)	268,809 (85.46)	
1-2	980 (24.51)	1,127 (28.36)		53,424 (17.00)	40,823 (12.98)	

Characteristic	Hospitalized on Time 0, COVID-19 diagnosis (exposure) group	Hospitalized on Time 0, Comparator group	Hospitalized on Time 0, ASD	Nonhospitalized on Time 0, COVID-19 diagnosis (exposure) group	Nonhospitalized on Time 0, Comparator group	Nonhospitalized on Time 0, ASD
≥ 3	226 (5.65)	408 (10.27)		8,312 (2.65)	4,918 (1.56)	
Outpatient provider visits [b] in previous 365 days			0.40			0.19
0	31 (0.78)	58 (1.46)		2,040 (0.65)	2,755 (0.88)	
1-2	493 (12.33)	255 (6.42)		56,377 (17.94)	78,229 (24.87)	
3-5	770 (19.25)	420 (10.57)		75,417 (24.00)	80,144 (25.48)	
6-10	917 (22.93)	738 (18.57)		75,717 (24.10)	67,533 (21.47)	
≥ 11	1,788 (44.71)	2,503 (62.98)		104,657 (33.31)	85,889 (27.31)	
SNF/LTC stay [c]	32 (0.80)	41 (1.03)	0.02	286 (0.09)	107 (0.03)	0.02
Influenza vaccination in previous year	1,174 (29.36)	1,289 (32.44)	0.07	88,470 (28.16)	93,602 (29.76)	0.04

ASD = absolute standardized difference; COVID-19 = coronavirus disease 2019; ED = emergency department; LTC = long-term care; Q1 = first quartile, Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] A unique individual may be included multiple times because of matching with replacement, and an individual may be included in both the exposure and comparator groups. This table counts each instance of an individual's entry separately as distinct observations; the number of unique individuals is reported separately.

[b] Unique days on which an outpatient visit occurred.

[c] SNF and LTC both identified in Medicare; SNF identified in MarketScan.

C. Nonhemorrhagic Stroke Analysis Set

Characteristic	Hospitalized on Time 0, COVID-19 diagnosis (exposure) group	Hospitalized on Time 0, Comparator group	Hospitalized on Time 0, ASD	Nonhospitalized on Time 0, COVID-19 diagnosis (exposure) group	Nonhospitalized on Time 0, Comparator group	Nonhospitalized on Time 0, ASD
Total selected individuals[a] (unique individuals)	3,975 (3,975)	3,876 (3,539)		313,909 (313,909)	314,143 (307,614)	
Demographic characteristics						
Age, years						
Mean (SD)	48.7 (12.5)	48.5 (12.6)	0.02	41.6 (13.6)	41.7 (13.6)	0.00
Median (Q1, Q3)	53 (40, 59)	52 (39, 59)		43 (30, 53)	43 (30, 53)	
Age groups, n (%)						
18-34 years	711 (17.89)	711 (18.34)		105,033 (33.46)	105,061 (33.44)	
35-49 years	945 (23.77)	921 (23.76)		99,793 (31.79)	99,862 (31.79)	
50-64 years	2,319 (58.34)	2,244 (57.89)		109,083 (34.75)	109,220 (34.77)	
Sex, n (%)			0.00			0.00
Female	2,007 (50.49)	1,964 (50.67)		176,208 (56.13)	176,395 (56.15)	
Male	1,968 (49.51)	1,912 (49.33)		137,701 (43.87)	137,748 (43.85)	
US geographic region, n (%)			0.03			0.14
Northeast	676 (17.01)	657 (16.95)		61,175 (19.49)	61,291 (19.51)	
North central	759 (19.09)	747 (19.27)		70,155 (22.35)	70,166 (22.34)	
South	2,058 (51.77)	1,994 (51.44)		147,124 (46.87)	147,222 (46.86)	
West	482 (12.13)	478 (12.33)		35,445 (11.29)	35,454 (11.29)	
Unknown				10 (0.00)	10 (0.00)	
Hospitalized on Time 0, n (%)	3,975 (100.0)	3,876 (100.0)	0.00	0 (0.00)	0 (0.00)	0.00
Comorbidities, n (%)						
Autoimmune disorders	163 (4.10)	127 (3.28)	0.04	12,349 (3.93)	12,717 (4.05)	0.01
Cancer	233 (5.86)	381 (9.83)	0.15	13,023 (4.15)	13,745 (4.38)	0.01

Characteristic	Hospitalized on Time 0, COVID-19 diagnosis (exposure) group	Hospitalized on Time 0, Comparator group	Hospitalized on Time 0, ASD	Nonhospitalized on Time 0, COVID-19 diagnosis (exposure) group	Nonhospitalized on Time 0, Comparator group	Nonhospitalized on Time 0, ASD
Chronic kidney disease or renal disease (other than end-stage renal disease)	323 (8.13)	404 (10.42)	0.08	5,470 (1.74)	4,481 (1.43)	0.03
Chronic liver disease	245 (6.16)	422 (10.89)	0.17	10,366 (3.30)	8,406 (2.68)	0.04
Chronic lung diseases	647 (16.28)	625 (16.12)	0.00	31,648 (10.08)	24,508 (7.80)	0.08
Dementia or other neurologic condition	266 (6.69)	403 (10.40)	0.13	18,936 (6.03)	15,638 (4.98)	0.05
Diabetes, Type 1 or 2	1,127 (28.35)	777 (20.05)	0.19	31,537 (10.05)	24,295 (7.73)	0.08
Heart conditions	840 (21.13)	1,214 (31.32)	0.23	35,795 (11.40)	29,346 (9.34)	0.07
Hemiplegia or paraplegia	27 (0.68)	43 (1.11)	0.05	497 (0.16)	482 (0.15)	0.00
Hypertension	1,844 (46.39)	1,803 (46.52)	0.00	75,851 (24.16)	66,327 (21.11)	0.07
Immunocompromised state	582 (14.64)	566 (14.60)	0.00	36,614 (11.66)	36,738 (11.69)	0.00
Lipid abnormality	1,457 (36.65)	1,360 (35.09)	0.03	71,126 (22.66)	64,437 (20.51)	0.05
Obese or severely obese	1,332 (33.51)	1,070 (27.61)	0.13	61,693 (19.65)	48,190 (15.34)	0.11
Peripheral vascular disease	161 (4.05)	225 (5.80)	0.08	4,042 (1.29)	3,317 (1.06)	0.02
Pneumonia or lower respiratory tract infection	751 (18.89)	629 (16.23)	0.07	40,257 (12.82)	27,500 (8.75)	0.13
Pregnancy	41 (1.03)	16 (0.41)	0.07	2,571 (0.82)	2,270 (0.72)	0.01
Sickle cell disease or thalassemia	15 (0.38)	17 (0.44)	0.01	723 (0.23)	613 (0.20)	0.01
Smoking/nicotine dependency	192 (4.83)	644 (16.62)	0.39	11,172 (3.56)	13,891 (4.42)	0.04
Stroke or cerebrovascular disease	96 (2.42)	165 (4.26)	0.10	3,218 (1.03)	2,575 (0.82)	0.02
Thrombophilia	16 (0.40)	38 (0.98)	0.07	999 (0.32)	801 (0.25)	0.01
Trauma	13 (0.33)	75 (1.93)	0.15	177 (0.06)	176 (0.06)	0.00
Healthcare utilization, n (%)						
Inpatient stays in previous 365 days			0.79			0.00
0	3,505 (88.18)	2,117 (54.62)		300,691 (95.79)	300,702 (95.72)	
1-2	384 (9.66)	1,287 (33.20)		12,329 (3.93)	12,719 (4.05)	
≥ 3	86 (2.16)	472 (12.18)		889 (0.28)	722 (0.23)	
ED visits in previous 365 days			0.21			0.19

Characteristic	Hospitalized on Time 0, COVID-19 diagnosis (exposure) group	Hospitalized on Time 0, Comparator group	Hospitalized on Time 0, ASD	Nonhospitalized on Time 0, COVID-19 diagnosis (exposure) group	Nonhospitalized on Time 0, Comparator group	Nonhospitalized on Time 0, ASD
0	2,778 (69.89)	2,366 (61.04)		252,358 (80.39)	268,624 (85.51)	
1-2	973 (24.48)	1,107 (28.56)		53,308 (16.98)	40,630 (12.93)	
≥ 3	224 (5.64)	403 (10.40)		8,243 (2.63)	4,889 (1.56)	
Outpatient provider visits [b] in previous 365 days			0.37			0.20
0	32 (0.81)	56 (1.44)		2,038 (0.65)	2,756 (0.88)	
1-2	493 (12.40)	252 (6.50)		56,362 (17.95)	78,216 (24.90)	
3-5	771 (19.40)	409 (10.55)		75,393 (24.02)	80,112 (25.50)	
6-10	912 (22.94)	729 (18.81)		75,691 (24.11)	67,467 (21.48)	
≥ 11	1,767 (44.45)	2,430 (62.69)		104,425 (33.27)	85,592 (27.25)	
SNF/LTC stay [c]	25 (0.63)	33 (0.85)	0.03	229 (0.07)	96 (0.03)	0.02
Influenza vaccination in previous year	1,166 (29.33)	1,258 (32.46)	0.07	88,367 (28.15)	93,442 (29.75)	0.04

ASD = absolute standardized difference; COVID-19 = coronavirus disease 2019; ED = emergency department; LTC = long-term care; Q1 = first quartile, Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

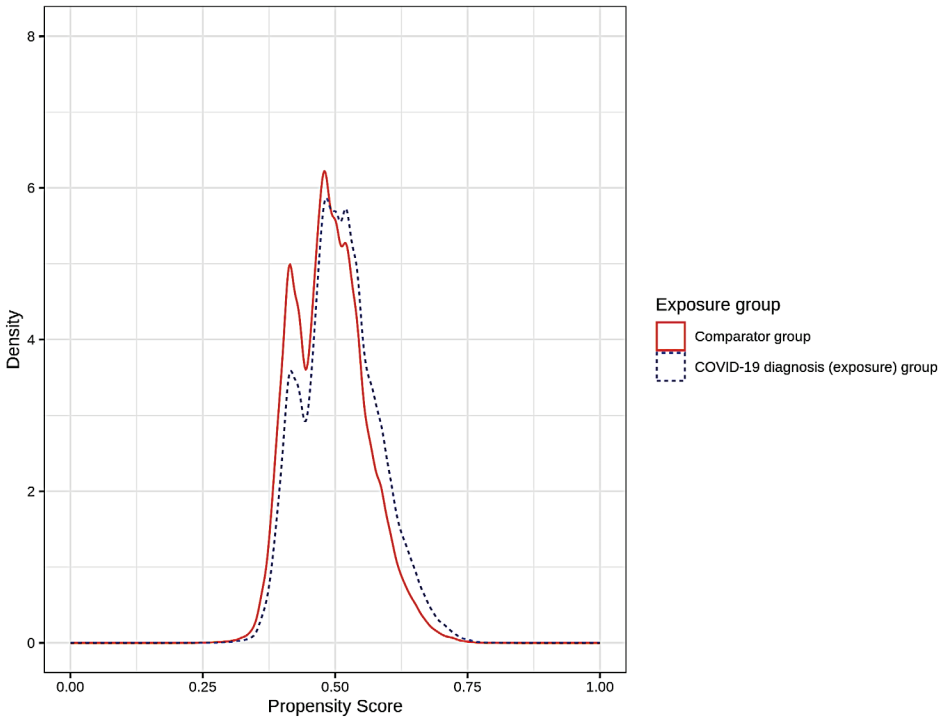
[a] A unique individual may be included multiple times because of matching with replacement, and an individual may be included in both the exposure and comparator groups. This table counts each instance of an individual's entry separately as distinct observations; the number of unique individuals is reported separately.

[b] Unique days on which an outpatient visit occurred.

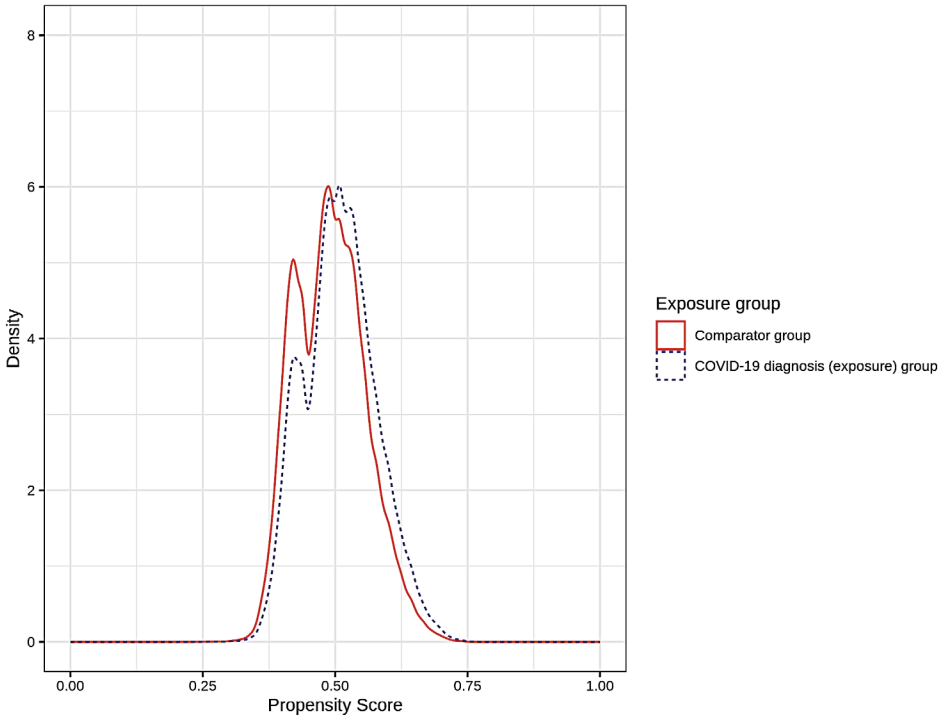
[c] SNF and LTC both identified in Medicare; SNF identified in MarketScan.

Figure B-1-MarketScan. Propensity Score Distributions Among Individuals With a COVID-19 Diagnosis and Comparators Without a COVID-19 Diagnosis, MarketScan

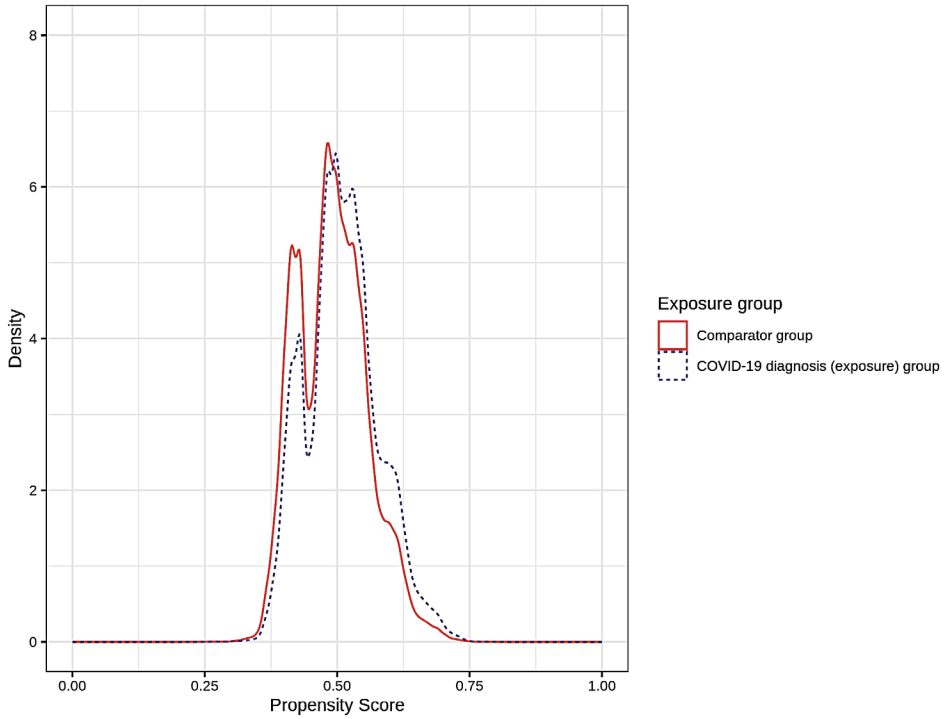
A. Guillain-Barré Syndrome



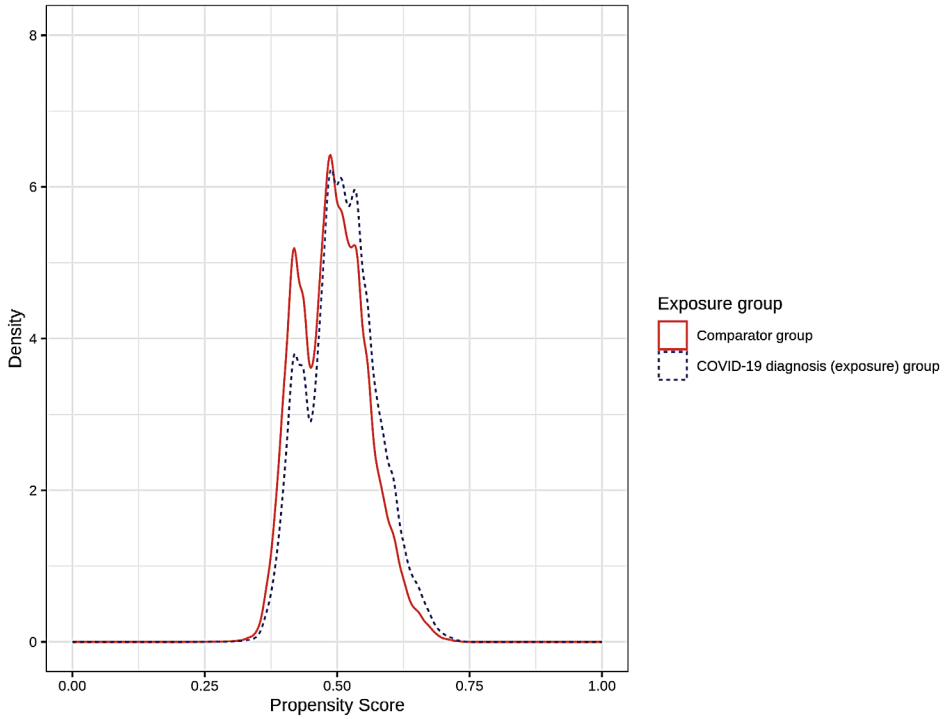
B. Bell's Palsy



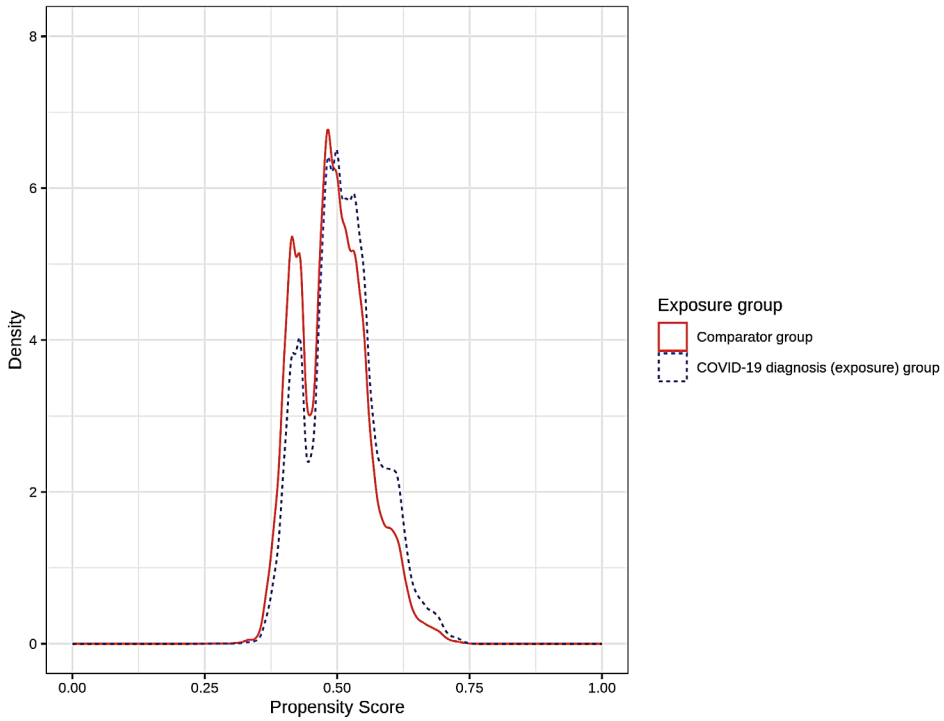
C. Encephalitis/Encephalomyelitis



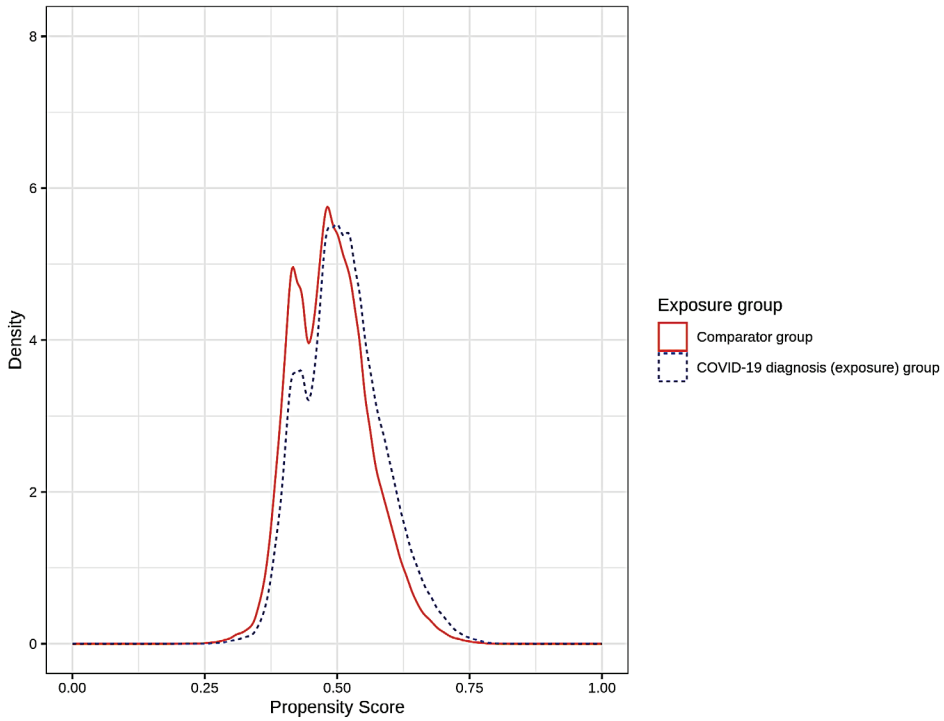
D. Narcolepsy



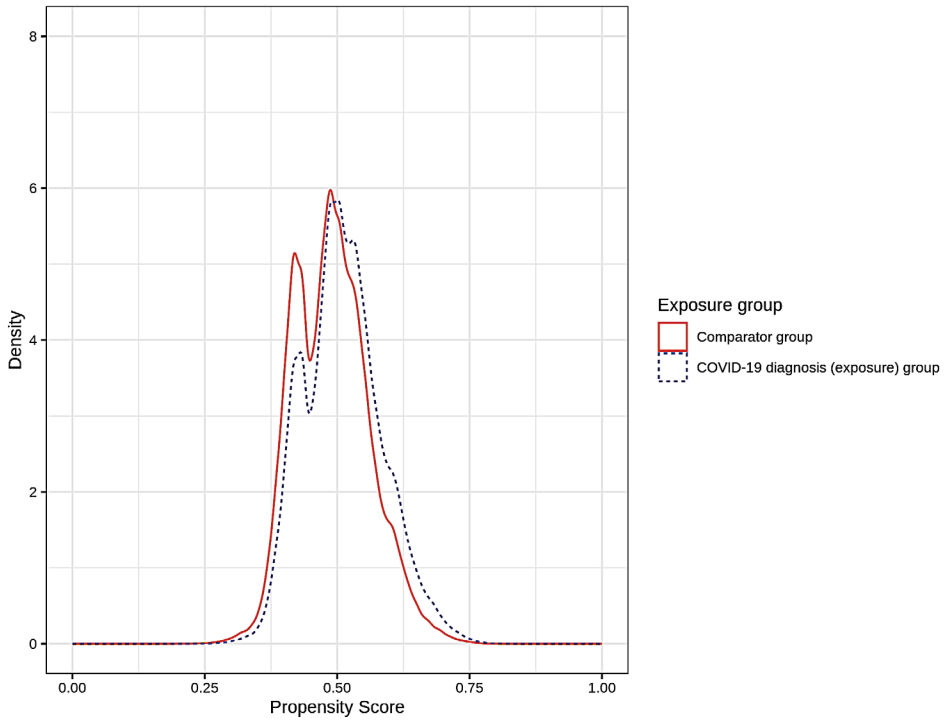
E. Appendicitis



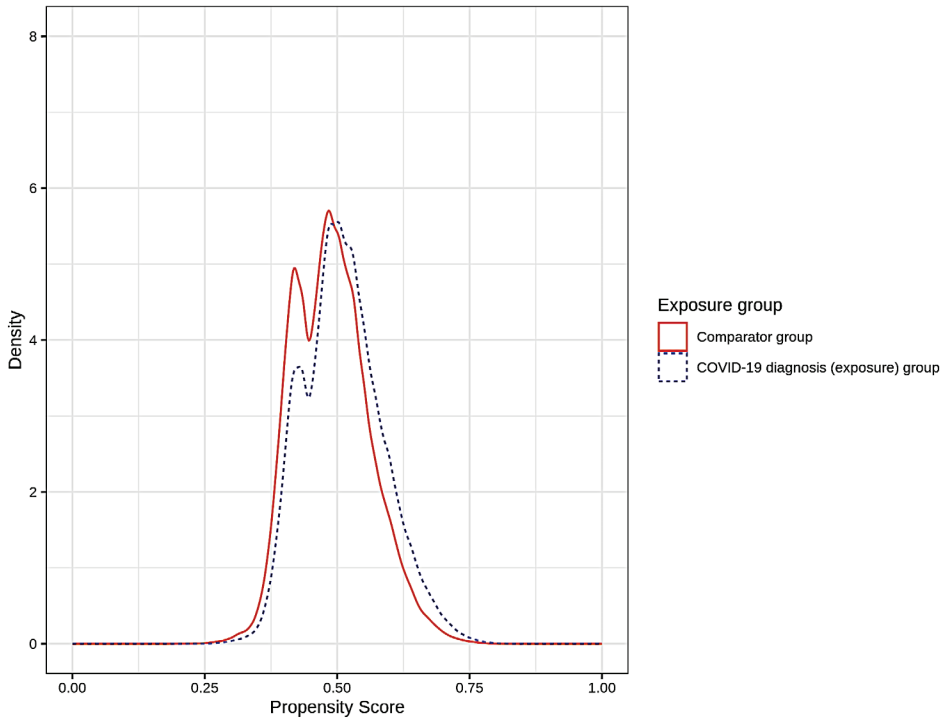
F. Nonhemorrhagic Stroke



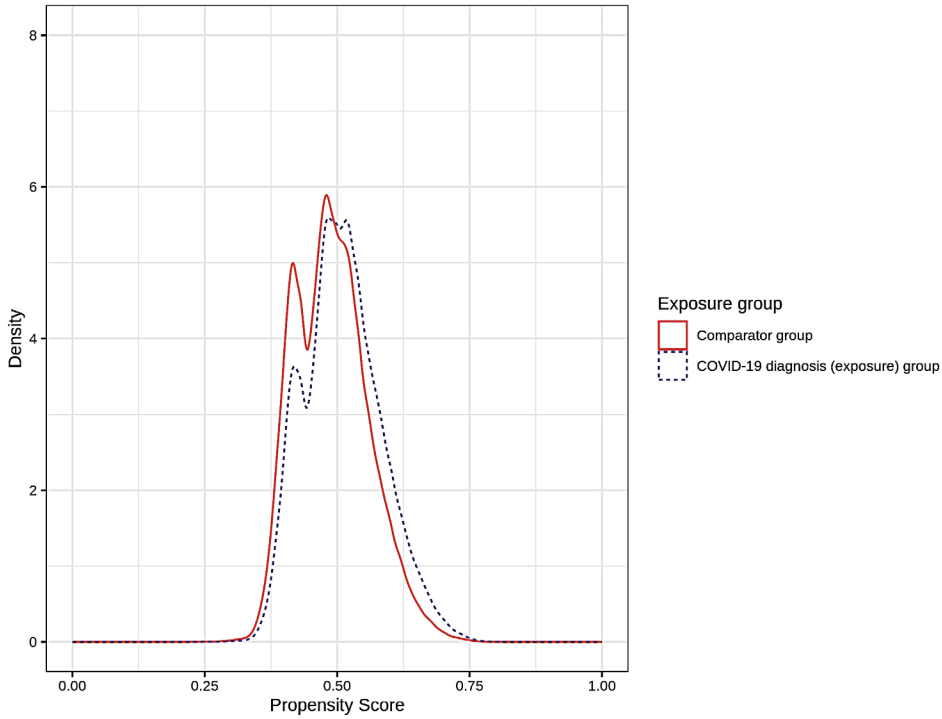
G. Hemorrhagic Stroke



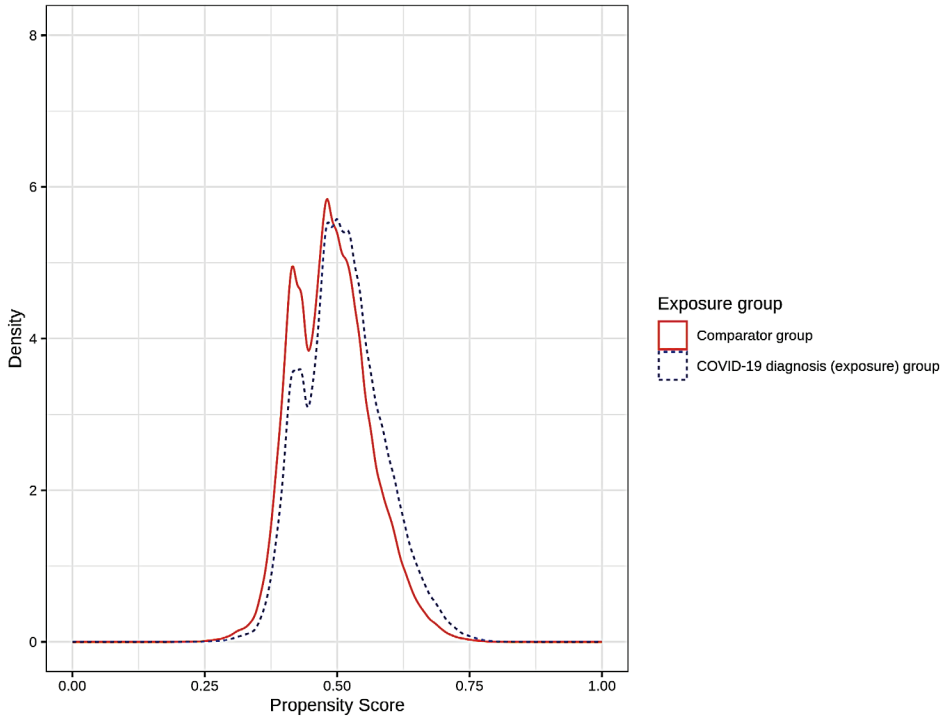
H. Acute Myocardial Infarction



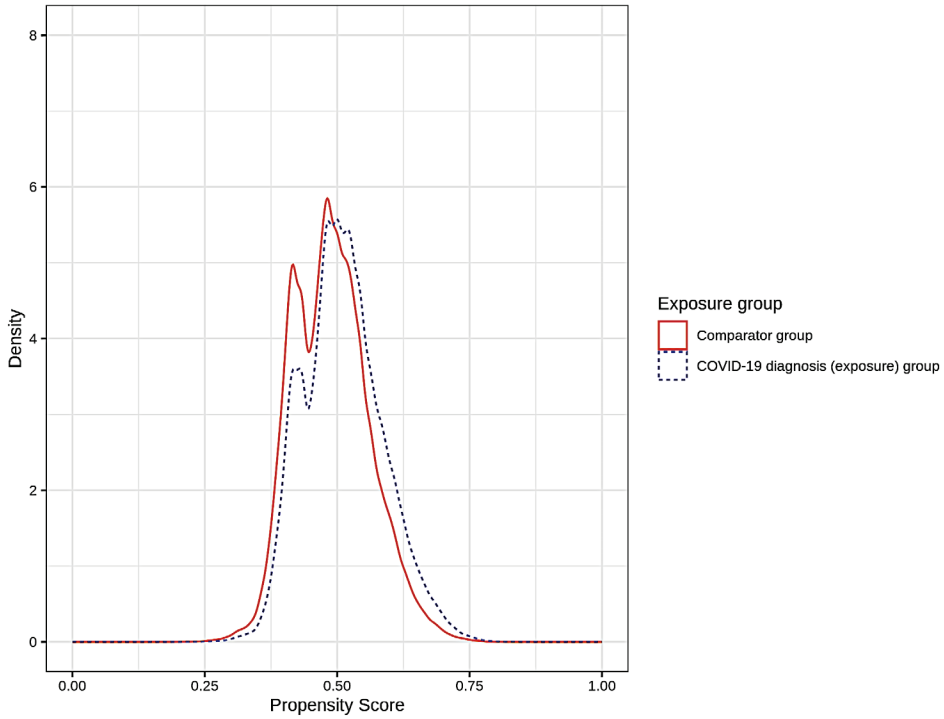
I. Myocarditis/Pericarditis



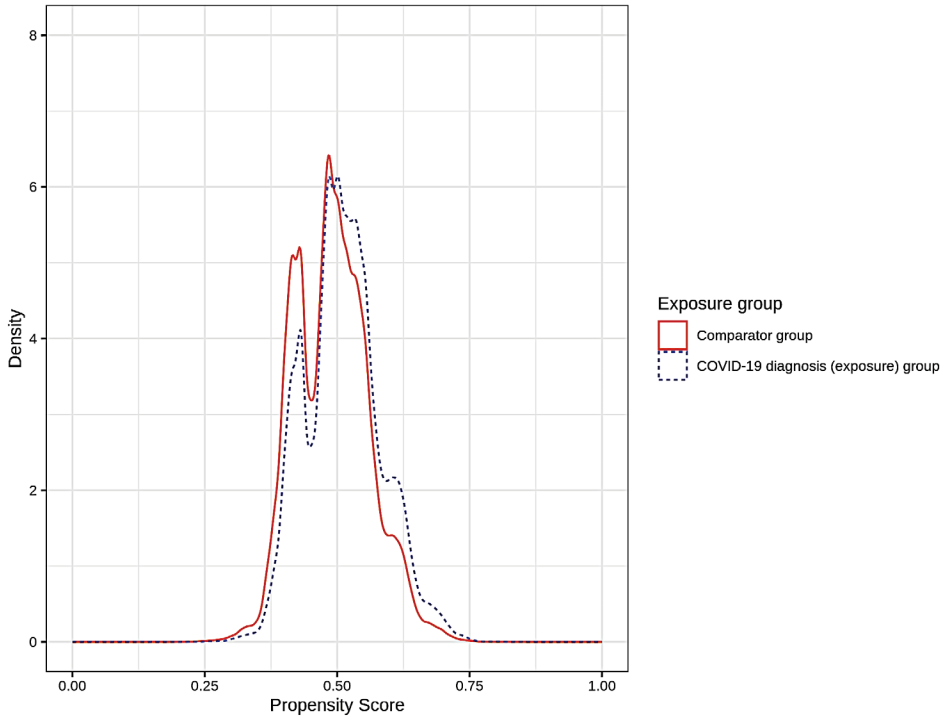
J. Deep Vein Thrombosis



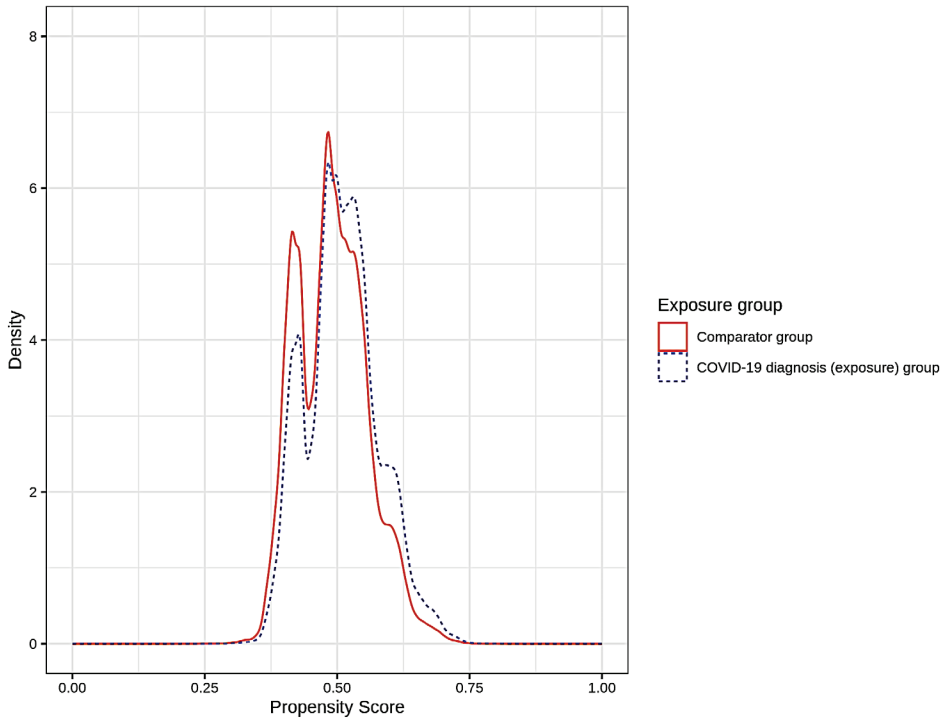
K. Pulmonary Embolism



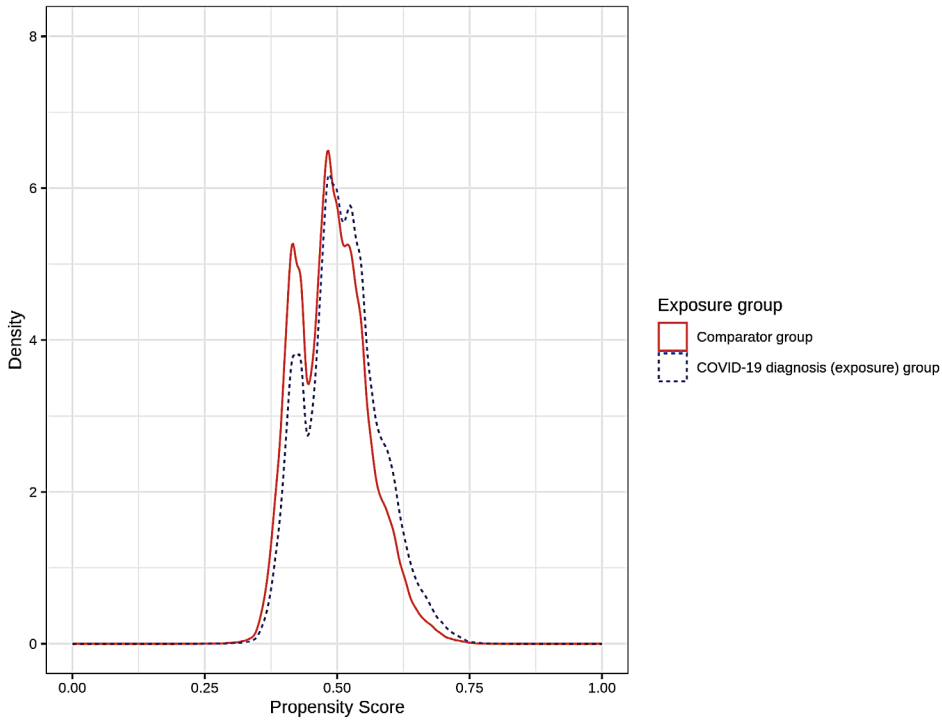
L. Disseminated Intravascular Coagulation



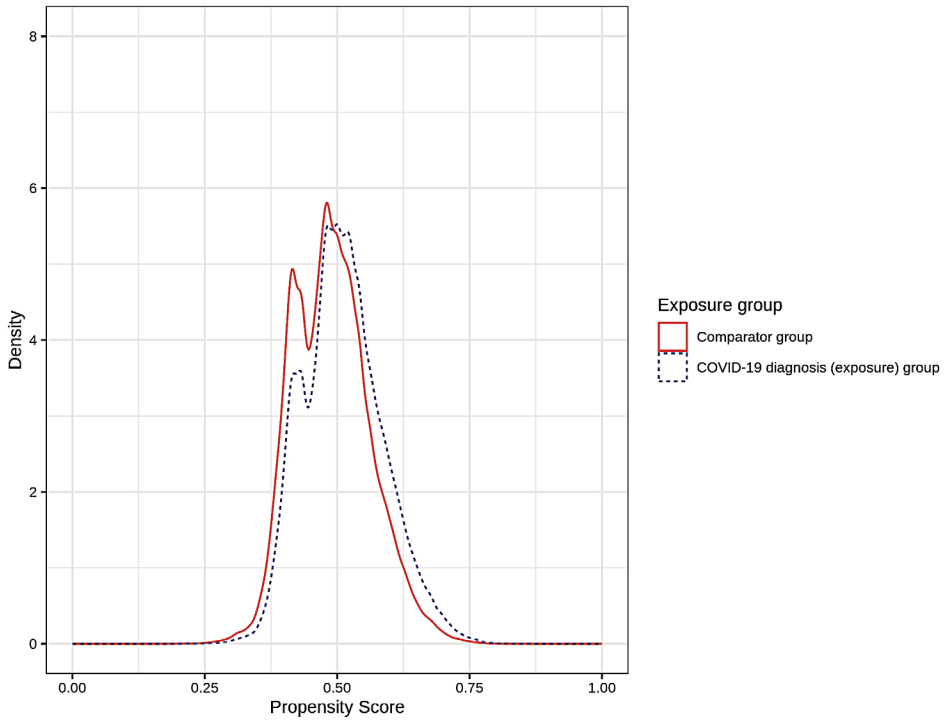
M. Immune Thrombocytopenia



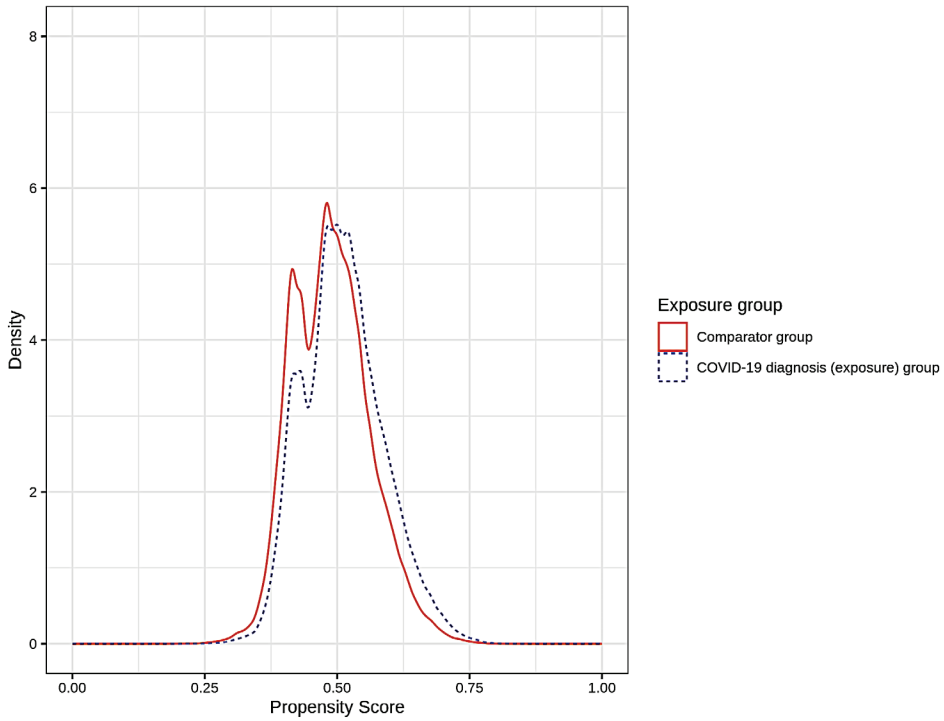
N. Transverse Myelitis



O. Unusual Site Thrombosis With Thrombocytopenia Syndrome



P. Common Site Thrombosis With Thrombocytopenia Syndrome

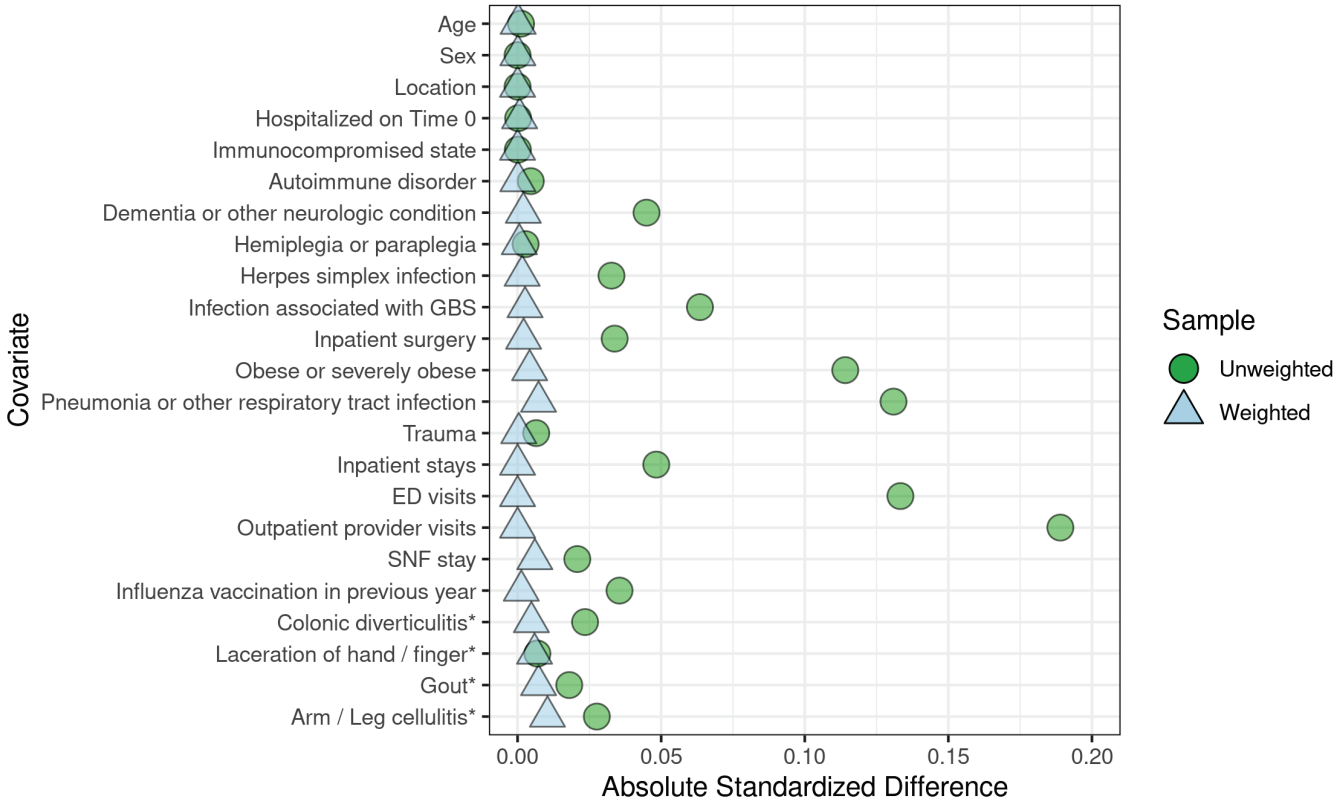


COVID-19 = coronavirus disease 2019.

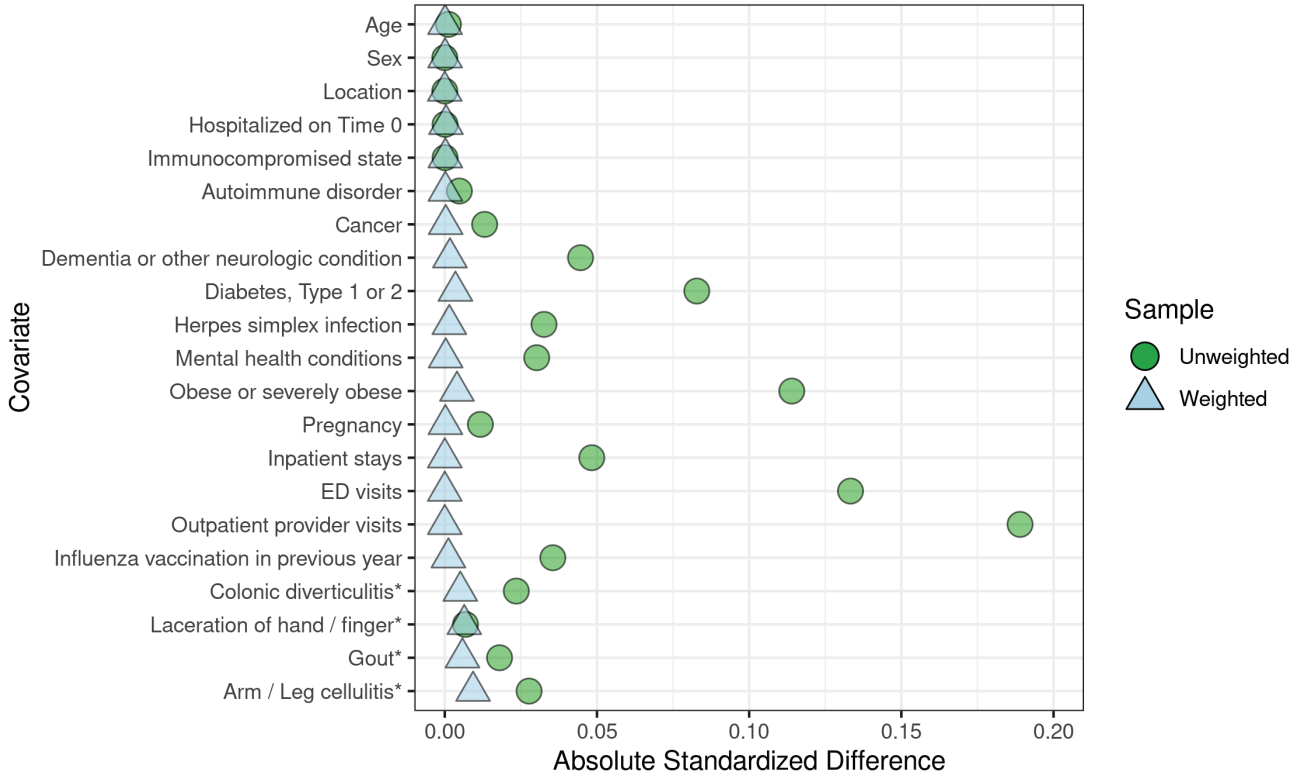
Note: A unique individual may be included multiple times and may appear in both exposure groups. This plot evaluates each instance where an individual is selected independently.

Figure B-2-MarketScan. Balance of Covariate Distributions Among Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis, Cohort Design, Before and After Stabilized Inverse Probability of Treatment Weighting, MarketScan

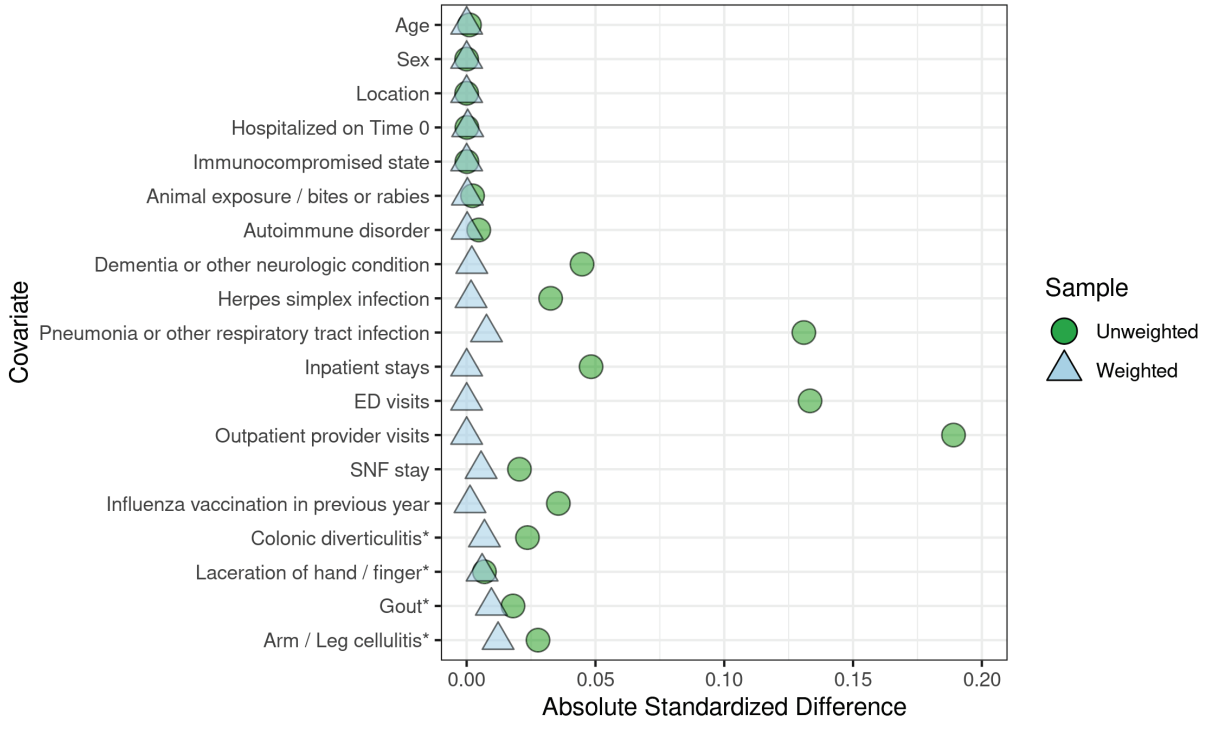
A. Guillain-Barré Syndrome



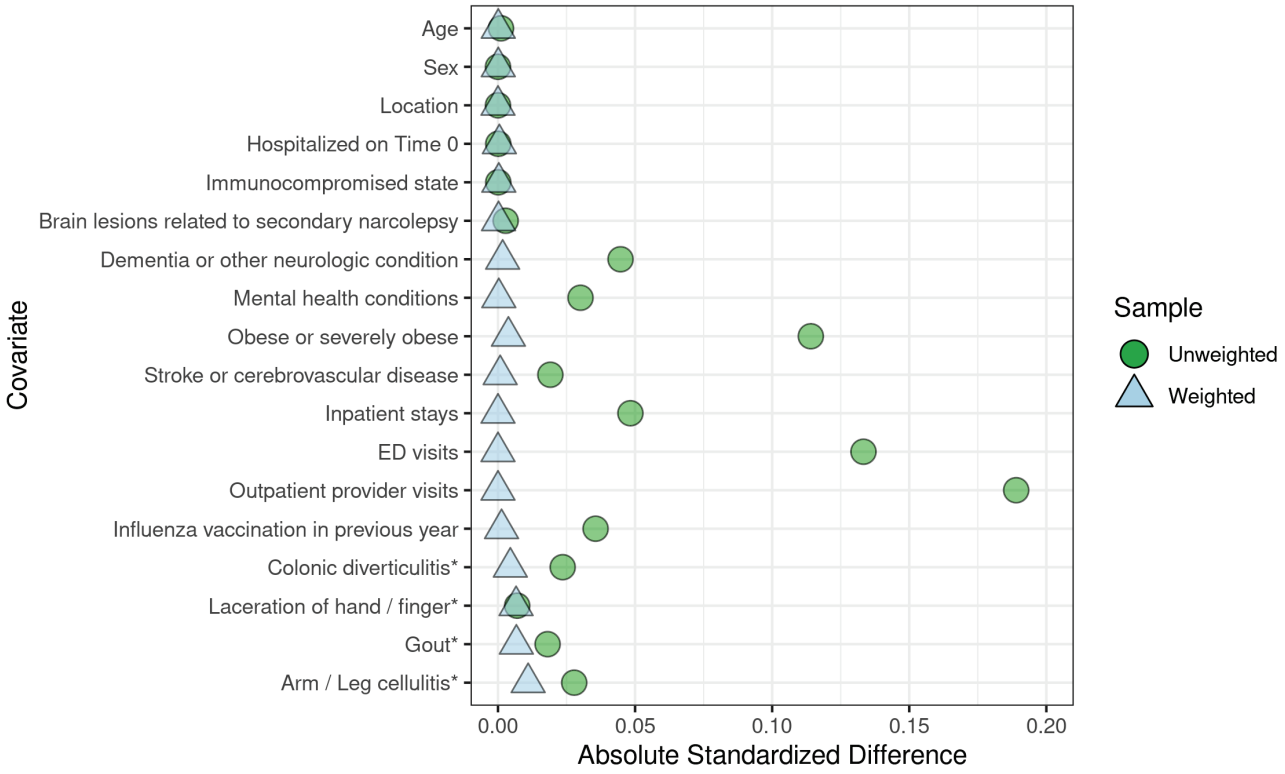
B. Bell's Palsy



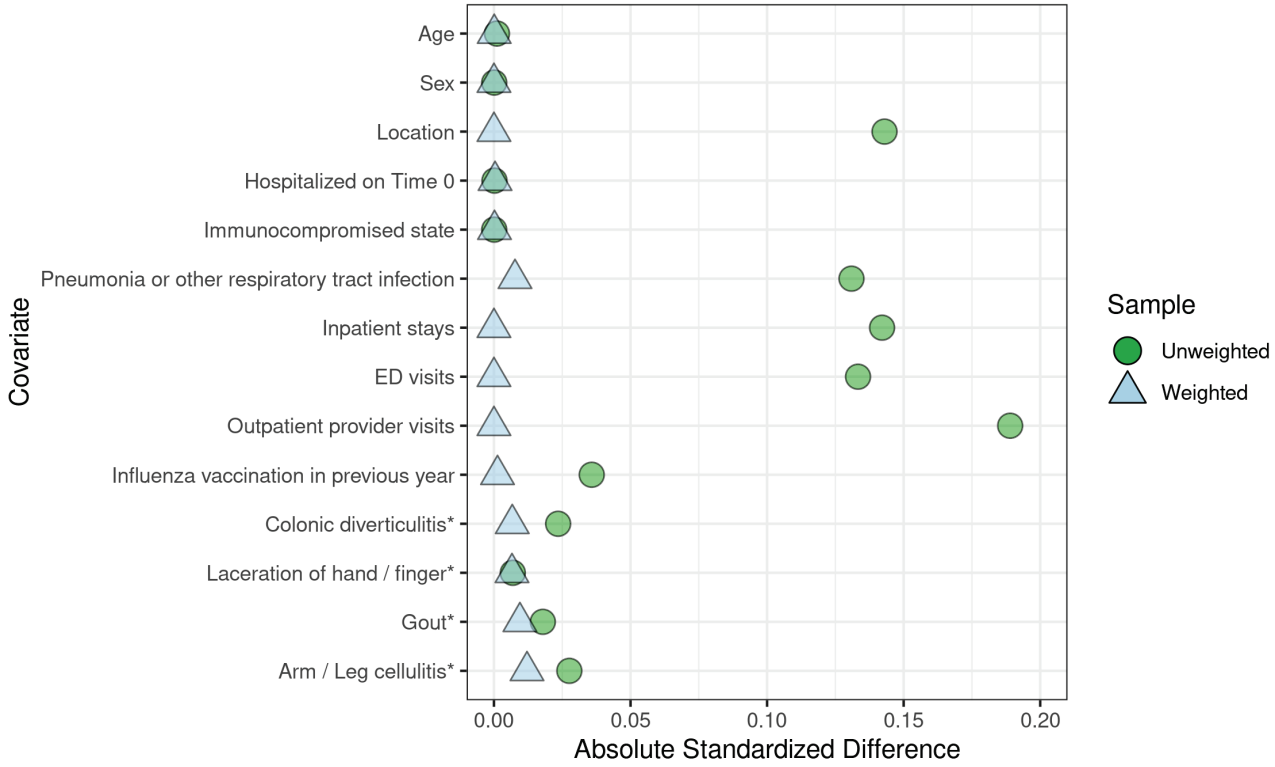
C. Encephalitis/Encephalomyelitis



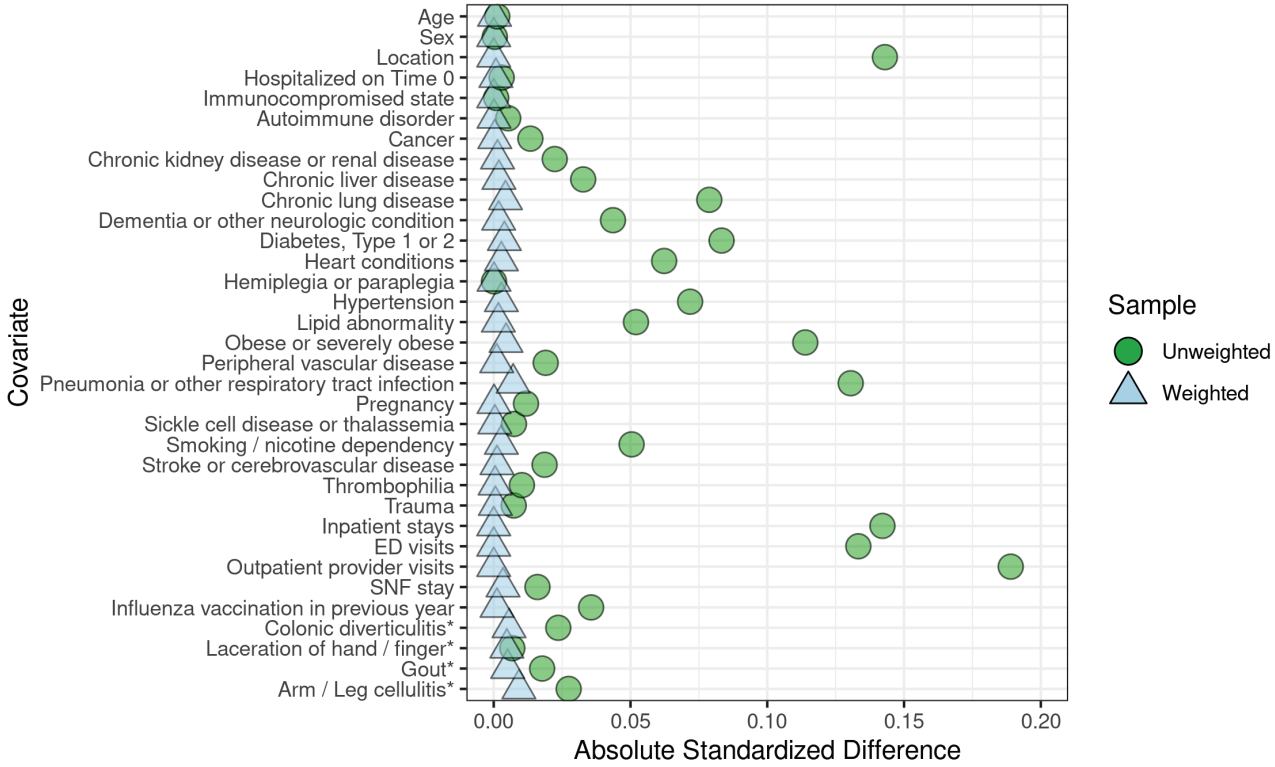
D. Narcolepsy



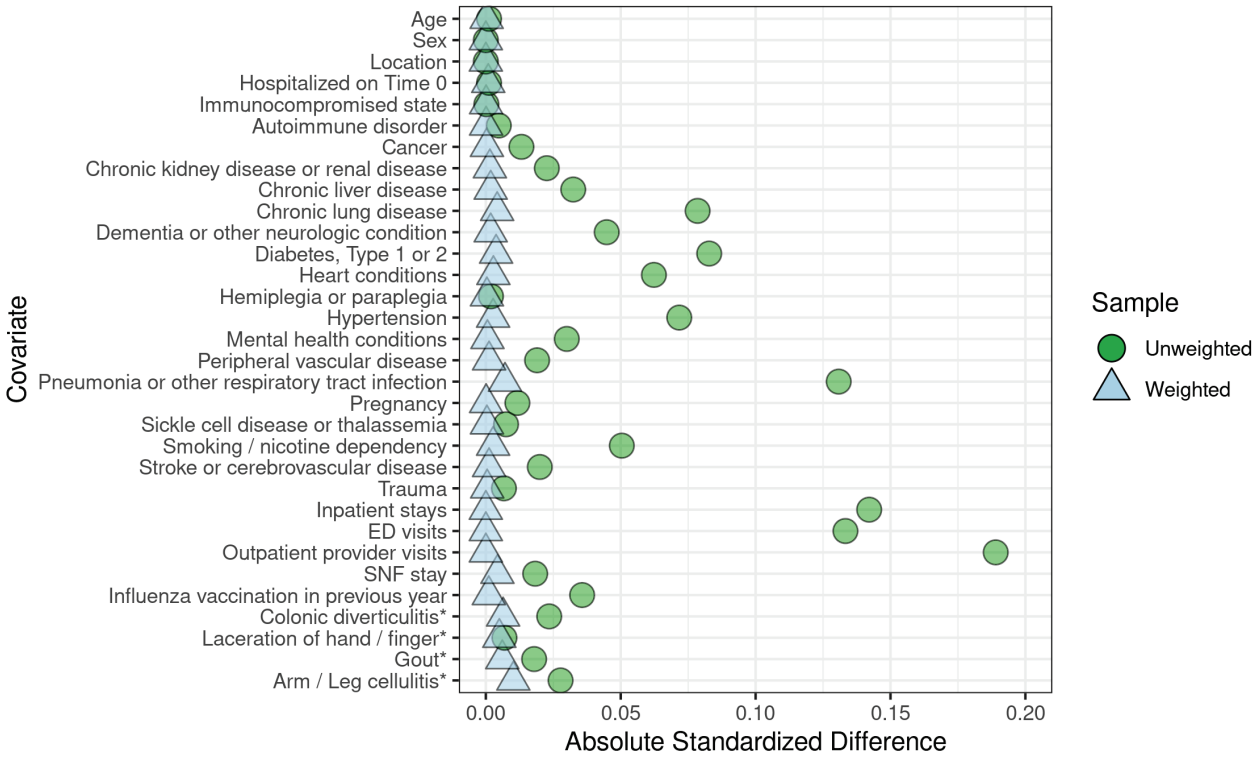
E. Appendicitis



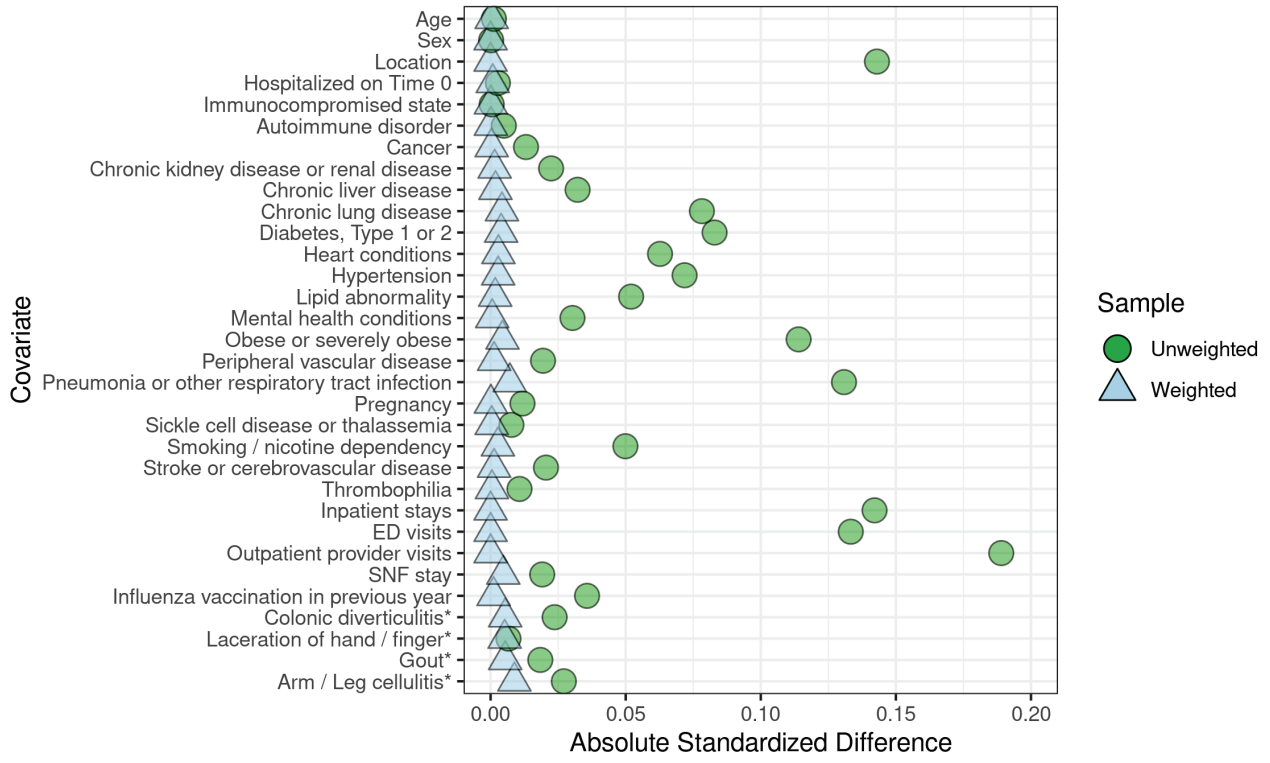
F. Nonhemorrhagic Stroke



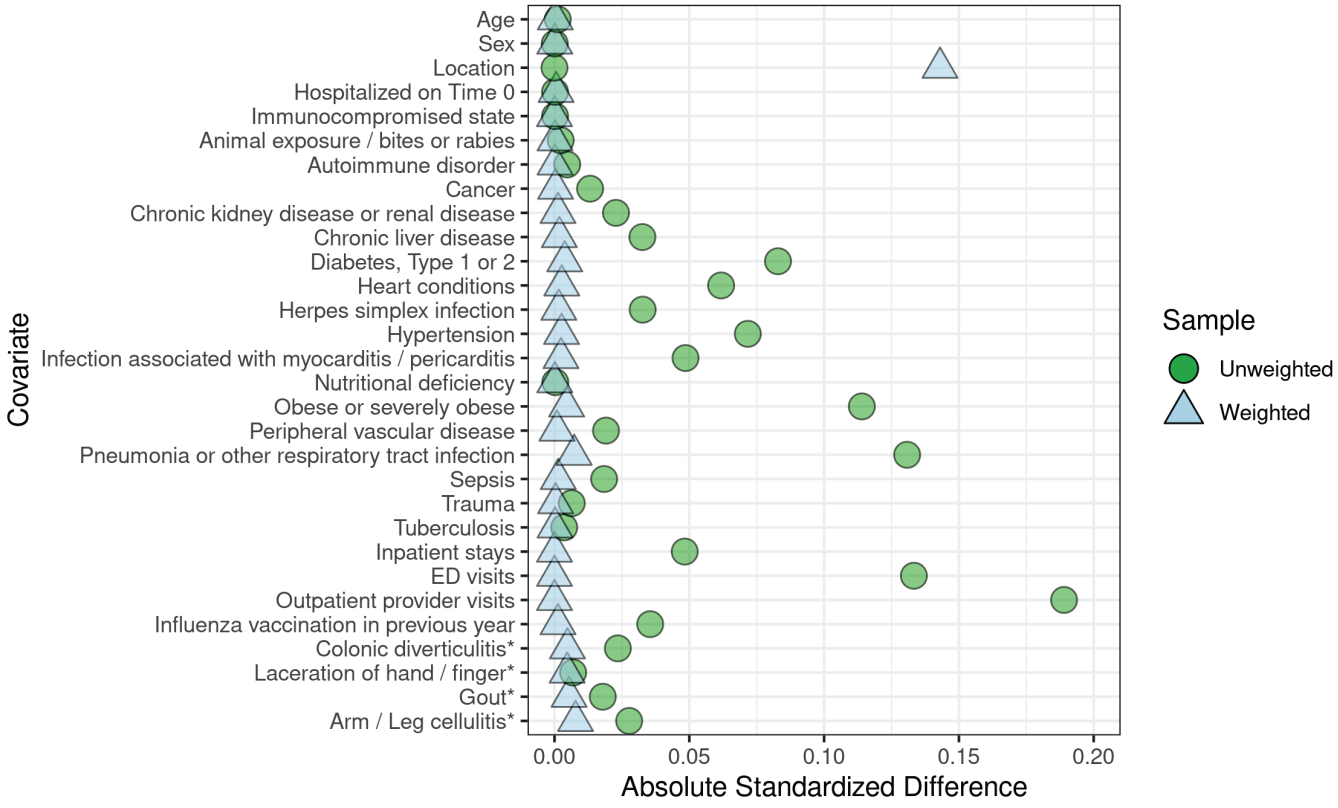
G. Hemorrhagic Stroke



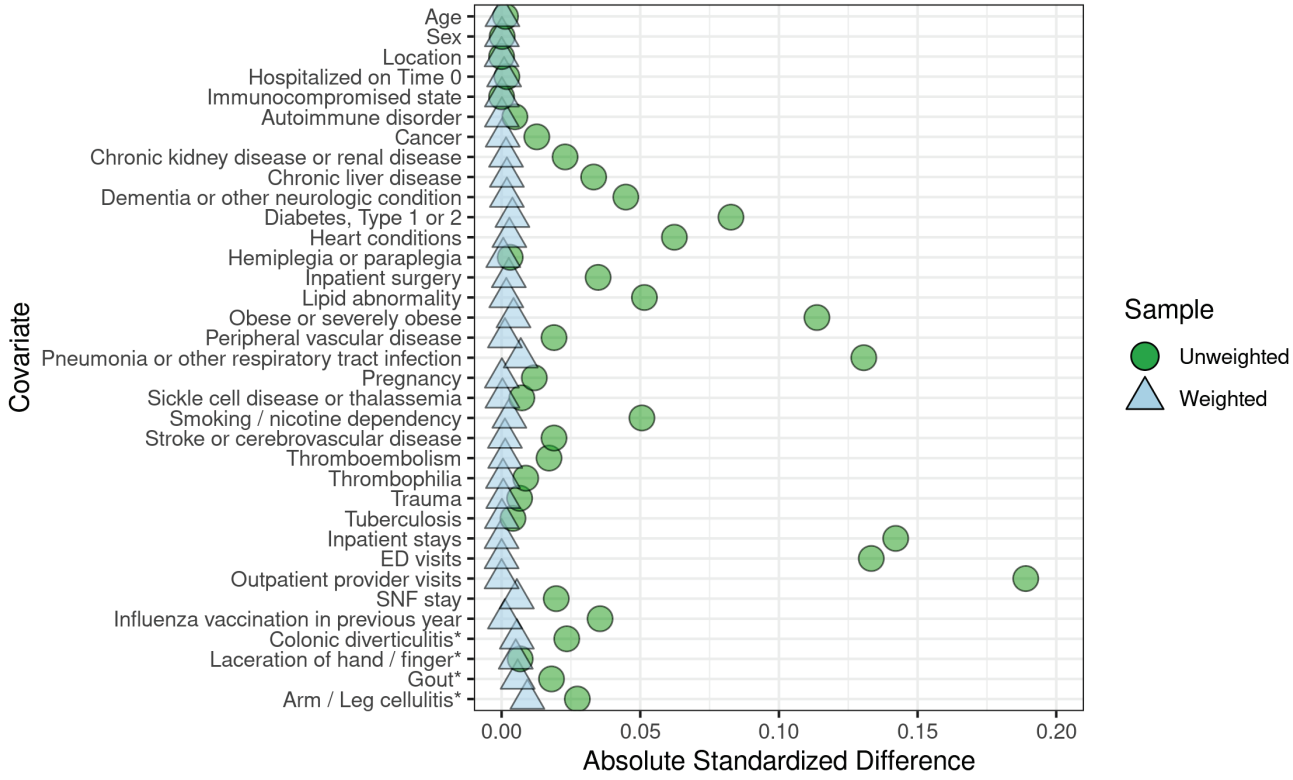
H. Acute Myocardial Infarction



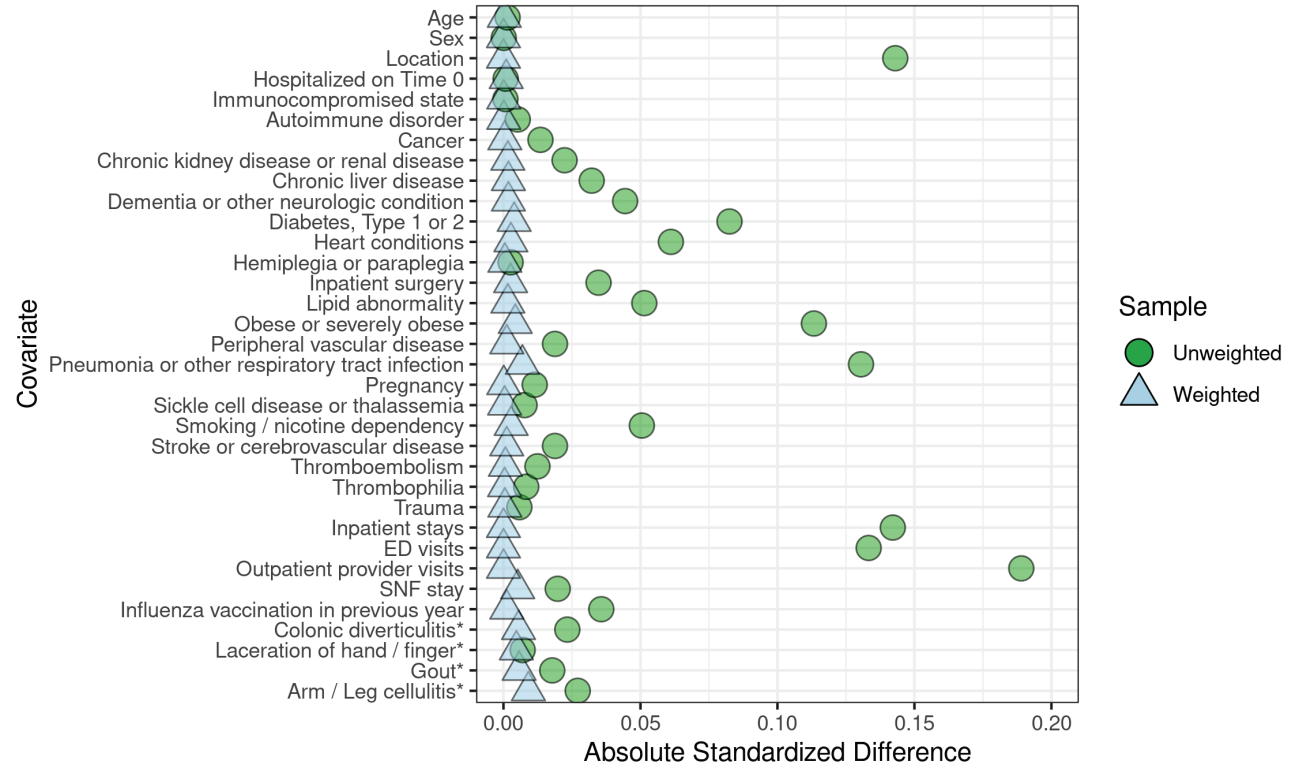
I. Myocarditis/Pericarditis



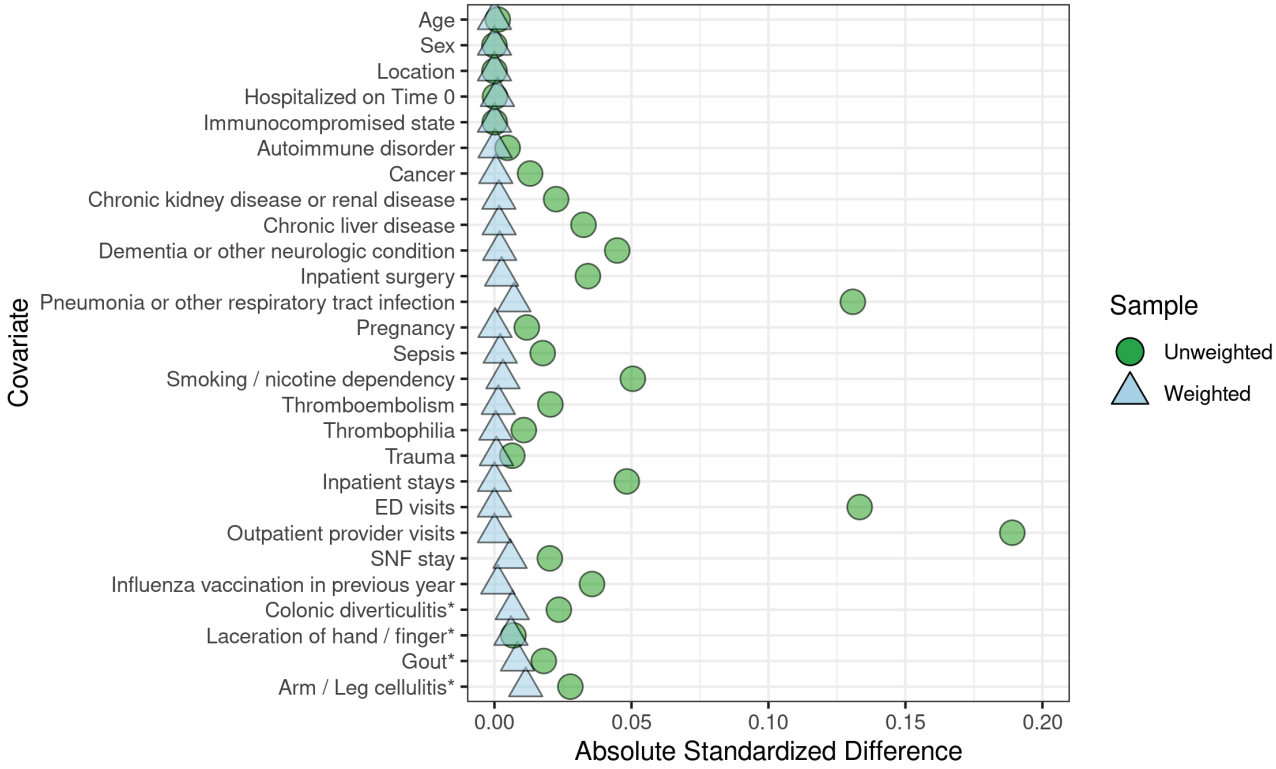
J. Deep Vein Thrombosis



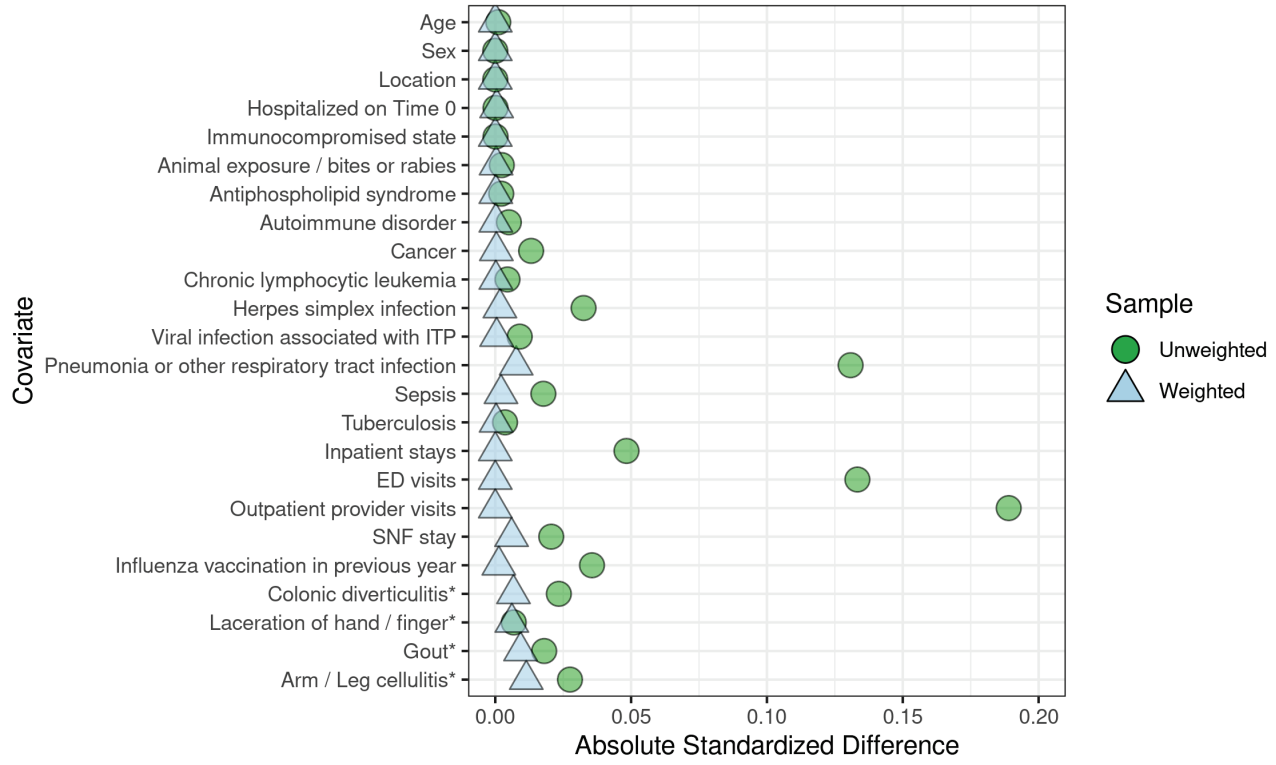
K. Pulmonary Embolism



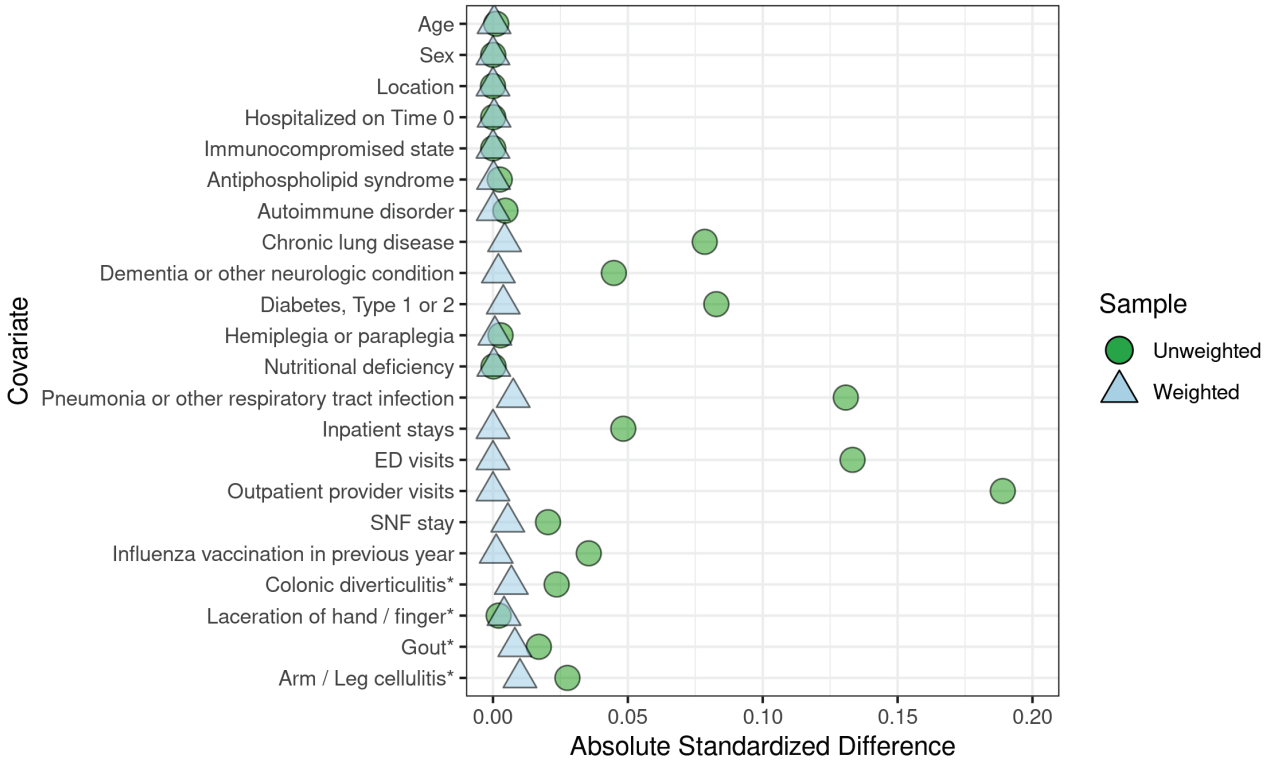
L. Disseminated Intravascular Coagulation



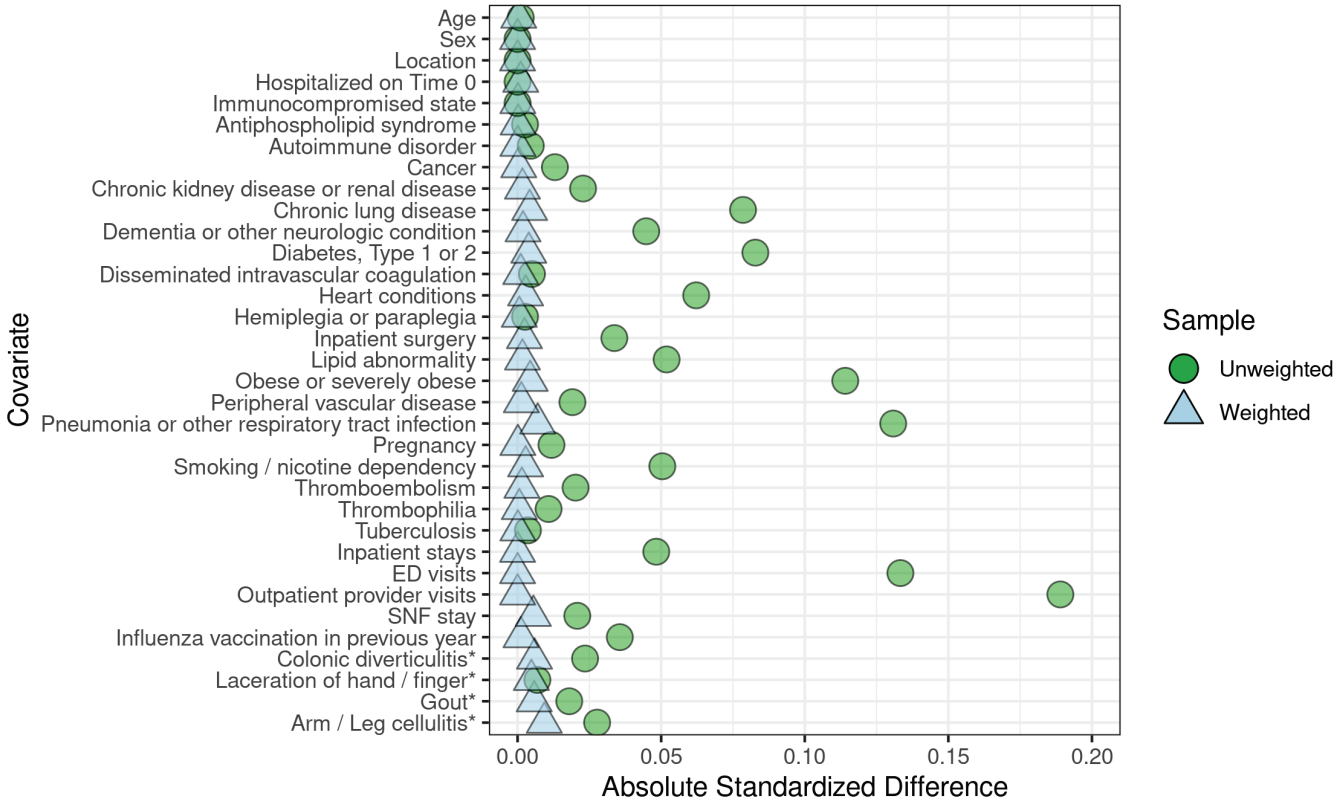
M. Immune Thrombocytopenia



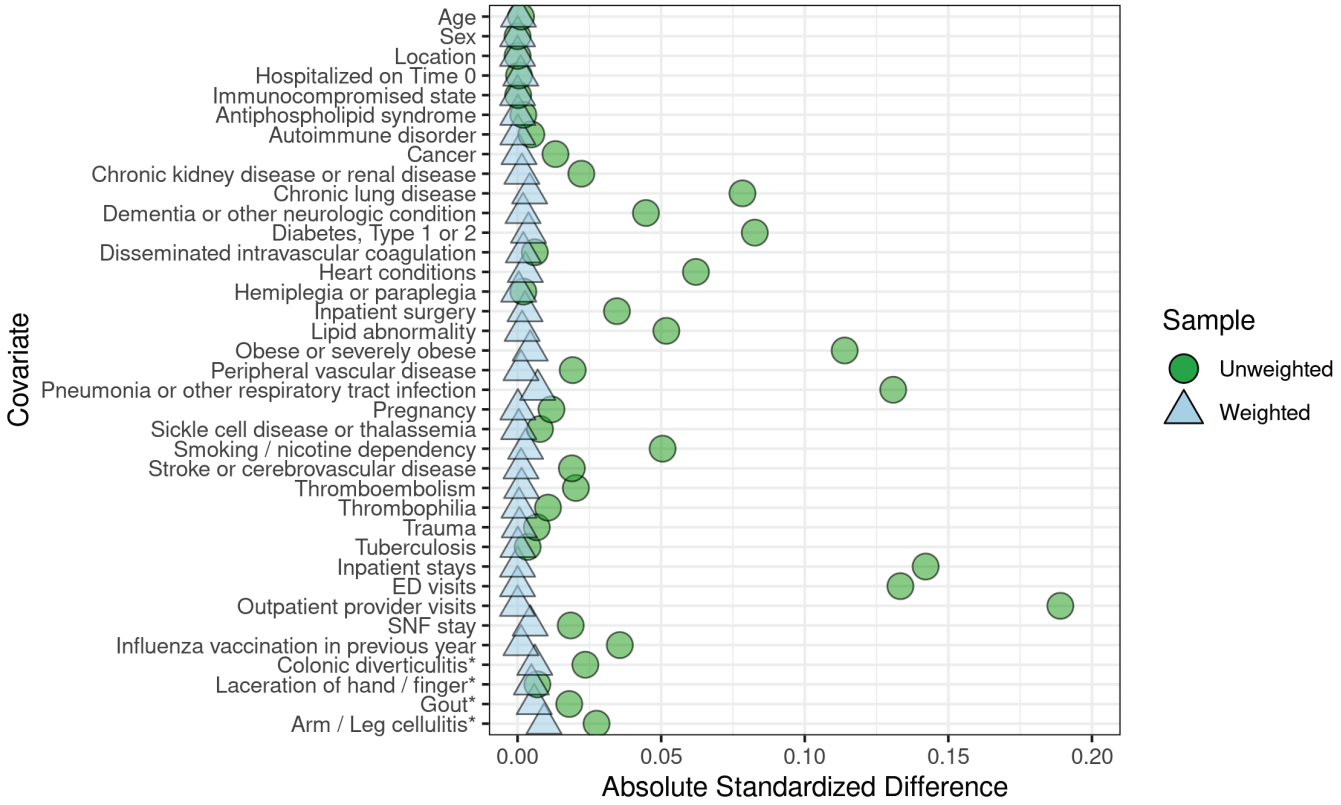
N. Transverse Myelitis



O. Unusual Site Thrombosis With Thrombocytopenia Syndrome



P. Common Site Thrombosis With Thrombocytopenia Syndrome



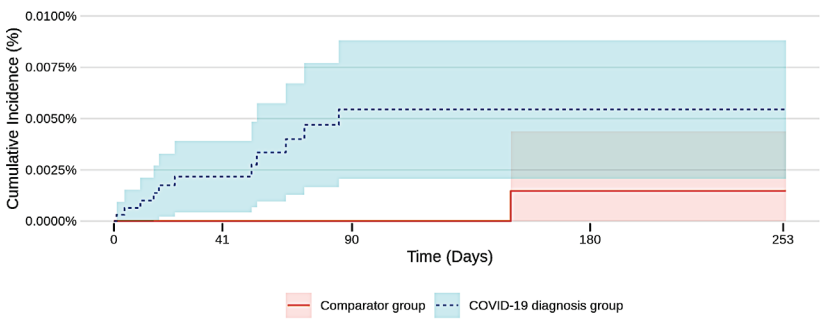
COVID-19 = coronavirus disease 2019; ED = emergency department; GBS = Guillain Barré Syndrome, SNF = skilled nursing facility.

* Indicates the history of negative control conditions occurring before Time 0.

Figure B-3-MarketScan. Cumulative Incidence of Adverse Events Among Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis, Cohort Design, Before and After sIPT Weighting, MarketScan

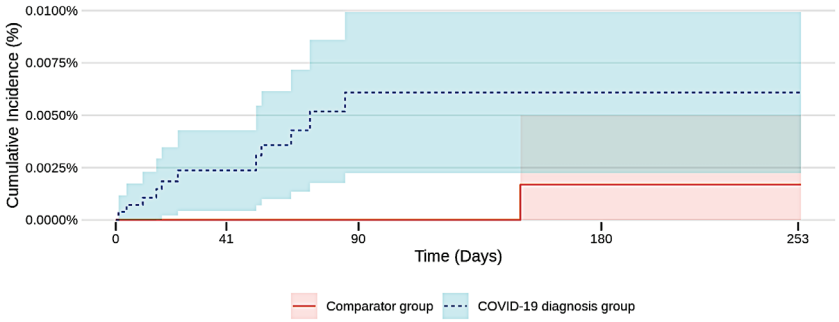
A. Guillain-Barré Syndrome

Unweighted



Comparator group					
At Risk	319249	187831	128066	36967	540
Censored	4503	133396	192294	282531	319248
Events	0	0	0	1	1
COVID-19 diagnosis group					
At Risk	319254	188088	127973	36926	546
Censored	4440	133149	192377	282555	319243
Events	1	6	11	11	11

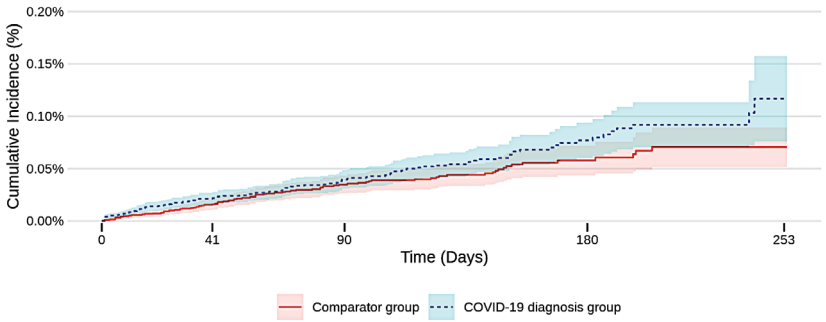
Weighted



Comparator group					
At Risk	318556	187743	128056	37008	541
Censored	4472	132782	191610	281796	318555
Events	0	0	0	1	1
COVID-19 diagnosis group					
At Risk	319279	187288	127083	36261	527
Censored	4476	133980	193290	283240	319267
Events	1	7	12	12	12

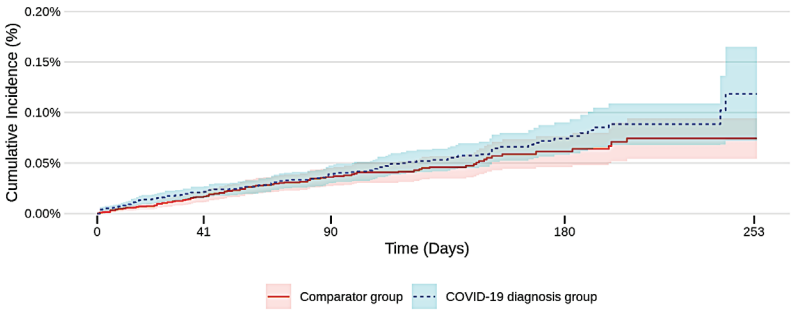
B. Bell's Palsy

Unweighted



Comparator group					
At Risk	319068	187706	127958	36932	541
Censored	4503	133298	192151	282297	318975
Events	3	41	71	89	93
COVID-19 diagnosis group					
At Risk	319031	187910	127813	36850	546
Censored	4436	133052	192240	282302	318909
Events	13	58	86	115	122

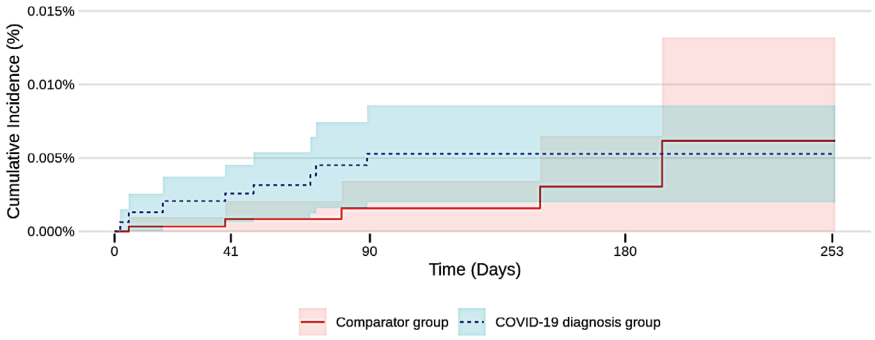
Weighted



Comparator group					
At Risk	318573	187580	127909	36972	540
Censored	4485	132924	191701	281756	318476
Events	3	43	74	93	98
COVID-19 diagnosis group					
At Risk	319045	187314	127144	36325	527
Censored	4460	133667	192922	282840	318926
Events	13	57	84	112	119

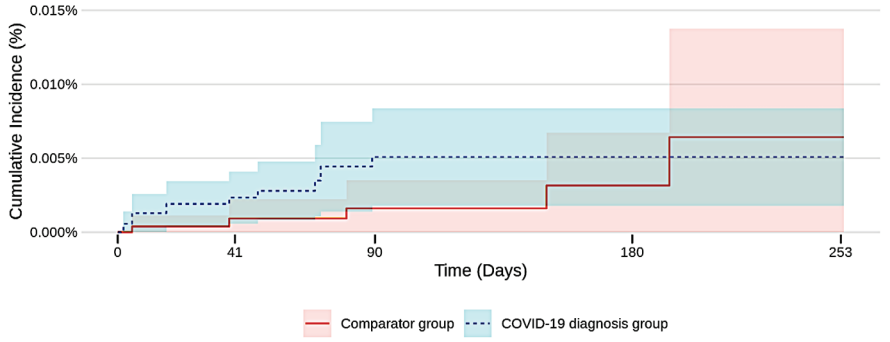
C. Encephalitis/Encephalomyelitis

Unweighted



Comparator group					
At Risk	319264	187839	128078	36969	541
Censored	4504	133401	192294	282541	319259
Events	0	2	3	4	5
COVID-19 diagnosis group					
At Risk	319264	188086	127958	36915	546
Censored	4441	133159	192401	282575	319253
Events	0	7	11	11	11

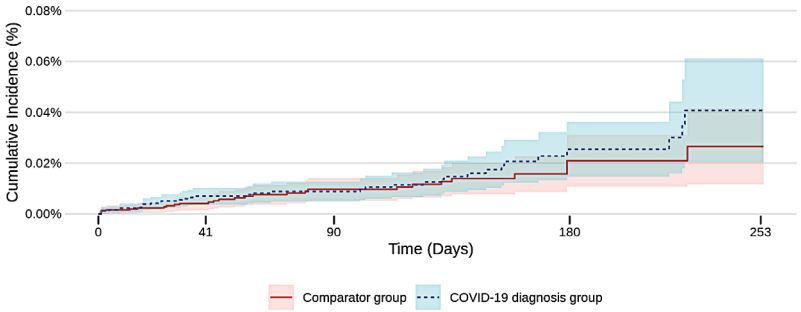
Weighted



Comparator group					
At Risk	318553	187716	128033	37000	540
Censored	4472	132804	191627	281798	318548
Events	0	2	3	4	5
COVID-19 diagnosis group					
At Risk	319305	187342	127143	36306	528
Censored	4477	133951	193259	283222	319295
Events	0	6	10	10	10

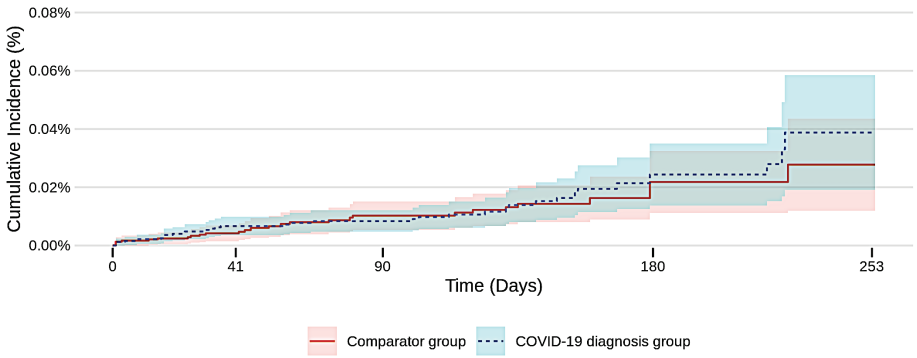
D. Narcolepsy

Unweighted



Comparator group					
At Risk	318970	187673	127950	36932	541
Censored	4502	133264	192108	282261	318942
Events	4	12	20	27	28
COVID-19 diagnosis group					
At Risk	318932	187902	127841	36886	546
Censored	4435	132997	192176	282251	318896
Events	4	18	21	33	36

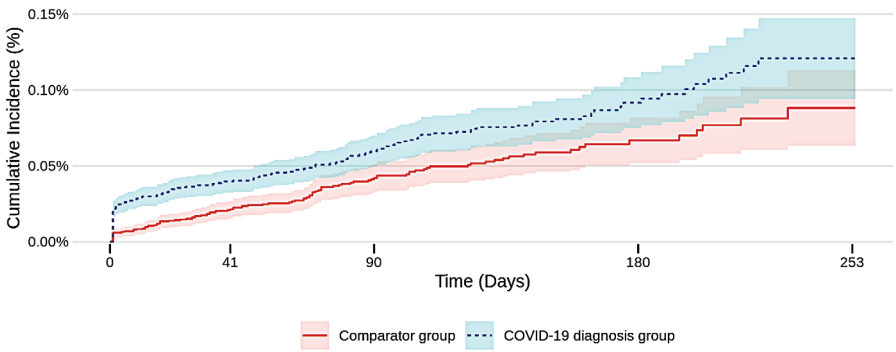
Weighted



Comparator group					
At Risk	318512	187572	127914	36990	542
Censored	4484	132903	191681	281742	318482
Events	4	12	21	28	29
COVID-19 diagnosis group					
At Risk	318927	187338	127231	36399	529
Censored	4458	133561	192780	282731	318893
Events	4	17	20	31	34

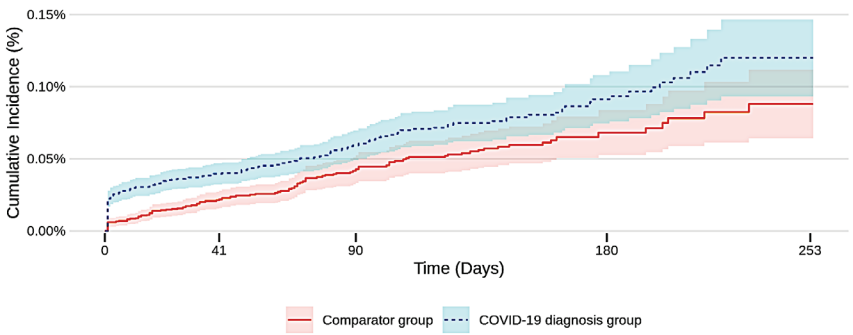
E. Appendicitis

Unweighted



Comparator group					
At Risk	318665	187454	127788	36907	539
Censored	4498	133129	191895	281899	318551
Events	19	59	90	109	114
COVID-19 diagnosis group					
At Risk	318640	187643	127652	36824	545
Censored	4428	132862	191945	281878	318458
Events	70	118	149	175	182

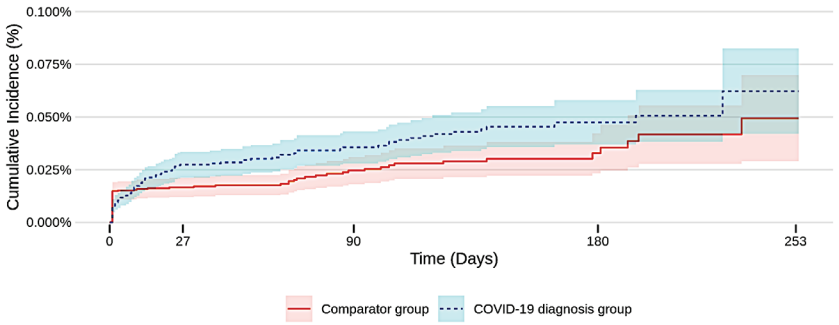
Weighted



Comparator group					
At Risk	317982	187344	127757	36949	539
Censored	4466	132546	191238	281171	317866
Events	19	60	92	111	116
COVID-19 diagnosis group					
At Risk	318684	186907	126850	36222	527
Censored	4462	133649	192793	282521	318503
Events	71	118	148	174	181

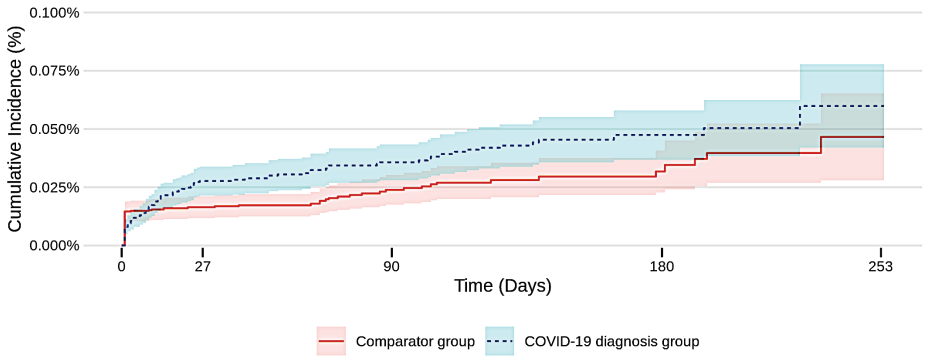
F. Nonhemorrhagic Stroke

Unweighted



Comparator group					
At Risk	318019	224061	127525	36770	536
Censored	4480	97295	191537	281425	317944
Events	47	52	64	72	75
COVID-19 diagnosis group					
At Risk	317884	224343	127276	36652	542
Censored	4418	96877	191619	281365	317778
Events	25	79	92	103	106

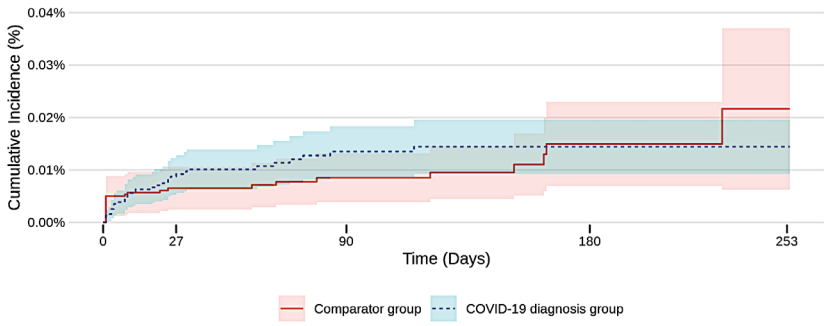
Weighted



Comparator group					
At Risk	317294	223841	127494	36790	534
Censored	4451	96787	190843	280680	317221
Events	46	51	62	70	73
COVID-19 diagnosis group					
At Risk	317828	223657	126311	35917	518
Censored	4449	97530	192529	282040	317723
Events	25	80	92	103	106

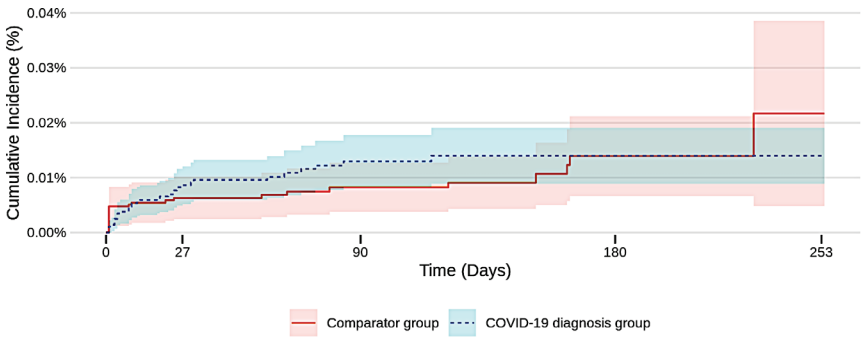
G. Hemorrhagic Stroke

Unweighted



Comparator group					
At Risk	319026	224794	127976	36927	539
Censored	4500	97609	192136	282322	318998
Events	16	20	23	27	28
COVID-19 diagnosis group					
At Risk	319035	225224	127851	36878	545
Censored	4439	97203	192258	282361	319001
Events	4	26	33	34	34

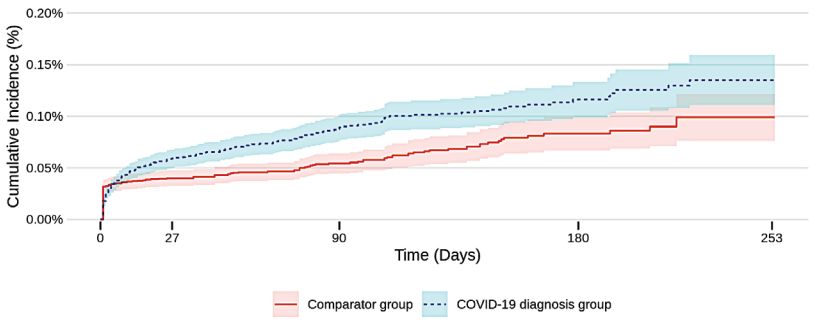
Weighted



Comparator group					
At Risk	318328	224608	127985	36978	536
Censored	4470	97092	191431	281575	318302
Events	15	19	22	26	27
COVID-19 diagnosis group					
At Risk	318970	224519	126864	36135	522
Censored	4473	97869	193183	283035	318937
Events	4	24	31	33	33

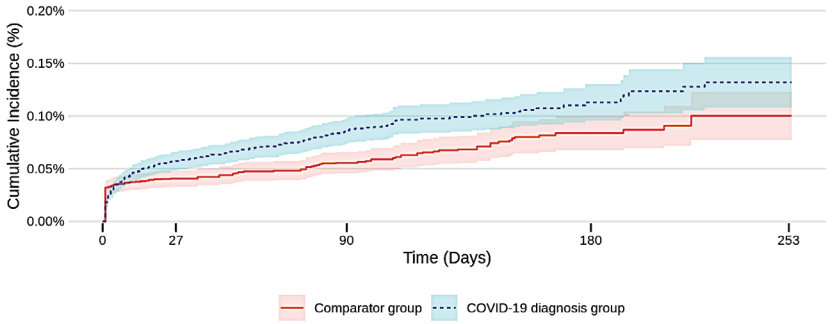
H. Acute Myocardial Infarction

Unweighted



Comparator group					
At Risk	318319	224208	127606	36792	534
Censored	4485	97375	191676	281603	318143
Events	101	124	147	172	176
COVID-19 diagnosis group					
At Risk	318271	224589	127449	36737	542
Censored	4420	96922	191699	281525	318019
Events	57	177	225	247	252

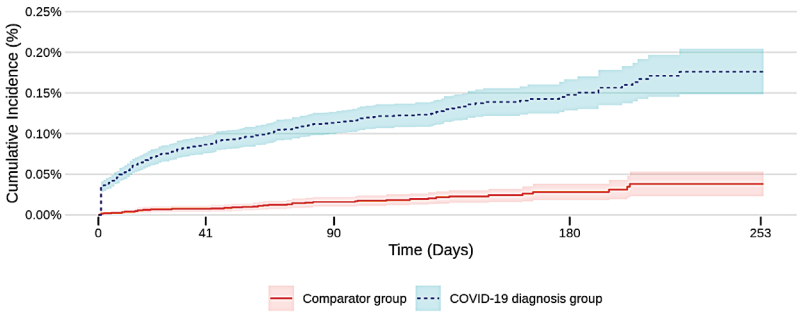
Weighted



Comparator group					
At Risk	317587	223997	127599	36832	533
Censored	4454	96849	190947	280827	317408
Events	102	126	150	174	178
COVID-19 diagnosis group					
At Risk	318220	223897	126456	35976	518
Censored	4454	97592	192649	282238	317976
Events	58	173	219	239	244

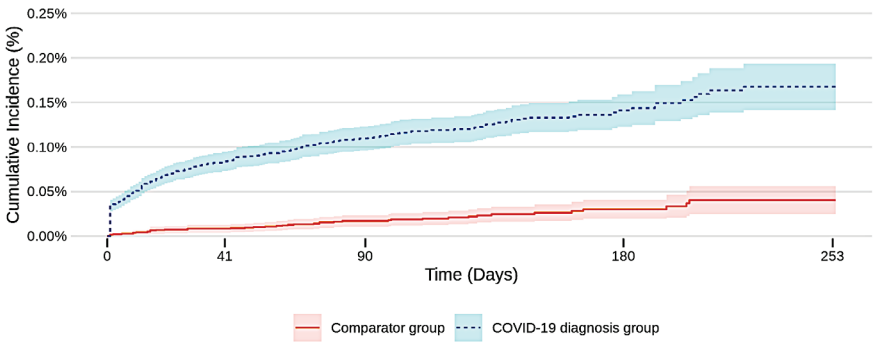
I. Myocarditis/Pericarditis

Unweighted



Comparator group					
At Risk	319163	187770	128007	36942	539
Censored	4502	133350	192233	282427	319116
Events	5	21	34	44	47
COVID-19 diagnosis group					
At Risk	319096	187811	127772	36846	545
Censored	4437	133024	192136	282170	318770
Events	111	248	290	318	326

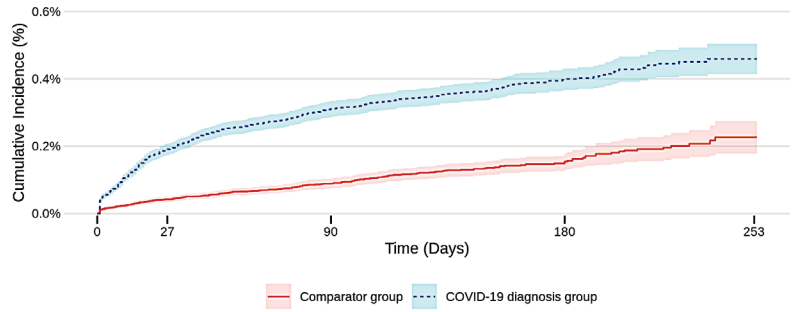
Weighted



Comparator group					
At Risk	318407	187643	127973	36965	538
Censored	4471	132710	191508	281643	318356
Events	5	23	37	48	51
COVID-19 diagnosis group					
At Risk	319156	186973	126822	36131	523
Censored	4474	133937	193156	282952	318843
Events	109	241	281	306	314

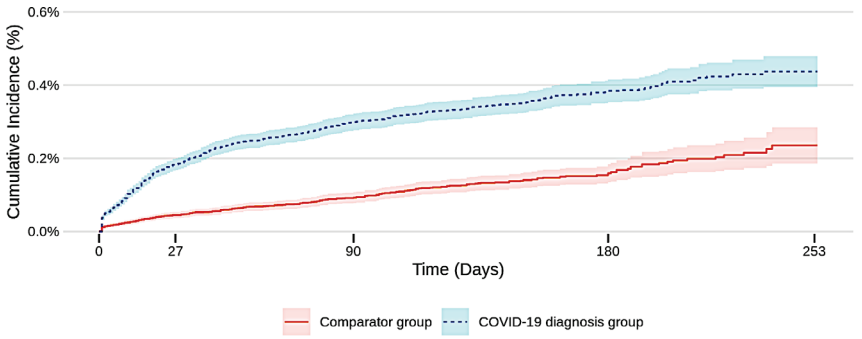
J. Deep Vein Thrombosis

Unweighted



Comparator group					
At Risk	318133	224069	127488	36745	532
Censored	4494	97329	191552	281377	317860
Events	38	121	201	257	273
COVID-19 diagnosis group					
At Risk	317909	224000	126975	36516	538
Censored	4420	96765	191284	280808	317074
Events	123	545	748	820	835

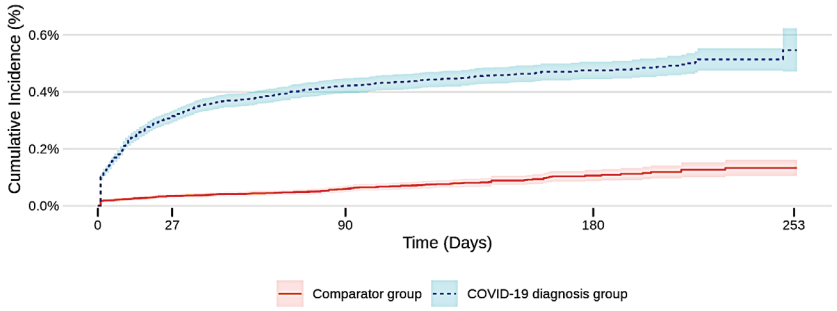
Weighted



Comparator group					
At Risk	317445	223867	127478	36780	529
Censored	4466	96831	190867	280643	317161
Events	39	128	210	267	284
COVID-19 diagnosis group					
At Risk	317812	223300	126005	35785	515
Censored	4451	97412	192186	281469	317011
Events	120	525	720	788	801

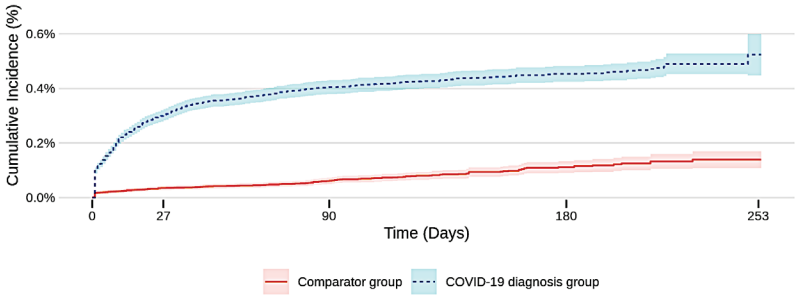
K. Pulmonary Embolism

Unweighted (any setting)



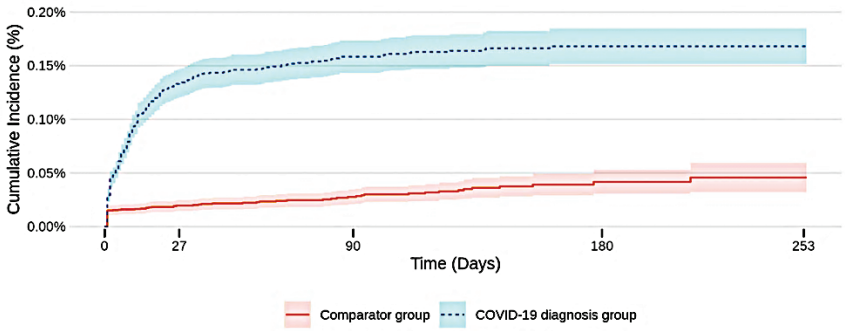
Comparator group					
At Risk	318524	224332	127685	36823	536
Censored	4496	97475	191804	281769	318337
Events	56	103	143	180	187
COVID-19 diagnosis group					
At Risk	318207	223975	127011	36578	539
Censored	4420	96719	191185	280709	317040
Events	324	926	1110	1156	1167

Weighted (any setting)



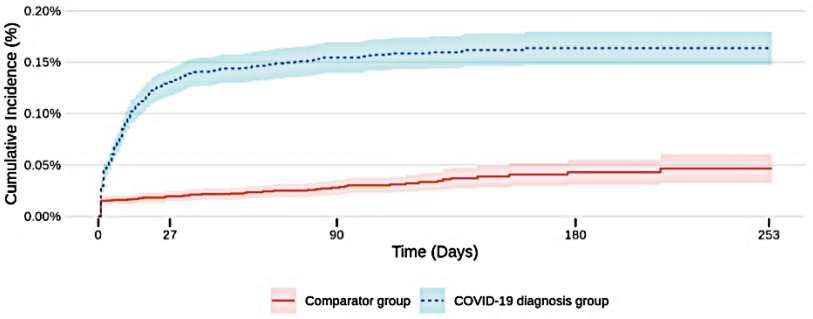
Comparator group					
At Risk	317841	224139	127677	36850	534
Censored	4467	96980	191126	281051	317647
Events	56	104	146	186	194
COVID-19 diagnosis group					
At Risk	318107	223272	126041	35856	515
Censored	4451	97377	192101	281375	316990
Events	315	893	1066	1108	1118

Unweighted (inpatient only)



Comparator group					
At Risk	318524	224369	127732	36851	536
Censored	4496	97481	191826	281836	318438
Events	48	60	74	85	86
COVID-19 diagnosis group					
At Risk	318207	224376	127352	36723	541
Censored	4424	96852	191524	281279	317765
Events	93	391	433	442	442

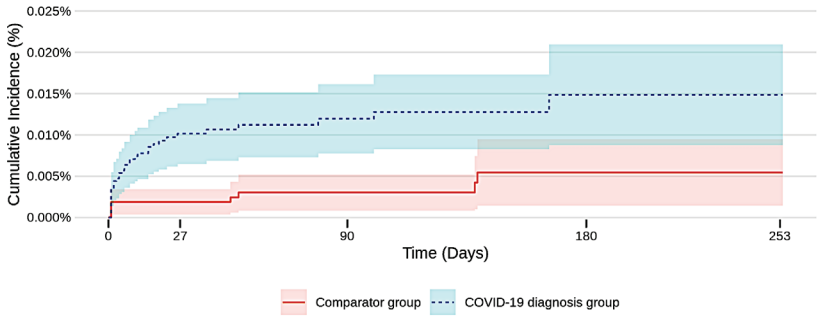
Weighted (inpatient only)



Comparator group					
At Risk	317841	224177	127726	36880	534
Censored	4467	96986	191148	281121	317753
Events	48	60	74	86	87
COVID-19 diagnosis group					
At Risk	318107	223656	126365	35992	518
Censored	4455	97503	192422	281916	317675
Events	94	382	423	432	432

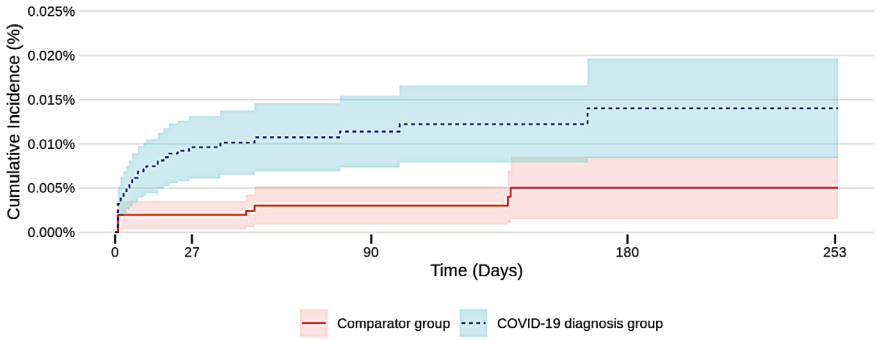
L. Disseminated Intravascular Coagulation

Unweighted



Comparator group					
At Risk	319279	224978	128085	36973	540
Censored	4504	97693	192297	282546	319269
Events	6	6	8	10	10
COVID-19 diagnosis group					
At Risk	319264	225390	127965	36923	546
Censored	4441	97268	192373	282544	319229
Events	11	30	33	35	35

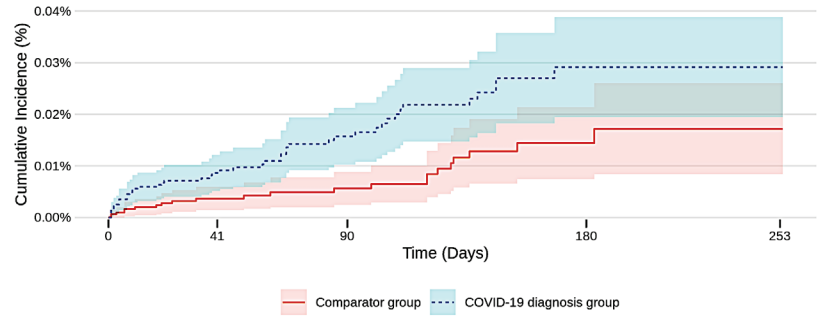
Weighted



Comparator group					
At Risk	318650	224821	128086	37017	539
Censored	4472	97219	191667	281872	318640
Events	6	6	8	10	10
COVID-19 diagnosis group					
At Risk	319108	224664	127052	36266	525
Censored	4472	97857	193133	283042	319074
Events	10	28	31	33	33

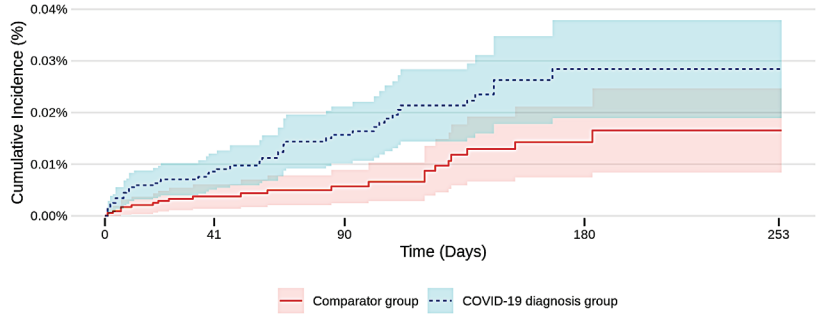
M. Immune Thrombocytopenia

Unweighted



Comparator group					
At Risk	319075	187723	127993	36936	540
Censored	4497	133320	192180	282368	319053
Events	2	10	13	21	22
COVID-19 diagnosis group					
At Risk	319058	187941	127852	36874	546
Censored	4433	133081	192277	282375	319011
Events	5	25	35	47	47

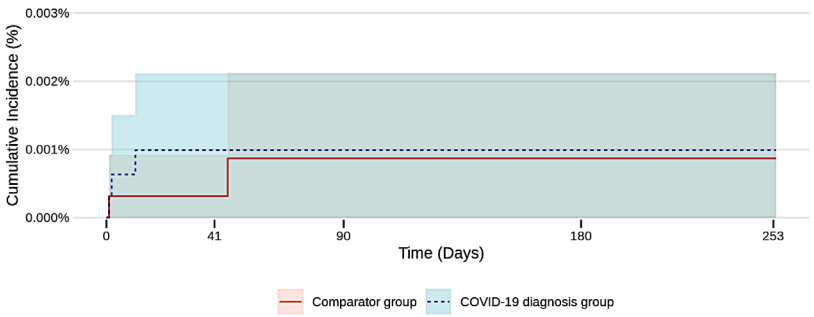
Weighted



Comparator group					
At Risk	318367	187594	127946	36959	539
Censored	4465	132731	191518	281636	318345
Events	2	10	13	21	22
COVID-19 diagnosis group					
At Risk	319082	187175	127015	36255	528
Censored	4469	133878	193139	283014	319035
Events	5	25	35	46	46

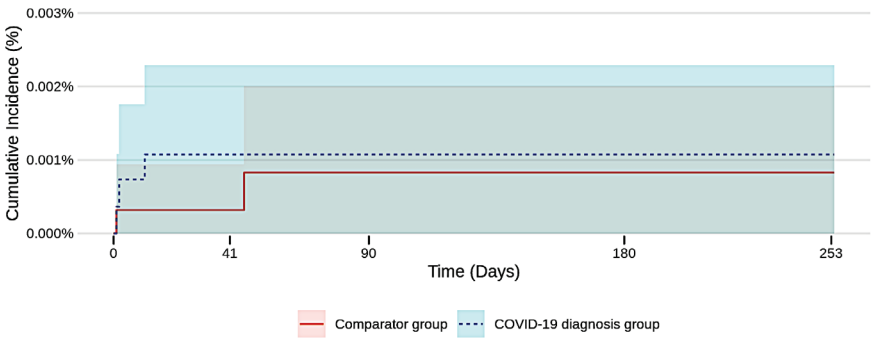
N. Transverse Myelitis

Unweighted



Comparator group					
At Risk	319244	187838	128074	36973	541
Censored	4502	133382	192279	282519	319242
Events	1	1	2	2	2
COVID-19 diagnosis group					
At Risk	319250	188087	127965	36924	546
Censored	4441	133149	192389	282561	319247
Events	1	3	3	3	3

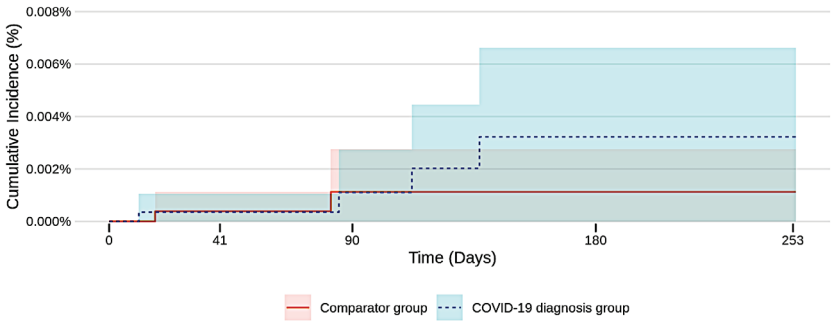
Weighted



Comparator group					
At Risk	318524	187708	128029	37002	539
Censored	4470	132784	191604	281770	318522
Events	1	1	2	2	2
COVID-19 diagnosis group					
At Risk	319305	187299	127085	36253	527
Censored	4477	134000	193325	283282	319302
Events	1	3	3	3	3

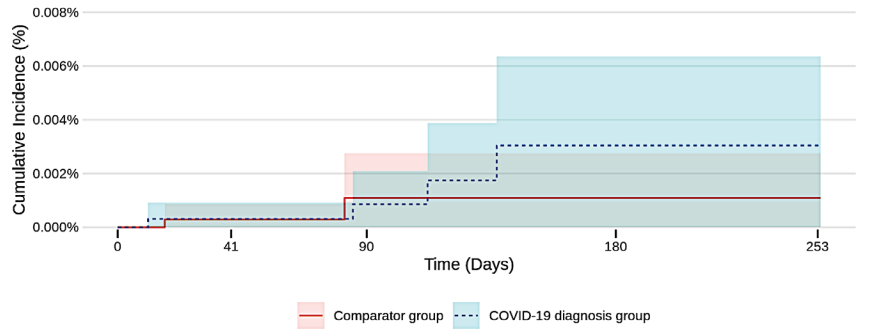
O. Unusual Site Thrombosis With Thrombocytopenia Syndrome

Unweighted



Comparator group					
At Risk	319277	187852	128086	36974	541
Censored	4503	133402	192300	282551	319275
Events	0	1	2	2	2
COVID-19 diagnosis group					
At Risk	319276	188104	127980	36927	546
Censored	4441	133160	192401	282583	319272
Events	0	1	2	4	4

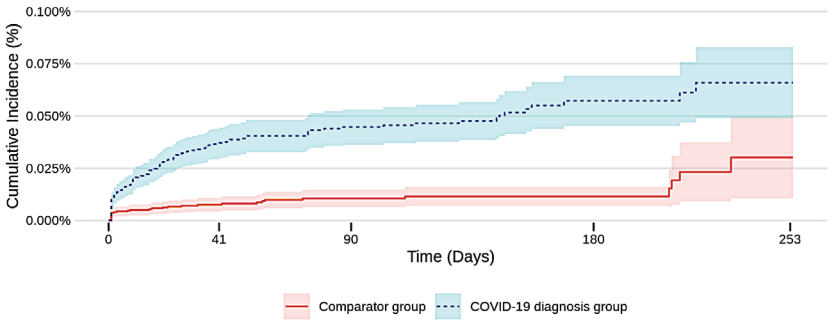
Weighted



Comparator group					
At Risk	318569	187758	128082	37009	540
Censored	4472	132779	191597	281807	318567
Events	0	1	2	2	2
COVID-19 diagnosis group					
At Risk	319183	187200	126982	36180	523
Censored	4472	133979	193306	283232	319179
Events	0	1	2	4	4

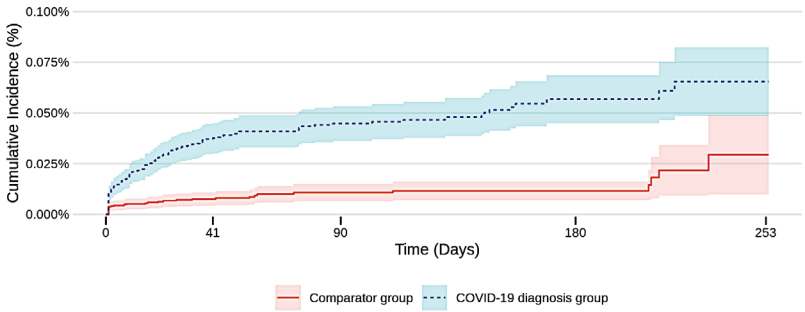
P. Common Site Thrombosis With Thrombocytopenia Syndrome

Unweighted



Comparator group					
At Risk	319172	187774	128032	36955	539
Censored	4502	133352	192223	282439	319140
Events	12	23	27	28	32
COVID-19 diagnosis group					
At Risk	319147	187942	127863	36872	543
Censored	4440	133091	192276	282389	319021
Events	32	103	115	124	126

Weighted



Comparator group					
At Risk	318474	187687	128031	36991	537
Censored	4472	132732	191526	281703	318442
Events	12	23	27	28	32
COVID-19 diagnosis group					
At Risk	319051	187034	126862	36125	519
Censored	4471	133910	193181	283035	318925
Events	33	104	116	124	126

COVID-19 = coronavirus disease 2019; sIPT = stabilized inverse probability of treatment.

Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

B.1.2. SCRI Analyses

Table B-10-MarketScan. Selection of Individuals With a COVID-19 Diagnosis for the Self-Controlled Risk Interval Study, MarketScan

Characteristic	Value
Overall SCRI population	
Individuals with COVID-19 diagnosis during the study period	509,875
Excluded for being aged outside age range, N (%)	51,848 (10.2)
Excluded for lacking 365 days of continuous database enrollment before Time 0, N (%)	128,310 (25.2)
Excluded for having a previous COVID-19 diagnosis	2,135 (0.4)
Excluded for having a previous select respiratory infection	119 (0.0)
Excluded for lacking ≥ 1 day in the pre-exposure reference window	25,306 (5.0)
Total SCRI population	330,799
Adverse event-specific analysis sets with 42-day risk windows[a]	
Excluded for not having Guillain-Barré syndrome in risk or reference window	330,779 (100.0)
Excluded for lacking 365 days of continuous database enrollment before outcome date	0 (0.0)
Excluded for having Guillain-Barré syndrome in outcome washout window	5 (0.0)
Guillain-Barré syndrome analysis set	12
Excluded for not having Bell's palsy in risk or reference window	330,507 (99.9)
Excluded for lacking 183 days of continuous database enrollment before outcome date	0 (0.0)
Excluded for having Bell's palsy in outcome washout window	61 (0.0)
Bell's palsy analysis set	192
Excluded for not having narcolepsy in risk or reference window	330,506 (99.9)
Excluded for lacking 365 days of continuous database enrollment before outcome date	0 (0.0)
Excluded for having narcolepsy in outcome washout window	197 (0.1)
Narcolepsy analysis set	86
Excluded for not having appendicitis in risk or reference window	330,453 (99.9)
Excluded for lacking 365 days of continuous database enrollment before outcome date	0 (0.0)
Excluded for having appendicitis in outcome washout window	24 (0.0)
Appendicitis analysis set	296
Excluded for not having myocarditis/pericarditis in risk or reference window	330,392 (99.9)
Excluded for lacking 365 days of continuous database enrollment before outcome date	0 (0.0)
Excluded for having myocarditis/pericarditis in outcome washout window	27 (0.0)
Myocarditis/pericarditis analysis set	339
Excluded for not having immune thrombocytopenia in risk or reference window	330,599 (99.9)
Excluded for lacking 365 days of continuous database enrollment before outcome date	0 (0.0)
Excluded for having immune thrombocytopenia in outcome washout window	111 (0.0)
Immune thrombocytopenia analysis set	78
Excluded for not having transverse myelitis in risk or reference window	330,785 (100.0)
Excluded for lacking 365 days of continuous database enrollment before outcome date	0 (0.0)
Excluded for having transverse myelitis in outcome washout window	5 (0.0)
Transverse myelitis analysis set	7
Adverse event-specific analysis sets with 28-day risk windows[a]	
Excluded for not having deep vein thrombosis in risk or reference window	329,228 (99.5)
Excluded for lacking 365 days of continuous database enrollment before outcome date	0 (0.0)
Excluded for having deep vein thrombosis in outcome washout window	374 (0.1)

Characteristic	Value
Deep vein thrombosis analysis set	1,013
Excluded for not having pulmonary embolism, inpatient, in risk or reference window	330,062 (99.8)
Excluded for lacking 365 days of continuous database enrollment before outcome date	0 (0.0)
Excluded for having pulmonary embolism in outcome washout window	118 (0.0)
Pulmonary embolism, inpatient, analysis set	560
Excluded for not having pulmonary embolism, overall, in risk or reference window	328,773 (99.4)
Excluded for lacking 365 days of continuous database enrollment before outcome date	0 (0.0)
Excluded for having pulmonary embolism in outcome washout window	382 (0.1)
Pulmonary embolism, overall, analysis set	1,444
Excluded for not having disseminated intravascular coagulation in risk or reference window	330,748 (100.0)
Excluded for lacking 365 days of continuous database enrollment before outcome date	0 (0.0)
Excluded for having disseminated intravascular coagulation in outcome washout window	0 (0.0)
Disseminated intravascular coagulation analysis set	42

COVID-19 = coronavirus disease 2019; SCRI = self-controlled risk interval.

[a] Denominators for all outcome-specific exclusions are the total SCRI after excluding those with ≥ 1 day in risk and reference windows; exclusions are noncumulative across analysis sets.

Table B-11-MarketScan. Characteristics of Individuals With a COVID-19 Diagnosis Included in the Self-Controlled Risk Interval Analysis Study Population, MarketScan

Overall

Characteristic	Value
Total included individuals	330,799
Age, years	
Mean (SD)	41.4 (13.7)
Median (Q1, Q3)	42 (29, 53)
Age groups, n (%)	
18-34 years	113,978 (34.5)
35-49 years	103,886 (31.4)
50-64 years	112,935 (34.1)
Sex	
Female	180,800 (54.7)
Male	149,999 (45.3)
US geographic region, n (%)	
Northeast	44,345 (13.4)
North central	69,166 (20.9)
South	172,142 (52.0)
West	44,841 (13.6)
Unknown	305 (0.1)
Hospitalized on Time 0, n (%)	10,129 (3.1)
Immunocompromised state, n (%)	35,924 (10.9)

A. Guillain-Barré Syndrome

Characteristic	Value
Total included individuals	12
Age, years	
Mean (SD)	48.7 (10.8)
Median (Q1, Q3)	50 (40, 57)
Age groups, n (%)	
18-34 years	1 (8.3)
35-49 years	5 (41.7)
50-64 years	6 (50.0)
Sex	
Female	5 (41.7)
Male	7 (58.3)
US geographic region, n (%)	
Northeast	2 (16.7)
North central	2 (16.7)
South	4 (33.3)
West	4 (33.3)
Unknown	0 (0.0)
Hospitalized on Time 0, n (%)	3 (25.0)
Immunocompromised state, n (%)	5 (41.7)

B. Bell's Palsy

Characteristic	Value
Total included individuals	192
Age, years	
Mean (SD)	47.1 (10.9)
Median (Q1, Q3)	49 (40, 57)
Age groups, n (%)	
18-34 years	28 (14.6)
35-49 years	75 (39.1)
50-64 years	89 (46.4)
Sex	
Female	107 (55.7)
Male	85 (44.3)
US geographic region, n (%)	
Northeast	22 (11.5)
North central	36 (18.8)
South	107 (55.7)
West	27 (14.1)
Unknown	0 (0.0)
Hospitalized on Time 0, n (%)	18 (9.4)
Immunocompromised state, n (%)	40 (20.8)

C. Encephalitis/Encephalomyelitis

Not evaluated with SCRI design.

D. Narcolepsy

Characteristic	Value
Total included individuals	86
Age, years	
Mean (SD)	40.0 (14.1)
Median (Q1, Q3)	40 (27, 52)
Age groups, n (%)	
18-34 years	36 (41.9)
35-49 years	22 (25.6)
50-64 years	28 (32.6)
Sex	
Female	64 (74.4)
Male	22 (25.6)
US geographic region, n (%)	
Northeast	4 (4.7)
North central	24 (27.9)
South	53 (61.6)
West	5 (5.8)
Unknown	0 (0.0)
Hospitalized on Time 0, n (%)	5 (5.8)
Immunocompromised state, n (%)	14 (16.3)

E. Appendicitis

Characteristic	Value
Total included individuals	296
Age, years	
Mean (SD)	36.1 (13.4)
Median (Q1, Q3)	34 (24, 47)
Age groups, n (%)	
18-34 years	149 (50.3)
35-49 years	93 (31.4)
50-64 years	54 (18.2)
Sex	
Female	134 (45.3)
Male	162 (54.7)
US geographic region, n (%)	
Northeast	32 (10.8)
North central	76 (25.7)
South	145 (49.0)
West	43 (14.5)
Unknown	0 (0.0)
Hospitalized on Time 0, n (%)	38 (12.8)
Immunocompromised state, n (%)	47 (15.9)

F. Nonhemorrhagic Stroke

Not evaluated with SCRI design.

G. Hemorrhagic Stroke

Not evaluated with SCRI design.

H. Acute Myocardial Infarction

Not evaluated with SCRI design.

I. Myocarditis/Pericarditis

Characteristic	Value
Total included individuals	339
Age, years	
Mean (SD)	33.9 (15.6)
Median (Q1, Q3)	27 (20, 49)
Age groups, n (%)	
18-34 years	194 (57.2)
35-49 years	63 (18.6)
50-64 years	82 (24.2)
Sex	
Female	146 (43.1)
Male	193 (56.9)
US geographic region, n (%)	
Northeast	44 (13.0)
North central	89 (26.3)
South	176 (51.9)
West	29 (8.6)
Unknown	1 (0.3)
Hospitalized on Time 0, n (%)	47 (13.9)
Immunocompromised state, n (%)	51 (15.0)

J. Deep Vein Thrombosis

Characteristic	Value
Total included individuals	1,013
Age, years	
Mean (SD)	51.1 (10.3)
Median (Q1, Q3)	53 (45, 59)
Age groups, n (%)	
18-34 years	82 (8.1)
35-49 years	288 (28.4)
50-64 years	643 (63.5)
Sex	
Female	423 (41.8)
Male	590 (58.2)
US geographic region, n (%)	
Northeast	102 (10.1)
North central	247 (24.4)
South	541 (53.4)
West	123 (12.1)
Unknown	0 (0.0)
Hospitalized on Time 0, n (%)	301 (29.7)
Immunocompromised state, n (%)	238 (23.5)

K. Pulmonary Embolism

Characteristic	PE, any setting Value	PE, inpatient only Value
Total included individuals	1,444	560
Age, years		
Mean (SD)	50.7 (10.8)	52.5 (9.8)
Median (Q1, Q3)	53 (44, 59)	55 (48, 60)
Age groups, n (%)		
18-34 years	145 (10.0)	41 (7.3)
35-49 years	384 (26.6)	130 (23.2)
50-64 years	915 (63.4)	389 (69.5)
Sex		
Female	663 (45.9)	219 (39.1)
Male	781 (54.1)	341 (60.9)
US geographic region, n (%)		
Northeast	141 (9.8)	43 (7.7)
North central	346 (24.0)	143 (25.5)
South	758 (52.5)	308 (55.0)
West	197 (13.6)	65 (11.6)
Unknown	2 (0.1)	1 (0.2)
Hospitalized on Time 0, n (%)	472 (32.7)	282 (50.4)
Immunocompromised state, n (%)	299 (20.7)	101 (18.0)

L. Disseminated Intravascular Coagulation

Characteristic	Value
Total included individuals	42
Age, years	
Mean (SD)	51.5 (10.3)
Median (Q1, Q3)	55 (43, 59)
Age groups, n (%)	
18-34 years	4 (9.5)
35-49 years	11 (26.2)
50-64 years	27 (64.3)
Sex	
Female	17 (40.5)
Male	25 (59.5)
US geographic region, n (%)	
Northeast	4 (9.5)
North central	7 (16.7)
South	26 (61.9)
West	5 (11.9)
Unknown	0 (0.0)
Hospitalized on Time 0, n (%)	17 (40.5)
Immunocompromised state, n (%)	13 (31.0)

M. Immune Thrombocytopenia

Characteristic	Value
Total included individuals	78
Age, years	
Mean (SD)	47.2 (12.3)
Median (Q1, Q3)	51 (40, 57)
Age groups, n (%)	
18-34 years	14 (17.9)
35-49 years	23 (29.5)
50-64 years	41 (52.6)
Sex	
Female	45 (57.7)
Male	33 (42.3)
US geographic region, n (%)	
Northeast	14 (17.9)
North central	27 (34.6)
South	27 (34.6)
West	9 (11.5)
Unknown	1 (1.3)
Hospitalized on Time 0, n (%)	14 (17.9)
Immunocompromised state, n (%)	54 (69.2)

N. Transverse Myelitis

Characteristic	Value
Total included individuals	7
Age, years	
Mean (SD)	48.1 (8.1)
Median (Q1, Q3)	49 (40, 54)
Age groups, n (%)	
18-34 years	0 (0.0)
35-49 years	4 (57.1)
50-64 years	3 (42.9)
Sex	
Female	5 (71.4)
Male	2 (28.6)
US geographic region, n (%)	
Northeast	0 (0.0)
North central	2 (28.6)
South	5 (71.4)
West	0 (0.0)
Unknown	0 (0.0)
Hospitalized on Time 0, n (%)	2 (28.6)
Immunocompromised state, n (%)	5 (71.4)

PE = pulmonary embolism; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; US = United States.

O. Unusual Site Thrombosis With Thrombocytopenia Syndrome

Not evaluated with SCRI design.

P. Common Site Thrombosis With Thrombocytopenia Syndrome
Not evaluated with SCRI design.

Table B-12-MarketScan. Association of COVID-19 Diagnosis With Adverse Events, Self-Controlled Risk Interval Analysis, MarketScan

Adverse event	N	Cases in risk window	Cases in reference window	Standard model[a] RI (95% CI)	Extended model[b] RI (95% CI)	Seasonality-adjusted extended model[c] RI (95% CI)	Attributable risk per 100,000 COVID-19 cases[c]
Guillain-Barré syndrome	12	7	5	5.84 (1.73-19.73)	7.95 (2.12-29.76)	14.30 (2.34-87.19)	1.97
Bell's palsy	192	62	130	2.41 (1.75-3.32)	2.48 (1.80-3.42)	2.60 (1.83-3.70)	11.53
Narcolepsy	86	22	64	1.77 (1.07-2.93)	1.82 (1.10-3.01)	1.87 (1.08-3.26)	3.09
Appendicitis	296	140	156	4.40 (3.45-5.60)	4.58 (3.59-5.85)	5.00 (3.75-6.67)	33.86
Myocarditis/pericarditis	339	274	65	20.16 (15.10-26.91)	21.33 (15.89-28.63)	24.64 (17.27-35.17)	79.47
Deep vein thrombosis	1,013	627	386	11.19 (9.79-12.79)	11.31 (9.89-12.94)	11.80 (10.11-13.77)	173.48
Pulmonary embolism, inpatient only	560	493	67	62.40 (47.53-81.92)	58.79 (44.86-77.06)	100.95 (67.05-151.97)	147.56
Pulmonary embolism, overall	1,444	1,136	308	28.50 (24.93-32.58)	28.58 (24.98-32.71)	30.49 (25.95-35.83)	332.15
Disseminated intravascular coagulation	42	33	9	20.07 (9.24-43.6)	21.00 (9.61-45.88)	83.52 (18.72-372.74)	9.86
Immune thrombocytopenia	78	29	49	2.80 (1.73-4.53)	2.91 (1.79-4.72)	3.03 (1.74-5.28)	5.87
Transverse myelitis	7	3	4	2.90 (0.64-13.08)	2.95 (0.65-13.31)	4.84 (0.78-30.11)	0.72

CI = confidence interval; COVID-19 = coronavirus disease 2019; RI = relative incidence.

[a] Conditional Poisson regression.

[b] Conditional Poisson model accounting for event-dependent observation windows.

[c] Conditional Poisson model accounting for event-dependent observation windows and adjusted for seasonality as calendar month groupings, with December treated as a full calendar month.

Table B-13-MarketScan. Association of COVID-19 Diagnosis With Adverse Events, Self-Controlled Risk Interval Analysis, Within Subgroups, MarketScan

A. Guillain-Barré Syndrome

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Sex				
Female	5	1	4	0.46 (0.05-4.40)
Male	7	6	1	NE
Age group				
18-34 years	1	0	1	NE
35-49 years	5	3	2	5.39 (0.52-56.18)
50-64 years	6	4	2	27.37 (4.28-174.85)
Immunocompromised state	5	1	4	1.03 (0.09-11.46)
Hospitalization status on Time 0				
Hospitalized on Time 0	3	2	1	NE
Nonhospitalized on Time 0	9	5	4	4.06 (0.89-18.56)

B. Bell's Palsy

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Sex				
Female	107	37	70	2.84 (1.80-4.48)
Male	85	25	60	2.33 (1.33-4.09)
Age group				
18-34 years	28	7	21	1.57 (0.55-4.50)
35-49 years	75	25	50	2.94 (1.64-5.28)
50-64 years	89	30	59	2.88 (1.73-4.80)
Immunocompromised state	40	11	29	2.36 (1.02-5.44)
Hospitalization status on Time 0				
Hospitalized on Time 0	18	5	13	2.19 (0.66-7.20)
Nonhospitalized on Time 0	174	57	117	2.76 (1.89-4.02)

C. Encephalitis/Encephalomyelitis

Not evaluated with SCRI design.

D. Narcolepsy

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Sex				
Female	64	19	45	2.33 (1.25-4.37)
Male	22	3	19	0.91 (0.24-3.44)
Age group				
18-34 years	36	12	24	3.06 (1.29-7.25)
35-49 years	22	4	18	1.01 (0.31-3.31)
50-64 years	28	6	22	1.29 (0.47-3.52)
Immunocompromised state	14	5	9	3.29 (0.91-11.94)
Hospitalization status on Time 0				
Hospitalized on Time 0	5	2	3	10.08 (0.86-118.46)
Nonhospitalized on Time 0	81	20	61	1.81 (1.01-3.27)

E. Appendicitis

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Sex				
Female	134	57	77	3.46 (2.28-5.24)
Male	162	83	79	6.92 (4.57-10.5)
Age group				
18-34 years	149	82	67	6.64 (4.44-9.94)
35-49 years	93	39	54	4.26 (2.53-7.17)
50-64 years	54	19	35	3.09 (1.56-6.12)
Immunocompromised state	47	15	32	1.84 (0.90-3.75)
Hospitalization status on Time 0				
Hospitalized on Time 0	38	33	5	818.13 (51.88-12,900.74)
Nonhospitalized on Time 0	258	107	151	3.67 (2.71-4.97)

F. Nonhemorrhagic Stroke

Not evaluated with SCRI design.

G. Hemorrhagic Stroke

Not evaluated with SCRI design.

H. Acute Myocardial Infarction

Not evaluated with SCRI design.

I. Myocarditis/Pericarditis

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Sex				
Female	146	110	36	14.77 (9.24-23.60)
Male	193	164	29	52.00 (27.56-98.08)
Age group				
18-34 years	194	174	20	60.29 (31.57-115.16)
35-49 years	63	42	21	9.17 (4.92-17.08)
50-64 years	82	58	24	18.41 (9.58-35.38)
Immunocompromised state	51	27	24	5.47 (2.84-10.54)
Hospitalization status on Time 0				
Hospitalized on Time 0	47	42	5	80.06 (23.45-273.36)
Nonhospitalized on Time 0	292	232	60	21.80 (14.89-31.93)

J. Deep Vein Thrombosis

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Sex				
Female	423	227	196	7.99 (6.39-9.99)
Male	590	400	190	16.58 (13.31-20.64)
Age group				
18-34 years	82	43	39	8.83 (5.18-15.05)
35-49 years	288	189	99	15.95 (11.68-21.77)
50-64 years	643	395	248	11.07 (9.13-13.42)
Immunocompromised state	238	110	128	5.61 (4.16-7.57)
Hospitalization status on Time 0				
Hospitalized on Time 0	301	247	54	50.53 (33.24-76.82)
Nonhospitalized on Time 0	712	380	332	7.88 (6.62-9.39)

K. Pulmonary Embolism

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Any setting				
Sex				
Female	663	500	163	24.77 (19.86-30.88)
Male	781	636	145	38.93 (30.79-49.21)
Age group				
18-34 years	145	101	44	16.56 (10.77-25.47)
35-49 years	384	304	80	30.37 (22.01-41.9)
50-64 years	915	731	184	34.55 (28.03-42.58)
Immunocompromised state	299	206	93	19.12 (13.81-26.49)
Hospitalization status on Time 0				
Hospitalized on Time 0	472	434	38	277.89 (155.44-496.81)
Nonhospitalized on Time 0	972	702	270	18.30 (15.45-21.67)

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Inpatient only				
Sex				
Female	219	188	31	68.14 (38.32-121.17)
Male	341	305	36	139.42 (78.36-248.03)
Age group				
18-34 years	41	32	9	78.04 (19.95-305.28)
35-49 years	130	115	15	99.29 (42.39-232.54)
50-64 years	389	346	43	117.83 (70.74-196.27)
Immunocompromised state				
Hospitalization status on Time 0	101	79	22	32.40 (16.85-62.31)
Hospitalized on Time 0	282	273	9	173,630.95 (20,821.58-1,447,906.93)
Nonhospitalized on Time 0	278	220	58	29.82 (20.38-43.64)

L. Disseminated Intravascular Coagulation

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Sex				
Female	17	15	2	NE
Male	25	18	7	64.73 (8.98-466.56)
Age group				
18-34 years	4	3	1	NE
35-49 years	11	8	3	32.47 (3.23-326.08)
50-64 years	27	22	5	103.45 (13.58-788.19)
Immunocompromised state	13	6	7	20.25 (1.70-241.60)
Hospitalization status on Time 0				
Hospitalized on Time 0	17	15	2	434.75 (17.29-10,931.04)
Nonhospitalized on Time 0	25	18	7	70.90 (11.44-439.28)

M. Immune Thrombocytopenia

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Sex				
Female	45	15	30	2.82 (1.32-6.01)
Male	33	14	19	3.76 (1.54-9.20)
Age group				
18-34 years	14	1	13	0.35 (0.04-3.09)
35-49 years	23	10	13	7.34 (2.16-24.95)
50-64 years	41	18	23	3.51 (1.66-7.41)
Immunocompromised state	54	10	44	1.58 (0.69-3.61)
Hospitalization status on Time 0				
Hospitalized on Time 0	14	13	1	NE
Nonhospitalized on Time 0	64	16	48	1.54 (0.80-2.96)

N. Transverse Myelitis

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Sex				
Female	5	2	3	2.00 (0.25-15.84)
Male	2	1	1	NE
Age group				
18-34 years	0	0	0	NE
35-49 years	4	2	2	NE
50-64 years	3	1	2	0.87 (0.05-14.65)
Immunocompromised state	5	1	4	0.81 (0.05-14.35)
Hospitalization status on Time 0				
Hospitalized on Time 0	2	1	1	0.95 (0.06-16.01)
Nonhospitalized on Time 0	5	2	3	4.07 (0.38-43.24)

O. Unusual Site Thrombosis With Thrombocytopenia Syndrome

Not evaluated with SCRI

P. Common Site Thrombosis With Thrombocytopenia Syndrome

Not evaluated with SCRI.

CI = confidence interval; RI = relative incidence; SCRI = self-controlled risk interval.

[a] Conditional Poisson model accounting for event-dependent observation windows and adjusted for seasonality.

Table B-14-MarketScan. Association of COVID-19 Diagnosis With Adverse Events Within Prespecified Risk Windows and Pre-Exposure and Postexposure Alternative Windows Compared With the Referent Window, Self-Controlled Risk Interval Analysis Using Extended Poisson Model for Event-Dependent Observation Windows, MarketScan

Adverse event	Risk period	N	Cases in risk window	Cases in reference window	Extended model [a] RI (95% CI)
Guillain-Barré syndrome	Pre-exposure window (days [−7, −1])	14	1	5	4.15 (0.53-32.42)
	Day 0 (day [0, 0])	14	2	5	73.37 (15.02-358.51)
	Modified, prespecified risk window (days [1, 41])	14	5	5	8.53 (2.45-29.65)
	Postexposure buffer (days [42, 69])	14	1	5	NE
Bell's palsy	Pre-exposure window (days [−7, −1])	222	11	130	1.89 (1.00-3.55)
	Day 0 (day [0, 0])	222	15	130	17.52 (10.33-29.73)
	Modified, prespecified risk window (days [1, 41])	222	47	130	1.95 (1.39-2.74)
	Postexposure buffer (days [42, 69])	222	19	130	5.41 (1.72-17.05)
Narcolepsy	Pre-exposure window (days [−7, −1])	95	5	64	1.97 (0.77-5.02)
	Day 0 (day [0, 0])	95	5	64	12.72 (5.13-31.53)
	Modified, prespecified risk window (days [1, 41])	95	17	64	1.44 (0.84-2.47)
	Postexposure buffer (days [42, 69])	95	4	64	NE
Appendicitis	Pre-exposure window (days [−7, −1])	316	5	156	0.70 (0.28-1.71)
	Day 0 (day [0, 0])	316	95	156	91.27 (71.38-116.70)
	Modified, prespecified risk window (days [1, 41])	316	45	156	1.38 (1.00-1.90)
	Postexposure buffer (days [42, 69])	316	15	156	1.43 (0.20-10.26)
Myocarditis/pericarditis	Pre-exposure window (days [−7, −1])	375	14	65	4.19 (2.45-7.16)
	Day 0 (day [0, 0])	375	128	65	260.47 (208.27-325.76)
	Modified, prespecified risk window (days [1, 41])	375	146	65	9.03 (7.22-11.29)
	Postexposure buffer (days [42, 69])	375	22	65	1.50 (0.19-11.55)
Deep vein thrombosis	Pre-exposure window (days [−7, −1])	1,175	38	386	2.08 (1.51-2.88)
	Day 0 (day [0, 0])	1,175	177	386	64.62 (54.77-76.25)
	Modified, prespecified risk window (days [1, 27])	1,175	450	386	8.04 (7.07-9.14)
	Postexposure buffer (days [28, 55])	1,175	124	386	1.52 (0.57-4.06)
Pulmonary embolism, inpatient	Pre-exposure window (days [−7, −1])	609	21	67	6.75 (4.37-10.45)
	Day 0 (day [0, 0])	609	245	67	556.35 (469.18-659.72)
	Modified, prespecified risk window (days [1, 27])	609	248	67	27.36 (23.01-32.55)
	Postexposure buffer (days [28, 55])	609	28	67	4.40 (1.10-17.66)
Pulmonary embolism, overall	Pre-exposure window (days [−7, −1])	1,612	56	308	3.65 (2.73-4.87)
	Day 0 (day [0, 0])	1,612	503	308	227.88 (204.11-254.42)

Adverse event	Risk period	N	Cases in risk window	Cases in reference window	Extended model [a] RI (95% CI)
	Modified, prespecified risk window (days [1, 27])	1,612	633	308	13.55 (12.17-15.09)
	Postexposure buffer (days [28, 55])	1,612	112	308	5.58 (3.16-9.86)
Disseminated intravascular coagulation	Pre-exposure window (days [−7, −1])	50	6	9	18.37 (7.72-43.70)
	Day 0 (day [0, 0])	50	12	9	361.01 (181.34-718.70)
	Modified, prespecified risk window (days [1, 27])	50	21	9	32.28 (17.06-61.09)
	Postexposure buffer (days [28, 55])	50	2	9	NE
Immune thrombocytopenia	Pre-exposure window (days [−7, −1])	88	3	49	1.29 (0.41-4.08)
	Day 0 (day [0, 0])	88	11	49	30.07 (15.72-57.50)
	Modified, prespecified risk window (days [1, 41])	88	18	49	1.74 (1.01-3.00)
	Postexposure buffer (days [42, 69])	88	7	49	NE
Transverse myelitis	Pre-exposure window (days [−7, −1])	9	1	4	9.18 (1.05-79.95)
	Day 0 (day [0, 0])	9	1	4	38.91 (4.17-363.36)
	Modified, prespecified risk window (days [1, 41])	9	2	4	3.14 (0.56-17.50)
	Postexposure buffer (days [42, 69])	9	1	4	NE

CI = confidence interval; COVID-19 = coronavirus disease 2019; NE = not estimable; RI = relative incidence.

[a] Conditional Poisson model accounting for event-dependent observation windows and adjusted for seasonality.

B.2. Medicare

B.2.1. Cohort Analyses

Table B-1-Medicare. Selection of Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis for the Cohort Study, Medicare

Characteristic	Value
Overall study cohort	
Individuals with COVID-19 diagnosis during the study period	1,807,670
Excluded for being aged outside age range, N (%)	253,377 (14.0%)
Excluded for lacking 365 days of continuous data base enrollment before Time 0, N (%)	436,595 (24.2%)
Excluded for lacking ≥ 1 healthcare claim during 365 days before Time 0, N (%)	9,722 (0.5%)
Excluded for having a COVID-19 diagnosis before Time 0, N (%)	10,510 (0.6%)
Excluded for having a select respiratory infection before Time 0, N (%)	12,048 (0.7%)
Eligible adults with new-onset COVID-19	1,085,418
Excluded for failing to match, N (%)	68,008 (6.3%)
Matched individuals with COVID-19	1,017,410
Matched comparator observations[a] (unique individuals)	1,017,410 (930,513)
Total study cohort	2,034,820
Adverse event-specific analysis sets[b]	
Excluded for having previous Guillain-Barré syndrome	1,602 (0.1%)
Guillain-Barré syndrome analysis set	2,033,218 (99.9%)
Excluded for having previous Bell's palsy	4,560 (0.2%)
Bell's palsy analysis set	2,030,260 (99.8%)
Excluded for having previous encephalitis/encephalomyelitis	1,039 (0.1%)
Encephalitis/encephalomyelitis analysis set	2,033,781 (99.9%)
Excluded for having previous narcolepsy	2,504 (0.1%)
Narcolepsy analysis set	2,032,316 (99.9%)
Excluded for having previous appendicitis	2,771 (0.1%)
Appendicitis analysis set	2,032,049 (99.9%)
Excluded for having previous nonhemorrhagic stroke	177,011 (8.7%)
Nonhemorrhagic stroke analysis set	1,857,809 (91.3%)
Excluded for having previous hemorrhagic stroke	28,459 (1.4%)
Hemorrhagic stroke analysis set	2,006,361 (98.6%)
Excluded for having previous acute myocardial infarction	83,837 (4.1%)
Acute myocardial infarction analysis set	1,950,983 (95.9%)
Excluded for having previous myocarditis pericarditis	3,297 (0.2%)
Myocarditis/pericarditis analysis set	2,031,523 (99.8%)
Excluded for having previous deep vein thrombosis	71,089 (3.5%)
Deep vein thrombosis analysis set	1,963,731 (96.5%)
Excluded for having previous pulmonary embolism	40,225 (2.0%)
Pulmonary embolism analysis set[c]	1,994,595 (98.0%)
Excluded for having previous disseminated intravascular coagulation	1,204 (0.1%)
Disseminated intravascular coagulation analysis set	2,033,616 (99.9%)
Excluded for having previous immune thrombocytopenia	5,517 (0.3%)
Immune thrombocytopenia analysis set	2,029,303 (99.7%)
Excluded for having previous transverse myelitis	532 (0.0%)

Characteristic	Value
Transverse myelitis analysis set	2,034,288 (100.0%)
Excluded for having previous unusual site thrombosis with thrombocytopenia	783 (0.0%)
Unusual site thrombosis with thrombocytopenia analysis set	2,034,037 (100.0%)
Excluded for having previous common site thrombosis with thrombocytopenia	22,400 (1.1%)
Common site thrombosis with thrombocytopenia analysis set	2,012,420 (98.9%)

COVID-19 = coronavirus disease 2019.

[a] A unique individual may be included multiple times because of matching with replacement, and an individual may be included in both the exposure and comparator groups. This table counts each instance of an individual's entry separately as distinct observations; the number of unique individuals is reported separately.

[b] Denominators for all adverse event-specific exclusions are the total study cohort; exclusions are noncumulative across analysis sets.

[c] Both pulmonary embolism outcomes (i.e., inpatient-only, and in any setting) were evaluated in the same analysis set.

Table B-2-Medicare. Characteristics of Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis Included in the Cohort Study, Medicare

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group	ASD
Total selected observations[a] (unique individuals)	1,017,410 (1,017,410)	1,017,410 (930,513)	
Demographic characteristics			
Age, years			
Mean (SD)	77.7 (8.6)	77.7 (8.6)	0.00
Median (Q1, Q3)	76 (71, 84)	76 (71, 84)	
Age groups, n (%)			
65-79 years	629,709 (61.9)	629,709 (61.9)	
≥ 80 years	387,701 (38.1)	387,701 (38.1)	
Sex, n (%)			0.00
Female	590,584 (58.0)	590,584 (58.0)	
Male	426,826 (42.0)	426,826 (42.0)	
US geographic region, n (%)			0.00
Northeast	218,277 (21.5)	218,107 (21.4)	
North central	250,139 (24.6)	250,130 (24.6)	
South	385,012 (37.8)	385,108 (37.9)	
West	161,002 (15.8)	161,085 (15.8)	
Unknown	2,980 (0.3)	2,980 (0.3)	
Race/ethnicity, n (%)[b]			0.08
American Indian/ Alaska Native	7,510 (0.7)	5,240 (0.5)	
Asian	16,819 (1.7)	19,101 (1.9)	
Black or African American	90,997 (8.9)	87,757 (8.6)	
Hispanic/Latin American/Latinx	26,460 (2.6)	16,390 (1.6)	
White	845,042 (83.1)	857,204 (84.3)	
A race/ethnicity not listed	13,898 (1.4)	14,649 (1.4)	
Not provided	16,684 (1.6)	17,069 (1.7)	
Dual Medicare/Medicaid eligibility, n (%)[b]	297,499 (29.2)	267,943 (26.3)	0.06
Original reason for Medicare eligibility, n (%)[b]			0.04
Age	860,430 (84.6)	871,968 (85.7)	
Disability	150,916 (14.8)	141,239 (13.9)	
End-stage renal disease	6,064 (0.6)	4,203 (0.4)	
Hospitalized on Time 0, n (%)	166,154 (16.3)	166,154 (16.3)	0.00
SNF/LTC[b] residence on Time 0, n (%)	250,193 (24.6)	250,193 (24.6)	0.00
Comorbidities, n (%)			
Animal exposure/bites or rabies	3,105 (0.3)	3,204 (0.3)	0.00
Antiphospholipid syndrome	829 (0.1)	855 (0.1)	0.00
Autoimmune disorders	93,071 (9.1)	89,588 (8.8)	0.01
Brain lesions related to secondary narcolepsy	519 (0.1)	517 (0.1)	0.00
Cancer	272,867 (26.8)	283,933 (27.9)	0.02
Chronic lymphocytic leukemia	6,995 (0.7)	6,673 (0.7)	0.00
Chronic kidney disease or renal disease (other than end-stage renal disease)	276,654 (27.2)	262,576 (25.8)	0.03
End-stage renal disease[b]	20,229 (2.0)	14,209 (1.4)	0.05

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group	ASD
Chronic liver disease	80,781 (7.9)	78,853 (7.8)	0.01
Chronic lung diseases	293,426 (28.8)	265,622 (26.1)	0.06
Dementia or other neurologic condition	350,351 (34.4)	308,057 (30.3)	0.09
Diabetes, Type 1 or 2	406,448 (39.9)	364,235 (35.8)	0.09
Disseminated intravascular coagulation[c]	324 (0.0)	331 (0.0)	0.00
Heart conditions	614,855 (60.4)	586,102 (57.6)	0.06
Hemiplegia or paraplegia	61,853 (6.1)	61,794 (6.1)	0.00
Herpes simplex infection	16,959 (1.7)	15,509 (1.5)	0.01
Hypertension	823,414 (80.9)	800,051 (78.6)	0.06
Immunocompromised state	438,954 (43.1)	438,954 (43.1)	0.00
Infection associated with GBS	51,279 (5.0)	43,254 (4.3)	0.04
Viral infection associated with ITP	3,702 (0.4)	3,358 (0.3)	0.01
Infection associated with myocarditis/pericarditis	111,923 (11.0)	104,135 (10.2)	0.02
Inpatient surgery	43,070 (4.2)	53,725 (5.3)	0.05
Lipid abnormality	733,659 (72.1)	714,996 (70.3)	0.04
Mental health conditions	441,954 (43.4)	404,912 (39.8)	0.07
Nutritional deficiency	80,039 (7.9)	79,309 (7.8)	0.00
Obese or severely obese	233,833 (23.0)	209,074 (20.5)	0.06
Peripheral vascular disease	318,384 (31.3)	292,986 (28.8)	0.05
Pneumonia or lower respiratory tract infection	237,118 (23.3)	188,874 (18.6)	0.12
Sepsis	59,822 (5.9)	58,347 (5.7)	0.01
Sickle cell disease or thalassemia	2,611 (0.3)	2,472 (0.2)	0.00
Smoking/nicotine dependency	64,705 (6.4)	80,909 (8.0)	0.06
Stroke or cerebrovascular disease	228,802 (22.5)	221,952 (21.8)	0.02
Thromboembolism	77,562 (7.6)	75,096 (7.4)	0.01
Thrombophilia	11,107 (1.1)	10,876 (1.1)	0.00
Trauma	24,546 (2.4)	29,888 (2.9)	0.03
Tuberculosis	2,585 (0.3)	2,299 (0.2)	0.01
Healthcare utilization, n (%)			
Inpatient stays in previous 365 days			0.02
0	729,890 (71.7)	721,877 (71.0)	
1-2	204,101 (20.1)	207,086 (20.4)	
≥ 3	83,419 (8.2)	88,447 (8.7)	
ED visits in previous 365 days			0.06
0	572,454 (56.3)	602,727 (59.2)	
1-2	282,442 (27.8)	259,078 (25.5)	
≥ 3	162,514 (16.0)	155,605 (15.3)	
Outpatient provider visits[d] in previous 365 days			0.17
0	93 (0.0)	172 (0.0)	
1-2	21,024 (2.1)	39,570 (3.9)	
3-5	51,668 (5.1)	75,724 (7.4)	
6-10	118,531 (11.7)	139,787 (13.7)	
≥ 11	826,094 (81.2)	762,157 (74.9)	
SNF/LTC stay[e]	295,527 (29.0)	286,390 (28.1)	0.02
Influenza vaccination in previous year	570,066 (56.0)	572,746 (56.3)	0.01

AE = adverse event; ASD = absolute standardized difference; COVID-19 = coronavirus disease 2019; ED = emergency department; GBS = Guillain-Barré syndrome; ITP = immune thrombocytopenia; LTC = long-term care; Q1 = first quartile, Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] A unique individual may be included multiple times because of matching with replacement, and an individual may be included in both the exposure and comparator groups. This table counts each instance of an individual's entry separately as distinct observations; the number of unique individuals is reported separately.

[b] Only available in Medicare.

[c] This serves as an AE-specific exclusion criterion when the condition is evaluated as an outcome, but history of the condition serves as a covariate for analyses of other AEs.

[d] Unique days on which an outpatient visit occurred.

[e] SNF and LTC both identified in Medicare; SNF identified in MarketScan.

Table B-3-Medicare. Characteristics of Individuals With a COVID-19 Diagnosis Included in the Cohort Study and Those Excluded for Failing to Match, Medicare

Characteristic	COVID-19 diagnosis (exposure) group retained by matching	Individuals with a COVID-19 diagnosis who failed to match
Total unique individuals	1,017,410 (1,017,410)	68,008 (68,008)
Demographic characteristics		
Age, years		
Mean (SD)	77.7 (8.6)	80.8 (9.0)
Median (Q1, Q3)	76.0 (71.0, 84.0)	81.0 (73.0, 88.0)
Age groups, n (%)		
65-79 years	629,709 (61.9)	31,064 (45.7)
≥ 80 years	387,701 (38.1)	36,944 (54.3)
Sex, n (%)		
Female	590,584 (58.0)	34,257 (50.4)
Male	426,826 (42.0)	33,751 (49.6)
US geographic region, n (%)		
Northeast	218,277 (21.5)	9,103 (13.4)
North central	250,139 (24.6)	19,879 (29.2)
South	385,012 (37.8)	31,590 (46.5)
West	161,002 (15.8)	7,093 (10.4)
Unknown	2,980 (0.3)	343 (0.5)
Race/ethnicity, n (%)		
American Indian/Alaska Native	7,510 (0.7)	928 (1.4)
Asian	16,819 (1.7)	904 (1.3)
Black or African American	90,997 (8.9)	9,789 (14.4)
Hispanic/Latin American/Latinx	26,460 (2.6)	1,640 (2.4)
White	845,042 (83.1)	53,588 (78.8)
A race/ethnicity not listed	13,898 (1.4)	730 (1.1)
Not provided	16,684 (1.6)	429 (0.6)
Dual Medicare/Medicaid eligibility, n (%)	297,499 (29.2)	30,409 (44.7)
Original reason for Medicare eligibility, n (%)		
Age	860,430 (84.6)	53,381 (78.5)
Disability	150,916 (14.8)	14,052 (20.7)
End-stage renal disease	6,064 (0.6)	575 (0.8)
Hospitalized on Time 0, n (%)	166,154 (16.3)	67,764 (99.6)
SNF/LTC[a] residence on Time 0, n (%)	250,193 (24.6)	33,311 (49.0)
Comorbidities, n (%)		
Animal exposure/bites or rabies	3,105 (0.3)	130 (0.2)
Antiphospholipid syndrome	829 (0.1)	40 (0.1)
Autoimmune disorders	93,071 (9.1)	5,722 (8.4)
Brain lesions related to secondary narcolepsy	519 (0.1)	54 (0.1)
Cancer	272,867 (26.8)	16,744 (24.6)
Chronic lymphocytic leukemia	6,995 (0.7)	576 (0.8)

Characteristic	COVID-19 diagnosis (exposure) group retained by matching	Individuals with a COVID-19 diagnosis who failed to match
Chronic kidney disease or renal disease (other than end-stage renal disease)	276,654 (27.2)	29,364 (43.2)
End-stage renal disease	20,229 (2.0)	2,489 (3.7)
Chronic liver disease	80,781 (7.9)	5,759 (8.5)
Chronic lung diseases	293,426 (28.8)	25,836 (38.0)
Dementia or other neurologic condition	350,351 (34.4)	34,022 (50.0)
Diabetes, Type 1 or 2	406,448 (39.9)	33,886 (49.8)
Disseminated intravascular coagulation[a]	324 (0.0)	28 (0.0)
Heart conditions	614,855 (60.4)	49,731 (73.1)
Hemiplegia or paraplegia	61,853 (6.1)	7,582 (11.1)
Herpes simplex infection	16,959 (1.7)	948 (1.4)
Hypertension	823,414 (80.9)	59,938 (88.1)
Immunocompromised state	438,954 (43.1)	27,919 (41.1)
Infection associated with GBS	51,279 (5.0)	4,484 (6.6)
Viral infection associated with ITP	3,702 (0.4)	237 (0.3)
Infection associated with myocarditis/pericarditis	111,923 (11.0)	11,207 (16.5)
Inpatient surgery	43,070 (4.2)	5,421 (8.0)
Lipid abnormality	733,659 (72.1)	48,762 (71.7)
Mental health conditions	441,954 (43.4)	35,803 (52.6)
Nutritional deficiency	80,039 (7.9)	9,196 (13.5)
Obese or severely obese	233,833 (23.0)	16,401 (24.1)
Peripheral vascular disease	318,384 (31.3)	28,432 (41.8)
Pneumonia or lower respiratory tract infection	237,118 (23.3)	22,636 (33.3)
Sepsis	59,822 (5.9)	8,147 (12.0)
Sickle cell disease or thalassemia	2,611 (0.3)	177 (0.3)
Smoking/nicotine dependency	64,705 (6.4)	5,848 (8.6)
Stroke or cerebrovascular disease	228,802 (22.5)	21,214 (31.2)
Thromboembolism	77,562 (7.6)	7,678 (11.3)
Thrombophilia	11,107 (1.1)	763 (1.1)
Trauma	24,546 (2.4)	3,371 (5.0)
Tuberculosis	2,585 (0.3)	218 (0.3)
Healthcare utilization, n (%)		
Inpatient stays in previous 365 days		
0	729,890 (71.7)	37,200 (54.7)
1-2	204,101 (20.1)	19,704 (29.0)
≥ 3	83,419 (8.2)	11,104 (16.3)
ED visits in previous 365 days		
0	572,454 (56.3)	26,433 (38.9)
1-2	282,442 (27.8)	22,149 (32.6)
≥ 3	162,514 (16.0)	19,426 (28.6)
Outpatient provider visits [b] in previous 365 days		
0	93 (0.0)	13 (0.0)
1-2	21,024 (2.1)	1,189 (1.7)

Characteristic	COVID-19 diagnosis (exposure) group retained by matching	Individuals with a COVID-19 diagnosis who failed to match
3-5	51,668 (5.1)	2,598 (3.8)
6-10	118,531 (11.7)	5,352 (7.9)
≥ 11	826,094 (81.2)	58,856 (86.5)
SNF/LTC stay	295,527 (29.0)	36,920 (54.3)
Influenza vaccination in previous year	570,066 (56.0)	33,767 (49.7)

AE = adverse event; COVID-19 = coronavirus disease 2019; ED = emergency department; GBS = Guillain-Barré syndrome; ITP = immune thrombocytopenia; LTC = long-term care; Q1 = first quartile, Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] This serves as an AE-specific exclusion criterion when the condition is evaluated as an outcome, but history of the condition serves as a covariate for analyses of other AEs.

[b] Unique days on which an outpatient visit occurred.

Table B-4-Medicare. Distribution of Stabilized Inverse Probability of Treatment Weights in Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis Included in the Cohort Study, Medicare

A. Guillain-Barré Syndrome

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	1,016,611	1,016,607
Total weighted sample size (sum of all sIPT weights)	1,015,994	1,015,672
Distribution of sIPT weights		
Mean (SD)	1.00 (0.14)	1.00 (0.14)
Median (Q1, Q3)	0.98 (0.91, 1.07)	0.99 (0.90, 1.07)
Minimum	0.74	0.74
Maximum	1.46	1.46

B. Bell's Palsy

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	1,015,088	1,015,172
Total weighted sample size (sum of all sIPT weights)	1,014,186	1,014,466
Distribution of sIPT weights		
Mean (SD)	1.00 (0.13)	1.00 (0.13)
Median (Q1, Q3)	0.98 (0.91, 1.06)	1.00 (0.91, 1.07)
Minimum	0.75	0.75
Maximum	1.44	1.44

C. Encephalitis/Encephalomyelitis

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	1,016,911	1,016,870
Total weighted sample size (sum of all sIPT weights)	1,016,281	1,015,921
Distribution of sIPT weights		
Mean (SD)	1.00 (0.14)	1.00 (0.13)
Median (Q1, Q3)	0.98 (0.91, 1.07)	0.99 (0.91, 1.07)
Minimum	0.74	0.74
Maximum	1.45	1.45

D. Narcolepsy

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	1,016,109	1,016,207
Total weighted sample size (sum of all sIPT weights)	1,015,223	1,015,531
Distribution of sIPT weights		
Mean (SD)	1.00 (0.13)	1.00 (0.12)
Median (Q1, Q3)	0.98 (0.92, 1.06)	1.00 (0.92, 1.07)
Minimum	0.75	0.75
Maximum	1.43	1.43

E. Appendicitis

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	1,016,139	1,015,910
Total weighted sample size (sum of all sIPT weights)	1,015,412	1,015,094
Distribution of sIPT weights		
Mean (SD)	1.00 (0.13)	1.00 (0.13)
Median (Q1, Q3)	0.98 (0.92, 1.06)	1.00 (0.91, 1.07)
Minimum	0.75	0.75
Maximum	1.44	1.44

F. Nonhemorrhagic Stroke

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	928,618	929,191
Total weighted sample size (sum of all sIPT weights)	927,951	928,031
Distribution of sIPT weights		
Mean (SD)	1.00 (0.15)	1.00 (0.15)
Median (Q1, Q3)	0.98 (0.89, 1.08)	0.98 (0.89, 1.08)
Minimum	0.73	0.73
Maximum	1.50	1.50

G. Hemorrhagic Stroke

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	1,003,495	1,002,866
Total weighted sample size (sum of all sIPT weights)	1,002,779	1,001,720
Distribution of sIPT weights		
Mean (SD)	1.00 (0.15)	1.00 (0.15)
Median (Q1, Q3)	0.98 (0.90, 1.07)	0.99 (0.90, 1.08)
Minimum	0.73	0.73
Maximum	1.48	1.48

H. Acute Myocardial Infarction

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	975,854	975,129
Total weighted sample size (sum of all sIPT weights)	975,114	974,158
Distribution of sIPT weights		
Mean (SD)	1.00 (0.14)	1.00 (0.14)
Median (Q1, Q3)	0.98 (0.90, 1.07)	0.99 (0.90, 1.08)
Minimum	0.73	0.73
Maximum	1.47	1.47

I. Myocarditis/Pericarditis

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	1,015,725	1,015,798
Total weighted sample size (sum of all sIPT weights)	1,015,041	1,014,903
Distribution of sIPT weights		
Mean (SD)	1.00 (0.13)	1.00 (0.13)
Median (Q1, Q3)	0.98 (0.91, 1.06)	0.99 (0.91, 1.07)
Minimum	0.74	0.74
Maximum	1.45	1.45

J. Deep Vein Thrombosis

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	981,125	982,606
Total weighted sample size (sum of all sIPT weights)	980,365	981,522
Distribution of sIPT weights		
Mean (SD)	1.00 (0.15)	1.00 (0.15)
Median (Q1, Q3)	0.98 (0.90, 1.07)	0.99 (0.90, 1.08)
Minimum	0.73	0.73
Maximum	1.49	1.49

K. Pulmonary Embolism

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	996,999	997,596
Total weighted sample size (sum of all sIPT weights)	996,236	996,510
Distribution of sIPT weights		
Mean (SD)	1.00 (0.15)	1.00 (0.15)
Median (Q1, Q3)	0.98 (0.90, 1.07)	0.99 (0.90, 1.08)
Minimum	0.73	0.73
Maximum	1.48	1.48

L. Disseminated Intravascular Coagulation

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	1,016,803	1,016,813
Total weighted sample size (sum of all sIPT weights)	1,016,029	1,015,784
Distribution of sIPT weights		
Mean (SD)	1.00 (0.14)	1.00 (0.14)
Median (Q1, Q3)	0.98 (0.90, 1.07)	0.99 (0.90, 1.08)
Minimum	0.74	0.74
Maximum	1.47	1.47

M. Immune Thrombocytopenia

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	1,014,639	1,014,664
Total weighted sample size (sum of all sIPT weights)	1,013,882	1,013,898
Distribution of sIPT weights		
Mean (SD)	1.00 (0.13)	1.00 (0.13)
Median (Q1, Q3)	0.98 (0.92, 1.06)	1.00 (0.91, 1.07)
Minimum	0.75	0.75
Maximum	1.44	1.44

N. Transverse Myelitis

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	1,017,133	1,017,155
Total weighted sample size (sum of all sIPT weights)	1,016,479	1,016,168
Distribution of sIPT weights		
Mean (SD)	1.00 (0.14)	1.00 (0.14)
Median (Q1, Q3)	0.98 (0.91, 1.07)	0.99 (0.90, 1.07)
Minimum	0.74	0.74
Maximum	1.46	1.46

O. Unusual Site Thrombosis With Thrombocytopenia Syndrome

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	1,017,065	1,016,972
Total weighted sample size (sum of all sIPT weights)	1,016,282	1,015,888
Distribution of sIPT weights		
Mean (SD)	1.00 (0.15)	1.00 (0.15)
Median (Q1, Q3)	0.98 (0.90, 1.07)	0.99 (0.90, 1.08)
Minimum	0.73	0.73
Maximum	1.48	1.48

P. Common Site Thrombosis With Thrombocytopenia Syndrome

Characteristic	COVID-19 diagnosis (exposure) group	Comparator group
Total included observations[a]	1,006,735	1,005,685
Total weighted sample size (sum of all sIPT weights)	1,005,959	1,004,591
Distribution of sIPT weights		
Mean (SD)	1.00 (0.15)	1.00 (0.15)
Median (Q1, Q3)	0.98 (0.90, 1.07)	0.99 (0.90, 1.08)
Minimum	0.73	0.73
Maximum	1.49	1.49

COVID-19 = coronavirus disease 2019; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; sIPT = stabilized inverse probability of treatment.

[a] A unique individual may be included multiple times because of matching with replacement, and an individual may be included in both the exposure and comparator groups. This table counts each instance of an individual's entry separately as distinct observations.

Table B-5-Medicare. Association of a COVID-19 Diagnosis With Adverse Events, Cohort Design, Medicare

A. Guillain-Barré syndrome

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	45	81,022,327	6.73 (4.58-8.89)	1.03 (0.66-1.62)	1.06 (0.67-1.68)
All of follow-up (day 0 – end)	Comparator	45	87,266,038	16.41 (0.00-37.81)	—	—
Day 0	COVID-19	11	1,016,611	1.08 (0.44-1.72)	0.44 (0.21-0.92)	0.45 (0.21-0.94)
Day 0	Comparator	25	1,016,607	2.46 (1.39-3.53)	—	—
Day 0-41	COVID-19	36	31,210,080	4.39 (2.93-5.86)	0.92 (0.57-1.49)	0.95 (0.58-1.55)
Day 0-41	Comparator	40	32,696,330	4.27 (2.75-5.79)	—	—
Day 0-90	COVID-19	41	53,253,214	5.42 (3.70-7.14)	1.03 (0.64-1.64)	1.06 (0.66-1.70)
Day 0-90	Comparator	41	56,621,277	4.48 (2.90-6.05)	—	—
Day 0-180	COVID-19	45	76,349,313	6.73 (4.58-8.89)	1.06 (0.68-1.65)	1.09 (0.69-1.71)
Day 0-180	Comparator	44	81,923,148	5.74 (3.56-7.91)	—	—
Alternative risk windows						
All of follow-up (day 1 - end)	COVID-19	31	80,000,492	5.06 (3.14-6.98)	1.93 (1.02-3.64)	1.97 (1.04-3.74)
All of follow-up (day 1 - end)	Comparator	17	86,246,732	13.59 (0.00-34.59)	—	—
Day 1-41	COVID-19	23	30,191,504	3.04 (1.78-4.30)	2.00 (0.92-4.33)	2.07 (0.95-4.51)
Day 1-41	Comparator	12	31,678,883	1.45 (0.51-2.39)	—	—
Day 1-90	COVID-19	28	52,233,046	4.07 (2.51-5.62)	2.26 (1.09-4.67)	2.34 (1.13-4.88)
Day 1-90	Comparator	13	55,603,154	1.66 (0.63-2.68)	—	—
Day 1-180	COVID-19	31	75,327,668	5.06 (3.14-6.98)	2.05 (1.07-3.93)	2.12 (1.10-4.10)
Day 1-180	Comparator	16	80,904,239	2.92 (1.10-4.73)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; GBS = Guillain Barré syndrome; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

— denotes the reference group.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, race/ethnicity, dual Medicare/Medicaid eligibility (Medicare only), reason for entering Medicare, hospitalization status on Time 0, SNF/LTC residence on Time 0, autoimmune disorders, dementia/neurologic conditions, hemiplegia/paraplegia, herpes simplex virus infection, immunocompromised state, infection associated with GBS, inpatient surgery, obesity, pneumonia or lower respiratory tract infection, trauma, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

B. Bell's Palsy

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	976	80,836,700	229.91 (208.74-251.07)	1.12 (1.01-1.23)	1.06 (0.96-1.17)
All of follow-up (day 0 – end)	Comparator	923	87,065,654	200.94 (178.86-223.02)	—	—
Day 0	COVID-19	220	1,015,088	21.67 (18.81-24.54)	0.94 (0.78-1.14)	0.92 (0.76-1.12)
Day 0	Comparator	233	1,015,172	22.95 (19.76-26.14)	—	—
Day 0-41	COVID-19	533	31,154,370	62.99 (57.52-68.45)	1.00 (0.88-1.13)	0.95 (0.84-1.08)
Day 0-41	Comparator	548	32,637,190	62.97 (56.76-69.19)	—	—
Day 0-90	COVID-19	742	53,148,672	109.41 (101.06-117.77)	1.09 (0.98-1.21)	1.04 (0.93-1.15)
Day 0-90	Comparator	710	56,508,381	95.99 (87.83-104.15)	—	—
Day 0-180	COVID-19	941	76,180,354	186.43 (172.48-200.38)	1.12 (1.01-1.23)	1.06 (0.97-1.17)
Day 0-180	Comparator	885	81,741,010	157.83 (144.55-171.11)	—	—
Alternative risk windows						
All of follow-up (day 1 - end)	COVID-19	756	79,823,029	208.27 (187.29-229.25)	1.18 (1.05-1.31)	1.11 (1.00-1.24)
All of follow-up (day 1 - end)	Comparator	690	86,050,482	178.03 (156.21-199.85)	—	—
Day 1-41	COVID-19	313	30,139,400	41.32 (36.67-45.97)	1.04 (0.88-1.23)	0.97 (0.82-1.15)
Day 1-41	Comparator	315	31,622,018	40.03 (34.74-45.32)	—	—
Day 1-90	COVID-19	522	52,134,026	87.76 (79.90-95.61)	1.16 (1.02-1.32)	1.09 (0.96-1.25)
Day 1-90	Comparator	477	55,493,209	73.06 (65.58-80.53)	—	—
Day 1-180	COVID-19	721	75,166,314	164.79 (151.13-178.45)	1.18 (1.06-1.32)	1.12 (1.00-1.25)
Day 1-180	Comparator	652	80,725,838	134.91 (122.04-147.78)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, race/ethnicity, dual Medicare/Medicaid eligibility, reason for entering Medicare, hospitalization status on Time 0, SNF/LTC residence on Time 0), autoimmune disorders, cancer, dementia/neurologic conditions, diabetes mellitus, type 1 or 2, herpes simplex virus infection, immunocompromised state, mental health conditions, obesity, inpatient hospital stays before Time 0, ED visits, outpatient visits, influenza vaccination in previous year.

C. Encephalitis/Encephalomyelitis

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	193	81,037,202	35.70 (27.29-44.1)	1.44 (1.12-1.85)	1.43 (1.10-1.85)
All of follow-up (day 0 – end)	Comparator	139	87,288,050	22.15 (17.02-27.28)	—	—
Day 0	COVID-19	82	1,016,911	8.06 (6.32-9.81)	1.41 (0.98-2.03)	1.47 (1.02-2.13)
Day 0	Comparator	58	1,016,870	5.70 (4.05-7.36)	—	—
Day 0-41	COVID-19	152	31,217,375	16.58 (13.91-19.26)	1.56 (1.16-2.10)	1.58 (1.16-2.16)
Day 0-41	Comparator	99	32,704,403	10.87 (8.04-13.71)	—	—
Day 0-90	COVID-19	174	53,264,710	21.36 (18.02-24.71)	1.54 (1.17-2.02)	1.53 (1.16-2.03)
Day 0-90	Comparator	116	56,634,947	14.32 (10.95-17.68)	—	—
Day 0-180	COVID-19	186	76,364,300	26.49 (21.97-31.00)	1.38 (1.07-1.78)	1.38 (1.06-1.78)
Day 0-180	Comparator	139	81,942,665	22.15 (17.02-27.28)	—	—
Alternative risk windows						
All of follow-up (day 1 - end)	COVID-19	109	80,018,307	27.43 (19.21-35.65)	1.43 (1.02-2.00)	1.36 (0.96-1.94)
All of follow-up (day 1 - end)	Comparator	81	86,269,166	16.45 (11.65-21.24)	—	—
Day 1-41	COVID-19	68	30,199,522	8.32 (6.31-10.33)	1.72 (1.05-2.84)	1.67 (0.99-2.84)
Day 1-41	Comparator	41	31,686,876	5.17 (2.89-7.45)	—	—
Day 1-90	COVID-19	90	52,246,349	13.10 (10.26-15.94)	1.63 (1.09-2.43)	1.55 (1.02-2.36)
Day 1-90	Comparator	58	55,616,901	8.61 (5.76-11.47)	—	—
Day 1-180	COVID-19	102	75,345,368	18.22 (14.07-22.38)	1.33 (0.95-1.87)	1.28 (0.90-1.82)
Day 1-180	Comparator	81	80,924,003	16.45 (11.65-21.24)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, race/ethnicity (Medicare only), dual Medicare/Medicaid eligibility, reason for entering Medicare, hospitalization status on Time 0, SNF/LTC residence on Time 0, animal exposure/bites or rabies, autoimmune disorders, dementia/neurologic conditions, herpes simplex virus infection, immunocompromised state, pneumonia or lower respiratory tract infection, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

D. Narcolepsy

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	218	80,972,196	49.87 (39.28-60.46)	1.32 (1.07-1.64)	1.22 (0.99-1.52)
All of follow-up (day 0 – end)	Comparator	174	87,225,920	52.25 (18.60-85.90)	—	—
Day 0	COVID-19	49	1,016,109	4.82 (3.47-6.17)	1.96 (1.21-3.17)	1.88 (1.16-3.06)
Day 0	Comparator	25	1,016,207	2.46 (1.50-3.42)	—	—
Day 0-41	COVID-19	134	31,192,395	15.78 (13.05-18.50)	1.53 (1.17-2.01)	1.45 (1.11-1.91)
Day 0-41	Comparator	90	32,682,357	10.82 (8.47-13.17)	—	—
Day 0-90	COVID-19	175	53,220,593	24.96 (21.04-28.89)	1.44 (1.13-1.82)	1.35 (1.06-1.71)
Day 0-90	Comparator	127	56,595,728	18.40 (14.72-22.07)	—	—
Day 0-180	COVID-19	210	76,302,265	38.81 (32.62-44.99)	1.32 (1.06-1.63)	1.22 (0.98-1.51)
Day 0-180	Comparator	168	81,884,679	32.19 (26.03-38.34)	—	—
Alternative risk windows						
All of follow-up (day 1 - end)	COVID-19	169	79,956,203	45.05 (34.55-55.56)	1.21 (0.96-1.54)	1.11 (0.88-1.42)
All of follow-up (day 1 - end)	Comparator	149	86,209,713	49.80 (16.16-83.42)	—	—
Day 1-41	COVID-19	85	30,176,311	10.96 (8.59-13.32)	1.37 (0.98-1.90)	1.28 (0.92-1.78)
Day 1-41	Comparator	65	31,666,150	8.36 (6.24-10.49)	—	—
Day 1-90	COVID-19	126	52,204,550	20.14 (16.45-23.82)	1.31 (1.00-1.72)	1.22 (0.93-1.60)
Day 1-90	Comparator	102	55,579,521	15.94 (12.40-19.47)	—	—
Day 1-180	COVID-19	161	75,286,272	33.98 (27.95-40.02)	1.20 (0.95-1.52)	1.10 (0.87-1.40)
Day 1-180	Comparator	143	80,868,472	29.73 (23.67-35.78)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, race/ethnicity (Medicare only), dual Medicare/Medicaid eligibility, reason for entering Medicare, hospitalization status on Time 0, SNF/LTC residence on Time 0, brain lesions related to secondary narcolepsy, dementia/neurologic conditions, immunocompromised state, mental health conditions, obesity, stroke/cerebrovascular disease, inpatient hospital stays before Time 0, ED visits, outpatient visits, influenza vaccination in previous year.

E. Appendicitis

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	310	80,967,062	73.76 (55.91-91.61)	0.72 (0.62-0.84)	0.73 (0.62-0.85)
All of follow-up (day 0 – end)	Comparator	442	87,170,269	75.48 (59.83-91.12)	—	—
Day 0	COVID-19	125	1,016,139	12.30 (10.15-14.46)	0.43 (0.34-0.53)	0.45 (0.36-0.56)
Day 0	Comparator	293	1,015,910	28.84 (25.21-32.48)	—	—
Day 0-41	COVID-19	203	31,191,851	22.60 (19.43-25.78)	0.61 (0.51-0.73)	0.62 (0.52-0.75)
Day 0-41	Comparator	338	32,664,585	34.60 (30.52-38.67)	—	—
Day 0-90	COVID-19	240	53,220,492	30.86 (26.71-35.02)	0.62 (0.52-0.73)	0.63 (0.53-0.75)
Day 0-90	Comparator	395	56,563,374	46.04 (40.85-51.22)	—	—
Day 0-180	COVID-19	300	76,298,427	55.10 (47.44-62.76)	0.72 (0.61-0.83)	0.72 (0.61-0.84)
Day 0-180	Comparator	432	81,835,282	58.59 (51.82-65.36)	—	—
Alternative risk windows						
All of follow-up (day 1 - end)	COVID-19	177	79,950,149	60.60 (42.89-78.31)	1.28 (1.02-1.61)	1.22 (0.97-1.53)
All of follow-up (day 1 - end)	Comparator	149	86,150,387	46.65 (31.44-61.86)	—	—
Day 1-41	COVID-19	70	30,174,988	9.44 (7.19-11.69)	1.63 (1.10-2.42)	1.55 (1.04-2.31)
Day 1-41	Comparator	45	31,647,329	5.76 (3.95-7.57)	—	—
Day 1-90	COVID-19	107	52,203,382	17.70 (14.20-21.20)	1.12 (0.84-1.48)	1.08 (0.81-1.43)
Day 1-90	Comparator	102	55,545,168	17.20 (13.51-20.89)	—	—
Day 1-180	COVID-19	167	75,281,311	41.94 (34.62-49.27)	1.29 (1.02-1.63)	1.23 (0.97-1.56)
Day 1-180	Comparator	139	80,815,851	29.76 (24.07-35.45)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, race/ethnicity, dual Medicare/Medicaid eligibility, reason for entering Medicare, hospitalization status on Time 0, SNF/LTC residence on Time 0, end-stage renal disease, immunocompromised state, pneumonia or lower respiratory tract infection, inpatient hospital stays before Time 0, ED visits, outpatient visits, influenza vaccination in previous year.

F. Nonhemorrhagic Stroke

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	5,569	74,436,513	1101.72 (1050.92-1152.49)	0.90 (0.87-0.93)	0.89 (0.86-0.93)
All of follow-up (day 0 – end)	Comparator	6,362	79,256,964	1210.21 (1133.79-1286.56)	—	—
Day 0	COVID-19	2,156	928,618	232.17 (222.38-241.96)	0.57 (0.54-0.60)	0.57 (0.54-0.61)
Day 0	Comparator	3,798	929,191	408.74 (394.35-423.13)	—	—
Day 0-27	COVID-19	3,900	20,937,812	453.11 (438.82-467.39)	0.86 (0.82-0.89)	0.86 (0.82-0.90)
Day 0-27	Comparator	4,596	21,619,604	511.54 (494.93-528.16)	—	—
Day 0-90	COVID-19	4,823	48,841,152	656.21 (636.74-675.67)	0.89 (0.85-0.92)	0.88 (0.85-0.92)
Day 0-90	Comparator	5,548	51,533,840	708.92 (686.76-731.07)	—	—
Day 0-180	COVID-19	5,447	70,124,074	914.38 (885.7-943.05)	0.90 (0.87-0.94)	0.89 (0.86-0.93)
Day 0-180	Comparator	6,204	74,470,470	965.55 (932.98-998.11)	—	—
Alternative risk windows						
All of follow-up (day 1 - end)	COVID-19	3,315	73,357,490	861.28 (811.29-911.24)	1.39 (1.31-1.47)	1.35 (1.28-1.43)
All of follow-up (day 1 - end)	Comparator	2,525	78,143,257	796.84 (721.69-871.94)	—	—
Day 1-27	COVID-19	1,654	19,961,517	211.86 (201.59-222.12)	2.18 (1.99-2.38)	2.14 (1.95-2.34)
Day 1-27	Comparator	781	20,643,092	101.38 (93.54-109.23)	—	—
Day 1-90	COVID-19	2,571	47,807,518	414.59 (397.83-431.35)	1.57 (1.47-1.67)	1.53 (1.43-1.63)
Day 1-90	Comparator	1,719	50,489,399	297.16 (280.67-313.64)	—	—
Day 1-180	COVID-19	3,192	69,051,155	672.44 (645.49-699.38)	1.42 (1.34-1.50)	1.38 (1.31-1.47)
Day 1-180	Comparator	2,369	73,371,954	553.25 (524.38-582.10)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED= emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, race/ethnicity, dual Medicare/Medicaid eligibility, reason for entering Medicare, hospitalization status on Time 0, SNF/LTC residence on Time 0, autoimmune disorders, cancer, chronic kidney disease/renal disease, end-stage renal disease, chronic liver disease, chronic lung disease, dementia/neurologic conditions, diabetes mellitus, type 1 or 2, heart conditions, hemiplegia/paraplegia, hypertension, immunocompromised state, lipid abnormality, obesity, peripheral vascular disease, pneumonia or lower respiratory tract infection, sickle cell disease/thalassemia, smoking/nicotine dependency, stroke/cerebrovascular disease, thrombophilia, trauma, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

G. Hemorrhagic Stroke

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	1,580	80,060,770	313.04 (287.48-338.58)	0.85 (0.80-0.92)	0.86 (0.80-0.92)
All of follow-up (day 0 – end)	Comparator	1,910	85,983,250	343.02 (300.53-385.49)	—	—
Day 0	COVID-19	561	1,003,495	55.90 (51.28-60.53)	0.50 (0.45-0.56)	0.52 (0.46-0.58)
Day 0	Comparator	1,119	1,002,866	111.58 (104.25-118.91)	—	—
Day 0-27	COVID-19	1,026	22,587,900	111.47 (104.59-118.34)	0.76 (0.70-0.83)	0.77 (0.71-0.84)
Day 0-27	Comparator	1,361	23,384,507	140.71 (132.30-149.12)	—	—
Day 0-90	COVID-19	1,320	52,604,402	172.20 (162.37-182.02)	0.81 (0.75-0.88)	0.82 (0.76-0.89)
Day 0-90	Comparator	1,656	55,813,852	196.81 (185.76-207.85)	—	—
Day 0-180	COVID-19	1,542	75,438,687	258.98 (243.54-274.42)	0.85 (0.79-0.92)	0.86 (0.80-0.92)
Day 0-180	Comparator	1,867	80,733,969	275.44 (257.40-293.48)	—	—
Alternative risk windows						
All of follow-up (day 1 - end)	COVID-19	997	79,037,154	253.78 (228.71-278.85)	1.38 (1.25-1.53)	1.35 (1.22-1.50)
All of follow-up (day 1 - end)	Comparator	771	84,917,216	228.58 (186.76-270.38)	—	—
Day 1-27	COVID-19	447	21,576,005	53.60 (48.59-58.61)	1.99 (1.69-2.34)	1.94 (1.64-2.29)
Day 1-27	Comparator	232	22,364,501	28.06 (24.22-31.91)	—	—
Day 1-90	COVID-19	740	51,584,501	114.13 (105.52-122.74)	1.50 (1.33-1.69)	1.47 (1.31-1.65)
Day 1-90	Comparator	520	54,771,472	83.02 (75.02-91.02)	—	—
Day 1-180	COVID-19	959	74,415,184	199.70 (185.07-214.32)	1.40 (1.26-1.55)	1.37 (1.24-1.52)
Day 1-180	Comparator	728	79,673,530	160.83 (144.60-177.06)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, race/ethnicity, dual Medicare/Medicaid eligibility, reason for entering Medicare, hospitalization status on Time 0, SNF/LTC residence on Time 0, autoimmune disorders, cancer, chronic kidney disease/renal disease, end-stage renal disease, chronic liver disease, chronic lung disease, dementia/neurologic conditions, diabetes mellitus, type 1 or 2, heart conditions, hemiplegia/paraplegia, hypertension, immunocompromised state, mental health conditions, peripheral vascular disease, pneumonia or lower respiratory tract infection, sickle cell disease/thalassemia, smoking/nicotine dependency, stroke/cerebrovascular disease, trauma, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

H. Acute Myocardial Infarction

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	18,774	77,328,845	2984.63 (2911.49-3057.72)	1.72 (1.67-1.76)	1.65 (1.61-1.70)
All of follow-up (day 0 – end)	Comparator	11,233	83,134,571	2044.85 (1956.60-2133.02)	—	—
Day 0	COVID-19	9,219	975,854	944.71 (925.52-963.90)	1.44 (1.39-1.49)	1.41 (1.36-1.46)
Day 0	Comparator	6,396	975,129	655.91 (638.01-673.81)	—	—
Day 0-27	COVID-19	15,125	21,800,656	1641.99 (1615.88-1668.09)	1.93 (1.87-1.98)	1.86 (1.81-1.92)
Day 0-27	Comparator	7,925	22,640,890	844.15 (823.33-864.96)	—	—
Day 0-90	COVID-19	17,155	50,828,080	2064.72 (2032.76-2096.68)	1.81 (1.76-1.86)	1.74 (1.69-1.79)
Day 0-90	Comparator	9,687	54,036,628	1191.86 (1164.07-1219.65)	—	—
Day 0-180	COVID-19	18,510	72,891,540	2607.53 (2563.75-2651.29)	1.73 (1.69-1.78)	1.67 (1.62-1.71)
Day 0-180	Comparator	10,968	78,108,375	1667.88 (1626.07-1709.66)	—	—
Alternative risk windows						
All of follow-up (day 1 - end)	COVID-19	9,168	76,240,828	2007.43 (1938.08-2076.73)	2.03 (1.95-2.11)	1.94 (1.86-2.01)
All of follow-up (day 1 - end)	Comparator	4,786	82,064,128	1388.83 (1302.22-1475.37)	—	—
Day 1-27	COVID-19	5,546	20,783,068	666.44 (648.84-684.04)	3.82 (3.60-4.06)	3.63 (3.42-3.86)
Day 1-27	Comparator	1,497	21,640,320	185.93 (175.82-196.03)	—	—
Day 1-90	COVID-19	7,561	49,766,942	1091.01 (1065.35-1116.66)	2.44 (2.34-2.55)	2.33 (2.23-2.43)
Day 1-90	Comparator	3,248	53,001,211	534.33 (513.50-555.15)	—	—
Day 1-180	COVID-19	8,906	71,806,699	1635.43 (1595.81-1675.04)	2.08 (2.00-2.16)	1.98 (1.91-2.06)
Day 1-180	Comparator	4,523	77,045,806	1011.57 (974.00-1049.11)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, race/ethnicity, dual Medicare/Medicaid eligibility, reason for entering Medicare, hospitalization status on Time 0, SNF/LTC residence on Time 0, autoimmune disorders, cancer, chronic kidney disease/renal disease, end-stage renal disease, chronic liver disease, chronic lung disease, diabetes mellitus, type 1 or 2, heart conditions, hypertension, immunocompromised state, lipid abnormality, mental health conditions, obesity, peripheral vascular disease, pneumonia or lower respiratory tract infection, sickle cell disease/thalassemia, smoking/nicotine dependency, stroke/cerebrovascular disease, thrombophilia, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

I. Myocarditis/Pericarditis

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	1,774	80,839,930	283.57 (264.64-302.49)	2.61 (2.37-2.89)	2.53 (2.29-2.79)
All of follow-up (day 0 – end)	Comparator	703	87,140,811	160.14 (112.49-207.77)	—	—
Day 0	COVID-19	669	1,015,725	65.86 (60.87-70.85)	4.21 (3.47-5.11)	4.08 (3.35-4.96)
Day 0	Comparator	159	1,015,798	15.65 (12.86-18.44)	—	—
Day 0-41	COVID-19	1,442	31,154,718	158.83 (150.51-167.14)	3.23 (2.86-3.63)	3.13 (2.77-3.53)
Day 0-41	Comparator	455	32,660,937	51.14 (45.68-56.61)	—	—
Day 0-90	COVID-19	1,599	53,150,219	193.63 (183.67-203.58)	2.80 (2.51-3.11)	2.72 (2.44-3.03)
Day 0-90	Comparator	587	56,552,689	77.60 (69.89-85.31)	—	—
Day 0-180	COVID-19	1,749	76,185,638	253.10 (239.00-267.19)	2.63 (2.38-2.90)	2.54 (2.30-2.81)
Day 0-180	Comparator	688	81,810,124	114.15 (102.75-125.55)	—	—
Alternative risk windows						
All of follow-up (day 1 - end)	COVID-19	1,105	79,824,722	217.84 (199.57-236.11)	2.14 (1.91-2.40)	2.07 (1.84-2.32)
All of follow-up (day 1 - end)	Comparator	544	86,125,013	144.51 (96.94-192.06)	—	—
Day 1-41	COVID-19	773	30,139,165	93.03 (86.37-99.69)	2.69 (2.32-3.13)	2.61 (2.24-3.04)
Day 1-41	Comparator	296	31,645,139	35.50 (30.85-40.14)	—	—
Day 1-90	COVID-19	930	52,134,790	127.84 (119.22-136.46)	2.27 (1.99-2.58)	2.20 (1.93-2.51)
Day 1-90	Comparator	428	55,536,891	61.95 (54.82-69.09)	—	—
Day 1-180	COVID-19	1,080	75,170,373	187.36 (174.16-200.55)	2.15 (1.91-2.41)	2.07 (1.84-2.33)
Day 1-180	Comparator	529	80,794,326	98.52 (87.50-109.53)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, race/ethnicity, dual Medicare/Medicaid eligibility, reason for entering Medicare, hospitalization status on Time 0, SNF/LTC residence on Time 0, animal exposure/bites or rabies, autoimmune disorders, cancer, chronic kidney disease/renal disease, end-stage renal disease, chronic liver disease, diabetes mellitus, type 1 or 2, heart conditions, herpes simplex virus infection, hypertension, immunocompromised state, infection associated with myocarditis/pericarditis, nutritional deficiencies, obesity, peripheral vascular disease, pneumonia or lower respiratory tract infection, sepsis, trauma, tuberculosis, inpatient hospital stays before Time 0, ED visits, outpatient visits, influenza vaccination in previous year.

J. Deep Vein Thrombosis

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	15,548	77,420,414	3122.9 (3029.32-3216.39)	1.68 (1.63-1.72)	1.67 (1.63-1.72)
All of follow-up (day 0 – end)	Comparator	9,735	83,606,920	2054.18 (1978.71-2129.59)	—	—
Day 0	COVID-19	3,676	981,125	374.67 (362.58-386.76)	1.62 (1.53-1.71)	1.64 (1.55-1.73)
Day 0	Comparator	2,278	982,606	231.83 (221.43-242.23)	—	—
Day 0-27	COVID-19	9,915	21,965,794	1136.47 (1114.01-1158.92)	1.92 (1.86-1.99)	1.94 (1.87-2.01)
Day 0-27	Comparator	5,267	22,847,333	589.01 (571.09-606.93)	—	—
Day 0-90	COVID-19	13,416	51,023,262	1862.1 (1829.16-1895.04)	1.78 (1.73-1.84)	1.78 (1.73-1.84)
Day 0-90	Comparator	7,834	54,419,810	1086.73 (1058.59-1114.85)	—	—
Day 0-180	COVID-19	15,196	73,010,983	2564.75 (2517.62-2611.86)	1.69 (1.64-1.73)	1.68 (1.64-1.73)
Day 0-180	Comparator	9,437	78,566,717	1673.53 (1628.69-1718.34)	—	—
Alternative risk windows						
All of follow-up (day 1 - end)	COVID-19	11,877	76,449,557	2759.71 (2666.57-2852.76)	1.70 (1.64-1.75)	1.69 (1.63-1.74)
All of follow-up (day 1 - end)	Comparator	7,457	82,624,314	1826.58 (1751.84-1901.27)	—	—
Day 1-27	COVID-19	6,239	20,985,616	764.63 (745.58-783.68)	2.16 (2.06-2.26)	2.18 (2.07-2.28)
Day 1-27	Comparator	2,989	21,864,727	358.01 (343.63-372.39)	—	—
Day 1-90	COVID-19	9,741	50,046,487	1493.1 (1462.27-1523.92)	1.85 (1.78-1.92)	1.85 (1.78-1.92)
Day 1-90	Comparator	5,556	53,437,204	856.88 (830.90-882.85)	—	—
Day 1-180	COVID-19	11,525	72,038,295	2199.78 (2153.97-2245.57)	1.71 (1.66-1.77)	1.70 (1.65-1.76)
Day 1-180	Comparator	7,159	77,584,111	1445.04 (1401.52-1488.55)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, race/ethnicity, dual Medicare/Medicaid eligibility, reason for entering Medicare, hospitalization status on Time 0, SNF/LTC residence on Time 0, autoimmune disorders, cancer, chronic kidney disease/renal disease, end-stage renal disease, chronic liver disease, dementia/neurologic conditions, diabetes mellitus, type 1 or 2, heart conditions, hemiplegia/paraplegia, immunocompromised state, inpatient surgery, lipid abnormality, obesity, peripheral vascular disease, pneumonia or lower respiratory tract infection, sickle cell disease/thalassemia, smoking/nicotine dependency, stroke/cerebrovascular disease, thromboembolism, thrombophilia, trauma, tuberculosis, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay e, influenza vaccination in previous year.

K. Pulmonary Embolism

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis, any setting						
All of follow-up (day 0 – end)	COVID-19	14,274	78,835,990	2264.96 (2196.78-2333.1)	2.46 (2.38-2.55)	2.47 (2.39-2.56)
All of follow-up (day 0 – end)	Comparator	6,021	85,281,541	1155.78 (1101.84-1209.69)	—	—
Day 0	COVID-19	5,030	996,999	504.51 (490.61-518.42)	2.32 (2.20-2.45)	2.4 (2.27-2.53)
Day 0	Comparator	2,175	997,596	218.02 (207.94-228.11)	—	—
Day 0-27	COVID-19	11,145	22,285,451	1231.02 (1208.11-1253.92)	3.05 (2.93-3.17)	3.10 (2.97-3.23)
Day 0-27	Comparator	3,725	23,220,447	399.93 (385.26-414.60)	—	—
Day 0-90	COVID-19	13,159	51,846,869	1634.83 (1605.88-1663.78)	2.68 (2.59-2.78)	2.71 (2.61-2.81)
Day 0-90	Comparator	5,058	55,398,687	654.26 (632.91-675.60)	—	—
Day 0-180	COVID-19	14,113	74,309,059	2004.66 (1966.83-2042.48)	2.50 (2.42-2.59)	2.52 (2.43-2.60)
Day 0-180	Comparator	5,848	80,094,538	936.72 (905.45-967.99)	—	—
Alternative risk windows, any setting						
All of follow-up (day 1 - end)	COVID-19	9,244	77,850,826	1769.03 (1701.94-1836.08)	2.55 (2.44-2.65)	2.53 (2.42-2.63)
All of follow-up (day 1 - end)	Comparator	3,846	84,283,945	939.80 (886.87-992.70)	—	—
Day 1-27	COVID-19	6,115	21,289,635	730.15 (711.78-748.51)	4.08 (3.84-4.34)	4.09 (3.85-4.36)
Day 1-27	Comparator	1,550	22,222,851	182.30 (171.86-192.74)	—	—
Day 1-90	COVID-19	8,129	50,854,708	1135.96 (1110.35-1161.57)	2.96 (2.83-3.10)	2.95 (2.81-3.09)
Day 1-90	Comparator	2,883	54,401,091	437.19 (418.62-455.76)	—	—
Day 1-180	COVID-19	9,083	73,321,591	1507.59 (1472.15-1543.02)	2.61 (2.51-2.73)	2.60 (2.49-2.71)
Day 1-180	Comparator	3,673	79,096,942	720.27 (690.85-749.68)	—	—
Overall analysis, inpatient only						
All of follow-up (day 0 – end)	COVID-19	8,776	79,173,482	1,311.14 (1,254.84-1,367.41)	2.56 (2.45-2.67)	2.60 (2.49-2.72)
All of follow-up (day 0 – end)	Comparator	3,539	85,457,650	631.56 (591.15-671.95)	—	—
Day 0	COVID-19	3,650	996,999	366.10 (354.24-377.95)	2.00 (1.88-2.12)	2.08 (1.95-2.21)
Day 0	Comparator	1,830	997,596	183.44 (174.15-192.73)	—	—
Day 0-27	COVID-19	7,253	22,345,091	793.86 (775.52-812.20)	3.04 (2.88-3.19)	3.11 (2.96-3.28)
Day 0-27	Comparator	2,426	23,241,125	256.07 (244.22-267.91)	—	—
Day 0-90	COVID-19	8,285	52,030,261	999.64 (977.36-1021.92)	2.75 (2.62-2.88)	2.80 (2.67-2.94)
Day 0-90	Comparator	3,093	55,478,006	382.26 (366.02-398.51)	—	—
Day 0-180	COVID-19	8,697	74,614,139	1,161.11 (1,133.51-1,188.69)	2.60 (2.49-2.72)	2.65 (2.53-2.77)
Day 0-180	Comparator	3,443	80,247,817	508.94 (486.39-531.47)	—	—
Alternative risk windows, inpatient only						
All of follow-up (day 1 - end)	COVID-19	4,924	78,114,621	927.56 (872.36-982.73)	3.06 (2.88-3.26)	3.06 (2.88-3.26)
All of follow-up (day 1 - end)	Comparator	1,702	84,436,728	448.23 (409.03-487.43)	—	—
Day 1-27	COVID-19	3,407	21,325,714	409.14 (395.34-422.94)	5.98 (5.41-6.61)	6.03 (5.45-6.67)

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Day 1-27	Comparator	590	22,236,532	72.14 (65.13-79.14)	—	—
Day 1-90	COVID-19	4,433	50,986,600	614.74 (595.98-633.49)	3.71 (3.45-3.98)	3.72 (3.46-3.99)
Day 1-90	Comparator	1,256	54,464,623	198.42 (185.44-211.39)	—	—
Day 1-180	COVID-19	4,845	73,556,340	776.93 (752.04-801.82)	3.18 (2.99-3.39)	3.19 (2.99-3.40)
Day 1-180	Comparator	1,606	79,228,251	325.36 (305.08-345.63)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, race/ethnicity, dual Medicare/Medicaid eligibility, reason for entering Medicare, hospitalization status on Time 0, SNF/LTC residence on Time 0, autoimmune disorders, cancer, chronic kidney disease/renal disease, end-stage renal disease, chronic liver disease, dementia/neurologic conditions, diabetes mellitus, type 1 or 2, heart conditions, hemiplegia/paraplegia, immunocompromised state, inpatient surgery, lipid abnormality, obesity, peripheral vascular disease, pneumonia or lower respiratory tract infection, sickle cell disease/thalassemia, smoking/nicotine dependency, stroke/cerebrovascular disease, thromboembolism, thrombophilia, trauma, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

L. Disseminated Intravascular Coagulation

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	1,269	81,006,596	176.97 (163.86-190.08)	2.71 (2.42-3.05)	2.73 (2.43-3.07)
All of follow-up (day 0 – end)	Comparator	480	87,276,904	81.90 (67.59-96.20)	—	—
Day 0	COVID-19	609	1,016,803	59.89 (55.14-64.65)	2.91 (2.47-3.44)	2.95 (2.49-3.49)
Day 0	Comparator	209	1,016,813	20.55 (17.54-23.57)	—	—
Day 0-27	COVID-19	1,061	22,867,666	110.80 (104.10-117.49)	3.38 (2.95-3.87)	3.41 (2.97-3.91)
Day 0-27	Comparator	317	23,719,923	33.18 (29.14-37.23)	—	—
Day 0-90	COVID-19	1,185	53,241,014	136.05 (127.98-144.12)	2.86 (2.53-3.23)	2.87 (2.54-3.25)
Day 0-90	Comparator	423	56,627,814	52.80 (46.88-58.72)	—	—
Day 0-180	COVID-19	1,253	76,334,984	160.47 (150.43-170.51)	2.72 (2.42-3.06)	2.74 (2.43-3.08)
Day 0-180	Comparator	472	81,932,629	69.59 (61.35-77.84)	—	—
Alternative risk windows						
All of follow-up (day 1 - end)	COVID-19	655	79,988,878	116.65 (104.42-128.87)	2.54 (2.18-2.97)	2.54 (2.17-2.98)
All of follow-up (day 1 - end)	Comparator	271	86,258,848	61.36 (47.41-75.29)	—	—
Day 1-27	COVID-19	447	21,850,577	50.43 (45.74-55.13)	4.24 (3.41-5.28)	4.27 (3.42-5.33)
Day 1-27	Comparator	108	22,702,691	12.63 (10.12-15.15)	—	—
Day 1-90	COVID-19	571	52,223,571	75.7 (69.19-82.21)	2.78 (2.34-3.30)	2.77 (2.33-3.29)
Day 1-90	Comparator	214	55,610,086	32.25 (27.28-37.22)	—	—
Day 1-180	COVID-19	639	75,317,347	100.13 (91.29-108.97)	2.55 (2.18-2.98)	2.55 (2.18-2.99)
Day 1-180	Comparator	263	80,914,620	49.05 (41.46-56.64)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, race/ethnicity, dual Medicare/Medicaid eligibility, reason for entering Medicare, hospitalization status on Time 0, SNF/LTC residence on Time 0, autoimmune disorders, cancer, chronic kidney disease/renal disease, end-stage renal disease, chronic liver disease, dementia/neurologic conditions, immunocompromised state, inpatient surgery, pneumonia or lower respiratory tract infection, sepsis, smoking/nicotine dependency, thromboembolism, thrombophilia, trauma, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

M. Immune Thrombocytopenia

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	693	80,830,449	127.49 (114.63-140.36)	1.46 (1.29-1.65)	1.43 (1.27-1.62)
All of follow-up (day 0 – end)	Comparator	496	87,072,175	115.09 (90.40-139.77)	—	—
Day 0	COVID-19	196	1,014,639	19.32 (16.61-22.02)	1.65 (1.30-2.09)	1.64 (1.29-2.08)
Day 0	Comparator	119	1,014,664	11.73 (9.50-13.96)	—	—
Day 0-41	COVID-19	498	31,141,633	56.89 (51.81-61.97)	1.69 (1.46-1.97)	1.65 (1.42-1.93)
Day 0-41	Comparator	301	32,629,074	34.34 (30.05-38.64)	—	—
Day 0-90	COVID-19	589	53,133,563	76.60 (70.09-83.11)	1.59 (1.39-1.82)	1.55 (1.35-1.78)
Day 0-90	Comparator	383	56,503,015	51.32 (45.39-57.26)	—	—
Day 0-180	COVID-19	682	76,171,365	115.55 (105.00-126.11)	1.51 (1.33-1.71)	1.48 (1.30-1.67)
Day 0-180	Comparator	472	81,744,405	83.23 (73.81-92.66)	—	—
Alternative risk windows						
All of follow-up (day 1 - end)	COVID-19	497	79,815,901	108.20 (95.62-120.78)	1.40 (1.22-1.61)	1.36 (1.18-1.57)
All of follow-up (day 1 - end)	Comparator	377	86,057,511	103.37 (78.81-127.93)	—	—
Day 1-41	COVID-19	302	30,127,030	37.58 (33.28-41.88)	1.72 (1.42-2.09)	1.66 (1.37-2.02)
Day 1-41	Comparator	182	31,614,410	22.62 (19.00-26.23)	—	—
Day 1-90	COVID-19	393	52,118,972	57.29 (51.37-63.21)	1.56 (1.33-1.84)	1.51 (1.28-1.78)
Day 1-90	Comparator	264	55,488,351	39.60 (34.2.-45.00)	—	—
Day 1-180	COVID-19	486	75,156,784	96.26 (86.05-106.46)	1.46 (1.26-1.69)	1.42 (1.23-1.64)
Day 1-180	Comparator	353	80,729,741	71.51 (62.43-80.60)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; ITP = immune thrombocytopenia; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, race/ethnicity, dual Medicare/Medicaid eligibility, reason for entering Medicare, hospitalization status on Time 0, SNF/LTC residence on Time 0, animal exposure/bites or rabies, antiphospholipid syndrome, autoimmune disorders, cancer, chronic lymphocytic leukemia, herpes simplex virus infection, immunocompromised state, infection associated with ITP, pneumonia or lower respiratory tract infection, sepsis, tuberculosis, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

N. Transverse Myelitis

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	< 11	81,061,561	1.54 (0.45-2.64)	0.54 (0.23-1.29)	0.59 (0.25-1.43)
All of follow-up (day 0 – end)	Comparator	17	87,313,779	2.22 (0.95-3.50)	—	—
Day 0	COVID-19	< 11	1,017,133	0.39 (0.01-0.78)	0.36 (0.11-1.24)	0.44 (0.13-1.52)
Day 0	Comparator	11	1,017,155	1.08 (0.29-1.88)	—	—
Day 0-41	COVID-19	< 11	31,226,537	0.39 (0.01-0.78)	0.29 (0.09-0.92)	0.36 (0.11-1.17)
Day 0-41	Comparator	14	32,714,215	1.40 (0.53-2.28)	—	—
Day 0-90	COVID-19	< 11	53,279,820	1.25 (0.32-2.19)	0.54 (0.22-1.37)	0.61 (0.24-1.56)
Day 0-90	Comparator	15	56,651,715	1.64 (0.65-2.63)	—	—
Day 0-180	COVID-19	< 11	76,386,353	1.54 (0.45-2.64)	0.54 (0.23-1.29)	0.59 (0.25-1.43)
Day 0-180	Comparator	17	81,966,974	2.22 (0.95-3.50)	—	—
Alternative risk windows						
All of follow-up (day 1 - end)	COVID-19	< 11	80,044,399	1.15 (0.13-2.18)	0.89 (0.27-2.94)	0.93 (0.28-3.09)
All of follow-up (day 1 - end)	Comparator	< 11	86,296,624	1.14 (0.14-2.14)	—	—
Day 1-41	COVID-19	0	30,209,375	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Day 1-41	Comparator	< 11	31,697,060	0.32 (0.00-0.69)	—	—
Day 1-90	COVID-19	< 11	52,262,658	0.86 (0.01-1.71)	1.06 (0.26-4.31)	1.17 (0.29-4.8.)
Day 1-90	Comparator	< 11	55,634,560	0.56 (0.00-1.15)	—	—
Day 1-180	COVID-19	< 11	75,369,191	1.15 (0.13-2.18)	0.89 (0.27-2.94)	0.93 (0.28-3.09)
Day 1-180	Comparator	< 11	80,949,819	1.14 (0.14-2.14)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, race/ethnicity, dual Medicare/Medicaid eligibility, reason for entering Medicare, hospitalization status on Time 0, SNF/LTC residence on Time 0, antiphospholipid syndrome, autoimmune disorders, chronic lung disease, dementia/neurologic conditions, diabetes mellitus, type 1 or 2, hemiplegia/paraplegia, immunocompromised state, nutritional deficiencies, pneumonia or lower respiratory tract infection, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

Note: Privacy rules require masking cell sizes of fewer than 11 individuals.

O. Unusual Site Thrombosis With Thrombocytopenia Syndrome

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	83	81,057,517	22.61 (6.43-38.79)	0.79 (0.59-1.06)	0.82 (0.61-1.10)
All of follow-up (day 0 – end)	Comparator	109	87,298,860	17.35 (11.89-22.82)	—	—
Day 0	COVID-19	29	1,017,065	2.85 (1.81-3.89)	0.46 (0.29-0.72)	0.50 (0.32-0.79)
Day 0	Comparator	63	1,016,972	6.19 (4.50-7.89)	—	—
Day 0-41	COVID-19	58	31,224,388	6.87 (5.06-8.69)	0.66 (0.47-0.93)	0.71 (0.50-0.99)
Day 0-41	Comparator	89	32,707,545	9.68 (7.45-11.92)	—	—
Day 0-90	COVID-19	68	53,276,112	9.07 (6.80-11.34)	0.71 (0.51-0.97)	0.73 (0.53-1.01)
Day 0-90	Comparator	99	56,641,033	11.70 (9.14-14.26)	—	—
Day 0-180	COVID-19	81	76,382,065	13.66 (10.21-17.10)	0.78 (0.58-1.05)	0.81 (0.60-1.09)
Day 0-180	Comparator	107	81,952,978	14.58 (11.27-17.89)	—	—
Alternative risk windows						
All of follow-up (day 1 - end)	COVID-19	55	80,040,985	19.86 (3.71-36.00)	1.25 (0.84-1.85)	1.26 (0.85-1.88)
All of follow-up (day 1 - end)	Comparator	47	86,281,346	10.62 (5.68-15.57)	—	—
Day 1-41	COVID-19	30	30,207,407	4.12 (2.62-5.62)	1.12 (0.66-1.90)	1.19 (0.70-2.02)
Day 1-41	Comparator	28	31,690,441	3.66 (2.22-5.10)	—	—
Day 1-90	COVID-19	40	52,259,229	6.32 (4.29-8.35)	1.11 (0.71-1.75)	1.13 (0.72-1.78)
Day 1-90	Comparator	38	55,623,801	5.67 (3.76-7.58)	—	—
Day 1-180	COVID-19	53	75,365,362	10.9 (7.62-14.19)	1.23 (0.82-1.83)	1.24 (0.83-1.85)
Day 1-180	Comparator	46	80,935,486	8.55 (5.72-11.39)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, race/ethnicity, dual Medicare/Medicaid eligibility, reason for entering Medicare, hospitalization status on Time 0, SNF/LTC residence on Time 0 (Medicare only), antiphospholipid syndrome, autoimmune disorders, cancer, chronic kidney disease/renal disease, end-stage renal disease, chronic lung disease, dementia/neurologic conditions, diabetes mellitus, type 1 or 2, disseminated intravascular coagulation, heart conditions, hemiplegia/paraplegia, immunocompromised state, inpatient surgery, lipid abnormality, obesity, peripheral vascular disease, pneumonia or lower respiratory tract infection, smoking/nicotine dependency, thromboembolism, thrombophilia, tuberculosis, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

P. Common Site Thrombosis With Thrombocytopenia Syndrome

Time period	Exposure group	Outcome cases	Person-time (days)	Crude cumulative incidence[a] (95% CI)	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Overall analysis						
All of follow-up (day 0 – end)	COVID-19	7,393	80,060,181	1141.83 (1098.92-1184.72)	2.21 (2.11-2.31)	2.19 (2.09-2.29)
All of follow-up (day 0 – end)	Comparator	3,453	86,171,433	625.25 (587.78-662.70)	—	—
Day 0	COVID-19	3,036	1,006,735	301.57 (290.86-312.28)	2.07 (1.94-2.21)	2.09 (1.95-2.23)
Day 0	Comparator	1,464	1,005,685	145.57 (137.56-153.59)	—	—
Day 0-41	COVID-19	6,281	30,822,517	697.26 (679.82-714.69)	2.59 (2.46-2.72)	2.57 (2.44-2.70)
Day 0-41	Comparator	2,468	32,307,477	271.95 (259.97-283.92)	—	—
Day 0-90	COVID-19	6,813	52,613,685	814.63 (794.53-834.73)	2.39 (2.28-2.50)	2.37 (2.26-2.48)
Day 0-90	Comparator	2,923	55,940,445	365.74 (350.19-381.29)	—	—
Day 0-180	COVID-19	7,293	75,448,038	1002.74 (976.10-1029.37)	2.23 (2.13-2.33)	2.21 (2.11-2.31)
Day 0-180	Comparator	3,365	80,914,018	525.65 (500.68-550.63)	—	—
Alternative risk windows						
All of follow-up (day 1 - end)	COVID-19	4,556	79,033,139	864.09 (822.22-905.95)	2.39 (2.25-2.53)	2.35 (2.22-2.49)
All of follow-up (day 1 - end)	Comparator	2,006	85,128,856	463.41 (429.48-497.32)	—	—
Day 1-41	COVID-19	3,447	29,805,445	418.04 (403.90-432.17)	3.35 (3.12-3.61)	3.32 (3.08-3.57)
Day 1-41	Comparator	1,062	31,287,149	131.60 (122.86-140.34)	—	—
Day 1-90	COVID-19	3,977	51,590,430	535.25 (517.93-552.57)	2.76 (2.59-2.94)	2.73 (2.56-2.92)
Day 1-90	Comparator	1,501	54,909,884	222.37 (209.33-235.40)	—	—
Day 1-180	COVID-19	4,455	74,421,287	723.09 (698.46-747.72)	2.42 (2.28-2.57)	2.39 (2.25-2.54)
Day 1-180	Comparator	1,929	79,873,754	377.33 (354.07-400.58)	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; ED = emergency department; HR = hazard ratio; LTC = long-term care; MSA = metropolitan statistical area; sIPT = stabilized inverse probability of treatment; SNF = skilled nursing facility.

[a] Estimated as the 1 minus the Kaplan-Meier survival estimator; expressed as risk per 100,000 individuals.

Note: Propensity score variables for the sIPT weight generation include age, sex, county/MSA and state of residence, race/ethnicity, dual Medicare/Medicaid eligibility, reason for entering Medicare, hospitalization status on Time 0, SNF/LTC residence on Time 0, antiphospholipid syndrome, autoimmune disorders, cancer, chronic kidney disease/renal disease, end-stage renal disease, chronic lung disease, dementia/neurologic conditions, diabetes mellitus, type 1 or 2, disseminated intravascular coagulation, heart conditions, hemiplegia/paraplegia, immunocompromised state, inpatient surgery, lipid abnormality, obesity, peripheral vascular disease, pneumonia or lower respiratory tract infection, sickle cell disease/thalassemia, smoking/nicotine dependency, stroke/cerebrovascular disease, thromboembolism, thrombophilia, trauma, tuberculosis, inpatient hospital stays before Time 0, ED visits, outpatient visits, SNF/LTC stay, influenza vaccination in previous year.

Table B-6-Medicare. Negative Control Outcomes Occurring Before Time 0 in Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis Included in the Cohort Study, sIPT-Weighted Exposure Groups, Medicare

Analysis set	Negative control outcome	COVID-19 diagnosis (exposure) group, N (%)	Comparator group, N (%)	ASD
Guillain-Barré syndrome	Colonic diverticulitis	106,366 (10.5)	106,437 (10.5)	0.00
	Laceration of hand/finger	10,236 (1.0)	9,914 (1.0)	0.00
	Gout	72,372 (7.1)	67,796 (6.7)	0.02
	Arm/leg cellulitis	84,285 (8.3)	80,328 (7.9)	0.01
Bell's palsy	Colonic diverticulitis	106,222 (10.5)	106,211 (10.5)	0.00
	Laceration of hand/finger	10,208 (1.0)	9,912 (1.0)	0.00
	Gout	71,978 (7.1)	67,863 (6.7)	0.02
	Arm/leg cellulitis	83,844 (8.3)	80,252 (7.9)	0.01
Encephalitis/encephalomyelitis	Colonic diverticulitis	106,574 (10.5)	106,255 (10.5)	0.00
	Laceration of hand/finger	10,228 (1.0)	9,922 (1.0)	0.00
	Gout	72,811 (7.2)	67,370 (6.6)	0.02
	Arm/leg cellulitis	84,639 (8.3)	79,954 (7.9)	0.02
Narcolepsy	Colonic diverticulitis	106,217 (10.5)	106,493 (10.5)	0.00
	Laceration of hand/finger	10,189 (1.0)	9,945 (1.0)	0.00
	Gout	72,461 (7.1)	67,579 (6.7)	0.02
	Arm/leg cellulitis	84,178 (8.3)	79,968 (7.9)	0.02
Appendicitis	Colonic diverticulitis	105,822 (10.4)	106,096 (10.5)	0.00
	Laceration of hand/finger	10,232 (1.0)	9,920 (1.0)	0.00
	Gout	72,201 (7.1)	67,697 (6.7)	0.02
	Arm/leg cellulitis	84,347 (8.3)	80,108 (7.9)	0.02
Nonhemorrhagic stroke	Colonic diverticulitis	95,894 (10.3)	95,497 (10.3)	0.00
	Laceration of hand/finger	9,289 (1.0)	8,964 (1.0)	0.00
	Gout	63,732 (6.9)	60,925 (6.6)	0.01
	Arm/leg cellulitis	73,312 (7.9)	70,755 (7.6)	0.01
Hemorrhagic stroke	Colonic diverticulitis	104,979 (10.5)	104,465 (10.4)	0.00
	Laceration of hand/finger	9,954 (1.0)	9,610 (1.0)	0.00
	Gout	70,740 (7.1)	67,037 (6.7)	0.01
	Arm/leg cellulitis	82,335 (8.2)	79,310 (7.9)	0.01
Acute myocardial infarction	Colonic diverticulitis	99,111 (10.2)	99,278 (10.2)	0.00
	Laceration of hand/finger	9,740 (1.0)	9,365 (1.0)	0.00
	Gout	66,275 (6.8)	63,484 (6.5)	0.01
	Arm/leg cellulitis	77,139 (7.9)	74,907 (7.7)	0.01
Myocarditis/pericarditis	Colonic diverticulitis	105,992 (10.4)	106,343 (10.5)	0.00
	Laceration of hand/finger	10,269 (1.0)	9,862 (1.0)	0.00
	Gout	71,376 (7.0)	68,343 (6.7)	0.01
	Arm/leg cellulitis	83,282 (8.2)	81,043 (8.0)	0.01
Deep vein thrombosis	Colonic diverticulitis	100,444 (10.2)	100,355 (10.2)	0.00
	Laceration of hand/finger	9,815 (1.0)	9,468 (1.0)	0.00
	Gout	67,533 (6.9)	64,590 (6.6)	0.01
	Arm/leg cellulitis	76,245 (7.8)	73,708 (7.5)	0.01

Analysis set	Negative control outcome	COVID-19 diagnosis (exposure) group, N (%)	Comparator group, N (%)	ASD
Pulmonary embolism	Colonic diverticulitis	102,978 (10.3)	102,635 (10.3)	0.00
	Laceration of hand/finger	10,006 (1.0)	9,660 (1.0)	0.00
	Gout	69,561 (7.0)	66,513 (6.7)	0.01
	Arm/leg cellulitis	80,902 (8.1)	78,246 (7.9)	0.01
Disseminated intravascular coagulation	Colonic diverticulitis	106,764 (10.5)	106,003 (10.4)	0.00
	Laceration of hand/finger	10,233 (1.0)	9,903 (1.0)	0.00
	Gout	72,324 (7.1)	67,863 (6.7)	0.02
	Arm/leg cellulitis	84,548 (8.3)	80,104 (7.9)	0.02
Immune thrombocytopenia	Colonic diverticulitis	105,960 (10.5)	106,060 (10.5)	0.00
	Laceration of hand/finger	10,212 (1.0)	9,884 (1.0)	0.00
	Gout	72,115 (7.1)	67,366 (6.6)	0.02
	Arm/leg cellulitis	83,998 (8.3)	79,969 (7.9)	0.01
Transverse myelitis	Colonic diverticulitis	106,586 (10.5)	106,333 (10.5)	0.00
	Laceration of hand/finger	10,239 (1.0)	9,919 (1.0)	0.00
	Gout	72,352 (7.1)	67,871 (6.7)	0.02
	Arm/leg cellulitis	84,238 (8.3)	80,452 (7.9)	0.01
Unusual site TTS	Colonic diverticulitis	106,486 (10.5)	106,332 (10.5)	0.00
	Laceration of hand/finger	10,251 (1.0)	9,883 (1.0)	0.00
	Gout	71,722 (7.1)	68,551 (6.7)	0.01
	Arm/leg cellulitis	83,793 (8.2)	80,997 (8.0)	0.01
Common site TTS	Colonic diverticulitis	104,326 (10.4)	104,042 (10.4)	0.00
	Laceration of hand/finger	10,097 (1.0)	9,726 (1.0)	0.00
	Gout	70,170 (7.0)	66,955 (6.7)	0.01
	Arm/leg cellulitis	81,889 (8.1)	78,975 (7.9)	0.01

ASD = absolute standardized difference; COVID-19 = coronavirus disease 2019; sIPT = stabilized inverse probability of treatment; TTS = thrombosis with thrombocytopenia syndrome.

Table B-7-Medicare. Negative Control Outcomes and Study Outcomes Occurring on the Same Day in Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis Included in the Cohort Study, Medicare

Analysis set	Negative control outcome	Outcome cases, N	Negative control outcome case, N	Cases occurring on same day, %[a]
Guillain-Barré syndrome	Colonic diverticulitis	94	88,725	0.00
	Laceration of hand/finger	94	5,120	0.00
	Gout	94	74,094	0.00
	Arm/leg cellulitis	94	64,423	0.00
Bell's palsy	Colonic diverticulitis	2,011	88,532	0.03
	Laceration of hand/finger	2,011	5,112	0.02
	Gout	2,011	73,970	0.06
	Arm/leg cellulitis	2,011	64,328	0.02
Encephalitis/encephalomyelitis	Colonic diverticulitis	367	88,752	0.01
	Laceration of hand/finger	367	5,120	0.00
	Gout	367	74,129	0.01
	Arm/leg cellulitis	367	64,475	0.00
Narcolepsy	Colonic diverticulitis	427	88,681	0.00
	Laceration of hand/finger	427	5,119	0.04
	Gout	427	74,056	0.01
	Arm/leg cellulitis	427	64,364	0.00
Appendicitis	Colonic diverticulitis	771	88,543	0.17
	Laceration of hand/finger	771	5,115	0.00
	Gout	771	74,053	0.04
	Arm/leg cellulitis	771	64,430	0.00
Nonhemorrhagic stroke	Colonic diverticulitis	12,594	80,552	0.36
	Laceration of hand/finger	12,594	4,652	0.19
	Gout	12,594	66,319	0.56
	Arm/leg cellulitis	12,594	56,581	0.20
Hemorrhagic stroke	Colonic diverticulitis	3,710	87,503	0.10
	Laceration of hand/finger	3,710	5,026	0.08
	Gout	3,710	72,945	0.12
	Arm/leg cellulitis	3,710	63,322	0.05
Acute myocardial infarction	Colonic diverticulitis	32,455	83,605	1.29
	Laceration of hand/finger	32,455	4,883	0.37
	Gout	32,455	69,012	1.79
	Arm/leg cellulitis	32,455	59,568	0.86
Myocarditis/pericarditis	Colonic diverticulitis	2,672	88,567	0.04
	Laceration of hand/finger	2,672	5,118	0.02
	Gout	2,672	73,948	0.10
	Arm/leg cellulitis	2,672	64,325	0.02
Deep vein thrombosis	Colonic diverticulitis	27,645	84,317	0.76
	Laceration of hand/finger	27,645	4,907	0.16
	Gout	27,645	70,015	0.68
	Arm/leg cellulitis	27,645	58,904	1.20
Pulmonary embolism	Colonic diverticulitis	21,841	86,126	0.68

Analysis set	Negative control outcome	Outcome cases, N	Negative control outcome case, N	Cases occurring on same day, %[a]
	Laceration of hand/finger	21,841	4,996	0.16
	Gout	21,841	72,020	0.67
	Arm/leg cellulitis	21,841	62,362	0.34
Disseminated intravascular coagulation	Colonic diverticulitis	1,890	88,718	0.09
	Laceration of hand/finger	1,890	5,119	0.02
	Gout	1,890	74,122	0.06
	Arm/leg cellulitis	1,890	64,447	0.05
Immune thrombocytopenia	Colonic diverticulitis	1,249	88,442	0.03
	Laceration of hand/finger	1,249	5,109	0.00
	Gout	1,249	73,804	0.06
	Arm/leg cellulitis	1,249	64,221	0.02
Transverse myelitis	Colonic diverticulitis	26	88,787	0.00
	Laceration of hand/finger	26	5,124	0.00
	Gout	26	74,160	0.00
	Arm/leg cellulitis	26	64,507	0.00
Unusual site TTS	Colonic diverticulitis	203	88,745	0.01
	Laceration of hand/finger	203	5,120	0.00
	Gout	203	74,139	0.01
	Arm/leg cellulitis	203	64,483	0.01
Common site TTS	Colonic diverticulitis	11,733	87,195	0.41
	Laceration of hand/finger	11,733	5,072	0.10
	Gout	11,733	72,586	0.50
	Arm/leg cellulitis	11,733	62,968	0.32

COVID-19 = coronavirus disease 2019; TTS = thrombosis with thrombocytopenia syndrome.

[a] Percentages calculated as the proportion of identified negative control outcome cases occurring on the same day as an adverse event.

Table B-8-Medicare. Association of a COVID-19 Diagnosis With Select Negative Control Outcomes, Medicare

A. Guillain-Barré Syndrome

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	43,711	77,809,678	1.12 (1.11-1.14)	1.11 (1.09-1.12)
	Comparator	41,088	84,139,577	—	—
Laceration of hand or finger	COVID-19	2,410	80,855,487	1.07 (1.02-1.14)	1.05 (0.99-1.11)
	Comparator	2,398	87,092,507	—	—
Gout	COVID-19	38,729	78,074,512	1.27 (1.25-1.29)	1.24 (1.23-1.26)
	Comparator	31,939	84,711,929	—	—
Arm/leg cellulitis	COVID-19	28,336	78,769,344	0.96 (0.95-0.98)	0.94 (0.92-0.95)
	Comparator	31,120	84,744,086	—	—

B. Bell's Palsy

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	43,635	77,702,124	1.12 (1.11-1.14)	1.11 (1.09-1.12)
	Comparator	40,986	84,016,391	—	—
Laceration of hand or finger	COVID-19	2,404	80,743,013	1.07 (1.01-1.13)	1.05 (0.99-1.11)
	Comparator	2,397	86,961,017	—	—
Gout	COVID-19	38,668	77,965,915	1.27 (1.25-1.29)	1.24 (1.22-1.25)
	Comparator	31,887	84,583,894	—	—
Arm/leg cellulitis	COVID-19	28,298	78,659,413	0.96 (0.94-0.98)	0.93 (0.92-0.95)
	Comparator	31,084	84,615,879	—	—

C. Encephalitis/Encephalomyelitis

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	43,743	77,831,516	1.12 (1.11-1.14)	1.11 (1.10-1.13)
	Comparator	41,083	84,167,112	—	—
Laceration of hand or finger	COVID-19	2,409	80,879,667	1.07 (1.01-1.14)	1.05 (0.99-1.11)
	Comparator	2,399	87,118,742	—	—
Gout	COVID-19	38,753	78,097,021	1.27 (1.25-1.29)	1.26 (1.24-1.28)
	Comparator	31,956	84,735,653	—	—
Arm/leg cellulitis	COVID-19	28,362	78,790,935	0.96 (0.94-0.98)	0.94 (0.93-0.96)
	Comparator	31,151	84,767,493	—	—

D. Narcolepsy

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	43,700	77,771,665	1.12 (1.11-1.14)	1.11 (1.09-1.12)
	Comparator	41,055	84,110,583	—	—
Laceration of hand or finger	COVID-19	2,409	80,817,315	1.07 (1.01-1.14)	1.05 (0.99-1.11)
	Comparator	2,398	87,060,481	—	—
Gout	COVID-19	38,708	78,037,258	1.27 (1.25-1.29)	1.25 (1.23-1.27)
	Comparator	31,929	84,679,707	—	—
Arm/leg cellulitis	COVID-19	28,324	78,731,756	0.96 (0.95-0.98)	0.94 (0.92-0.96)
	Comparator	31,076	84,715,798	—	—

E. Appendicitis

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	43,648	77,780,906	1.12 (1.11-1.14)	1.1 (1.09-1.12)
	Comparator	40,976	84,092,701	—	—
Laceration of hand or finger	COVID-19	2,407	80,821,230	1.07 (1.01-1.14)	1.06 (1.00-1.12)
	Comparator	2,397	87,035,852	—	—
Gout	COVID-19	38,717	78,041,274	1.27 (1.25-1.29)	1.24 (1.22-1.26)
	Comparator	31,924	84,654,872	—	—
Arm/leg cellulitis	COVID-19	28,345	78,735,151	0.96 (0.95-0.98)	0.94 (0.92-0.95)
	Comparator	31,121	84,686,855	—	—

F. Nonhemorrhagic Stroke

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	40,263	71,767,821	1.13 (1.12-1.15)	1.11 (1.10-1.13)
	Comparator	37,195	76,875,881	—	—
Laceration of hand or finger	COVID-19	2,207	74,587,568	1.06 (1.00-1.13)	1.04 (0.98-1.11)
	Comparator	2,199	79,542,814	—	—
Gout	COVID-19	35,243	72,038,661	1.3 (1.28-1.32)	1.23 (1.21-1.25)
	Comparator	28,395	77,443,194	—	—
Arm/leg cellulitis	COVID-19	25,303	72,711,658	0.97 (0.95-0.98)	0.92 (0.90-0.94)
	Comparator	27,440	77,483,067	—	—

G. Hemorrhagic Stroke

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	43,249	76,948,742	1.12 (1.11-1.14)	1.11 (1.09-1.12)
	Comparator	40,487	83,009,636	—	—
Laceration of hand or finger	COVID-19	2,372	79,965,397	1.07 (1.01-1.14)	1.05 (0.99-1.12)
	Comparator	2,355	85,917,207	—	—
Gout	COVID-19	38,247	77,211,036	1.28 (1.26-1.29)	1.23 (1.21-1.25)
	Comparator	31,388	83,578,190	—	—
Arm/leg cellulitis	COVID-19	27,940	77,903,997	0.96 (0.95-0.98)	0.93 (0.91-0.94)
	Comparator	30,584	83,610,259	—	—

H. Acute Myocardial Infarction

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	41,625	75,174,890	1.14 (1.12-1.15)	1.11 (1.09-1.12)
	Comparator	38,476	80,936,904	—	—
Laceration of hand or finger	COVID-19	2,330	78,082,660	1.09 (1.03-1.16)	1.07 (1.01-1.14)
	Comparator	2,269	83,698,164	—	—
Gout	COVID-19	36,419	75,457,022	1.29 (1.27-1.31)	1.22 (1.20-1.24)
	Comparator	29,544	81,504,826	—	—
Arm/leg cellulitis	COVID-19	26,520	76,122,059	0.97 (0.96-0.99)	0.92 (0.90-0.93)
	Comparator	28,635	81,532,862	—	—

I. Myocarditis/Pericarditis

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	43,641	77,744,891	1.12 (1.11-1.14)	1.10 (1.08-1.11)
	Comparator	41,008	84,076,936	—	—
Laceration of hand or finger	COVID-19	2,406	80,785,988	1.07 (1.01-1.13)	1.06 (1.00-1.12)
	Comparator	2,400	87,022,892	—	—
Gout	COVID-19	38,678	78,008,295	1.27 (1.25-1.29)	1.22 (1.20-1.23)
	Comparator	31,860	84,647,155	—	—
Arm/leg cellulitis	COVID-19	28,307	78,701,271	0.96 (0.95-0.98)	0.92 (0.90-0.93)
	Comparator	31,069	84,678,193	—	—

J. Deep Vein Thrombosis

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	41,853	75,356,328	1.13 (1.12-1.15)	1.12 (1.10-1.13)
	Comparator	38,959	81,357,555	—	—
Laceration of hand or finger	COVID-19	2,322	78,275,338	1.08 (1.02-1.14)	1.06 (1.00-1.12)
	Comparator	2,298	84,151,235	—	—
Gout	COVID-19	36,805	75,629,665	1.28 (1.26-1.30)	1.22 (1.20-1.24)
	Comparator	30,131	81,907,338	—	—
Arm/leg cellulitis	COVID-19	26,100	76,356,626	0.97 (0.95-0.98)	0.93 (0.91-0.94)
	Comparator	28,448	82,015,734	—	—

K. Pulmonary Embolism

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Overall					
Colonic diverticulitis	COVID-19	42,570	76,511,850	1.13 (1.11-1.14)	1.11 (1.10-1.13)
	Comparator	39,841	82,661,982	—	—
Laceration of hand or finger	COVID-19	2,363	79,485,483	1.08 (1.02-1.14)	1.06 (1.00-1.13)
	Comparator	2,335	85,524,634	—	—
Gout	COVID-19	37,751	76,769,351	1.28 (1.26-1.29)	1.22 (1.20-1.24)
	Comparator	31,026	83,212,959	—	—
Arm/leg cellulitis	COVID-19	27,487	77,457,238	0.96 (0.95-0.98)	0.92 (0.91-0.94)
	Comparator	30,133	83,253,735	—	—

L. Disseminated Intravascular Coagulation

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	43,726	77,827,860	1.12 (1.11-1.14)	1.11 (1.10-1.13)
	Comparator	41,071	84,163,206	—	—
Laceration of hand or finger	COVID-19	2,410	80,874,635	1.07 (1.02-1.14)	1.05 (1.00-1.12)
	Comparator	2,397	87,114,803	—	—
Gout	COVID-19	38,743	78,092,633	1.27 (1.25-1.29)	1.24 (1.22-1.26)
	Comparator	31,957	84,731,189	—	—
Arm/leg cellulitis	COVID-19	28,351	78,787,669	0.96 (0.95-0.98)	0.94 (0.93-0.96)
	Comparator	31,126	84,765,596	—	—

M. Immune Thrombocytopenia

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	43,595	77,668,134	1.12 (1.11-1.14)	1.11 (1.09-1.12)
	Comparator	40,937	83,988,723	—	—
Laceration of hand or finger	COVID-19	2,403	80,705,294	1.07 (1.01-1.13)	1.05 (0.99-1.11)
	Comparator	2,396	86,930,992	—	—
Gout	COVID-19	38,596	77,931,991	1.27 (1.25-1.29)	1.25 (1.23-1.26)
	Comparator	31,804	84,558,773	—	—
Arm/leg cellulitis	COVID-19	28,265	78,623,253	0.96 (0.95-0.98)	0.94 (0.92-0.95)
	Comparator	31,003	84,592,604	—	—

N. Transverse Myelitis

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	43,752	77,843,588	1.12 (1.11-1.14)	1.11 (1.09-1.12)
	Comparator	41,103	84,185,253	—	—
Laceration of hand or finger	COVID-19	2,411	80,891,991	1.07 (1.01-1.14)	1.05 (0.99-1.11)
	Comparator	2,401	87,138,205	—	—
Gout	COVID-19	38,763	78,108,597	1.27 (1.25-1.29)	1.24 (1.22-1.26)
	Comparator	31,975	84,754,245	—	—
Arm/leg cellulitis	COVID-19	28,376	78,802,292	0.96 (0.95-0.98)	0.93 (0.92-0.95)
	Comparator	31,161	84,786,955	—	—

O. Unusual Site Thrombosis With Thrombocytopenia Syndrome

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	43,741	77,843,881	1.12 (1.11-1.14)	1.11 (1.09-1.12)
	Comparator	41,076	84,177,480	—	—
Laceration of hand or finger	COVID-19	2,408	80,891,858	1.07 (1.01-1.14)	1.05 (1.00-1.12)
	Comparator	2,400	87,128,410	—	—
Gout	COVID-19	38,756	78,108,840	1.27 (1.25-1.29)	1.22 (1.20-1.24)
	Comparator	31,960	84,745,140	—	—
Arm/leg cellulitis	COVID-19	28,365	78,802,482	0.96 (0.95-0.98)	0.92 (0.91-0.94)
	Comparator	31,147	84,777,726	—	—

P. Common Site Thrombosis With Thrombocytopenia Syndrome

Negative control outcome	Exposure group	Outcome cases	Person-time (days)	Crude HR (95% CI)	sIPTW HR (95% CI)
Colonic diverticulitis	COVID-19	43,156	77,236,329	1.13 (1.11 – 1.14)	1.11 (1.09 – 1.13)
	Comparator	40,268	83,305,387	—	—
Laceration of hand or finger	COVID-19	2,392	80,247,085	1.07 (1.01 – 1.14)	1.05 (0.99 – 1.12)
	Comparator	2,378	86,200,414	—	—
Gout	COVID-19	38,107	77,504,221	1.28 (1.26 – 1.30)	1.22 (1.20 – 1.24)
	Comparator	31,177	83,878,226	—	—
Arm/leg cellulitis	COVID-19	27,851	78,192,910	0.97 (0.95 – 0.98)	0.93 (0.91 – 0.94)
	Comparator	30,319	83,913,369	—	—

CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; sIPTW = stabilized inverse probability of treatment weighted.

— denotes the reference group.

Table B-9-Medicare. Characteristics of Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis, by Hospitalization at Time 0, Medicare

Characteristic	Hospitalized on Time 0, COVID-19 diagnosis (exposure) group	Hospitalized on Time 0, Comparator group	Hospitalized on Time 0, ASD	Nonhospitalized on Time 0, COVID-19 diagnosis (exposure) group	Nonhospitalized on Time 0, Comparator group	Nonhospitalized on Time 0, ASD
Total selected observations [a] (unique individuals)	166,154 (166,154)	166,154 (146,571)		851,256 (851,256)	851,256 (791,689)	
Demographic characteristics						
Age, years						
Mean (SD)	78.1(8.0)	78.1(8.0)	0.00	77.6 (8.7)	77.6 (8.7)	0.00
Median (Q1, Q3)	77 (72, 84)	77 (72, 84)		76 (70, 84)	76 (70, 84)	
Age groups, n (%)						
65-79 years	97,335 (58.6)	97,335 (58.6)		532,374 (62.5)	532,374 (62.5)	
≥ 80 years	68,819 (41.4)	68,819 (41.4)		318,882 (37.5)	318,882 (37.5)	
Sex, n (%)			0.00			0.00
Female	85,276 (51.3)	85,276 (51.3)		505,308 (59.4)	505,308 (59.4)	
Male	80,878 (48.7)	80,878 (48.7)		345,948 (40.6)	345,948 (40.6)	
US geographic region, n (%)			0.00			0.00
Northeast	36,702 (22.1)	36,540 (22.0)		181,575 (21.3)	181,567 (21.3)	
North central	40,001 (24.1)	39,958 (24.0)		210,138 (24.7)	210,172 (24.7)	
South	62,861 (37.8)	63,003 (37.9)		322,151 (37.8)	322,105 (37.8)	
West	26,550 (16.0)	26,613 (16.0)		134,452 (15.8)	134,472 (15.8)	
Unknown	40 (0.0)	40 (0.0)		2,940 (0.3)	2,940 (0.3)	
Race/ethnicity, n (%)[b]			0.20			0.07
American Indian/Alaska Native	1,440 (0.9)	783 (0.5)		6,070 (0.7)	4,457 (0.5)	
Asian	4,082 (2.5)	3,033 (1.8)		12,737 (1.5)	16,068 (1.9)	
Black or African American	22,505 (13.5)	17,331 (10.4)		68,492 (8.0)	70,426 (8.3)	
Hispanic/Latin American/Latinx	6,891 (4.1)	2,847 (1.7)		19,569 (2.3)	13,543 (1.6)	
White	126,070 (75.9)	137,362 (82.7)		718,972 (84.5)	719,842 (84.6)	

Characteristic	Hospitalized on Time 0, COVID-19 diagnosis (exposure) group	Hospitalized on Time 0, Comparator group	Hospitalized on Time 0, ASD	Nonhospitalized on Time 0, COVID-19 diagnosis (exposure) group	Nonhospitalized on Time 0, Comparator group	Nonhospitalized on Time 0, ASD
A race/ethnicity not listed	2,861 (1.7)	2,437 (1.5)		11,037 (1.3)	12,212 (1.4)	
Not provided	2,305 (1.4)	2,361 (1.4)		14,379 (1.7)	14,708 (1.7)	
Dual Medicare/Medicaid eligibility, n (%)[b]	44,237 (26.6)	32,416 (19.5)	0.17	253,262 (29.8)	235,527 (27.7)	0.05
Original reason for Medicare eligibility, n (%) [b]			0.05			0.03
Age	135,171 (81.4)	138,126 (83.1)		725,259 (85.2)	733,842 (86.2)	
Disability	28,674 (17.3)	26,398 (15.9)		122,242 (14.4)	114,841 (13.5)	
End-stage renal disease	2,309 (1.4)	1,630 (1.0)		3,755 (0.4)	2,573 (0.3)	
Hospitalized on Time 0, n (%)	166,154 (100.0)	166,154 (100.0)	0.00	0 (0.0)	0 (0.0)	0.00
SNF/LTC[b] residence on Time 0, n (%)	10,656 (6.4)	10,656 (6.4)	0.00	239,537 (28.1)	239,537 (28.1)	0.00
Comorbidities, n (%)						
Animal exposure/bites or rabies	495 (0.3)	698 (0.4)	0.02	2,610 (0.3)	2,506 (0.3)	0.00
Antiphospholipid syndrome	171 (0.1)	244 (0.1)	0.01	658 (0.1)	611 (0.1)	0.00
Autoimmune disorders	16,815 (10.1)	17,383 (10.5)	0.01	76,256 (9.0)	72,205 (8.5)	0.02
Brain lesions related to secondary narcolepsy	103 (0.1)	138 (0.1)	0.01	416 (0.0)	379 (0.0)	0.00
Cancer	49,656 (29.9)	58,375 (35.1)	0.11	223,211 (26.2)	225,558 (26.5)	0.01
Chronic lymphocytic leukemia	1,809 (1.1)	1,745 (1.1)	0.00	5,186 (0.6)	4,928 (0.6)	0.00
Chronic kidney disease or renal disease (other than end-stage renal disease)	62,434 (37.6)	71,844 (43.2)	0.12	214,220 (25.2)	190,732 (22.4)	0.06
End-stage renal disease [b]	7,103 (4.3)	5,715 (3.4)	0.04	13,126 (1.5)	8,494 (1.0)	0.05
Chronic liver disease	17,134 (10.3)	23,454 (14.1)	0.12	63,647 (7.5)	55,399 (6.5)	0.04
Chronic lung diseases	59,580 (35.9)	62,585 (37.7)	0.04	233,846 (27.5)	203,037 (23.9)	0.08
Dementia or other neurologic condition	53,409 (32.1)	52,600 (31.7)	0.01	296,942 (34.9)	255,457 (30.0)	0.10
Diabetes, Type 1 or 2	81,608 (49.1)	74,701 (45.0)	0.08	324,840 (38.2)	289,534 (34.0)	0.09

Characteristic	Hospitalized on Time 0, COVID-19 diagnosis (exposure) group	Hospitalized on Time 0, Comparator group	Hospitalized on Time 0, ASD	Nonhospitalized on Time 0, COVID-19 diagnosis (exposure) group	Nonhospitalized on Time 0, Comparator group	Nonhospitalized on Time 0, ASD
Disseminated intravascular coagulation [c]	69 (0.0)	170 (0.1)	0.02	255 (0.0)	161 (0.0)	0.01
Heart conditions	112,906 (68.0)	128,981 (77.6)	0.22	501,949 (59.0)	457,121 (53.7)	0.11
Hemiplegia or paraplegia	10,793 (6.5)	13,834 (8.3)	0.07	51,060 (6.0)	47,960 (5.6)	0.02
Herpes simplex infection	2,684 (1.6)	3,031 (1.8)	0.02	14,275 (1.7)	12,478 (1.5)	0.02
Hypertension	142,424 (85.7)	145,476 (87.6)	0.05	680,990 (80.0)	654,575 (76.9)	0.08
Immunocompromised state	82,503 (49.7)	82,503 (49.7)	0.00	356,451 (41.9)	356,451 (41.9)	0.00
Infection associated with GBS	9,714 (5.8)	10,224 (6.2)	0.01	41,565 (4.9)	33,030 (3.9)	0.05
Viral infection associated with ITP	914 (0.6)	834 (0.5)	0.01	2,788 (0.3)	2,524 (0.3)	0.01
Infection associated with myocarditis/pericarditis	22,001 (13.2)	27,322 (16.4)	0.09	89,922 (10.6)	76,813 (9.0)	0.05
Inpatient surgery	10,819 (6.5)	25,685 (15.5)	0.29	32,251 (3.8)	28,040 (3.3)	0.03
Lipid abnormality	126,585 (76.2)	131,236 (79.0)	0.07	607,074 (71.3)	583,760 (68.6)	0.06
Mental health conditions	67,856 (40.8)	73,387 (44.2)	0.07	374,098 (43.9)	331,525 (38.9)	0.10
Nutritional deficiency	15,775 (9.5)	22,827 (13.7)	0.13	64,264 (7.5)	56,482 (6.6)	0.04
Obese or severely obese	48,362 (29.1)	47,187 (28.4)	0.02	185,471 (21.8)	161,887 (19.0)	0.07
Peripheral vascular disease	56,842 (34.2)	63,496 (38.2)	0.08	261,542 (30.7)	229,490 (27.0)	0.08
Pneumonia or lower respiratory tract infection	46,921 (28.2)	47,039 (28.3)	0.00	190,197 (22.3)	141,835 (16.7)	0.14
Sepsis	13,956 (8.4)	20,391 (12.3)	0.13	45,866 (5.4)	37,956 (4.5)	0.04
Sickle cell disease or thalassemia	552 (0.3)	628 (0.4)	0.01	2,059 (0.2)	1,844 (0.2)	0.01
Smoking/nicotine dependency	13,359 (8.0)	21,867 (13.2)	0.17	51,346 (6.0)	59,042 (6.9)	0.04
Stroke or cerebrovascular disease	42,407 (25.5)	53,240 (32.0)	0.14	186,395 (21.9)	168,712 (19.8)	0.05
Thromboembolism	17,129 (10.3)	22,397 (13.5)	0.10	60,433 (7.1)	52,699 (6.2)	0.04
Thrombophilia	2,388 (1.4)	3,344 (2.0)	0.04	8,719 (1.0)	7,532 (0.9)	0.01
Trauma	4,956 (3.0)	11,989 (7.2)	0.19	19,590 (2.3)	17,899 (2.1)	0.01

Characteristic	Hospitalized on Time 0, COVID-19 diagnosis (exposure) group	Hospitalized on Time 0, Comparator group	Hospitalized on Time 0, ASD	Nonhospitalized on Time 0, COVID-19 diagnosis (exposure) group	Nonhospitalized on Time 0, Comparator group	Nonhospitalized on Time 0, ASD
Tuberculosis	609 (0.4)	671 (0.4)	0.01	1,976 (0.2)	1,628 (0.2)	0.01
Healthcare utilization, n (%)						
Inpatient stays in previous 365 days			0.46			0.08
0	102,446 (61.7)	65,135 (39.2)		627,444 (73.7)	656,742 (77.1)	
1-2	41,039 (24.7)	63,162 (38.0)		163,062 (19.2)	143,924 (16.9)	
≥ 3	22,669 (13.6)	37,857 (22.8)		60,750 (7.1)	50,590 (5.9)	
ED visits in previous 365 days			0.32			0.13
0	73,774 (44.4)	50,116 (30.2)		498,680 (58.6)	552,611 (64.9)	
1-2	52,748 (31.7)	57,407 (34.6)		229,694 (27.0)	201,671 (23.7)	
≥ 3	39,632 (23.9)	58,631 (35.3)		122,882 (14.4)	96,974 (11.4)	
Outpatient provider visits [d] in previous 365 days			0.13			0.22
0	38 (0.0)	53 (0.0)		55 (0.0)	119 (0.0)	
1-2	4,185 (2.5)	3,284 (2.0)		16,839 (2.0)	36,286 (4.3)	
3-5	8,644 (5.2)	6,020 (3.6)		43,024 (5.1)	69,704 (8.2)	
6-10	18,130 (10.9)	13,560 (8.2)		100,401 (11.8)	126,227 (14.8)	
≥ 11	135,157 (81.3)	143,237 (86.2)		690,937 (81.2)	618,920 (72.7)	
SNF/LTC stay [e]	28,873 (17.4)	30,503 (18.4)	0.03	266,654 (31.3)	255,887 (30.1)	0.03
Influenza vaccination in previous year	93,215 (56.1)	97,178 (58.5)	0.05	476,851 (56.0)	475,568 (55.9)	0.00

AE = adverse event; ASD = absolute standardized difference; COVID-19 = coronavirus disease 2019; ED = emergency department; GBS = Guillain-Barré syndrome; ITP = immune thrombocytopenia; LTC = long-term care; Q1 = first quartile, Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] A unique individual may be included multiple times because of matching with replacement, and an individual may be included in both the exposure and comparator groups. This table counts each instance of an individual's entry separately as distinct observations; the number of unique individuals is reported separately.

[b] Only available in Medicare.

[c] This serves as an AE-specific exclusion criterion when the condition is evaluated as an outcome, but history of the condition serves as a covariate for analyses of other AEs.

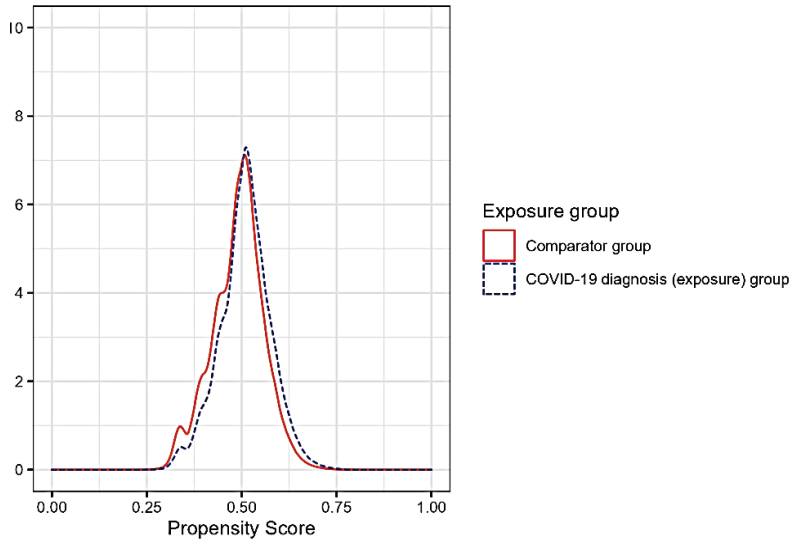
[d] Unique days on which an outpatient visit occurred.

[e] SNF and LTC both identified in Medicare; only SNF identified in MarketScan.

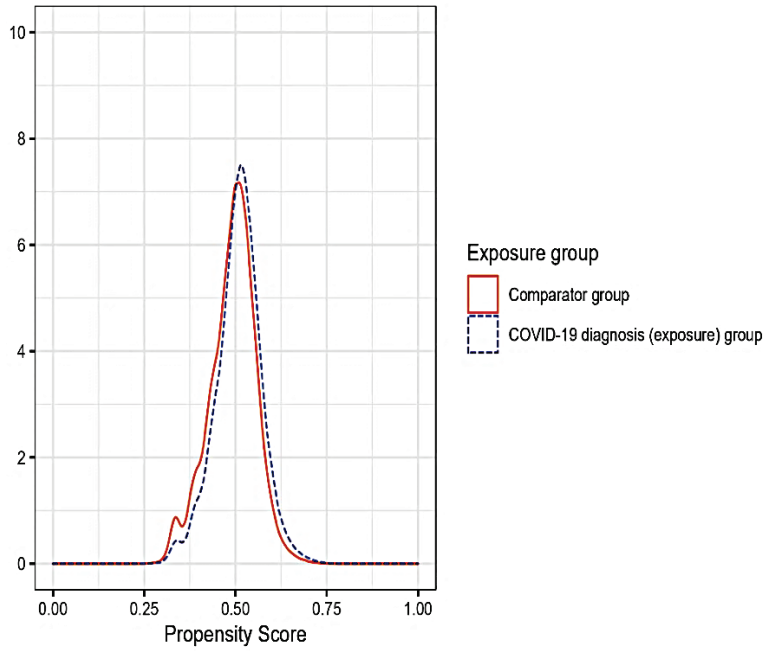
Note: Results presented in the overall, descriptive cohort before subdividing into adverse event-specific analysis sets.

Figure B-1-Medicare. Propensity Score Distributions Among Individuals With a COVID-19 Diagnosis and Comparators Without a COVID-19 Diagnosis, Medicare

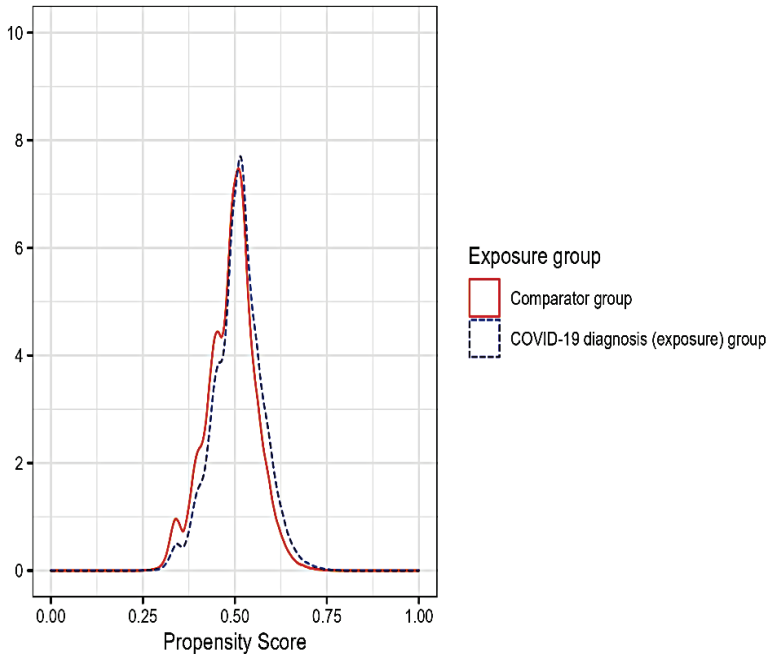
A. Guillain-Barré Syndrome



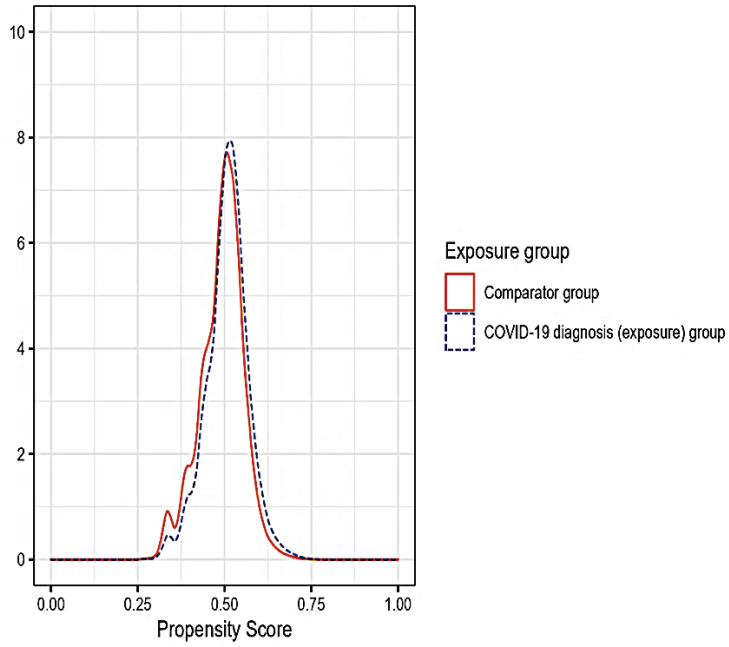
B. Bell's Palsy



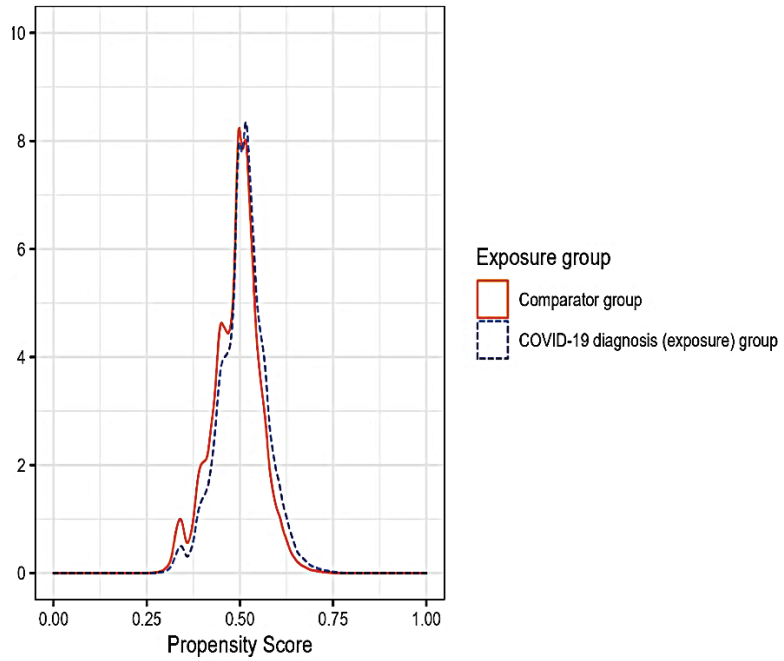
C. Encephalitis/Encephalomyelitis



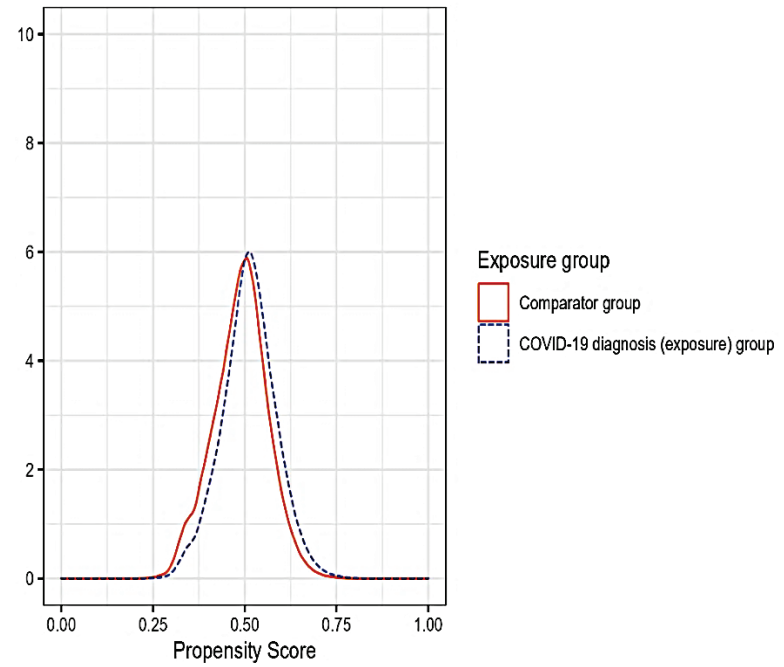
D. Narcolepsy



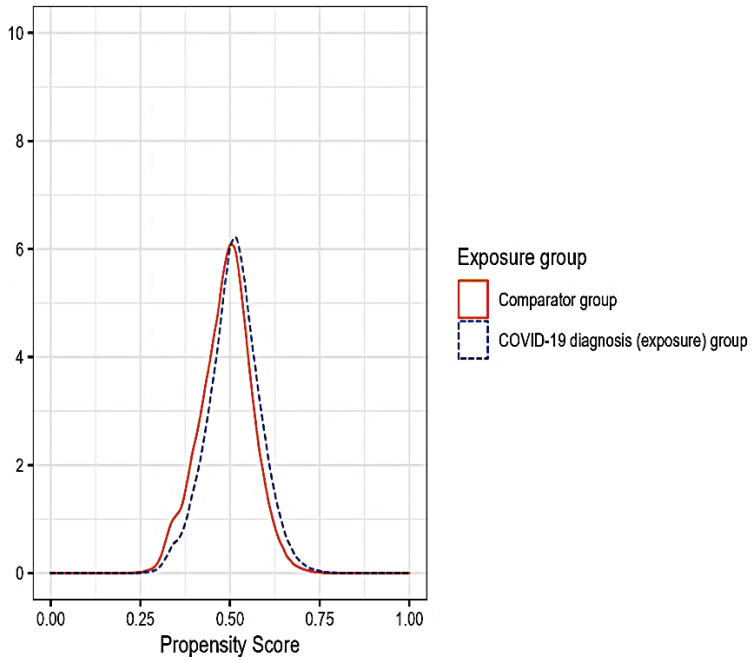
E. Appendicitis



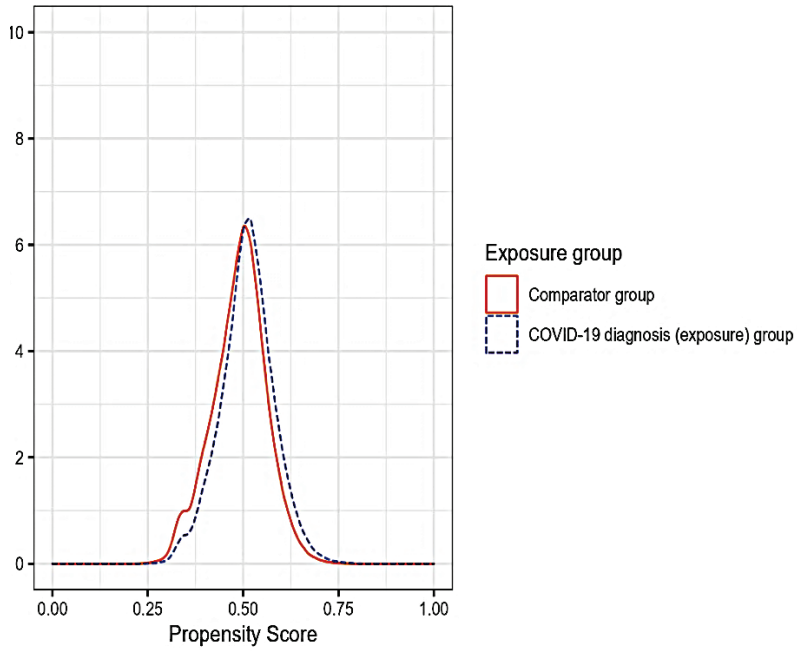
F. Nonhemorrhagic Stroke



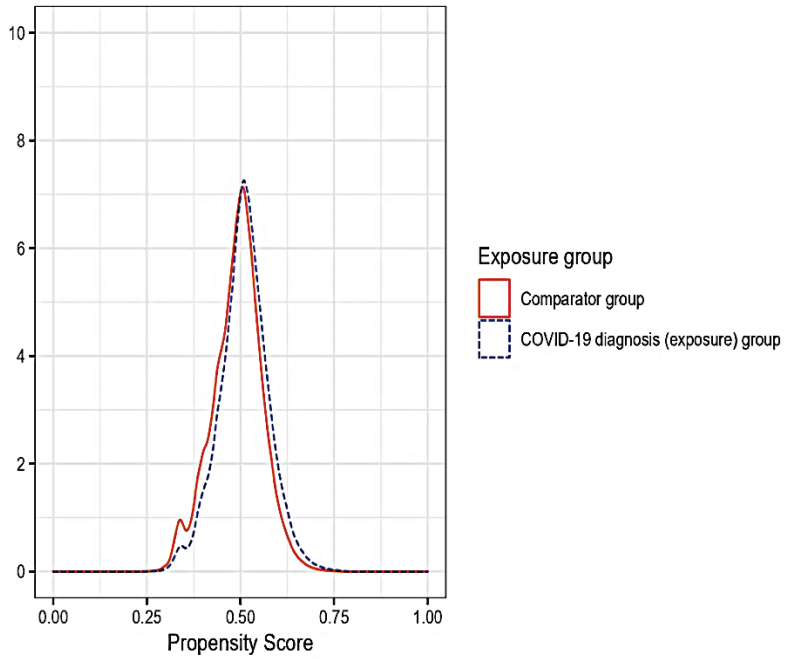
G. Hemorrhagic Stroke



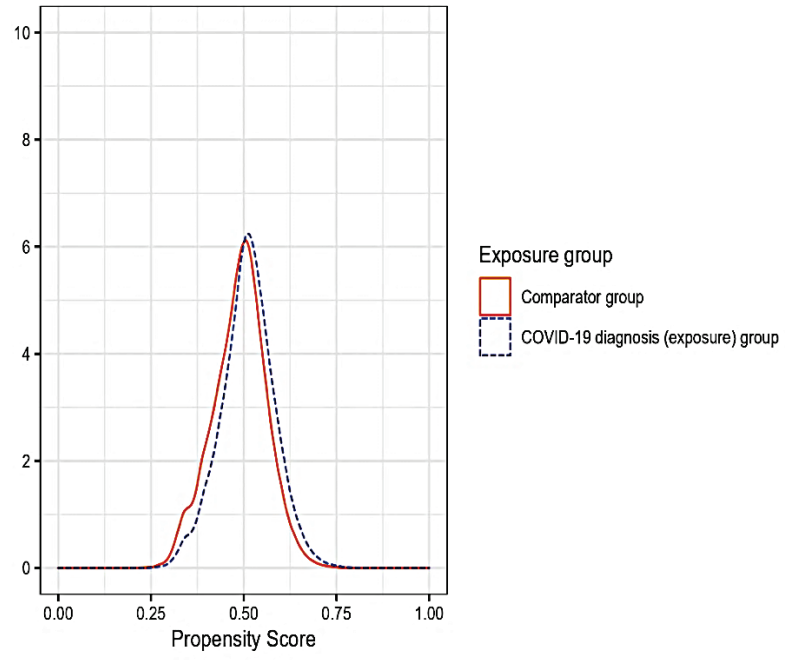
H. Acute Myocardial Infarction



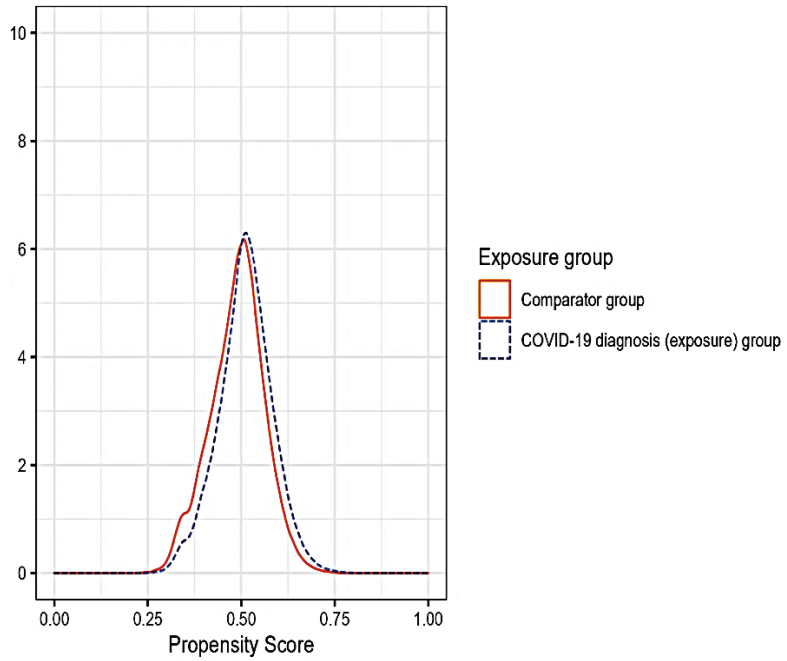
I. Myocarditis/Pericarditis



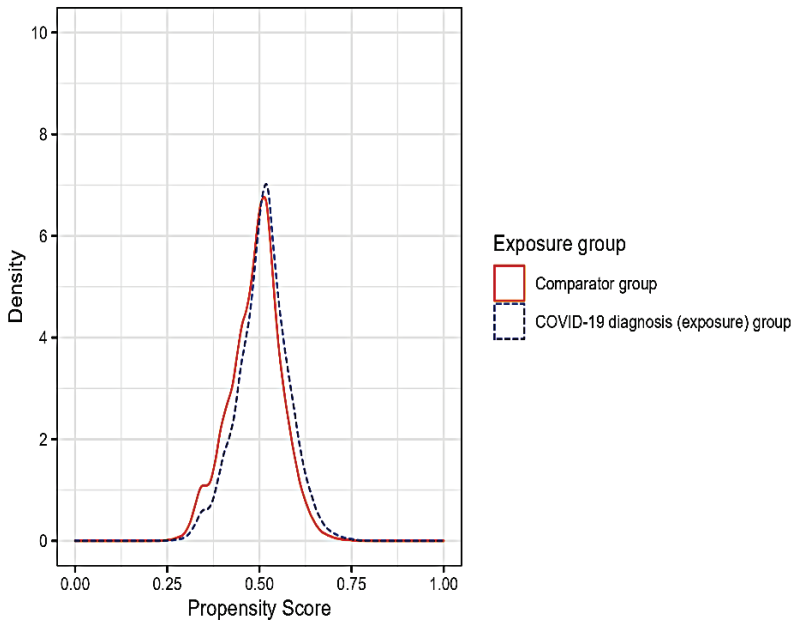
J. Deep Vein Thrombosis



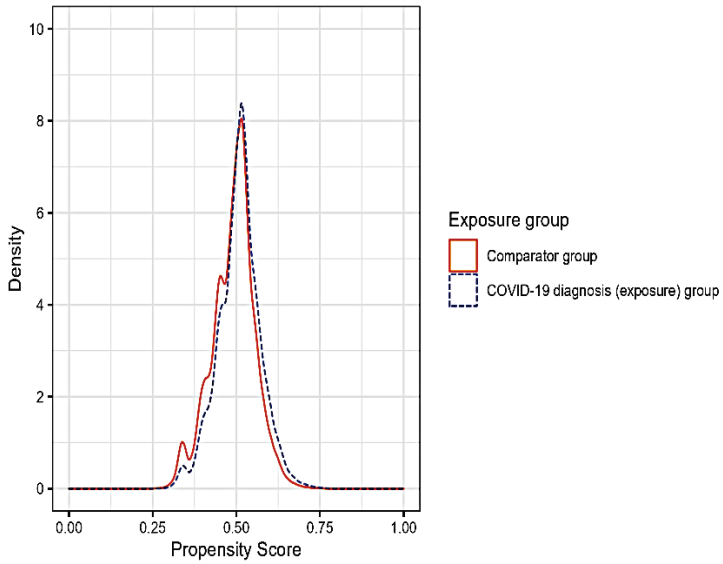
K. Pulmonary Embolism



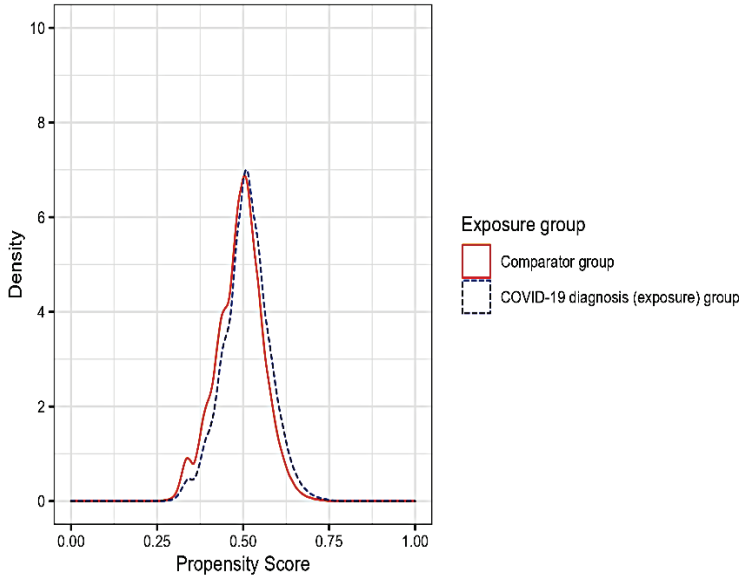
L. Disseminated Intravascular Coagulation



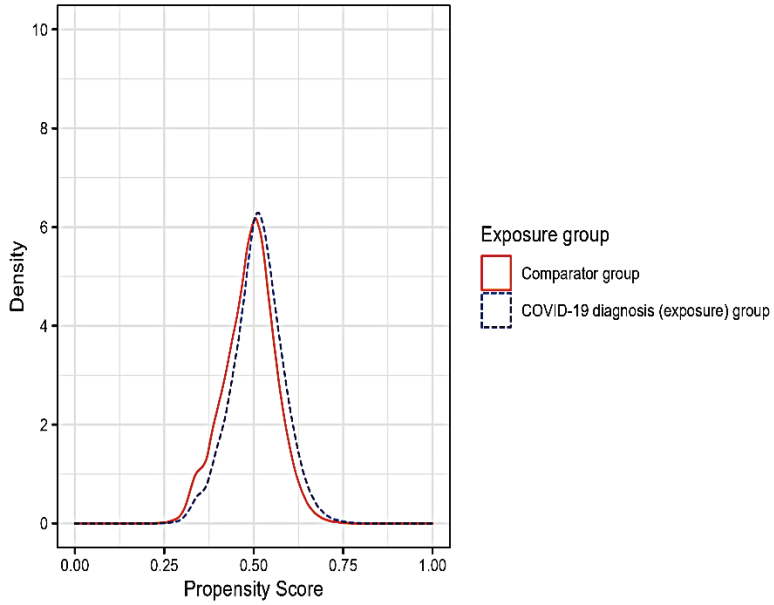
M. Immune Thrombocytopenia



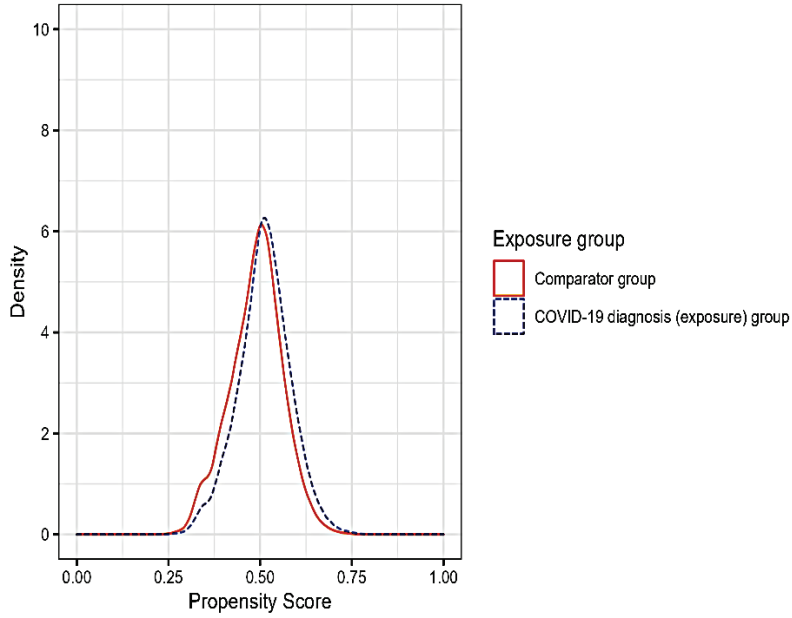
N. Transverse Myelitis



O. Unusual Site Thrombosis With Thrombocytopenia Syndrome



P. Common Site Thrombosis With Thrombocytopenia Syndrome

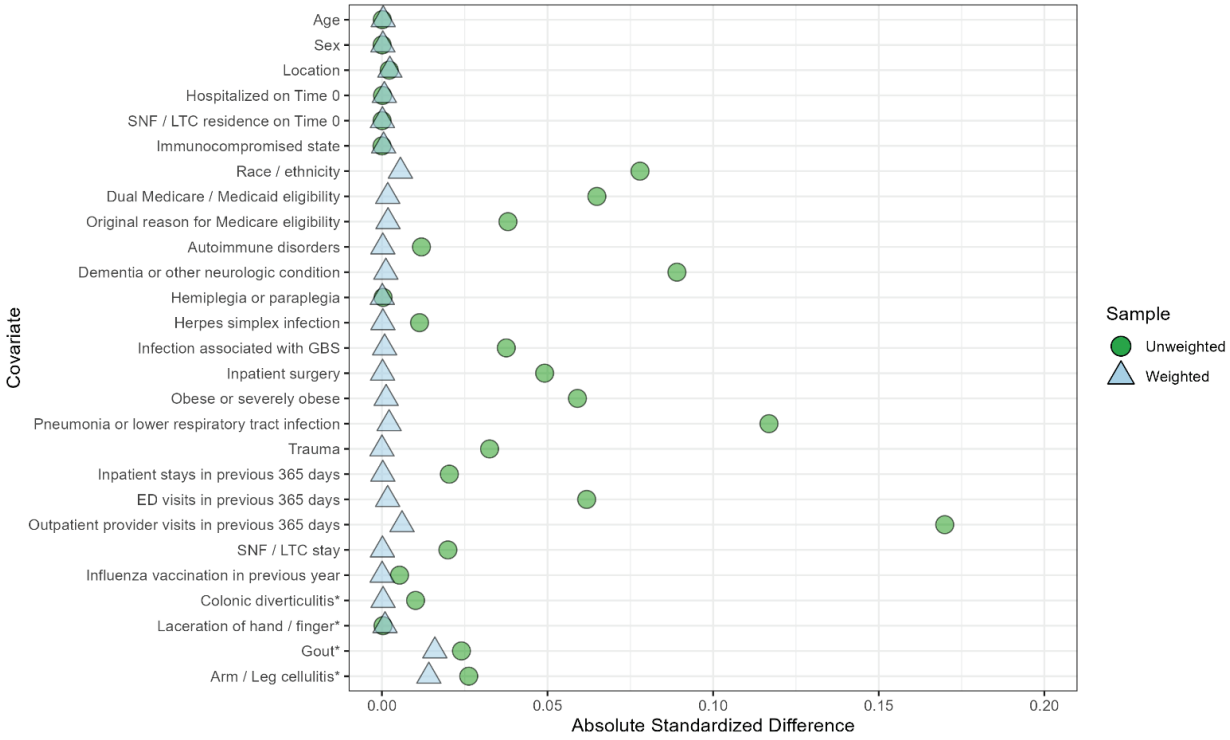


COVID-19 = coronavirus disease 2019.

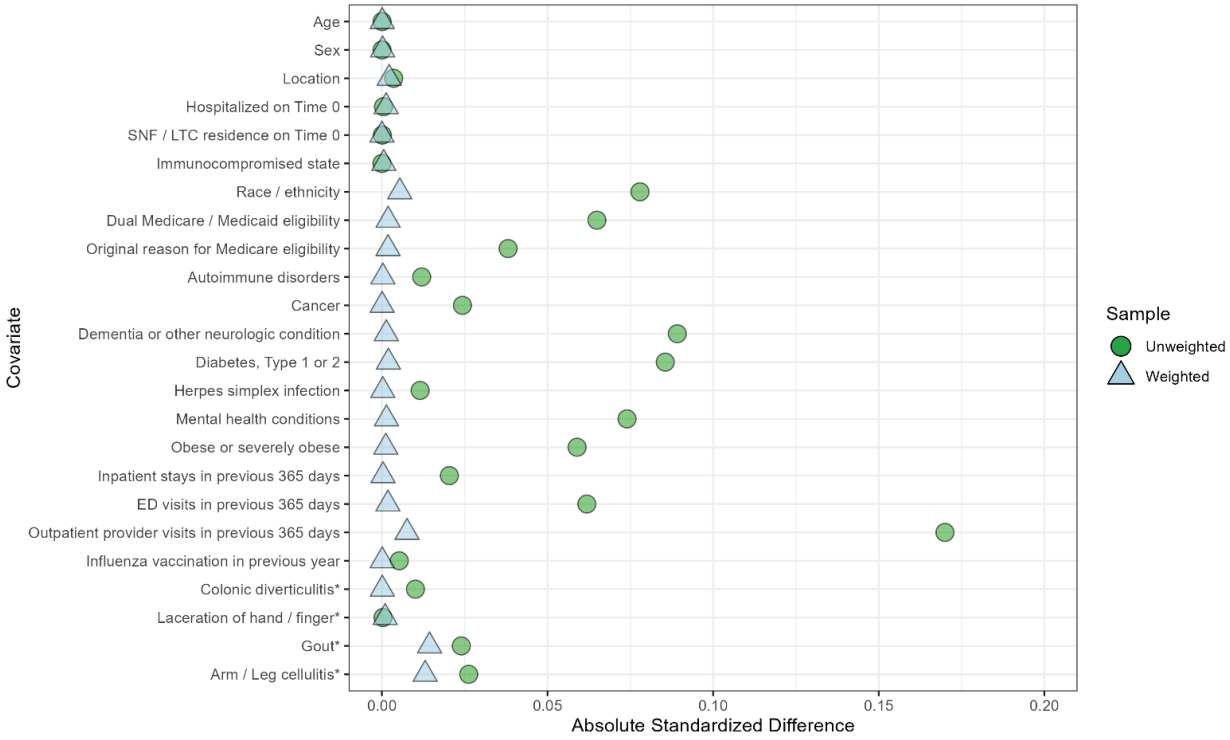
Note: A unique individual may be included multiple times and may appear in both exposure groups. This plot evaluates each instance where an individual is selected independently.

Figure B-2-Medicare. Balance of Covariate Distributions Among Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis, Cohort Design, Before and After Stabilized Inverse Probability of Treatment Weighting, Medicare

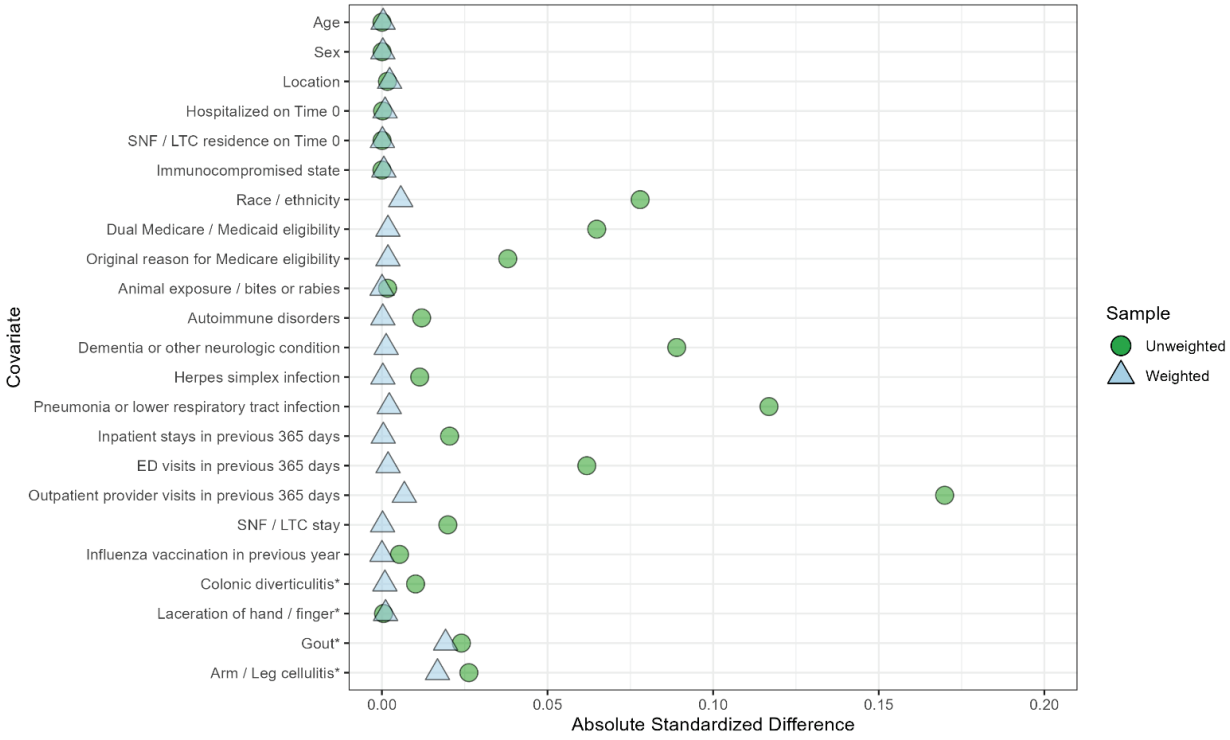
A. Guillain-Barré Syndrome



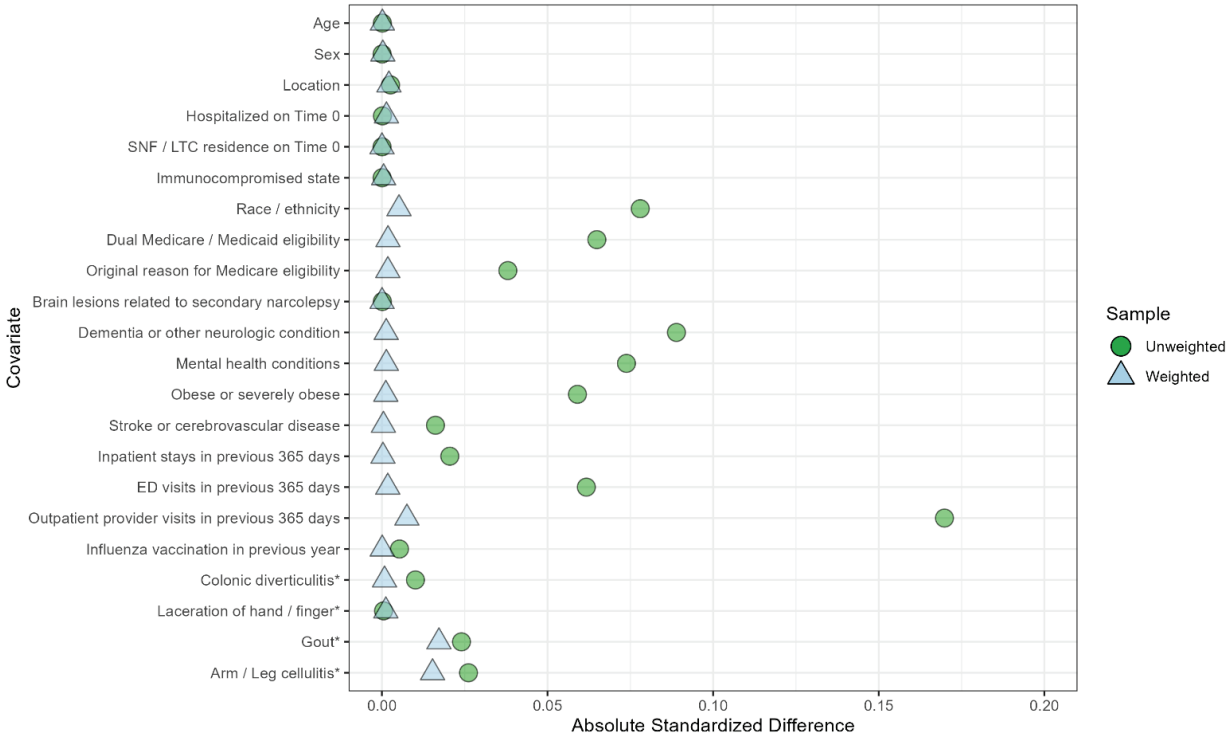
B. Bell's Palsy



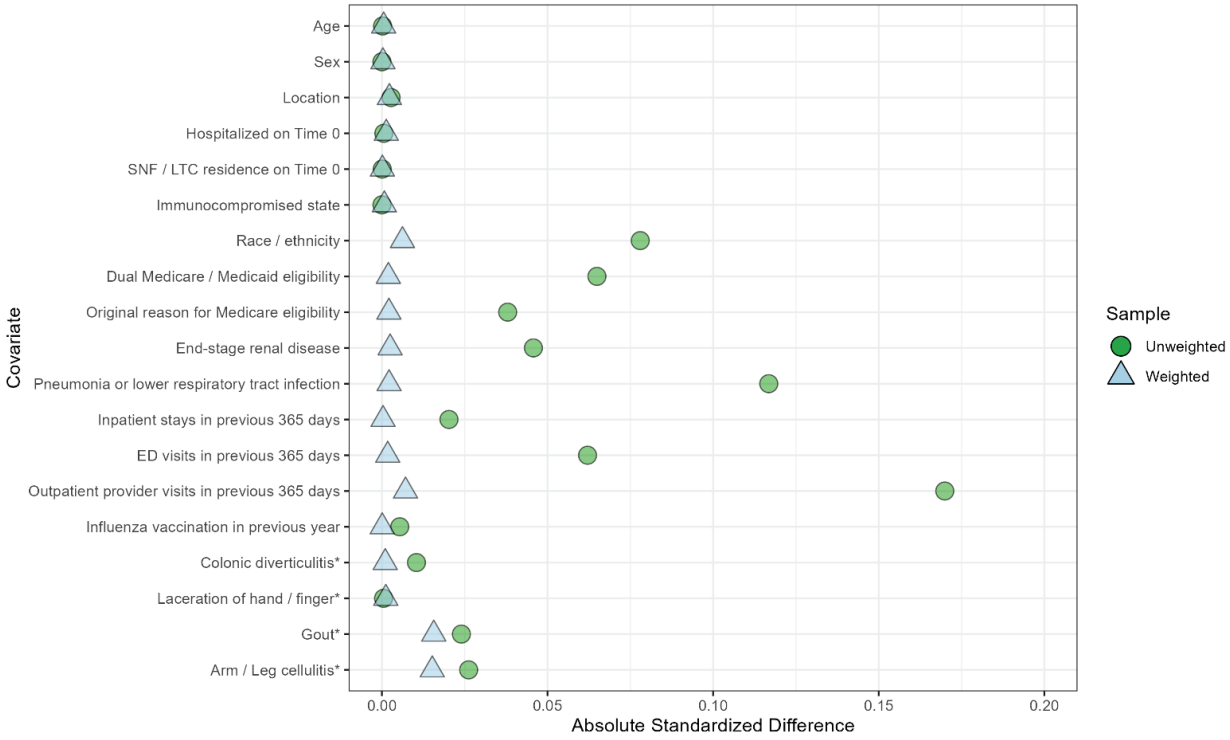
C. Encephalitis/Encephalomyelitis



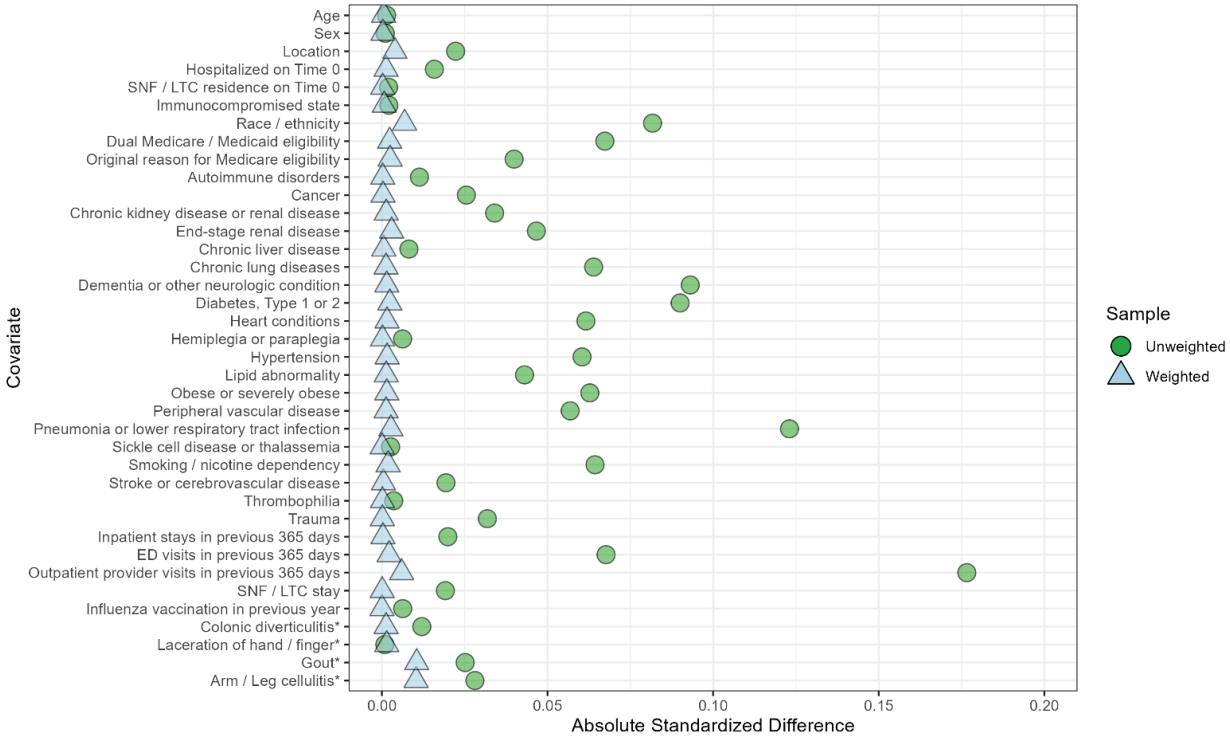
D. Narcolepsy



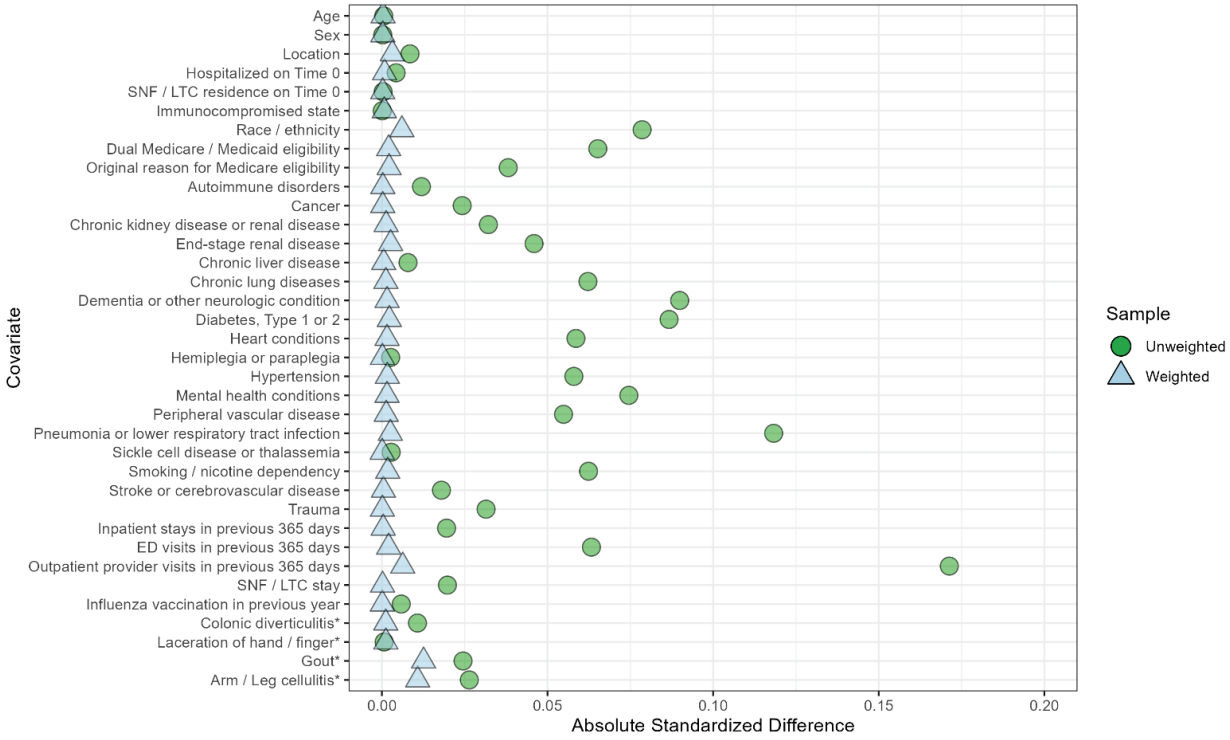
E. Appendicitis



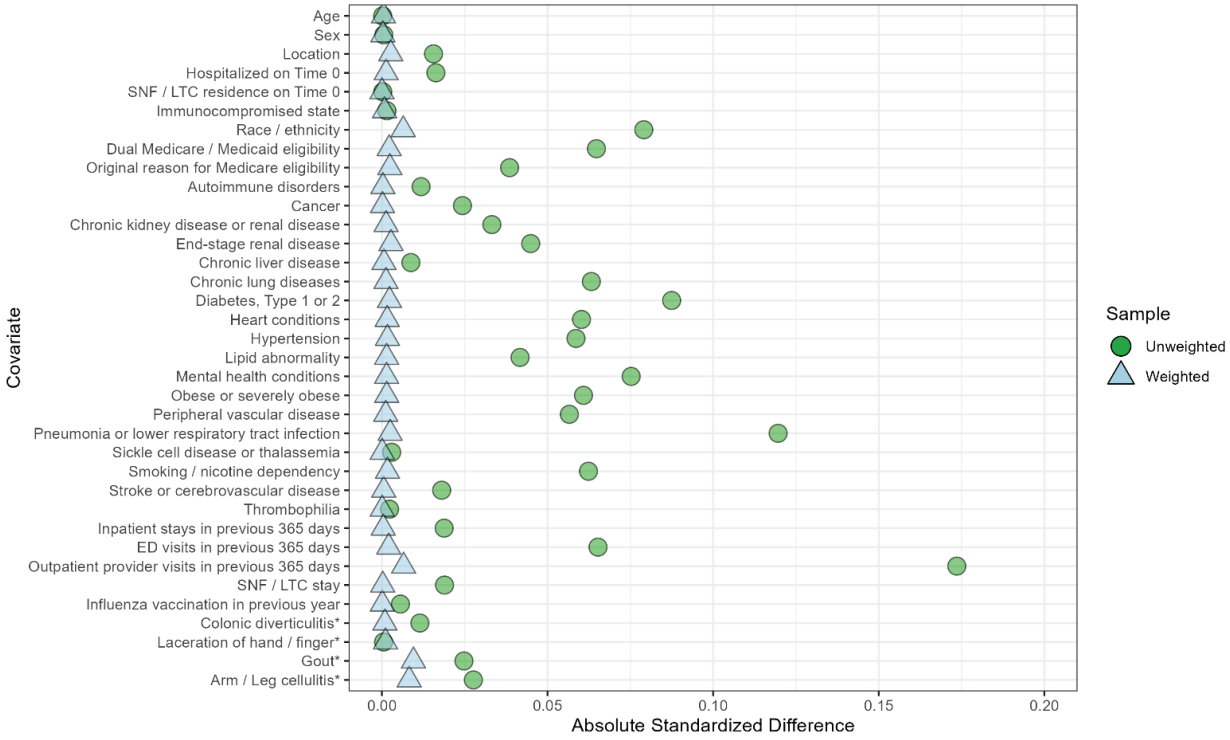
F. Nonhemorrhagic Stroke



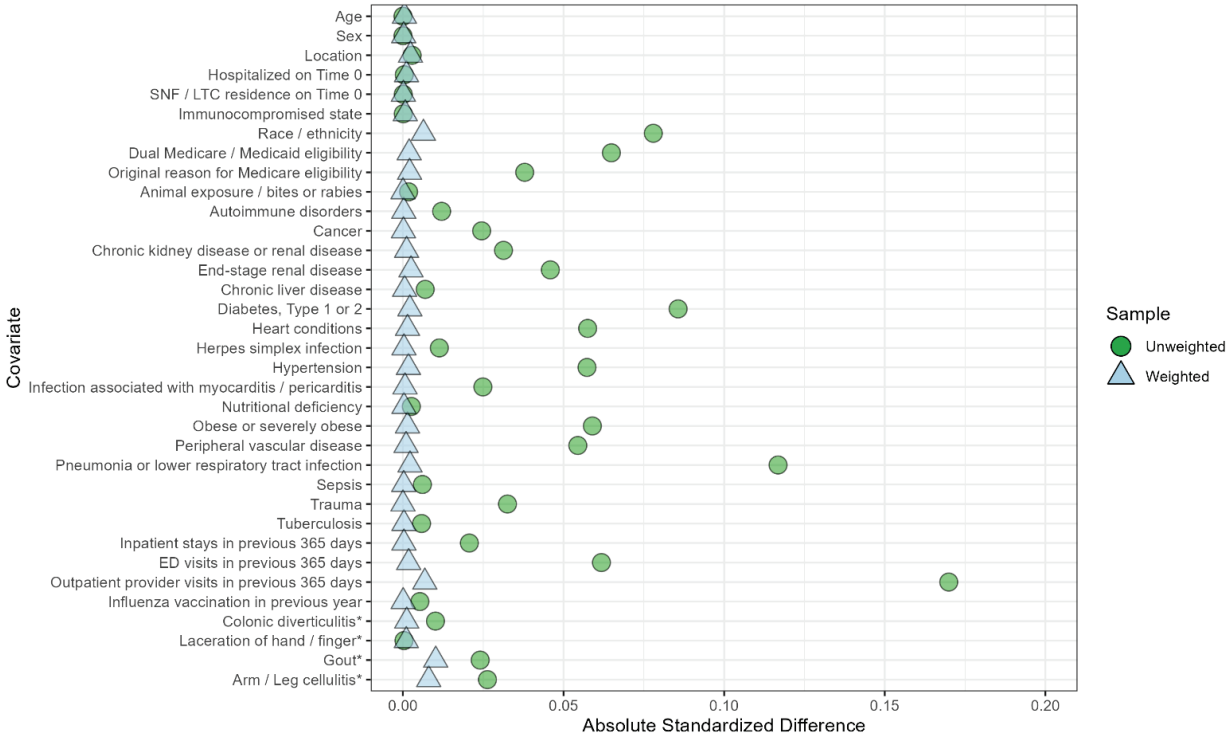
G. Hemorrhagic Stroke



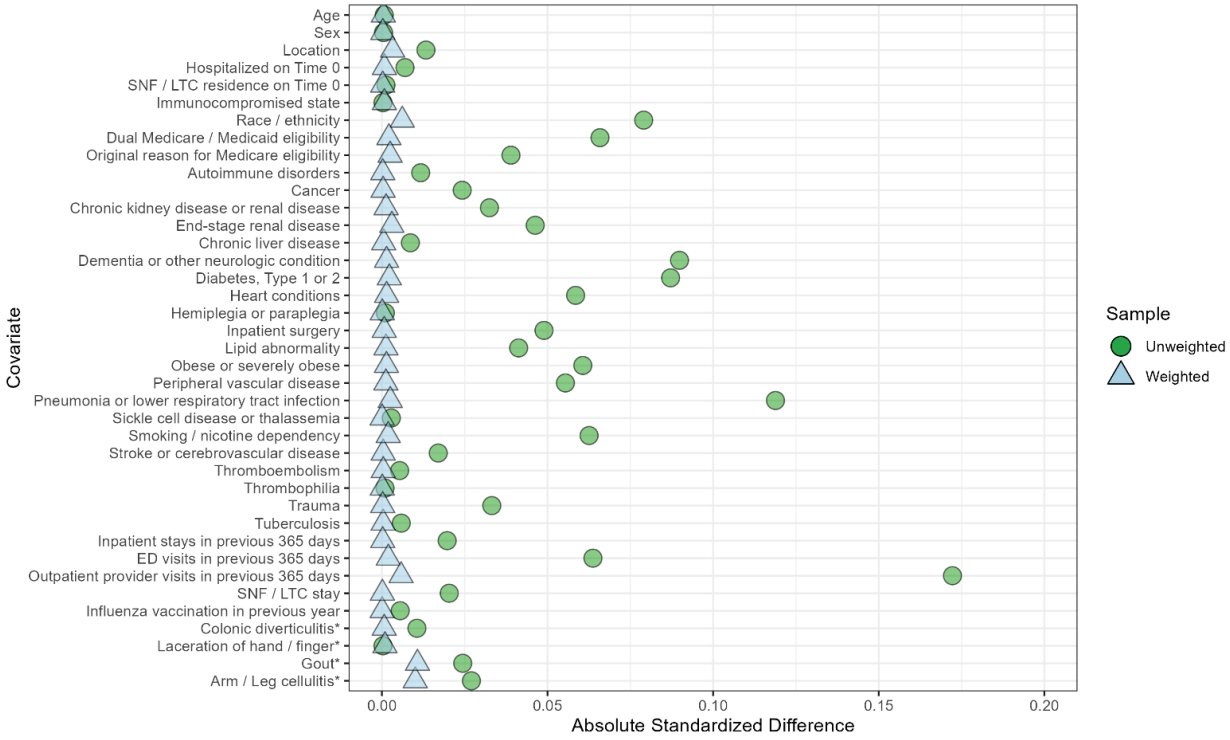
H. Acute Myocardial Infarction



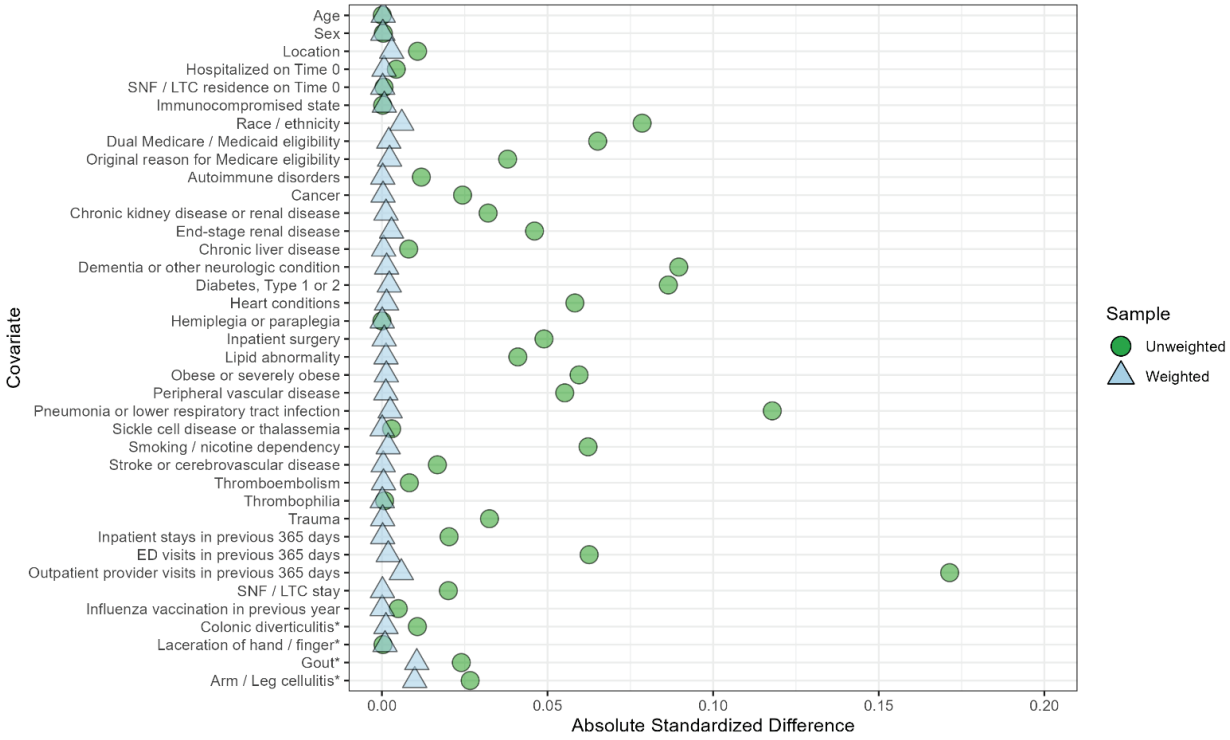
I. Myocarditis/Pericarditis



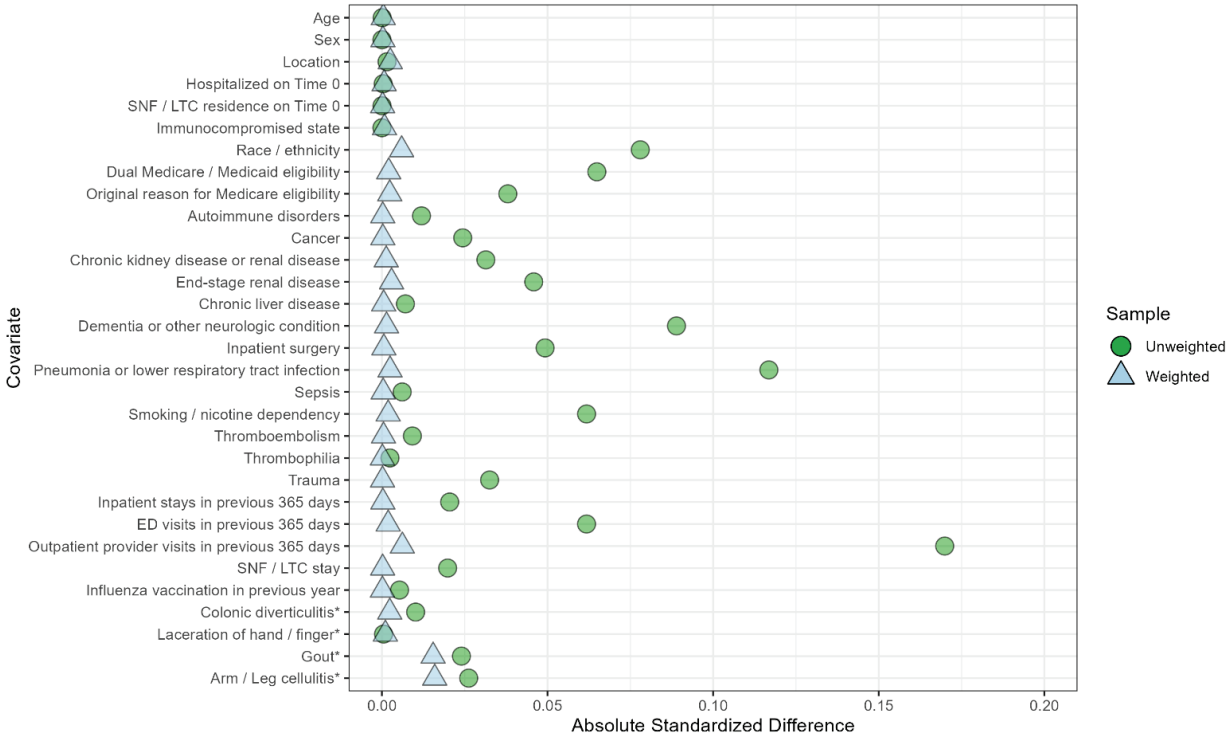
J. Deep Vein Thrombosis



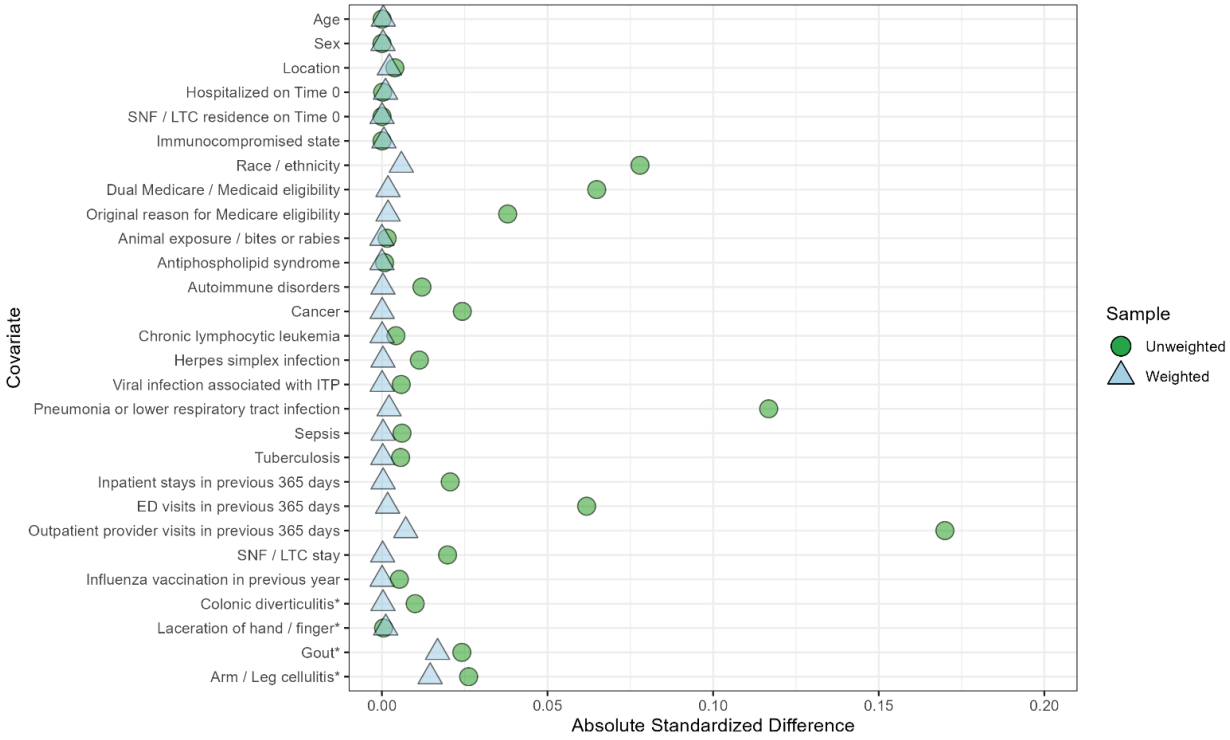
K. Pulmonary Embolism



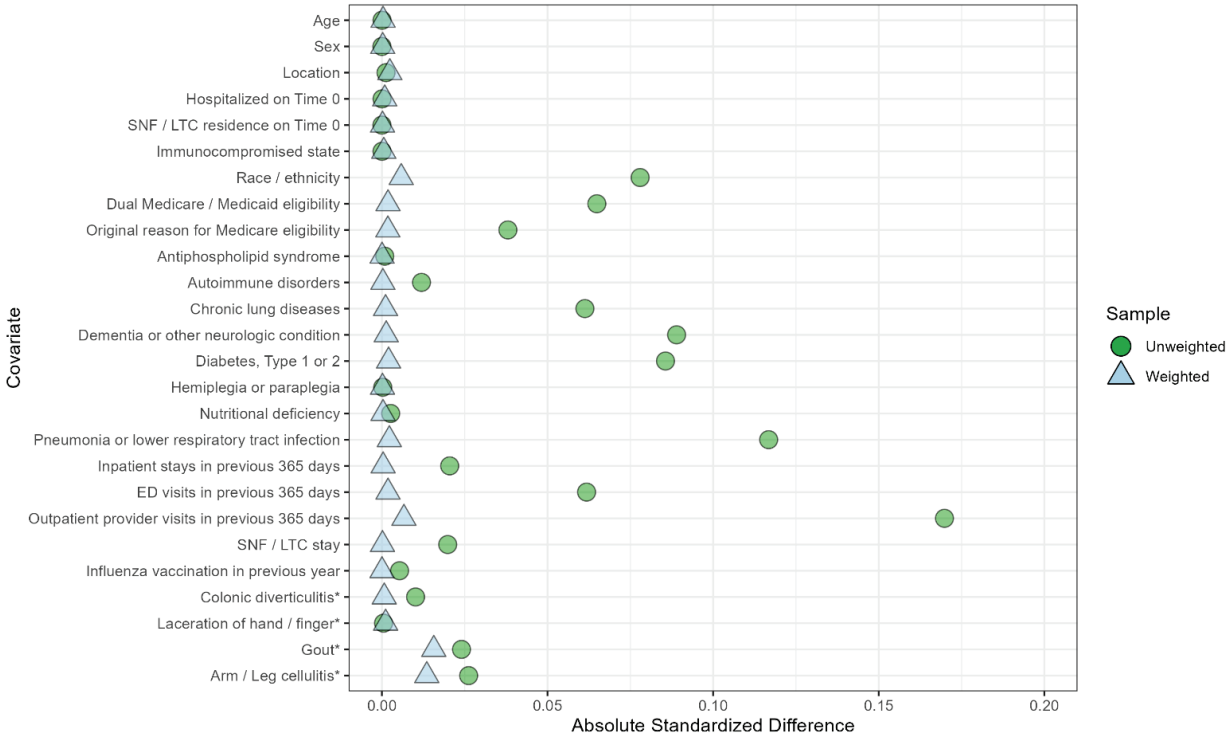
L. Disseminated Intravascular Coagulation



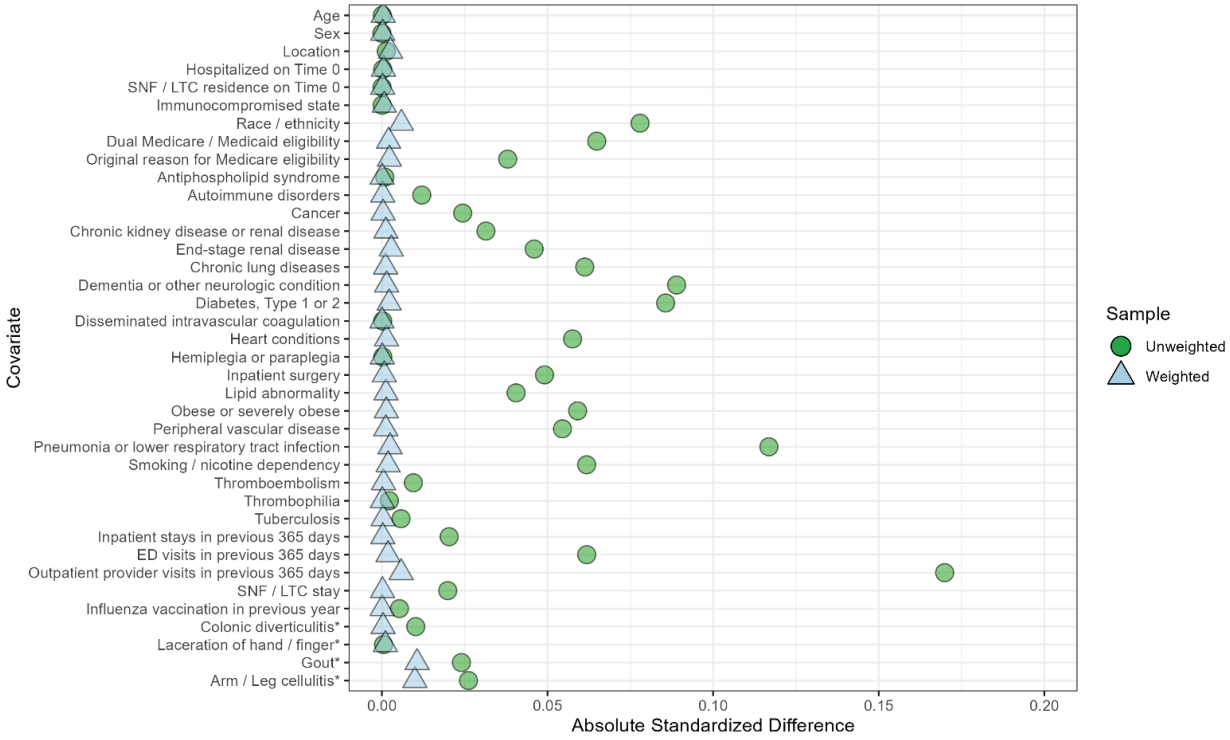
M. Immune Thrombocytopenia



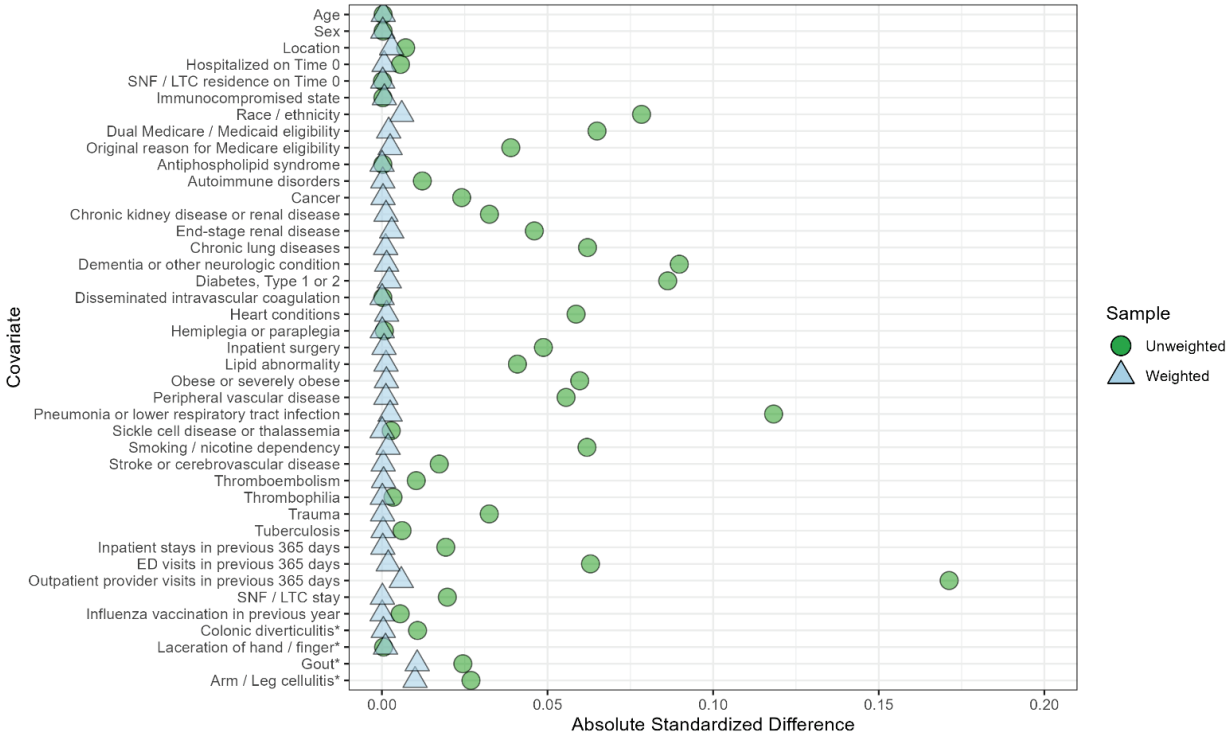
N. Transverse Myelitis



O. Unusual Site Thrombosis With Thrombocytopenia Syndrome



P. Common Site Thrombosis With Thrombocytopenia Syndrome



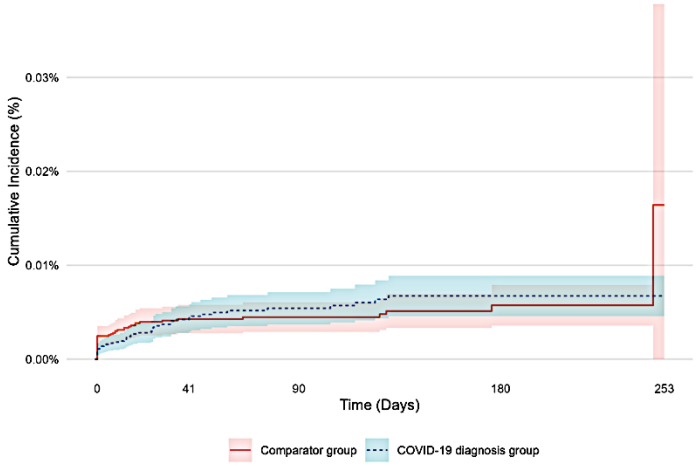
ASD = absolute standardized difference; COVID-19 = coronavirus disease 2019; ED = emergency department; LTC = long-term care; SNF = skilled nursing facility.

* Indicates the history of negative control conditions occurring before Time 0.

Figure B-3-Medicare. Cumulative Incidence of Adverse Events Among Individuals With a COVID-19 Diagnosis and Comparator Individuals Without a COVID-19 Diagnosis, Cohort Design, Before and After sIPT Weighting, Medicare

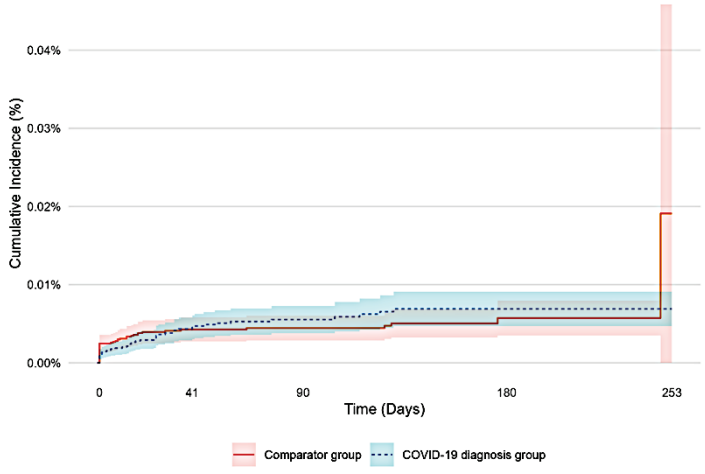
A. Guillain-Barré Syndrome

Unweighted



Comparator group					
At Risk	1016607	597718	409539	153827	1890
Censored	16268	425078	610298	863758	1016562
Events	25	40	41	44	45
COVID-19 diagnosis group					
At Risk	1016611	553207	376000	138143	1551
Censored	18210	469345	643681	879354	1016566
Events	11	36	41	45	45

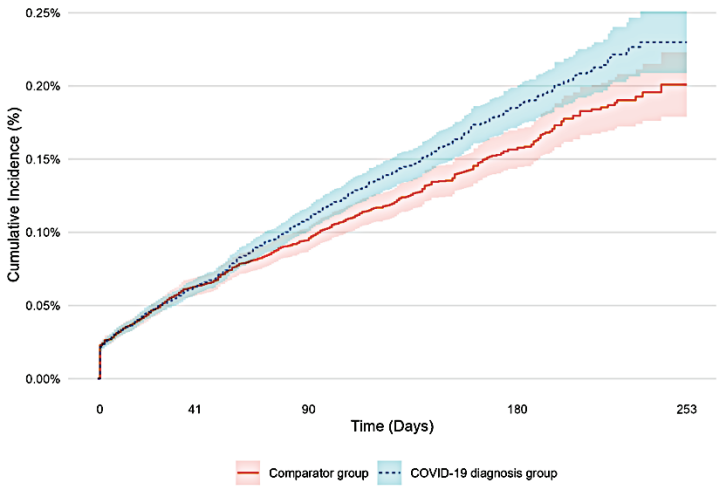
Weighted



Comparator group					
At Risk	1015672	598068	409943	154215	1889
Censored	16195	423788	608951	862438	1015627
Events	25	40	41	44	45
COVID-19 diagnosis group					
At Risk	1015994	550786	372865	136057	1521
Censored	18316	471179	646181	880805	1015948
Events	11	37	42	46	46

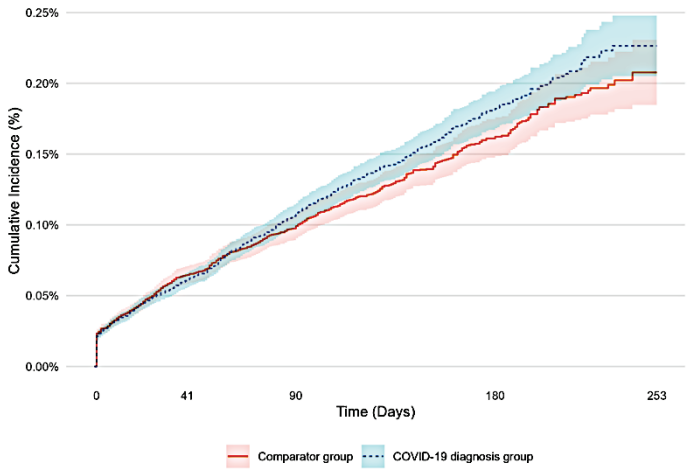
B. Bell's Palsy

Unweighted



Comparator group					
At Risk	1015172	596494	408541	153347	1876
Censored	16248	424347	609192	861959	1014249
Events	233	548	710	885	923
COVID-19 diagnosis group					
At Risk	1015088	552134	375065	137698	1550
Censored	18160	468386	642394	877377	1014112
Events	220	533	742	941	976

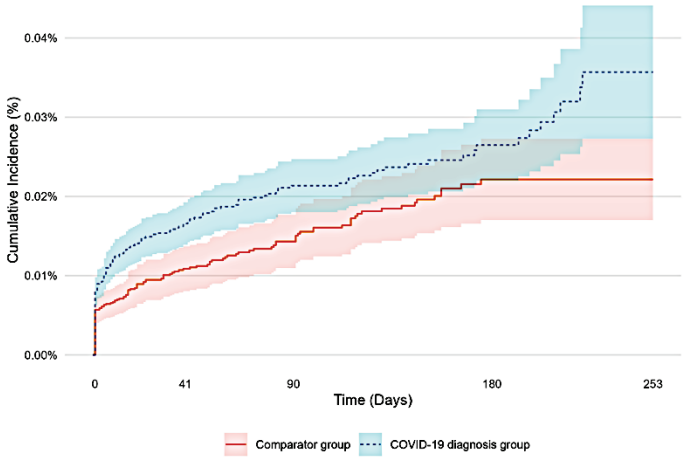
Weighted



Comparator group					
At Risk	1014466	596499	408484	153402	1871
Censored	16194	423623	608520	861173	1013517
Events	237	561	730	909	949
COVID-19 diagnosis group					
At Risk	1014186	550138	372541	136139	1530
Censored	18217	469515	644023	878047	1013234
Events	218	520	724	917	952

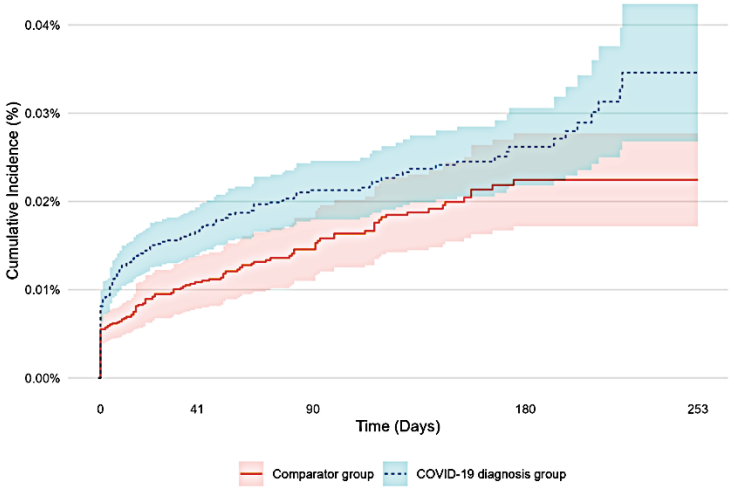
C. Encephalitis/Encephalomyelitis

Unweighted



Comparator group					
At Risk	1016870	597871	409635	153882	1891
Censored	16261	425130	610391	863871	1016731
Events	58	99	116	139	139
COVID-19 diagnosis group					
At Risk	1016911	553341	376069	138151	1555
Censored	18213	469397	643780	879507	1016718
Events	82	152	174	186	193

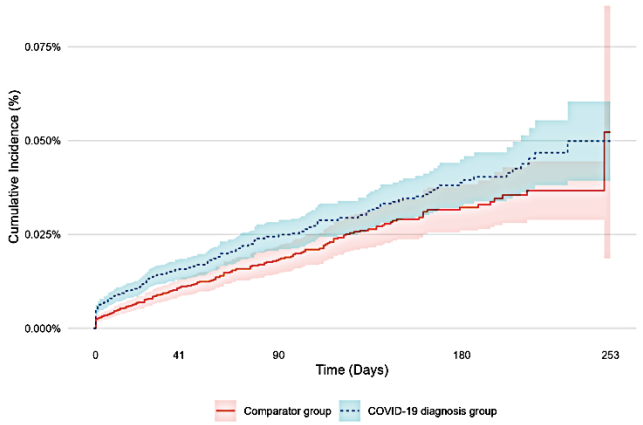
Weighted



Comparator group					
At Risk	1015921	598063	409831	154179	1892
Censored	16188	423986	609236	862626	1015781
Events	56	98	117	140	140
COVID-19 diagnosis group					
At Risk	1016281	550894	372959	136078	1527
Censored	18313	471241	646243	880932	1016088
Events	83	153	174	186	192

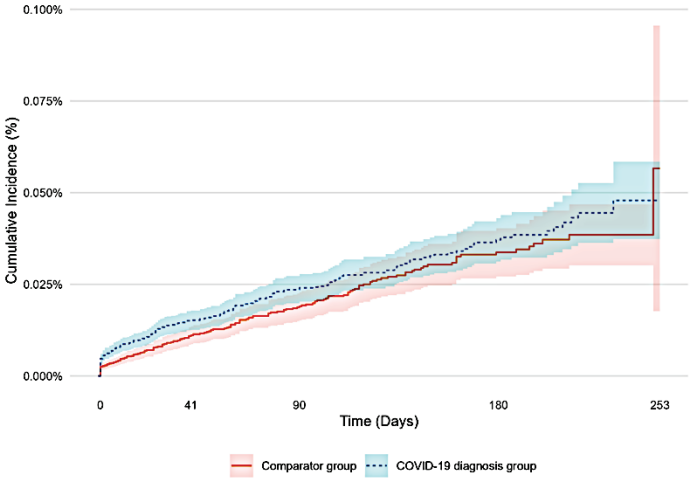
D. Narcolepsy

Unweighted



Comparator group					
At Risk	1016207	597432	409329	153764	1885
Censored	16261	424911	610025	863297	1016033
Events	25	90	127	168	174
COVID-19 diagnosis group					
At Risk	1016109	552865	375737	138061	1554
Censored	18207	469090	643308	878772	1015891
Events	49	134	175	210	218

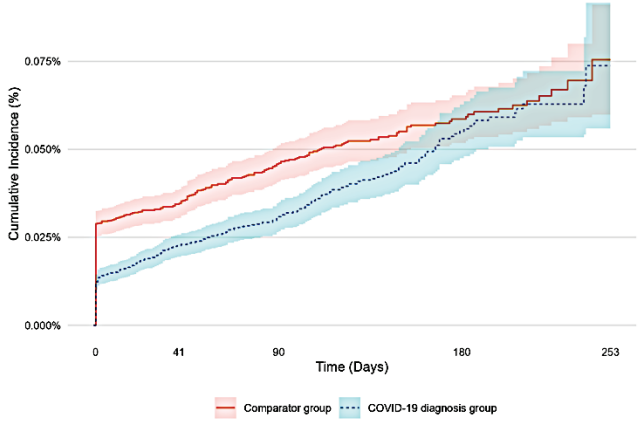
Weighted



Comparator group					
At Risk	1015531	597486	409345	153850	1883
Censored	16203	424176	609326	862526	1015350
Events	25	92	131	174	181
COVID-19 diagnosis group					
At Risk	1015223	550877	373265	136529	1535
Censored	18271	470210	644890	879416	1015015
Events	48	129	168	201	209

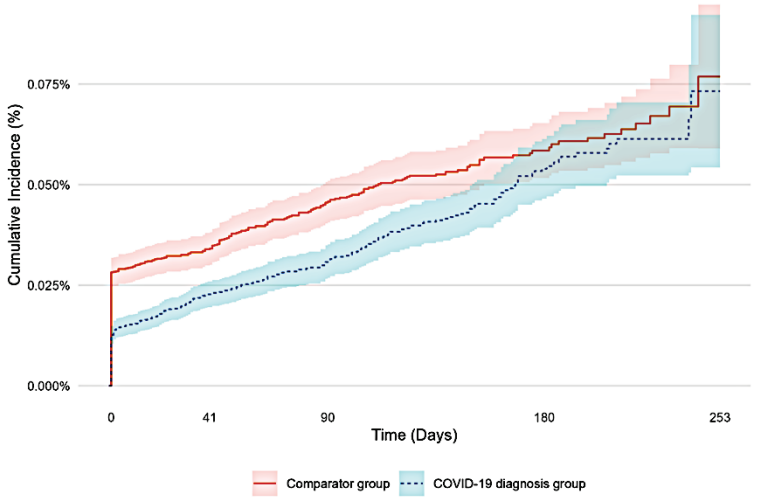
E. Appendicitis

Unweighted



Comparator group					
At Risk	1015910	597113	409064	153631	1890
Censored	16257	424681	609723	862866	1015468
Events	293	338	395	432	442
COVID-19 diagnosis group					
At Risk	1016139	552885	375738	138004	1553
Censored	18208	469030	643271	878765	1015829
Events	125	203	240	300	310

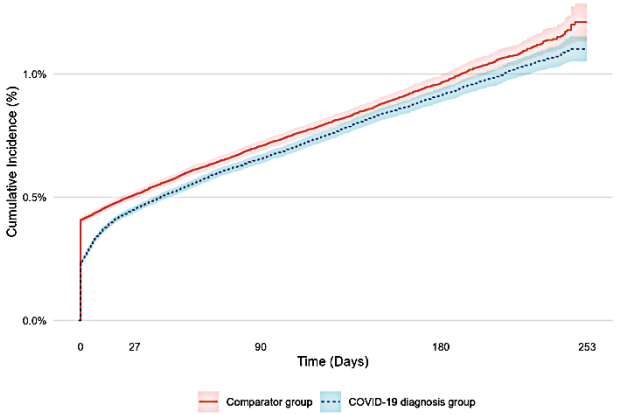
Weighted



Comparator group					
At Risk	1015094	597478	409443	153981	1890
Censored	16193	423505	608524	861705	1014655
Events	287	333	391	428	439
COVID-19 diagnosis group					
At Risk	1015412	550535	372933	136184	1519
Censored	18312	470680	645331	879847	1015105
Events	128	205	242	298	307

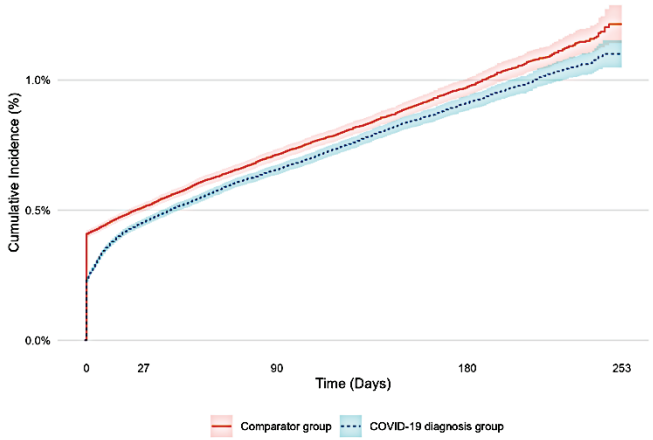
F. Nonhemorrhagic Stroke

Unweighted



Comparator group					
At Risk	929191	644374	371825	138565	1644
Censored	14562	289814	554759	785325	922829
Events	3798	4596	5548	6204	6362
COVID-19 diagnosis group					
At Risk	928618	605323	345747	127193	1454
Censored	15973	328863	580871	796813	923049
Events	2156	3900	4823	5447	5569

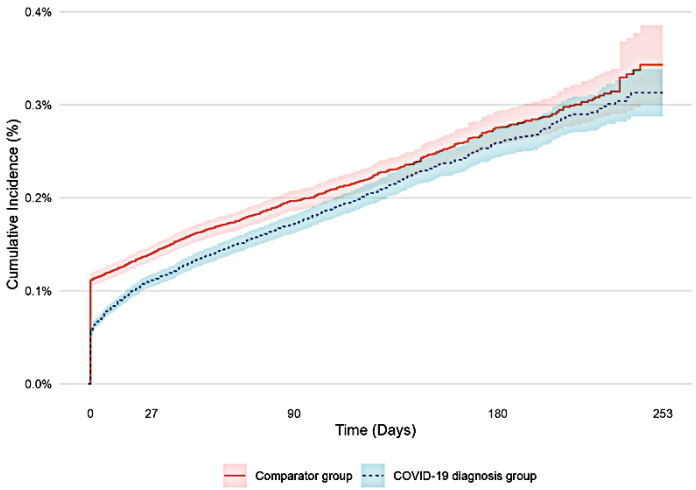
Weighted



Comparator group					
At Risk	928031	643872	371650	138713	1641
Censored	14523	289115	553733	783981	921630
Events	3802	4607	5576	6243	6401
COVID-19 diagnosis group					
At Risk	927951	604023	343271	125366	1414
Censored	16073	329557	582668	797970	922394
Events	2182	3918	4825	5437	5556

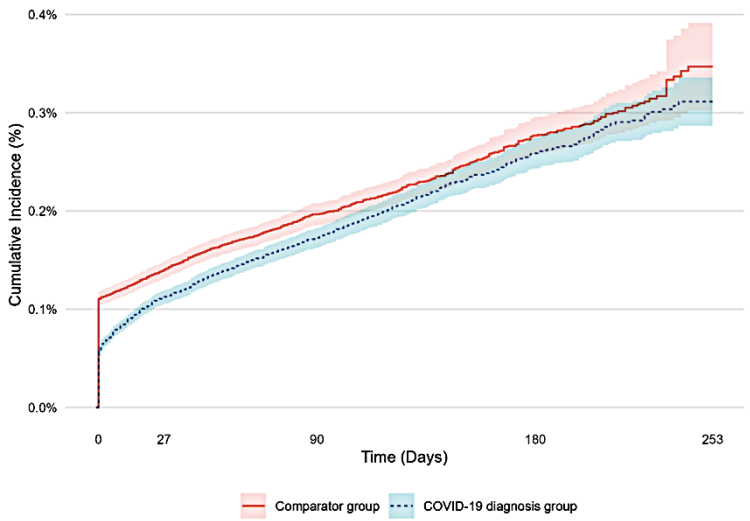
G. Hemorrhagic Stroke

Unweighted



Comparator group					
At Risk	1002866	697078	403507	151301	1861
Censored	15981	314749	600922	850705	1000956
Events	1119	1361	1656	1867	1910
COVID-19 diagnosis group					
At Risk	1003495	651531	371587	136602	1546
Censored	17817	361162	633664	866272	1001915
Events	561	1026	1320	1542	1580

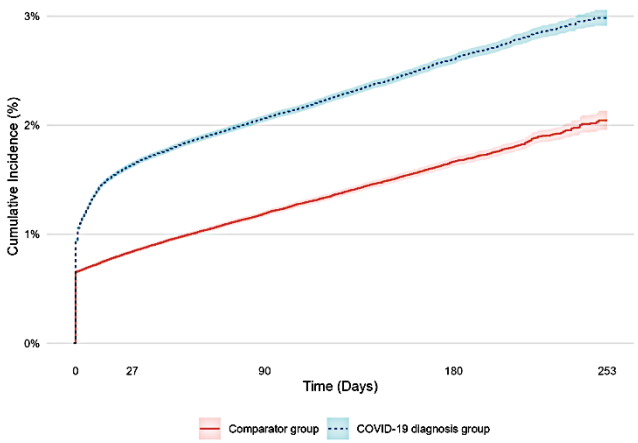
Weighted



Comparator group					
At Risk	1001720	696729	403422	151445	1854
Censored	15937	313923	599858	849420	999812
Events	1108	1354	1651	1864	1908
COVID-19 diagnosis group					
At Risk	1002779	649781	368648	134575	1509
Censored	17908	362267	635874	867565	1001198
Events	574	1036	1326	1544	1581

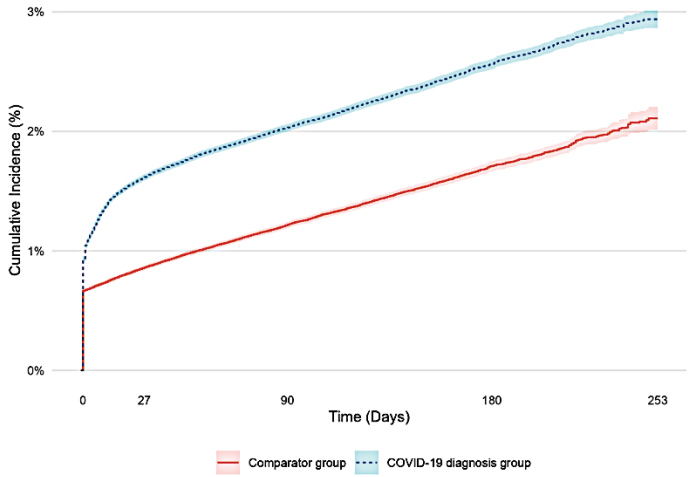
H. Acute Myocardial Infarction

Unweighted



Comparator group					
At Risk	975129	675181	390343	145575	1783
Censored	15264	302088	578222	819553	963896
Events	6396	7925	9687	10968	11233
COVID-19 diagnosis group					
At Risk	975854	629813	359317	131520	1464
Censored	16950	340790	602355	826695	957080
Events	9219	15125	17155	18510	18774

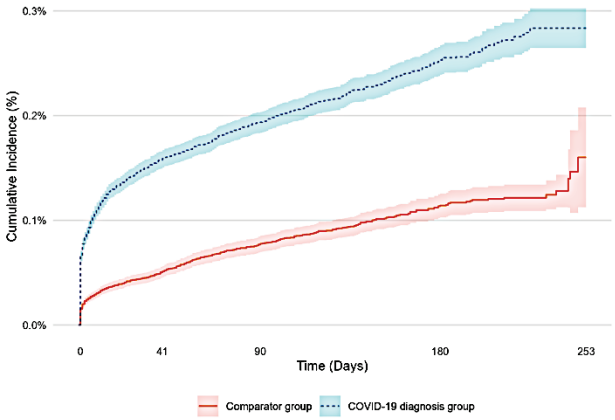
Weighted



Comparator group					
At Risk	974158	674827	390336	145793	1781
Censored	15221	301284	577050	818126	962676
Events	6493	8074	9885	11208	11482
COVID-19 diagnosis group					
At Risk	975114	628470	356950	129760	1425
Censored	17046	341699	604257	828018	956664
Events	9125	14894	16877	18194	18451

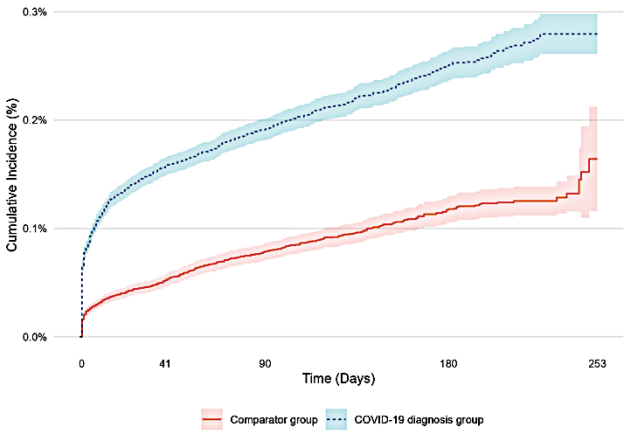
I. Myocarditis/Pericarditis

Unweighted



Comparator group					
At Risk	1015798	596996	408901	153498	1889
Censored	16249	424569	609582	862634	1015095
Events	159	455	587	688	703
COVID-19 diagnosis group					
At Risk	1015725	552145	375090	137686	1539
Censored	18183	468115	642136	877220	1013951
Events	669	1442	1599	1749	1774

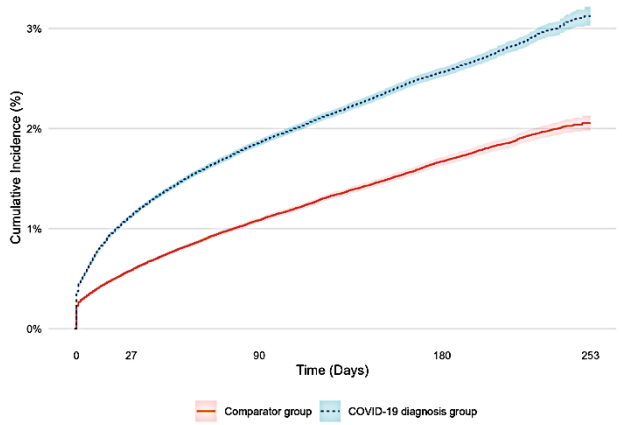
Weighted



Comparator group					
At Risk	1014903	597318	409253	153828	1883
Censored	16189	423345	608317	861393	1014182
Events	164	466	599	706	721
COVID-19 diagnosis group					
At Risk	1015041	549840	372223	135813	1503
Censored	18286	469786	644319	878414	1013286
Events	668	1431	1584	1732	1755

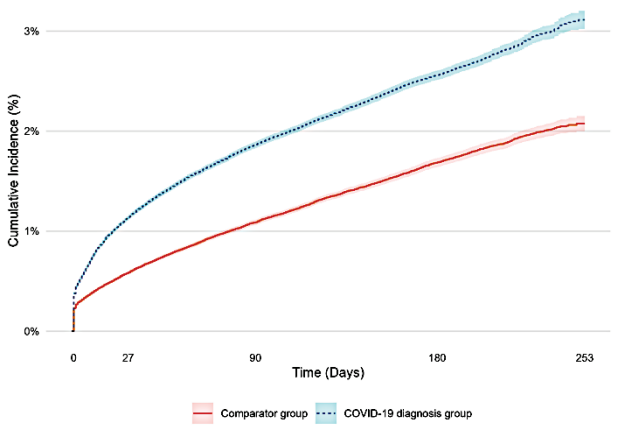
J. Deep Vein Thrombosis

Unweighted



Comparator group					
At Risk	982606	680188	391999	145872	1775
Censored	15641	307311	585918	828282	972871
Events	2278	5267	7834	9437	9735
COVID-19 diagnosis group					
At Risk	981125	632489	358811	130809	1473
Censored	17255	348720	611879	835999	965577
Events	3676	9915	13416	15196	15548

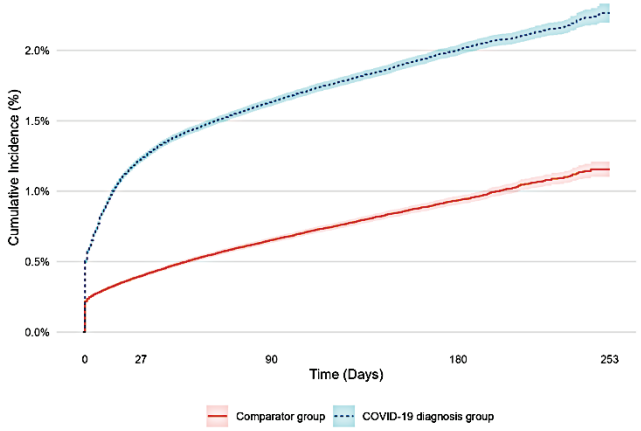
Weighted



Comparator group					
At Risk	981522	679935	392058	146088	1770
Censored	15584	306460	584765	826953	971748
Events	2270	5246	7835	9468	9774
COVID-19 diagnosis group					
At Risk	980365	630830	356024	128894	1434
Censored	17361	349664	613887	837165	964851
Events	3710	9953	13429	15171	15514

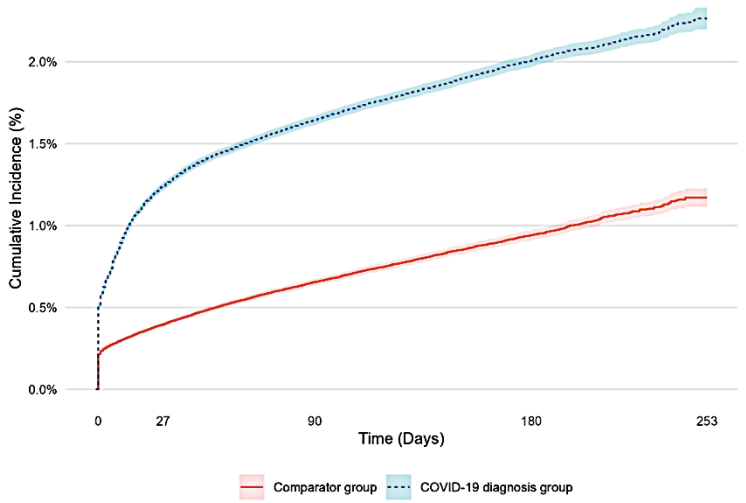
K. Pulmonary Embolism

Unweighted (any setting)



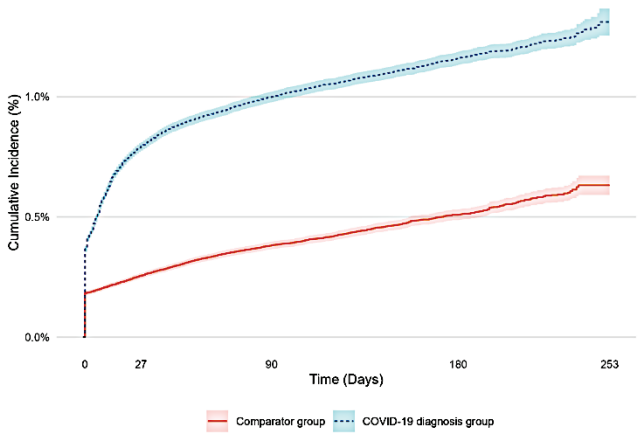
Comparator group					
At Risk	997596	691966	400084	149715	1825
Censored	15889	312178	595646	843036	991575
Events	2175	3725	5058	5848	6021
COVID-19 diagnosis group					
At Risk	996999	641870	365838	134112	1501
Censored	17633	354057	621041	849673	982725
Events	5030	11145	13159	14113	14274

Weighted (any setting)



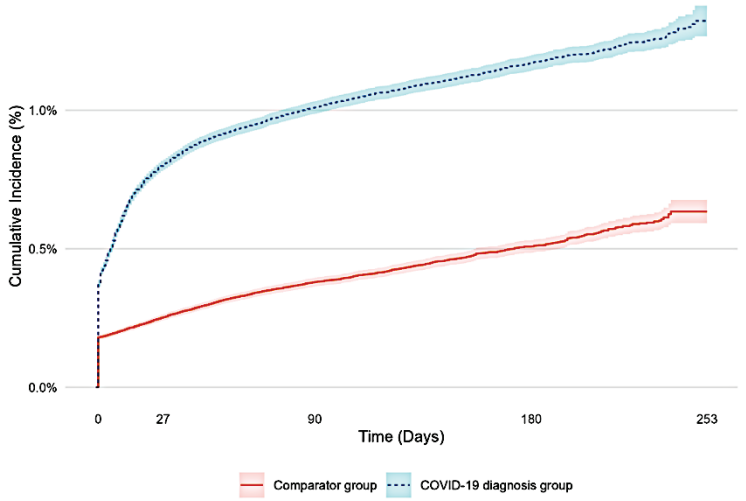
Comparator group					
At Risk	996510	691789	400267	150011	1817
Censored	15827	311251	594371	841654	990479
Events	2149	3702	5053	5853	6031
COVID-19 diagnosis group					
At Risk	996236	640054	362875	132106	1464
Censored	17735	355084	623144	850838	981903
Events	5138	11253	13245	14176	14333

Unweighted (inpatient only)



Comparator group					
At Risk	997596	692841	401060	150294	1837
Censored	15902	312597	596642	844865	994057
Events	1830	2426	3093	3443	3539
COVID-19 diagnosis group					
At Risk	996999	644170	367589	134961	1516
Censored	17666	355670	624171	854244	988223
Events	3650	7253	8285	8697	8776

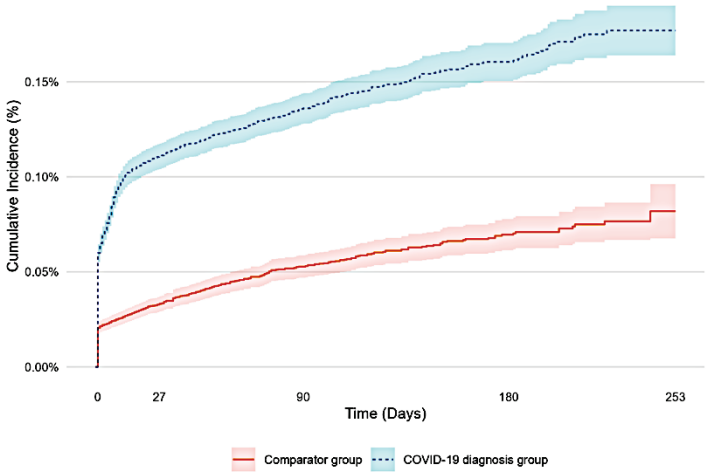
Weighted (inpatient only)



Comparator group					
At Risk	996510	692667	401257	150599	1829
Censored	15841	311674	595373	843499	992990
Events	1803	2396	3068	3423	3520
COVID-19 diagnosis group					
At Risk	996236	642364	364610	132935	1479
Censored	17768	356701	626285	855403	987371
Events	3739	7348	8376	8786	8865

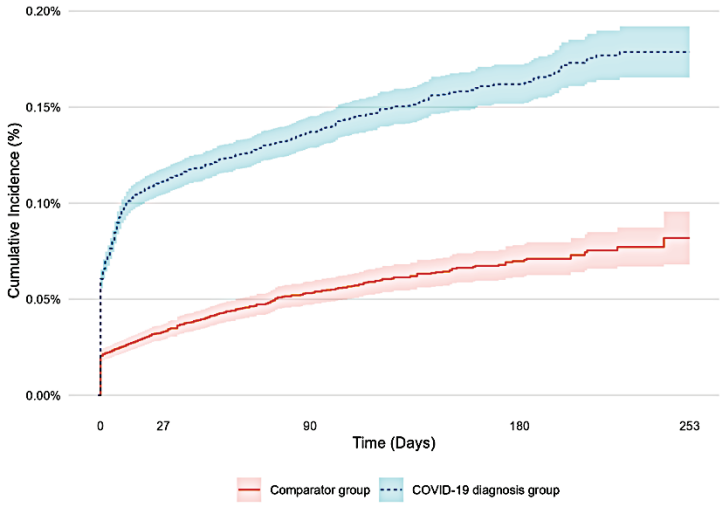
L. Disseminated Intravascular Coagulation

Unweighted



Comparator group					
At Risk	1016813	707032	409575	153862	1894
Censored	16260	319937	610086	863501	1016333
Events	209	317	423	472	480
COVID-19 diagnosis group					
At Risk	1016803	659331	375959	138127	1556
Censored	18193	366749	642771	878354	1015534
Events	609	1061	1185	1253	1269

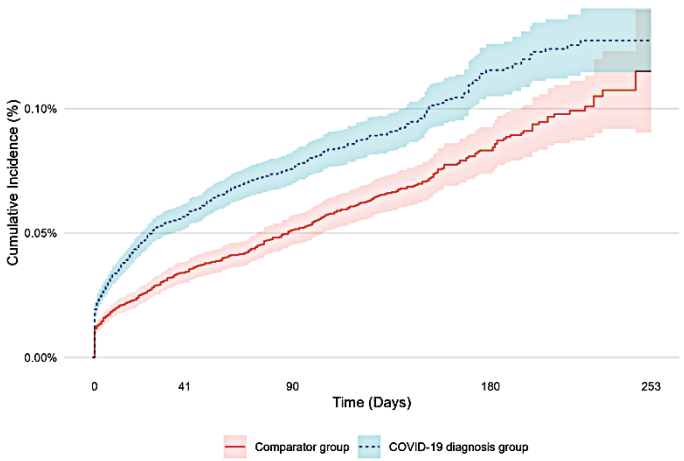
Weighted



Comparator group					
At Risk	1015784	706948	409846	154196	1891
Censored	16202	318950	608773	862140	1015303
Events	209	316	424	473	481
COVID-19 diagnosis group					
At Risk	1016029	657368	372891	136048	1520
Censored	18301	368014	645047	879636	1014753
Events	615	1066	1191	1261	1277

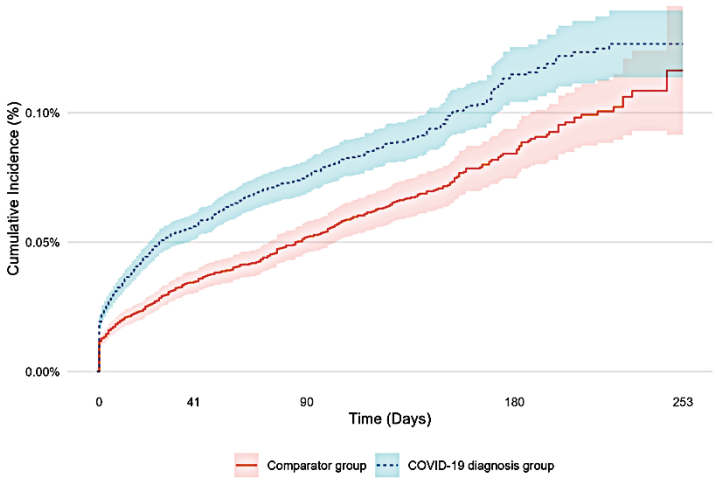
M. Immune Thrombocytopenia

Unweighted



Comparator group					
At Risk	1014664	596480	408628	153426	1891
Censored	16234	424098	608921	861784	1014168
Events	119	301	383	472	496
COVID-19 diagnosis group					
At Risk	1014639	551954	375101	137750	1553
Censored	18167	468147	642061	877138	1013946
Events	196	498	589	682	693

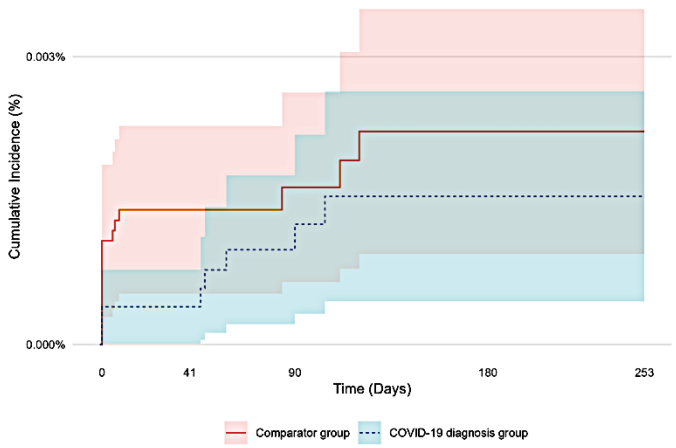
Weighted



Comparator group					
At Risk	1013898	596927	409113	153865	1894
Censored	16167	422879	607656	860576	1013396
Events	119	304	388	477	502
COVID-19 diagnosis group					
At Risk	1013882	549428	372060	135772	1523
Censored	18268	469956	644335	878354	1013199
Events	195	491	580	672	683

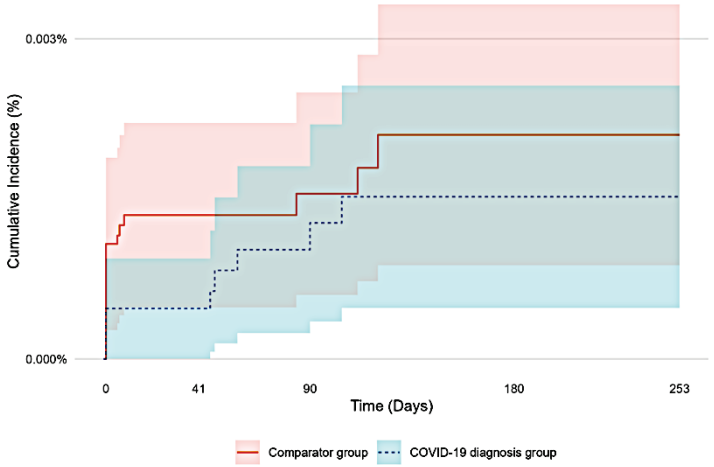
N. Transverse Myelitis

Unweighted



Comparator group					
At Risk	1017155	598043	409742	153926	1892
Censored	16278	425329	610673	864235	1017138
Events	11	14	15	17	17
COVID-19 diagnosis group					
At Risk	1017133	553488	376170	138209	1555
Censored	18222	469624	644069	879849	1017124
Events	< 11	< 11	< 11	< 11	< 11

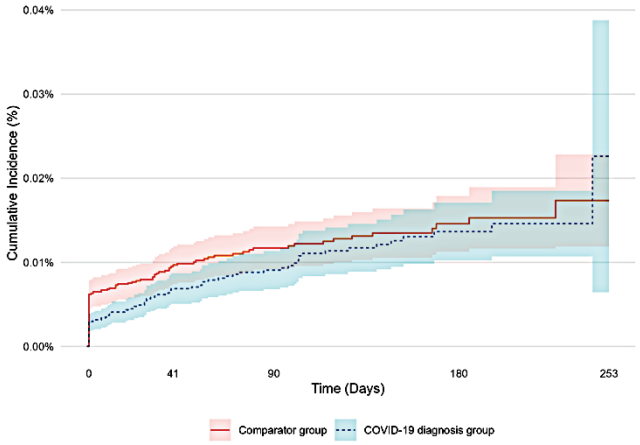
Weighted



Comparator group					
At Risk	1016168	598179	409864	154174	1891
Censored	16209	424205	609558	863003	1016152
Events	11	13	14	16	16
COVID-19 diagnosis group					
At Risk	1016479	551104	373073	136158	1527
Censored	18316	471391	646495	881231	1016470
Events	< 11	< 11	< 11	< 11	< 11

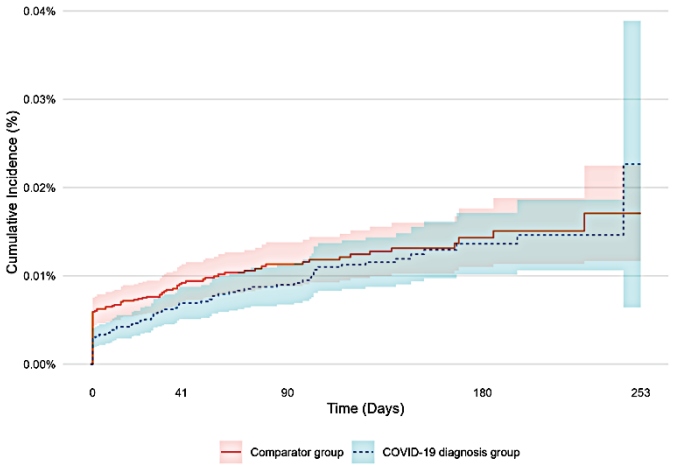
O. Unusual Site Thrombosis With Thrombocytopenia Syndrome

Unweighted



Comparator group					
At Risk	1016972	597929	409690	153911	1895
Censored	16271	425181	610455	863976	1016863
Events	63	89	99	107	109
COVID-19 diagnosis group					
At Risk	1017065	553440	376144	138210	1555
Censored	18217	469546	643967	879706	1016982
Events	29	58	68	81	83

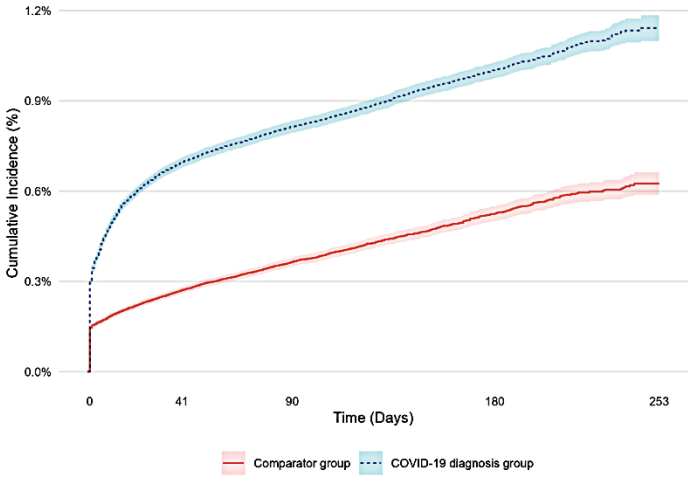
Weighted



Comparator group					
At Risk	1015888	598128	409941	154214	1888
Censored	16216	423893	609115	862595	1015782
Events	60	85	95	104	106
COVID-19 diagnosis group					
At Risk	1016282	551081	373080	136141	1519
Censored	18324	471159	646236	880978	1016199
Events	30	59	68	81	83

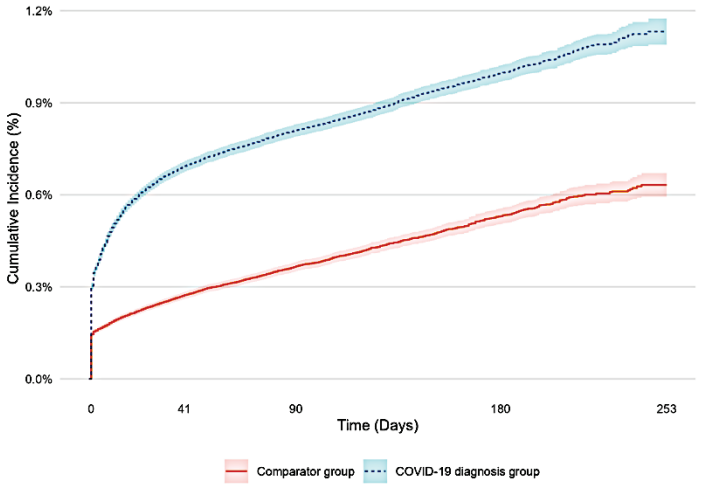
P. Common Site Thrombosis With Thrombocytopenia Syndrome

Unweighted



Comparator group					
At Risk	1005685	590591	404469	151624	1865
Censored	16034	418797	601544	851705	1002232
Events	1464	2468	2923	3365	3453
COVID-19 diagnosis group					
At Risk	1006735	546732	371730	136431	1525
Censored	17839	459623	631266	863929	999342
Events	3036	6281	6813	7293	7393

Weighted



Comparator group					
At Risk	1004591	590725	404657	151902	1860
Censored	15984	417551	600246	850318	1001119
Events	1461	2476	2931	3382	3472
COVID-19 diagnosis group					
At Risk	1005959	544536	368789	134407	1488
Censored	17946	461108	633455	865208	998615
Events	3050	6252	6778	7247	7343

COVID-19 = coronavirus disease 2019; sIPT = stabilized inverse probability of treatment.

Note: Time 0 (index date) is the first day of follow-up; it is represented as the first day at risk on the cumulative incidence plots.

B.2.2. SCRI Analyses

Table B-10-Medicare. Selection of Individuals With a COVID-19 Diagnosis for the Self-Controlled Risk Interval Study, Medicare

Characteristic	Value
Overall SCRI population	
Individuals with COVID-19 diagnosis during the study period	1,571,901
Excluded for being aged outside age range, N (%)	219,427 (14.0)
Excluded for lacking 365 days of continuous database enrollment before Time 0, N (%)	366,363 (23.3)
Excluded for having a previous COVID-19 diagnosis	85,728 (5.5)
Excluded for having a previous select respiratory infection	407 (0.0)
Excluded for lacking ≥ 1 day in the pre-exposure reference window	44,911 (2.9)
Total SCRI population	855,065 (54.4)
Adverse event-specific analysis sets with 42-day risk windows[a]	
Excluded for not having Guillain-Barré syndrome in risk or reference window	854,999 (100.0)
Excluded for lacking 365 days of continuous database enrollment before outcome date	0 (0.0)
Excluded for having Guillain-Barré syndrome in outcome washout window	19 (0.0)
Guillain-Barré syndrome analysis set	47 (0.0)
Excluded for not having Bell's palsy in risk or reference window	853,077 (99.8)
Excluded for lacking 183 days of continuous database enrollment before outcome date	< 11
Excluded for having Bell's palsy in outcome washout window	> 11
Bell's palsy analysis set	1,480 (0.2)
Excluded for not having narcolepsy in risk or reference window	854,206 (99.9)
Excluded for lacking 365 days of continuous database enrollment before outcome date	< 11
Excluded for having narcolepsy in outcome washout window	> 11
Narcolepsy analysis set	338 (0.0)
Excluded for not having appendicitis in risk or reference window	854,633 (99.9)
Excluded for lacking 365 days of continuous database enrollment before outcome date	0 (0.0)
Excluded for having appendicitis in outcome washout window	36 (0.0)
Appendicitis analysis set	396 (0.0)
Excluded for not having myocarditis/pericarditis in risk or reference window	853,313 (99.8)
Excluded for lacking 365 days of continuous database enrollment before outcome date	< 11
Excluded for having myocarditis/pericarditis in outcome washout window	> 11
Myocarditis/pericarditis analysis set	1,605 (0.2)
Excluded for not having immune thrombocytopenia in risk or reference window	853,053 (99.8)
Excluded for lacking 365 days of continuous database enrollment before outcome date	0 (0.0)
Excluded for having immune thrombocytopenia in outcome washout window	1,092 (0.1)
Immune thrombocytopenia analysis set	920 (0.1)
Excluded for not having transverse myelitis in risk or reference window	854,995 (100.0)
Excluded for lacking 365 days of continuous database enrollment before outcome date	0 (0.0)
Excluded for having transverse myelitis in outcome washout window	48 (0.0)
Transverse myelitis analysis set	22 (0.0)
Adverse event-specific analysis sets with 28-day risk windows[a]	
Excluded for not having deep vein thrombosis in risk or reference window	828,927 (96.9)
Excluded for lacking 365 days of continuous database enrollment before outcome date	13 (0.0)
Excluded due to having deep vein thrombosis in outcome washout window	9,079 (1.1)

Characteristic	Value
Deep vein thrombosis analysis set	17,046 (2.0)

COVID-19 = coronavirus disease 2019; SCRI = self-controlled risk interval.

[a] Denominators for all adverse event-specific exclusions are the total SCRI after excluding those with ≥ 1 day in risk and reference windows; exclusions are noncumulative across analysis sets.

Note: Privacy rules require masking cell sizes containing fewer than 11 individuals.

Table B-11-Medicare. Characteristics of Individuals With a COVID-19 Diagnosis Included in the Self-Controlled Risk Interval Analysis Study Population, Medicare

Overall

Characteristic	Value
Total included individuals	855,065
Age, years	
Mean (SD)	77.4 (8.4)
Median (Q1, Q3)	76 (70, 83)
Age groups, n (%)	
65-79 years	539,002 (63.0)
≥ 80 years	316,063 (37.0)
Sex	
Female	486,381 (56.9)
Male	368,684 (43.1)
US geographic region, n (%)	
Northeast	125,327 (14.7)
North central	233,154 (27.3)
South	355,853 (41.6)
West	138,058 (16.1)
Unknown	2,673 (0.3)
Race/ethnicity, n (%)[a]	
American Indian /Alaska Native	7,165 (0.8)
Asian	12,648 (1.5)
Black or African American	67,441 (7.9)
Hispanic/Latin American/Latinx	21,394 (2.5)
White	722,056 (84.4)
A race/ethnicity not listed	10,840 (1.3)
Not provided	13,521 (1.6)
Hospitalized on Time 0, n (%)	182,913 (21.4)
SNF/LTC[a] residence on Time 0, n (%)	186,367 (21.8)
Immunocompromised state, n (%)	357,587 (41.8)

COVID-19 = coronavirus disease 2019; LTC = long-term care; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] Only available in Medicare.

A. Guillain-Barré Syndrome

Characteristic	Value
Total included individuals	47
Age, years	
Mean (SD)	76.4 (7.3)
Median (Q1, Q3)	75 (71, 81)
Age groups, n (%)	
65-79 years	31 (66.0)
≥ 80 years	16 (34.0)
Sex	
Female	14 (29.8)
Male	33 (70.2)
US geographic region, n (%)	
Northeast	< 11
North central	20 (42.6)
South	< 11
West	< 11
Unknown	0
Race/ethnicity, n (%)[a]	
American Indian/Alaska Native	< 11
Asian	0
Black or African American	< 11
Hispanic/Latin American/Latinx	< 11
White	42 (89.4)
A race/ethnicity not listed	0
Not provided	0
Hospitalized on Time 0, n (%)	24 (51.1)
SNF/LTC[a] residence on Time 0, n (%)	< 11
Immunocompromised state, n (%)	24 (51.1)

LTC = long-term care; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] Only available in Medicare.

Note: Privacy rules require masking cells containing fewer than 11 individuals.

B. Bell's Palsy

Characteristic	Value
Total included individuals	1,480
Age, years	
Mean (SD)	77.1 (8.0)
Median (Q1, Q3)	76 (71, 83)
Age groups, n (%)	
65-79 years	954 (64.5)
≥ 80 years	526 (35.5)
Sex	
Female	828 (55.9)
Male	652 (44.1)
US geographic region, n (%)	
Northeast	243 (16.4)
North central	392 (26.5)
South	588 (39.7)
West	252 (17.0)
Unknown	< 11
Race/ethnicity, n (%)[a]	
American Indian/Alaska Native	19 (1.3)
Asian	23 (1.6)
Black or African American	127 (8.6)
Hispanic/Latin American/Latinx	59 (4.0)
White	1,202 (81.2)
A race/ethnicity not listed	26 (1.8)
Not provided	24 (1.6)
Hospitalized on Time 0, n (%)	509 (34.4)
SNF/LTC[a] residence on Time 0, n (%)	320 (21.6)
Immunocompromised state, n (%)	765 (51.7)

LTC = long-term care; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] Only available in Medicare.

Note: Privacy rules require masking cells consisting of fewer than 11 individuals and ensuring that they cannot be back-calculated from other data in the table.

C. Encephalitis/Encephalomyelitis

Not evaluated with SCRI design.

D. Narcolepsy

Characteristic	Value
Total included individuals	338
Age, years	
Mean (SD)	76.2 (7.5)
Median (Q1, Q3)	75 (70, 81)
Age groups, n (%)	
65-79 years	233 (68.9)
≥ 80 years	105 (31.1)
Sex	
Female	174 (51.5)
Male	164 (48.5)
US geographic region, n (%)	
Northeast	36 (10.7)
North central	73 (21.6)
South	167 (49.4)
West	60 (17.8)
Unknown	< 11
Race/ethnicity, n (%)[a]	
American Indian/Alaska Native	< 11
Asian	< 11
Black or African American	31 (9.2)
Hispanic/Latin American/Latinx	< 11
White	290 (85.8)
A race/ethnicity not listed	< 11
Not provided	< 11
Hospitalized on Time 0, n (%)	91 (26.9)
SNF/LTC[a] residence on Time 0, n (%)	103 (30.5)
Immunocompromised state, n (%)	192 (56.8)

LTC = long-term care; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] Only available in Medicare.

Note: Privacy rules requiring masking cell sizes consisting of fewer than 11 individuals.

E. Appendicitis

Characteristic	Value
Total included individuals	396
Age, years	
Mean (SD)	75.4 (7.6)
Median (Q1, Q3)	73 (69, 80)
Age groups, n (%)	
65-79 years	285 (72.0)
≥ 80 years	111 (28.0)
Sex	
Female	192 (48.5)
Male	204 (51.5)
US geographic region, n (%)	
Northeast	49 (12.4)
North central	112 (28.3)
South	162 (40.9)
West	72 (18.2)
Unknown	< 11
Race/ethnicity, n (%)[a]	
American Indian/Alaska Native	< 11
Asian	< 11
Black or African American	24 (6.1)
Hispanic/Latin American/Latinx	13 (3.3)
White	328 (82.8)
A race/ethnicity not listed	< 11
Not provided	12 (3.0)
Hospitalized on Time 0, n (%)	173 (43.7)
SNF/LTC[a] residence on Time 0, n (%)	58 (14.6)
Immunocompromised state, n (%)	200 (50.5)

LTC = long-term care; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] Only available in Medicare.

Note: Privacy rules require masking cell sizes consisting of fewer than 11 individuals and ensuring that they cannot be back-calculated from other data in the table.

F. Nonhemorrhagic Stroke

Not evaluated with SCRI design.

G. Hemorrhagic Stroke

Not evaluated with SCRI design.

H. Acute Myocardial Infarction

Not evaluated with SCRI design.

I. Myocarditis/Pericarditis

Characteristic	Value
Total included individuals	1,605
Age, years	
Mean (SD)	77.5 (8.0)
Median (Q1, Q3)	76 (71, 83)
Age groups, n (%)	
65-79 years	1,006 (62.7)
≥ 80 years	599 (37.3)
Sex	
Female	772 (48.1)
Male	833 (51.9)
US geographic region, n (%)	
Northeast	239 (14.9)
North central	461 (28.7)
South	651 (40.6)
West	248 (15.5)
Unknown	< 11
Race/ethnicity, n (%)[a]	
American Indian/Alaska Native	14 (0.9)
Asian	28 (1.7)
Black or African American	175 (10.9)
Hispanic/Latin American/Latinx	55 (3.4)
White	1,283 (79.9)
A race/ethnicity not listed	26 (1.6)
Not provided	24 (1.5)
Hospitalized on Time 0, n (%)	892 (55.6)
SNF/LTC[a] residence on Time 0, n (%)	269 (16.8)
Immunocompromised state, n (%)	860 (53.6)

LTC = long-term care; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] Only available in Medicare.

Note: Privacy rules require masking cell sizes consisting of fewer than 11 individuals and ensuring that they cannot be back-calculated from other data in the table.

J. Deep Vein Thrombosis

Characteristic	Value
Total included individuals	17,046
Age, years	
Mean (SD)	78.2 (8.2)
Median (Q1, Q3)	77 (72, 84)
Age groups, n (%)	
65-79 years	10,072 (59.1)
≥ 80 years	6,974 (40.9)
Sex	
Female	8,834 (51.8)
Male	8,212 (48.2)
US geographic region, n (%)	
Northeast	2,448 (14.4)
North central	4,588 (26.9)
South	7,199 (42.2)
West	2,781 (16.3)
Unknown	30 (0.2)
Race/ethnicity, n (%)[a]	
American Indian/Alaska Native	114 (0.7)
Asian	254 (1.5)
Black or African American	2,163 (12.7)
Hispanic/Latin American/Latinx	517 (3.0)
White	13,564 (79.6)
A race/ethnicity not listed	212 (1.2)
Not provided	222 (1.3)
Hospitalized on Time 0, n (%)	8,257 (48.4)
SNF/LTC[a] residence on Time 0, n (%)	4,937 (29.0)
Immunocompromised state, n (%)	8,836 (51.8)

CLTC = long-term care; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] Only available in Medicare.

K. Pulmonary Embolism

Not evaluated with SCRI design in Medicare.

L. Disseminated Intravascular Coagulation

Not evaluated with SCRI design in Medicare.

M. Immune Thrombocytopenia

Characteristic	Value
Total included individuals	920
Age, years	
Mean (SD)	77.9 (8.0)
Median (Q1, Q3)	77 (71, 84)
Age groups, n (%)	
65-79 years	545 (59.2)
≥ 80 years	375 (40.8)
Sex	
Female	428 (46.5)
Male	492 (53.5)
US geographic region, n (%)	
Northeast	144 (15.7)
North central	286 (31.1)
South	357 (38.8)
West	129 (14.0)
Unknown	< 11
Race/ethnicity, n (%)[a]	
American Indian/Alaska Native	< 11
Asian	< 11
Black or African American	76 (8.3)
Hispanic/Latin American/Latinx	22 (2.4)
White	790 (85.9)
A race/ethnicity not listed	< 11
Not provided	11 (1.2)
Hospitalized on Time 0, n (%)	403 (43.8)
SNF/LTC[a] residence on Time 0, n (%)	190 (20.7)
Immunocompromised state, n (%)	705 (76.6)

LTC = long-term care; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] Only available in Medicare.

Note: Privacy rules require masking cell sizes consisting of fewer than 11 individuals and ensuring they cannot be back-calculated from other data in the table.

N. Transverse Myelitis

Characteristic	Value
Total included individuals	22
Age, years	
Mean (SD)	74.4 (7.1)
Median (Q1, Q3)	72 (69, 79)
Age groups, n (%)	
65-79 years	> 11
≥ 80 years	< 11
Sex	
Female	< 11
Male	> 11
US geographic region, n (%)	
Northeast	< 11
North central	< 11
South	12 (54.5)
West	< 11
Unknown	0
Race/ethnicity, n (%)[a]	
American Indian/Alaska Native	0
Asian	0
Black or African American	< 11
Hispanic/Latin American/Latinx	0
White	> 11
A race/ethnicity not listed	0
Not provided	0
Hospitalized on Time 0, n (%)	14 (63.6)
SNF/LTC[a] residence on Time 0, n (%)	< 11
Immunocompromised state, n (%)	16 (72.7)

LTC = long-term care; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SNF = skilled nursing facility; US = United States.

[a] Only available in Medicare.

Note: Privacy rules require masking cell sizes consisting of fewer than 11 individuals and ensuring that they cannot be back-calculated from other data in the table.

O. Unusual Site Thrombosis With Thrombocytopenia Syndrome

Not evaluated with SCRI design.

P. Common Site Thrombosis With Thrombocytopenia Syndrome

Not evaluated with SCRI design.

Table B-12-Medicare. Association of COVID-19 Diagnosis With Adverse Events, Self-Controlled Risk Interval Analysis, Medicare

Adverse event	N	Cases in risk window	Cases in reference window	Standard model[a] RI (95% CI)	Extended model[b] RI (95% CI)	Seasonality-adjusted extended model[c] RI (95% CI)	Attributable risk per 100,000 COVID-19 diagnoses[c]
Guillain-Barré syndrome	47	29	18	8.17 (4.33-15.43)	6.85 (3.64-12.9)	11.65 (4.28-31.69)	3.10
Bell's palsy	1,480	450	1,030	1.98 (1.76-2.23)	1.92 (1.70-2.15)	1.94 (1.71-2.21)	25.56
Narcolepsy	338	113	225	2.15 (1.69-2.73)	2.01 (1.59-2.56)	2.05 (1.58-2.66)	6.75
Appendicitis	396	163	233	3.35 (2.7-4.16)	3.22 (2.59-4.00)	3.53 (2.73-4.56)	13.67
Myocarditis/pericarditis	1,605	1,176	429	17.39 (15.38-19.66)	10.50 (9.27-11.89)	11.73 (10.05-13.69)	125.81
Deep vein thrombosis	17,046	9,068	7,978	7.39 (7.15-7.63)	5.59 (5.41-5.78)	5.58 (5.38-5.79)	870.48
Immune thrombocytopenia	920	451	469	4.83 (4.19-5.56)	3.87 (3.36-4.46)	3.86 (3.28-4.54)	39.07
Transverse myelitis	22	< 11	> 11	2.86 (1.15-7.11)	2.9 (1.16-7.24)	3.76 (1.25-11.35)	0.77

CI = confidence interval; COVID-19 = coronavirus disease 2019; RI = relative incidence.

[a] Conditional Poisson regression.

[b] Conditional Poisson model accounting for event-dependent observation windows.

[c] Conditional Poisson model accounting for event-dependent observation windows and adjusted for seasonality as calendar month groupings, with December treated as a full calendar month.

Note: privacy rules require masking cells containing fewer than 11 individuals and ensuring that they cannot be back-calculated from other data in the table.

Table B-13-Medicare. Association of COVID-19 Diagnosis With Adverse Events, Self-Controlled Risk Interval Analysis, Within Subgroups, Medicare

A. Guillain-Barré Syndrome

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Sex				
Female	14	< 11	< 11	2.21 (0.51-9.50)
Male	33	> 11	< 11	30.40 (6.71-137.78)
Age group				
65-79 years	31	> 11	< 11	15.27 (4.18-55.82)
≥ 80 years	16	< 11	< 11	9.78 (1.11-86.32)
Immunocompromised state	24	11	13	9.48 (2.00-44.95)
Hospitalized on Time 0	24	> 11	< 11	189.25 (12.46-2873.44)

B. Bell's Palsy

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Sex				
Female	828	261	567	2.02 (1.71-2.39)
Male	652	189	463	1.80 (1.48-2.20)
Age group				
65-79 years	954	271	683	1.82 (1.55-2.13)
≥ 80 years	526	179	347	2.16 (1.75-2.68)
Immunocompromised state	765	211	554	1.62 (1.35-1.94)
Hospitalized on Time 0	509	224	285	4.09 (3.27-5.13)

C. Encephalitis/Encephalomyelitis

Not evaluated with SCRI design.

D. Narcolepsy

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Sex				
Female	174	56	118	1.76 (1.22-2.55)
Male	164	57	107	2.38 (1.64-3.47)
Age group				
65-79 years	233	78	155	2.04 (1.50-2.79)
≥ 80 years	105	35	70	2.28 (1.38-3.76)
Immunocompromised state	192	59	133	1.81 (1.28-2.57)
Hospitalized on Time 0	91	37	54	3.56 (2.13-5.97)

E. Appendicitis

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Sex				
Female	192	79	113	3.99 (2.72-5.87)
Male	204	84	120	3.13 (2.21-4.42)
Age group				
65-79 years	285	127	158	3.90 (2.90-5.25)
≥ 80 years	111	36	75	2.65 (1.60-4.41)
Immunocompromised state	200	68	132	2.29 (1.59-3.29)
Hospitalized on Time 0	173	107	66	9.31 (6.07-14.27)

F. Nonhemorrhagic Stroke

Not evaluated with SCRI design.

G. Hemorrhagic Stroke

Not evaluated with SCRI design.

H. Acute Myocardial Infarction

Not evaluated with SCRI design.

I. Myocarditis/Pericarditis

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Sex				
Female	772	544	228	10.57 (8.52-13.12)
Male	833	632	201	13.11 (10.49-16.39)
Age group				
65-79 years	1,006	728	278	11.75 (9.70-14.22)
≥ 80 years	599	448	151	11.65 (8.94-15.19)
Immunocompromised state	860	557	303	7.63 (6.31-9.22)
Hospitalized on Time 0	892	765	127	71.31 (48.40-105.08)

J. Deep Vein Thrombosis

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Sex				
Female	8,834	4,321	4,513	4.83 (4.60-5.08)
Male	8,212	4,747	3,465	6.58 (6.23-6.95)
Age group				
65-79 years	10,072	5,561	4,511	6.12 (5.83-6.42)
≥ 80 years	6,974	3,507	3,467	4.89 (4.62-5.18)
Immunocompromised state	8,836	4,122	4,714	4.38 (4.16-4.60)
Hospitalized on Time 0	8,257	5,710	2,547	12.59 (11.84-13.38)

K. Pulmonary Embolism
Not evaluated with SCRI design.

L. Disseminated Intravascular Coagulation
Not evaluated with SCRI design.

M. Immune Thrombocytopenia

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Sex				
Female	428	208	220	3.46 (2.74-4.37)
Male	492	243	249	3.95 (3.15-4.96)
Age group				
65-79 years	545	264	281	3.74 (3.04-4.61)
≥ 80 years	375	187	188	3.77 (2.91-4.89)
Immunocompromised state	705	260	445	2.49 (2.06-3.00)
Hospitalized on Time 0	403	268	135	10.63 (7.80-14.48)

N. Transverse Myelitis

Subgroup	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Sex				
Female	< 11	< 11	< 11	10.49 (1.41-78.13)
Male	> 11	< 11	< 11	2.87 (0.67-12.34)
Age group				
65-79 years	> 11	< 11	< 11	4.00 (1.21-13.25)
≥ 80 years	< 11	< 11	< 11	NE [b]
Immunocompromised state	> 11	< 11	> 11	1.85 (0.45-7.68)
Hospitalized on Time 0	> 11	< 11	< 11	124.71 (5.58-2787.87)

O. Unusual Site Thrombosis With Thrombocytopenia Syndrome
Not evaluated with SCRI.

P. Common Site Thrombosis With Thrombocytopenia Syndrome
Not evaluated with SCRI.

CI = confidence interval; COVID-19 = coronavirus disease 2019; NE = not estimable; RI = relative incidence; SCRI = self-controlled risk interval.

[a] Conditional Poisson model accounting for event-dependent observation windows and adjusted for seasonality.

[b] Error on estimate for ≥ 80 years because of a single beneficiary having an interval of 1 day in combination of risk window and calendar month.

Note: privacy rules require masking cells containing fewer than 11 individuals and ensuring that they cannot be back-calculated from other data in the table.

Table B-14-Medicare. Association of COVID-19 Diagnosis With Adverse Events Within Prespecified Risk Windows and Pre-Exposure and Postexposure Alternative Windows Compared With the Referent Window, Self-Controlled Risk Interval Analysis Using Extended Poisson Model [a] for Event-Dependent Observation Windows, Medicare

Adverse event	Risk period	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
Guillain-Barré syndrome	Pre-exposure window (days [−7, −1])	51	< 11	18	2.03 (0.43-9.57)
	Day 0 (day [0, 0])	51	12	18	84.71 (33.94-211.44)
	Modified, prespecified risk window (days [1, 41])	51	17	18	4.63 (1.78-12.01)
	Postexposure buffer (days [42, 69])	51	< 11	18	1.85 (0.32-10.72)
Bell's palsy	Pre-exposure window (days [−7, −1])	1,649	65	1,030	1.11 (0.86-1.43)
	Day 0 (day [0, 0])	1,649	197	1,030	23.17 (19.74-27.19)
	Modified, prespecified risk window (days [1, 41])	1,649	253	1,030	1.05 (0.91-1.22)
	Postexposure buffer (days [42, 69])	1,649	104	1,030	1.05 (0.84-1.30)
Narcolepsy	Pre-exposure window (days [−7, −1])	374	16	225	1.18 (0.70-1.97)
	Day 0 (day [0, 0])	374	46	225	23.38 (16.78-32.58)
	Modified, prespecified risk window (days [1, 41])	374	67	225	1.15 (0.85-1.55)
	Postexposure buffer (days [42, 69])	374	20	225	0.82 (0.50-1.33)
Appendicitis	Pre-exposure window (days [−7, −1])	430	21	233	1.61 (1.02-2.55)
	Day 0 (day [0, 0])	430	111	233	59.69 (46.24-77.04)
	Modified, prespecified risk window (days [1, 41])	430	52	233	0.98 (0.70-1.36)
	Postexposure buffer (days [42, 69])	430	13	233	0.61 (0.34-1.11)
Myocarditis/pericarditis	Pre-exposure window (days [−7, −1])	1,729	43	429	1.33 (0.96-1.83)
	Day 0 (day [0, 0])	1,729	584	429	118 (102.10-136.39)
	Modified, prespecified risk window (days [1, 41])	1,729	592	429	4.53 (3.89-5.27)
	Postexposure buffer (days [42, 69])	1,729	81	429	1.80 (1.38-2.34)
Deep vein thrombosis	Pre-exposure window (days [−7, −1])	19,291	675	7,978	1.23 (1.14-1.33)
	Day 0 (day [0, 0])	19,291	3,608	7,978	43.61 (41.78-45.51)
	Modified, prespecified risk window (days [1, 27])	19,291	5,460	7,978	3.18 (3.05-3.30)
	Postexposure buffer (days [28, 55])	19,291	1,570	7,978	1.59 (1.49-1.68)
Immune thrombocytopenia	Pre-exposure window (days [−7, −1])	985	22	469	0.70 (0.45-1.08)
	Day 0 (day [0, 0])	985	200	469	41.78 (34.82-50.13)
	Modified, prespecified risk window (days [1, 41])	985	251	469	1.91 (1.60-2.28)
	Postexposure buffer (days [42, 69])	985	43	469	0.93 (0.66-1.30)
Transverse myelitis	Pre-exposure window (days [−7, −1])	24	0	13	0 (0-NE)
	Day 0 (day [0, 0])	24	< 11	13	83.45 (34.67-200.86)

Adverse event	Risk period	N	Cases in risk window	Cases in reference window	Extended model[a] RI (95% CI)
	Modified, prespecified risk window (days [1, 41])	24	0	13	0 (0-NE)
	Postexposure buffer (days [42, 69])	24	< 11	13	1.95 (0.41-9.26)

CI = confidence interval; COVID-19 = coronavirus disease 2019; NE = not estimable; RI = relative incidence.

[a] Conditional Poisson model accounting for event-dependent observation windows, adjusted for seasonality, and modified to support 1-day periods.

Note: Privacy rules require masking cell sizes consisting of fewer than 11 individuals.