Incidence of Epilepsy and Seizures Over the First 6 Months After a COVID-19 Diagnosis: A Retrospective Cohort Study

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Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

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Figure Count:
4

Table Count:
3
Search Terms:

Acknowledgment:
M. Taquet and P.J. Harrison were granted unrestricted access to the TriNetX Analytics network for the purposes of research, and with no constraints on the analyses done or the decision to publish. M. Taquet is an NIHR Academic Clinical Fellow and Oxford Health BRC Senior Research Fellow. A. Sen is an Oxford University Hospitals NHS Foundation Trust BRC Senior Research Fellow. The views expressed are those of the authors and not necessarily those of the National Health Service, NIHR, or the Department of Health and Social Care.

Study Funding:
The work was supported by the National Institute for Health and Care Research (NIHR) Oxford Health Biomedical Research Centre (BRC), grant BRC-1215-20005.

Disclosures:
The authors report no relevant disclosures.

Preprint DOI:

Received Date:
2022-05-04

Accepted Date:
2022-10-06
Handling Editor Statement:

Submitted and externally peer reviewed. The handling editor was Barbara Jobst, MD, PhD, FAAN.

Abstract

Background: The relationship between COVID-19 and epilepsy is uncertain. We studied the potential association between COVID-19 and seizures or epilepsy in the six months after infection.

Methods: We applied validated methods to an electronic health records network (TriNetX Analytics) of 81 million people. We closely matched people with COVID-19 infections to those with influenza. In each cohort, we measured the incidence and hazard ratios (HRs) of seizures and of epilepsy. We stratified data by age and by whether the person was hospitalized during the acute infection. We then explored time-varying HRs to assess temporal patterns of seizure or epilepsy diagnoses.

Results: We analyzed 860,934 electronic health records. After matching, this yielded two cohorts each of 152,754 patients. COVID-19 was associated with an increased risk of seizures and epilepsy compared to influenza. The incidence of seizures within 6 months of COVID-19 was 0.81% (95% CI, 0.75-0.88; HR compared to influenza 1.55 (1.39-1.74)). The incidence of epilepsy was 0.30% (0.26-0.34; HR compared to influenza 1.87 (1.54-2.28)). The HR of epilepsy after COVID-19 compared to influenza was greater in people who had not been hospitalized and in individuals aged under 16 years. The time of peak HR after infection differed by age and hospitalization status.
Conclusions: The incidence of new seizures or epilepsy diagnoses in the six months following COVID-19 was low overall, but higher than in matched patients with influenza. This difference was more marked in people who were not hospitalized, highlighting the risk of epilepsy and seizures even in those with less severe infection. Children appear at particular risk of seizures and epilepsy after COVID-19 providing another motivation to prevent COVID-19 infection in pediatric populations. That the varying time of peak risk related to hospitalization and age may provide clues as to the underlying mechanisms of COVID-associated seizures and epilepsy.

Introduction

The SARS-CoV-2 pandemic is associated with serious morbidities and mortality. By end April 2022, there were ~513 million COVID-19 cases worldwide with over 6.23 million deaths.\(^1\) COVID-19 infection is associated with acute neurological manifestations, particularly encephalopathy, agitation, confusion, anosmia, aguesia and stroke.\(^2,3\) Compared to influenza, people who contract COVID-19 also show an increased risk of many neurological and psychiatric sequelae in the subsequent 6 months, with incidence highest in those admitted to an intensive care setting.\(^4\) COVID-19 may impair neurological function through effects on brain endothelial cells, inflammation, cytokine storm, and other mechanisms.\(^5,6\)

Any severe infection can cause cortical hyperexcitability through metabolic disturbances. Acute symptomatic seizures and status epilepticus are, however, rare with COVID-19.\(^7-9\) Electroencephalography (EEG) studies in those with COVID-19 demonstrate frequent interictal epileptiform abnormalities and occasionally electrographic seizures.\(^10-12\) The significance of these findings and their implication for outcomes is not, though, fully understood. The incidence of acute symptomatic seizures with COVID-19 infection (~1%) is, lower than with SARS (~2.7%)
and MERS (~8.6%).\textsuperscript{13} Given the heterogeneous literature, it remains uncertain if COVID-19 infection predisposes patients to develop seizures or epilepsy.

Most investigations of COVID-19 and seizures have focused on the acute setting while assessments of medium-term neurological outcomes have not included epilepsy or had low case numbers.\textsuperscript{4,14} We, therefore, examined a large dataset of healthcare records to determine the incidence of seizures and epilepsy in the six months after COVID-19 infection, and compare these risks with matched patients following infection with influenza.

Material and Methods
Data and study design
The study used TriNetX Analytics, a federated network of linked EHRs recording anonymized data from 59 healthcare organizations (HCOs), primarily in the USA, totaling 81 million patients. Available data include demographics, diagnoses (ICD-10 codes), procedures (Current Procedural Terminology CPT codes), and measurements (e.g., blood pressure). The HCOs consist of a mixture of primary care centers, hospitals, and specialist units. They provide data from uninsured as well as insured individuals. Using the TriNetX user interface, cohorts are created based on inclusion and exclusion criteria, matched for confounding variables, and compared for outcomes of interest over specified time periods. For further details about TriNetX, see eMethods in the Supplement.
Standard Protocol Approvals, Registrations, and Patient Consents

Data de-identification within TriNetX is formally attested as per Section §164.514(b)(1) of the HIPAA Privacy Rule, superseding TriNetX’s waiver from the Western Institutional Review Board; no further ethical approval was thus needed. As we used anonymized routinely collected data, no participant consent was required.

Cohorts

The primary cohort was defined as all patients who had a confirmed diagnosis of COVID-19 (ICD-10 code U07.1). The World Health Organization recommends using this code when COVID-19 has been confirmed by laboratory testing irrespective of severity of clinical signs or symptoms. This was compared to a matched cohort of patients diagnosed with influenza (ICD-10 codes J09-J11) who did not have either a diagnosis of COVID-19 or a positive test for COVID-19. Cohorts included all patients who had the index event (COVID-19 or influenza) between January 20, 2020 (the date of the first recorded COVID-19 case in the USA) and May 31, 2021 and who were still alive at the end of follow-up (August 24, 2021). Individuals who had a pre-existing diagnosis of epilepsy or recurrent seizures (ICD-10 G40 code) were excluded from both cohorts. More details about the cohort definition including the ICD-10/CPT codes used are provided in the eMethods in the Supplement.

Covariates

We assessed established and suspected risk factors for COVID-19 and for more severe COVID-19 illness: age, sex, race, ethnicity, obesity, hypertension, diabetes, chronic kidney disease, asthma, chronic lower respiratory diseases, nicotine dependence, substance misuse, previous psychiatric illness, ischemic heart disease and other forms of heart disease, socioeconomic deprivation, cancer (and hematological cancer in particular), chronic liver disease, stroke, dementia, organ transplant, rheumatoid arthritis, lupus, psoriasis, and disorders
involving an immune mechanism. To capture these risk factors in patients’ health records, 58 variables were used. More details including ICD-10 codes are presented in the eMethods in the Supplement. Cohorts were matched for all these variables, as described below.

Outcomes
The primary outcome was the 6-month incidence of the composite endpoint of epilepsy (ICD-10 code G40) or seizures (ICD-10 code R56). Secondary outcomes included either code separately.

Statistical analyses
Propensity score matching (carried out within the TriNetX network) created cohorts with matched baseline characteristics.\(^{15}\) Propensity score 1:1 matching used a greedy nearest neighbor approach with a caliper distance of 0.1 pooled standard deviations of the logit of the propensity score. Any characteristic with a standardized mean difference (SMD) between cohorts lower than 0.1 is considered well matched.\(^{16}\) The Kaplan-Meier estimator was used to estimate the incidence of each outcome. Hazard ratios (HRs) with 95% confidence intervals were calculated using the Cox model and the null hypothesis of no difference between cohorts was tested using log-rank tests. The proportional hazard assumption was tested using the generalized Schoenfeld approach. If the assumption was violated, a time-varying HR was estimated using natural cubic splines fitted to the log-cumulative hazard.\(^{17}\)

Further details are in the eMethods in the Supplement. Statistical analyses were conducted in R version 3.6.3 except for the log-rank tests which were performed within TriNetX. Statistical significance was set at two-sided p-values <0.05. A Reporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement was completed.
Secondary analyses
To analyze the influence of age on the results, we repeated the primary analysis in pediatric (≤ 16 years old) and adult (> 16 years old) populations. To explore whether, and how, associations between COVID-19 and epilepsy or seizures are affected by the severity of the acute infection, we repeated the analysis separately in those who were hospitalized and those not hospitalized within 14 days of their COVID-19 or influenza diagnosis. A moderation analysis by age group (≤ vs. > 16 years-old) and hospitalization status was also conducted (see eMethods in the Supplement).

Data availability
The TriNetX system returned the results of these analyses as csv files which were downloaded and archived. Data presented in this paper and the Supplement can be freely accessed at https://osf.io/m8ht2.

Results
The baseline demographic data of the cohorts, before and after matching, are presented in Table 1 (and eTable 1 in the Supplement). Prior to matching, the COVID-19 dataset consisted of 681,283 individuals with a mean age that was higher than the influenza data set that contained 179,561 people. There were more females in both groups and this was maintained after matching. While most of the COVID-19 and influenza cohorts were White, there was good representation of people of Black/African American and Hispanic heritage. To reduce confounders, groups were then closely matched for demographic characteristics as well as multiple systemic and psychiatric co-morbidities, leading to matched cohorts of individuals diagnosed with COVID-19 and influenza each consisting of 152,754 individuals.
I) Seizures and epilepsy after COVID-19: incidence and hazard ratios compared to influenza
There was an increased incidence of the composite endpoint of seizures or epilepsy in the COVID-19 cohort compared to the influenza cohort (6-month cumulative incidence 0.94% vs. 0.60%, HR 1.55, 95% CI 1.40-1.72, p < 0.0001; Figure 1; Table 2). Separately, there was an increased risk of seizures (0.81% vs. 0.51%, HR 1.55, 95% CI 1.39-1.74, p < 0.0001) and epilepsy (0.30% vs. 0.17%, HR 1.87, 95% CI 1.54-2.28, p < 0.0001). These findings indicate that COVID-19 infection is associated with a higher risk of both epilepsy and seizures compared to influenza.

II) Secondary analyses
1. Is the increased risk of seizures and epilepsy age dependent?
Results for the analysis stratified by age between children (aged ≤16 years, n=43,231 after matching; see eTable 2 in the Supplement for baseline characteristics) and adults (aged > 16 years, n=108,116 after matching; eTable 3 in the Supplement) are summarized in Figure 2 and Table 3. Compared to influenza, there was an increased risk of the composite endpoint of seizures or epilepsy after COVID-19 in both children (1.34% vs. 0.69%, HR 1.85, 95% CI 1.54-2.22, p < 0.0001) and adults (0.84% vs. 0.54%, HR 1.56, 95% CI 1.37-1.77, p < 0.0001). While the contrast between COVID-19 and influenza appears more marked among children (Figure 2), there was no significant moderation by age of this composite endpoint (moderation coefficient 0.20, 95% CI -0.025-0.42, p=0.082). There was a significantly increased risk for both seizures and epilepsy measured individually in both age groups (Figure 2). The risk of epilepsy after COVID-19 vs influenza was significantly moderated by age and more marked among children than adults (moderation coefficient 0.68, 95% CI 0.23-1.13, p=0.0031).

2. Is the increased risk of seizures and epilepsy dependent on the severity of COVID-19 infection as proxied by hospitalization?
Results for the analysis stratified by hospitalization status, between non-hospitalized (n=139,490 after matching; see eTable 4 in the Supplement for baseline characteristics) and hospitalized individuals (n=11,090 after matching; see eTable 5 in the Supplement) are summarized in Figure 3 and Table 3. Compared to influenza, there was a significantly increased risk of the composite endpoint of seizures or epilepsy after COVID-19 in non-hospitalized individuals (0.72% vs. 0.48%, HR 1.44, 95% CI 1.27-1.63, p < 0.0001) but not in hospitalized individuals (2.90% vs. 2.40%, HR 1.14, 95% CI 0.95-1.38, p=0.16). However, hospitalization status was not a significant moderator (moderation coefficient 0.12, 95% CI -0.10-0.35, p = 0.28). Similarly, there were significantly increased risks in both seizures and epilepsy measured individually in the non-hospitalized group only (Figure 3). Hospitalization status was a significant moderator for the association between COVID-19 and epilepsy (with the association being more marked among non-hospitalized patients; moderation coefficient 0.52, 95% CI 0.11-0.93, p=0.012), but not for seizures (moderation coefficient 0.047, 95% CI -0.20-0.29, p=0.70).

3. When is the peak risk of ‘seizures or epilepsy’ after COVID-19 compared to influenza?

We performed a post-hoc analysis of time-varying HRs for the composited endpoint of seizures or epilepsy across the whole cohort (Figure 4) and separately according to hospitalization status, and in the two age groups. Across the whole cohort, the peak time for the HR of seizures or epilepsy between COVID-19 and influenza was 23 days after infection. The peak time for the HR was 21 days in adults and 50 days in children. At 50 days post-infection, children were almost three times more likely to have seizures or epilepsy diagnosed following COVID-19 infection than after influenza. Amongst individuals hospitalized with COVID-19 or influenza, the HR for seizures or epilepsy peaked at 9 days versus 41 days in those who were not hospitalized. At that timepoint, non-hospitalized people were more than twice as likely to have seizures or epilepsy diagnosed post COVID-19 compared to influenza.
Discussion

In a large electronic health records network, our study revealed that COVID-19 is associated with an increased risk of seizures or epilepsy when compared to matched patients with influenza over six-month time horizon from the date of infection. While the risk of epilepsy or seizures was significantly raised after COVID-19 compared to influenza, the absolute risk remains low (affecting less than 1% of all COVID-19 patients), consistent with other studies.\textsuperscript{13,18,19} The relative risk of epilepsy or seizures after COVID-19 infection, compared to after being infected with influenza, was more marked amongst children and non-hospitalized individuals over the six-month time horizon.

The elevated risk among children was unexpected even though it is appreciated that COVID-19 affects adults and children differently.\textsuperscript{20-23} Pulmonary disease is the main manifestation in adults while immune-mediated inflammatory response with or without multi-system inflammatory syndrome in children (MIS-C) were the major manifestations of COVID in children. Children with neurological manifestations can be more likely to have positive COVID-19 antibodies either alone or in combination with COVID-19 PCR positivity. Those without neurological manifestations often only had positive COVID-19 PCR results, suggestive of acute infection.\textsuperscript{20}

Many immune-mediated parainfectious central nervous system illnesses manifest some time after the offending viral infection\textsuperscript{24}, consistent with the delayed peak in the risk of epilepsy in our COVID-19 pediatric cohort. Immune- or inflammatory-mediated mechanisms of COVID-19 could contribute to epileptogenesis in the developing brain or unmask a previous predisposition to seizures. Epilepsy has neurodevelopmental, psychological, social and educational consequences.\textsuperscript{25,26} While the infection is often mild in children, neurological consequences of COVID-19 may potentially be more severe.\textsuperscript{27} Our data provide additional support for preventing
COVID-19 infection in children, which can inform the risks-benefits balance of vaccination in pediatric populations.

A similar immune-mediated mechanism might account for the differences seen in non-hospitalized patients. In this group, there was a higher risk of seizures or epilepsy after COVID-19 compared to influenza, and this relative risk gradually increased over time, peaking at around six weeks after the acute infection. An increasing HR over time only implies that the incidence in one group increases relative to the other group. Cautious interpretation is therefore warranted. The observation of an increasing risk of seizures or epilepsy over a few weeks post-COVID is, though, potentially consistent with an immune-mediated etiology. There should be greater attention to those presenting with subtle features of seizures, for example focal aware seizures, particularly in the three months following less severe COVID infection. By contrast, severe infections can directly lower seizure threshold owing to metabolic disturbances, fever, sleep deprivation, and other factors. This is consistent with our observation that the risk of epilepsy or seizure in hospitalized patients with COVID-19 peaks shortly after infection, whilst not being significantly greater than in hospitalized patients with influenza over the whole 6-months follow-up period.

Whilst these data offer insights into whether COVID-19 may contribute to seizures and epileptogenesis, much remains unanswered. We sought to determine if an underlying cause for seizures could be identified, particularly considering if stroke, a potential consequence of COVID-19, may be the main cause of COVID-19 related seizures or epilepsy. The data did not allow this to be answered due to the limited number of patients with a sequential diagnosis of COVID, stroke and subsequent epilepsy or seizures. Since most people who experienced a stroke were likely hospitalized, and that the increased risk of seizures or epilepsy was mainly
seen in non-hospitalized patients, it is perhaps less likely that stroke was a major factor in the development of epilepsy.

The long-term outcomes of patients diagnosed with seizures post COVID-19 remains poorly characterized. People and clinicians may choose not to initiate medication, even after two unprovoked seizures, if these occur proximal to COVID-19 infection and perhaps particularly if EEG and MRI do not suggest an underlying substrate for seizures. It will be important to monitor these individuals to determine if further seizures supervene. In those who do start medication, especially children, it will be crucial to track seizure profiles and long term neurodevelopmental/neurocognitive outcomes.

Conclusions

Our study shows that the absolute risk of epilepsy and seizures after COVID-19 infection is comparatively low. The relative risk is, though, greater after COVID-19 infection than after influenza, particularly in people who were not hospitalized and in children (aged less than 16 years). The peak HR in these more susceptible groups occurred some weeks after infection with COVID-19, potentially suggesting an immune-mediated etiology. Other study designs are required to further investigate possible underlying mechanisms.

As seizures and epilepsy remain relatively rare outcomes following COVID-19, we support continued pooling of data across multiple centers and establishing long-term open access repositories for the reporting of post COVID-19 seizures and epilepsy. Transparent reporting of outcomes is crucial to better understanding how COVID-19 may interrelate with seizure disorders.
Limitations:

This study has several limitations beyond those inherent to research using EHRs
(summarized in the eMethods in the Supplement) such as the unknown completeness of
records, no validation of diagnoses, and sparse information on socioeconomic and lifestyle
factors. We cannot comment on people who were infected with COVID-19 but could not be
matched to those from our influenza cohort. We do not know with which SARS-CoV-2 variant
individual patients were infected, nor whether they had previously been vaccinated against
SARS-CoV-2, and this might influence the likelihood of developing seizures. As the study is
entirely reliant on people being coded as having COVID-19 to enter the dataset, this study
cannot comment on outcomes in patients infected with SARS-CoV-2 but who were not tested or
diagnosed with COVID-19.

We matched a large number of people who had influenza to COVID-19 cases. The comparison
cohort was selected to be contemporaneous to the COVID-19 cohort to limit the impact of
contextual factors (e.g. strained health services) on outcomes. The incidence of influenza has
decreased during the COVID-19 pandemic so those affected might not be representative of
people diagnosed with influenza before the pandemic. Very similar hazard ratios were, though,
observed for other neurological outcomes when comparison was made with cohorts of patients
diagnosed with influenza in 2018 and 2019. Conversely, we did not compare the risk of
epilepsy and seizures between a COVID-19 cohort and the general population and it is possible
that the corresponding HR would be greater that those observed when comparing COVID-19 to
influenza. Also, we cannot compare post COVID-19 sequelae to infections with more
‘epileptogenic’ viruses, such as herpes simplex virus, as there are insufficient case numbers.

There are intrinsic difficulties when coding for epilepsy and seizures. COVID-19 associates with
psychological co-morbidity, both in those with pre-existing seizures and those who do not
have epilepsy. While psychological stresses can contribute to the development of epilepsy, this can also precipitate psychological non-epileptic attacks (PNES; dissociative seizures; functional seizures). PNES may be mis-categorized as seizures or epilepsy and this may be over-represented in the COVID-19 cohort. Seizures are also a nuanced, clinical diagnosis and it is possible that, for example, cardiovascular episodes of collapse or metabolic derangement (for example hypoglycaemia) may be coded as ‘seizure’ or even ‘epilepsy.’ Similar limitations do, though, also apply to those infected with either COVID-19 or influenza helping to validate the approach presented here.

http://links.lww.com/WNL/C480

REFERENCES:


Figure 1: Kaplan-Meier curves comparing the 6-months cumulative incidence of the primary outcome between matched cohorts of patients with COVID-19 vs. influenza.

An increased probability of being diagnosed with seizures or epilepsy is observed in the six months after COVID-19 compared to after influenza. The shaded areas around the curves represent 95% CI.
Figure 2 – Kaplan-Meier curves comparing the 6-months cumulative incidence of the primary outcome between matched subgroups of patients with COVID-19 vs. influenza.

Compared to influenza, COVID-19 associates with an increased probability of being diagnosed with seizures and/or epilepsy in both age groups. The risk of epilepsy was more marked in individuals younger than 16 years. The shaded areas around the curves represent 95% CI.

Seizures (R56) or epilepsy

(G40) (HR 1.85, p < 0.0001)

Seizures (R56)

Patients ≤ 16 years old

(HR 1.83, p < 0.0001)

Epilepsy (G40)

Patients > 16 years old

(HR 2.85, p < 0.0001)

(HR 1.56, p < 0.0001)

(HR 1.64, p < 0.0001)

(HR 1.48, p = 0.00056)
Figure 3 – Kaplan-Meier curves comparing the 6-month cumulative incidence of the primary outcome between matched subgroups of non-hospitalised and hospitalised patients with COVID-19 vs. influenza.

In people who were hospitalized the risks of seizures and/or epilepsy were similar following COVID-19 and influenza infections. In non-hospitalized patients, COVID-19 associated with significantly increased risks of seizures and/or epilepsy. The shaded areas around the curves represent 95% CI.
Figure 4 – Time varying hazard ratios for the primary analysis (left) and non-hospitalized/hospitalized and paediatric/adult subgroups. The time of the peak HR is noted on the x-axis.

The left-most panel in each row is identical to facilitate comparison. The peak HR in the whole cohort is at 23 days, similar to that seen in those aged over 16 years. In those under 16 years, the peak is delayed to 50 days and at that point the HR is nearly 3.0. Hospitalized patients show a peak HR at 9 days while in non-hospitalized patients the peak HR is at 41 days.
**Table 1** – Baseline characteristics for COVID-19 and influenza cohorts before and after matching. Only characteristics with a prevalence higher than 5% after matching are presented here. For all other baseline characteristics, see eTable 1. SMD=Standardized mean difference.

<table>
<thead>
<tr>
<th>Before matching</th>
<th>After matching</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COVID-19</strong></td>
<td><strong>Influenza</strong></td>
</tr>
<tr>
<td><strong>Influenza</strong></td>
<td><strong>COVID-19</strong></td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td>681283</td>
</tr>
<tr>
<td><strong>DEMOGRAPHICS</strong></td>
<td></td>
</tr>
<tr>
<td>Age; mean (SD); y</td>
<td>45.6 (21.1)</td>
</tr>
<tr>
<td>Sex; n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>377061 (55.3)</td>
</tr>
<tr>
<td>Male</td>
<td>303898 (44.6)</td>
</tr>
<tr>
<td>Race; n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>416830 (61.2)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>116220 (17.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>122781 (18.0)</td>
</tr>
<tr>
<td>Ethnicity; n (%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>96390 (14.1)</td>
</tr>
<tr>
<td>Not Hispanic of Latino</td>
<td>424617 (62.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>152276 (23.5)</td>
</tr>
<tr>
<td>COMORBIDITIES; n (%)</td>
<td></td>
</tr>
<tr>
<td>Overweight and obesity</td>
<td>139368 (20.5)</td>
</tr>
<tr>
<td>Hypertensive disease</td>
<td>219503 (32.2)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>109869 (16.1)</td>
</tr>
<tr>
<td>Chronic lower respiratory diseases</td>
<td></td>
</tr>
<tr>
<td>Bronchitis; not specified as acute or chronic</td>
<td>35075 (5.1)</td>
</tr>
<tr>
<td>Asthma</td>
<td>79654 (11.7)</td>
</tr>
<tr>
<td>Nicotine dependence</td>
<td>55991 (8.2)</td>
</tr>
<tr>
<td>Psychiatric comorbidities</td>
<td></td>
</tr>
<tr>
<td>Substance misuse</td>
<td>77411 (11.4)</td>
</tr>
<tr>
<td>Mood disorders</td>
<td>108333 (15.9)</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>137335 (20.2)</td>
</tr>
<tr>
<td>Heart disease</td>
<td></td>
</tr>
<tr>
<td>Ischemic heart diseases</td>
<td>65745 (9.7)</td>
</tr>
<tr>
<td>Other forms of heart disease</td>
<td>127337 (18.7)</td>
</tr>
<tr>
<td>Neoplasms (any)</td>
<td>133697 (19.6)</td>
</tr>
</tbody>
</table>
Table 2 – Incidence in the whole COVID-19 cohort and HR for the comparison between matched COVID-19 and influenza cohorts for the primary composite outcome and its constituents. Numbers in brackets are 95% confidence intervals.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Incidence at 6 months %</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures (R56) or epilepsy (G40)</td>
<td>0.94 (0.87-1.01)</td>
<td>1.55 (1.40-1.72)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Seizures (R56)</td>
<td>0.81 (0.75-0.88)</td>
<td>1.55 (1.39-1.74)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Epilepsy (G40)</td>
<td>0.30 (0.26-0.34)</td>
<td>1.87 (1.54-2.28)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
Table 3: Moderation by age and hospitalization status of risk of the different outcomes after COVID-19 vs. influenza.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Moderation Coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderation by age (≤ 16 years vs. &gt;16 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures (R56) or Epilepsy (G40)</td>
<td>0.20 (-0.025 – 0.42)</td>
<td>0.082</td>
</tr>
<tr>
<td>Seizures (R56)</td>
<td>0.12 (-0.11 – 0.36)</td>
<td>0.32</td>
</tr>
<tr>
<td>Epilepsy (G40)</td>
<td>0.68 (0.23 – 1.13)</td>
<td>0.0031</td>
</tr>
<tr>
<td>Moderation by hospitalization status (hospitalized vs. not hospitalized)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures (R56) or Epilepsy (G40)</td>
<td>0.12 (-0.10 – 0.35)</td>
<td>0.28</td>
</tr>
<tr>
<td>Seizures (R56)</td>
<td>0.047 (-0.20 – 0.29)</td>
<td>0.70</td>
</tr>
<tr>
<td>Epilepsy (G40)</td>
<td>0.52 (0.11 – 0.93)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

When examining age, a significantly positive moderation coefficient indicates that the HR among children is significantly greater than the HR among adults. While there is no significant moderation by age for a diagnosis of seizures or the composite endpoint of seizures or epilepsy, the HR for epilepsy was significantly greater in children than in adults.

In investigating hospitalization status, as a surrogate for disease severity, a significantly positive moderation coefficient indicates that the HR among non-hospitalized individuals is significantly greater than the HR among hospitalized patients. While there is no significant moderation by hospitalization status for a diagnosis of seizures or the composite endpoint of seizures or epilepsy, the HR for epilepsy was significantly greater in non-hospitalized than in hospitalized patients.
Incidence of Epilepsy and Seizures Over the First 6 Months After a COVID-19 Diagnosis: A Retrospective Cohort Study
Maxime Taquet, Orrin Devinsky, J. Helen Cross, et al.
Neurology published online November 16, 2022
DOI 10.1212/WNL.0000000000201595

This information is current as of November 16, 2022