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Original Article

Pandemic Effect on Healthcare Use and Death in Adults with Epilepsy: A Population Study

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ABSTRACT: ***Objectives:*** We conducted a population-based study using Ontario health administrative data to describe trends in healthcare utilization and mortality in adults with epilepsy during the first pandemic year (March 2020–March 2021) compared to historical data (2016–2019). We also investigated if changes in outpatient visits and diagnostic testing during the first pandemic year were associated with increased risk for hospitalizations, emergency department (ED) visits, or death. ***Methods:*** Projected monthly visit rates (per 100,000 people) for outpatient visits, electroencephalography, magnetic resonance, computed tomography, all-cause ED visits, hospitalizations, and mortality were calculated based on historical data by fitting monthly time series autoregressive integrated moving-average models. Two-way interactions were calculated using Quasi-Poisson models. ***Results:*** In adults with epilepsy during the first quarter of the pandemic, we demonstrated a reduction in all-cause outpatient visits, diagnostic testing, ED visits and hospitalizations, and a temporary increase in mortality (observed rates of 355.8 vs projected 308.8, 95% CI: 276.3–345.1). By the end of the year, outpatient visits increased (85,535.4 vs 76,620.6, 95% CI: 71,546.9–82,059.4), and most of the diagnostic test rates returned to the projected. The increase in the rate of all-cause mortality during the pandemic, compared to pre-pandemic, was greater during months with the lower frequency of diagnostic tests than months with higher frequency (interaction *p*-values <.0001). ***Conclusion:*** We described the impact of the pandemic on healthcare utilization and mortality in adults with epilepsy during the first year. We demonstrated that access to relevant diagnostic testing is likely important for this population while planning restrictions on non-urgent health services.

RÉSUMÉ : Effets de la pandémie sur l'utilisation des soins de santé et les décès chez des adultes atteints d'épilepsie : une étude basée sur la population. ***Objectifs :*** Nous avons mené une étude basée sur la population en utilisant des données administratives de santé de l'Ontario afin de décrire les tendances d'utilisation des soins de santé et de mortalité chez des adultes atteints d'épilepsie au cours de la première année pandémique (mars 2020-mars 2021), et ce, par rapport à des données historiques (2016-2019). Nous avons également cherché à savoir si les changements dans les consultations externes et les tests diagnostiques au cours de la première année pandémique peuvent être associés à un risque accru d'hospitalisation, de visite aux urgences ou de décès. ***Méthodes :*** Les taux mensuels projetés (pour 100 000 personnes) pour les consultations externes, l'électroencéphalographie, l'imagerie par résonance magnétique (IRM), la tomodensitométrie, les visites aux urgences toutes causes confondues, les hospitalisations et la mortalité ont été calculés sur la base de données historiques en ajustant les séries temporelles mensuelles à des modèles autorégressifs intégrés de moyenne mobile. Notons par ailleurs que les interactions à double sens ont été calculées à l'aide de modèles de quasi-Poisson. ***Résultats :*** Chez les adultes atteints d'épilepsie au cours du premier trimestre de la pandémie, nous avons constaté une réduction des consultations externes toutes causes confondues, des tests diagnostiques, des visites aux urgences et des hospitalisations, ainsi qu'une augmentation temporaire de la mortalité (taux observés de 355,8 contre 308,8 prévus, IC à 95 % : 276,3-345,1). À la fin de l'année, le nombre de consultations externes avait augmenté (85 535,4 contre 76 620,6 ; IC à 95 % : 71 546,9-82 059,4) et la plupart des taux de tests diagnostiques étaient revenus au niveau projeté. Par rapport à la période prépandémique, l'augmentation des taux de mortalité toutes causes confondues pendant la pandémie était plus importante pendant les mois où la fréquence des tests diagnostiques était plus faible que pendant les mois où cette même fréquence était plus élevée (valeurs de *p* d'interaction < 0,0001). ***Conclusion :*** Nous avons décrit l'impact

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de la pandémie sur l'utilisation des soins de santé et la mortalité chez des adultes atteints d'épilepsie au cours de la première année pandémique. Nous avons ainsi démontré que l'accès à des tests diagnostiques pertinents s'avère probablement important pour cette population même si des restrictions portant sur les services de santé non urgents sont planifiées.

Keywords: Epilepsy; pandemic; healthcare utilization; mortality

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Introduction

The COVID-19 pandemic posed unprecedented challenges to healthcare systems across the world.[1] The World Health Organization (WHO) declared the COVID-19 global pandemic on March 11, 2020,[2] forcing many countries to lockdown and restrict their outpatient care, ambulatory testing, and procedures.

Epilepsy is a chronic and debilitating condition requiring regular monitoring of seizure control, as well as the use of anti-seizure medications (ASMs) and their side effects.[3] The disease burden of epilepsy ranked second among neurologic conditions in terms of disability-adjusted life years by the WHO's 2010 Global Burden of Disease study.[2] At the beginning of the COVID-19 pandemic, health care for individuals with epilepsy changed dramatically, including the increased use of telemedicine, decreased electroencephalogram (EEG) use, limited availability of epilepsy surgery,[4,5] and a reduction in the new prescription and renewals of ASMs.[6] In studies conducted in the United Kingdom and the United States during the initial phase of the pandemic, 25%–34% of individuals with epilepsy[2,7] and 29% of caregivers[7] reported increased perceived seizures; 31% of patients and 20% of caregivers reported difficulties accessing medication;[7] and 5% of patients reported stopping or reducing ASMs due to health care access or cost.[2] Similarly, the International League Against Epilepsy COVID-19 and Telemedicine Task Force, which aimed to assess the international patient experience during the COVID-19 pandemic,[8] found that 23% of people with epilepsy and 28% of caregivers reported increased seizure frequency; difficulty obtaining medication was reported by 20% of individuals with epilepsy and 26% of caregivers; and difficulty with health care access was reported by 28% of individuals with epilepsy and 30% of caregivers.[8]

However, most of the studies that described the impact of the COVID-19 pandemic on individuals with epilepsy were mainly survey or interview-based,[2,7,9] limited by small sample sizes,[3,7] lacking long-term data (most published evidence is focused on one to four months since the pandemic),[1–3,7–9] and had limited data on healthcare utilization and mortality.[1–3,7–9] Importantly, no studies investigated the extent to which pandemic restrictions on non-urgent health services result in increased morbidity and death in individuals with epilepsy during the pandemic. To address these limitations, we conducted a population-based study with the primary objective to describe trends in healthcare utilization and mortality in adults with epilepsy during the first year of the pandemic restrictions compared to similar periods in previous years. As the secondary objective, we investigated the association between changes in non-urgent healthcare services since the pandemic compared to pre-pandemic historical data and adverse health outcomes during the pandemic. We hypothesize that there are lower rates of non-urgent health service use during the pandemic compared to the same periods pre-pandemic. We also hypothesize that periods with lower rates of non-urgent health service use during the pandemic are associated with increased rates of adverse health outcomes compared to the same periods pre-pandemic.

Methods

Study Design

We conducted a retrospective population-based study via open-cohort sampling strategy using Ontario health administrative data, from the most populous province of Canada, on adults with a previous diagnosis of epilepsy during the first year of the COVID-19 pandemic (March 2020–March 2021) and compared their healthcare utilization and mortality to similar periods in the previous years (Jan 2016–Dec 2019).

The use of data in this study was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

Data Sources

ICES, an independent non-profit institution, houses individual-level high-quality administrative databases on publicly funded services, including outpatient and inpatient visits (emergency department [ED] visits or hospitalizations) and diagnostic testing in Ontario.[10] These databases are regularly updated and validated for accuracy (https://datadictionary.ices.on.ca/Applications/DataDictionary/Default.aspx).[11,12] The Registered Persons (RPDB) database contains data on vital statistics and demographics. The Ontario Health Insurance Plan (OHIP) database captures 95% of physician billing. The National Ambulatory Care Reporting System Database (NACRS) records ED visits. The Discharge Abstract Database (DAD) records hospitalizations, and the Canadian Census includes neighborhood socioeconomic details. Ontario Mental Health Reporting System contains information on inpatient mental health admissions. The COVID-19 Integrated Testing Dataset includes all available COVID-19 diagnostic laboratory results in Ontario. These databases were linked using unique encoded identifiers. In Ontario, physician billing codes in response to the COVID-19 pandemic, including virtual visits (phone or video), were implemented on March 14, 2020, and extended until December 1, 2022.[13]

Population and Setting

In an open cohort, all adults (18 years and older) Ontario residents with a prior diagnosis of epilepsy between January 2016–March 2021 who were alive at the beginning of each month were considered for inclusion. *Prior diagnosis of epilepsy* was identified by the presence of one inpatient visit (hospitalization) at any time or two physician claims within 2 years with epilepsy-specific diagnostic codes (ICD-9: 345; ICD-10: G40 or G41; OHIP: 345).[14,15] The open-cohort sampling strategy allows individuals to

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enter the cohort as they age and leave when they die or move out of the province. We considered March 17, 2020, when the state of emergency was declared in Ontario,[16] as the start of the pandemic. Follow-up continued until March 31, 2021.

Time frame Definitions

Observed versus projected event rates with 95% confidence intervals (CIs) were visualized monthly over the first year of the pandemic. For comparison, similar to our previous study,[17] four time periods were considered: (i) *pre-COVID-19*: Jan–Feb 2020; (ii) *Wave I*: March–May 2020; (iii) *Summer lull*: June–August 2020; and (iv) *Wave II*: September 2020–March 2021.

Outcomes

Primary Objective

The primary outcomes were all-cause outpatient visits, relevant diagnostic tests used to work up the etiology of a seizure[18] (EEG, sleep studies, magnetic resonance imaging [MRI], and a computerized tomography [CT] scan), all-cause ED visits and hospitalizations (from NACRS and DAD databases), and all-cause mortality (from RPDB database). Outpatient visits were categorized by: (i) total (virtual or in-person) primary care visits, (ii) total (virtual or in-person) visits from other than family medicine specialists, and (ii) total virtual outpatient visits.

Health system costs were considered in the secondary analysis. We estimated *costs associated with health care utilization* from a public payer's perspective using the hybrid costing methods developed for Ontario health administrative data (see more details in the Data Supplement).[19] All costs were standardized using health sector-specific consumer price indices to their equivalent 2021 Canadian dollar value.[20]

Secondary Objective

All-cause outpatient visits and epilepsy-relevant diagnostic testing were considered *non-urgent healthcare services*. All-cause ED visits, hospitalization, and mortality were considered separately as *adverse health outcomes*.

Covariates

Covariates considered were sex, age group (18–24, 25–34, 35–49, 50–64, 65+), residence location (rural vs. urban), neighborhood income quintiles, and mental health status (based on mental health and addictions-related outpatient and inpatient services within the last year; please see details in the Data Supplement).

Statistical Analyses

Primary Objective

We used a similar analytic approach as from our previous study to describe trends in healthcare utilization and mortality.[17] Briefly, we created a 63-period time series from January 2016 to March 2021 and calculated monthly rates as the number of events per 100,000 people. Autoregressive integrated moving-average (ARIMA) models were used to calculate projected outcome rates using observed monthly rates from similar periods pre-COVID (Jan 2016–Dec 2019). ARIMA models regress observed rates on past observed values, fitting autoregressive and moving-average terms to account for seasonality and other underlying trends and correlation structures.[21] We used SAS software's adaption of the United States Census Bureau's X-13ARIMA-SEATS program (X13) for ARIMA,[22,23] including its automated model selection feature.[24] This algorithm selects the best-fitting model using the Bayesian Information Criterion.[22]

We used the best-fitting model for each outcome to project monthly rates for 13 months following February 2020. We considered observed rates outside the projected 95% CIs to be significantly different from projected rates.[5] We presented comparisons between observed and projected monthly rates graphically as a time series and mean rates across the four time periods in tabular form.

We conducted all analyses in the whole sample and stratified by sex and age group (18–24, 25–34, 35–49, 50–64, 65+).

Secondary Objective

To investigate how the pandemic interacted with non-urgent healthcare (outpatient visits and epilepsy-relevant diagnostic testing) and its association with adverse health outcomes (all-cause ED visits, hospitalizations, or death) since the pandemic, we used a two-way statistical interaction term between frequency of non-urgent healthcare services and pandemic. We operationalized non-urgent healthcare utilization as a categorical variable in two steps: (1) calculating the rate of healthcare utilization for each month in the time series and then (2) categorizing months of the time series into quantiles based on these rates to compare months with high vs. lower frequency of healthcare services. The effect of the pandemic was operationalized using a binary indicator: months in the time series from January 2015 to February 2020 were categorized as "pre-COVID," and all subsequent months were categorized as "post-COVID." We used contrast statements to compare outcome rates during the "post-COVID" period to the "pre-COVID" period within each quantile of non-urgent healthcare services. Quasi-Poisson models were used to estimate crude and adjusted rate ratios (RRs) for outcomes of interest.[25] Significant interactions were explored by calculating RRs for post- vs pre-COVID at each level of frequency of service use. Interaction p-values < 0.05 indicated a significant interaction. Covariates considered in the statistical model were sex, age, rurality, income, and mental health status.

Given that an increase in the frequency of virtual care visits was a pandemic-specific phenomenon, its effect was explored within the pandemic period only.

We performed all data analyses in SAS (version 9.4 using SAS Enterprise guide version 7.15.3) in the secure environment at ICES following Ontario privacy standards.

Results

In March 2020, 98,267 adults had a prior diagnosis of epilepsy: 50,702 (51.6%) male, 24,742 (25.2%) 65 years and older, and 45,782 (46.6%) resided in low-income areas.

Crude rates and rate ratios for outcomes of interest compared to similar periods in previous years are presented in Table 1. Tables 2, 3, and Supplementary Tables 1–11 present observed and projected monthly rates and 95% CI estimated by ARIMA Models. Adjusted rate ratios are presented in Tables 4 and 5. Figures 1 and Supplementary Figures 1–3 present observed versus projected monthly rates for outcomes of interest.

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Table 1: Monthly crude rates, crude rate ratios (RR), and 95% confidence intervals (CI) for all-cause outpatient, inpatient visits, mortality, and diagnostic tests in adults with a previous diagnosis of epilepsy during the first year of the pandemic compared to pre-pandemic

	Pre-COVID			Wave I			Summer Lull			Wave II		
	2017–19	(2020)		2017–19	(2020)		2017–19	(2020)		2017–19	(2020–21)	
	Jan–Feb			Mar–May			Jun–Aug			Sep–Mar		
Outcome	Monthly rates per 100,000 people		RR (95%CI)	Monthly rates per 100,000 people		RR (95%CI)	Monthly rates per 100,000 people		RR (95%CI)	Monthly rates per 100,000 people		RR (95%CI)
All-cause outpatient visits	77,515.68	76,922.81	0.99(0.89–1.11)	81,989.68	71,262.71	**0.87(0.83–0.91)**	78,321.25	79,337.19	1.01 (0.97–1.05)	77,958.41	85,535.37	**1.10 (1.03–1.17)**
Primary care visits	47,091.41	45,761.4	0.97 (0.86–1.09)	48,964.34	43,975.48	**0.90 (0.86–0.94)**	47,275.6	48,261.52	1.02 (0.98–1.06)	46,824.74	50,765.8	**1.08 (1.02–1.15)**
Other Specialist visits	30,424.61	31,161.92	1.02 (0.92–1.13)	33,025.34	27,287.23	**0.83(0.77–0.88)**	31,045.76	31,076.01	1.00 (0.96–1.05)	31,133.82	34,769.57	**1.12 (1.04–1.20)**
Outpatient virtual visits	1303.73	2095.12	**1.61 (1.24–2.09)**	1444.47	40,590.38	**28.10 (20.51–38.51)**	1515.23	46,017.95	**30.37 (24.78–37.21)**	2589.6	48,091.56	**18.57 (9.97–34.60)**
All-cause ED visits	10,107.94	10,100.69	1.00 (0.92–1.08)	10,769.32	7493.03	**0.70 (0.64–0.76)**	11,306.77	9521.78	**0.84 (0.80–0.88)**	10,370.64	8665.09	**0.84 (0.79–0.88)**
All-cause hospitalizations	2232.46	2286.45	1.02 (0.94–1.12)	2296.83	1754.93	**0.76 (0.72–0.81)**	2242.05	2130.06	0.95 (0.89–1.01)	2262.64	2190.15	0.97 (0.92–1.01)
All-cause mortality	322.74	332.72	1.03 (0.92–1.16)	302.52	355.78	**1.18 (1.06–1.31)**	274.9	301.28	**1.10 (1.01–1.18)**	316.6	342.71	1.08 (1.00–1.17)
Sleep Studies	221.98	207.16	0.93 (0.83–1.04)	225.6	52.92	**0.23 (0.13–0.41)**	223.7	114.38	**0.51 (0.44–0.60)**	208.97	208.97	**0.88 (0.78–0.99)**
Electroencephalography (EEG)	1847.56	1808.74	0.98 (0.92–1.05)	1973.97	700.13	**0.35 (0.23–0.54)**	1827.95	1199.39	**0.66 (0.56–0.77)**	1792.43	1347.96	**0.75 (0.68–0.83)**
Magnetic resonance imaging (MRI)	1966.56	2024.73	1.03 (0.96–1.10)	2028.59	1353.05	**0.67 (0.57–0.78)**	1959.05	1870.51	**0.95 (0.92–0.99)**	1992.9	2112.39	**1.06 (1.01–1.12)**
Computed Tomography (CT)	3623.56	3884.55	1.07 (0.99–1.16)	3904.5	2926.87	**0.75 (0.67–0.84)**	3884.07	3875.36	1.00 (0.95–1.04)	3813.1	4096.44	**1.07 (1.03–1.12)**

CI=confidence intervals; ED=emergency department; RR=rate ratios.
In bold: statistically significant.

Table 2: Observed and projected monthly rates and 95% confidence intervals (CI) estimated by ARIMA models for all-cause mortality and hospitalizations, emergency department (ED), and outpatient visits in adults with a prior diagnosis of epilepsy: rates were calculated as the number of events per 100,000 people at risk. Similar periods in previous years (2016–2019) were used to calculate projected rates

	Observed	Projected (95% CI)	Observed	Projected (95% CI)	Observed	Projected (95% CI)	Observed	Projected (95% CI)
Entire population	Pre-COVID Jan–Feb 2020		Wave I Mar–May 2020		Summer Lull Jun–Aug 2020		Wave II Sep 2020–Mar 2021	
All-cause outpatient visits	76,922.81	73,897.67 (69,688.25–78361.36)	↓**71262.71**	80,347.15 (75,471.30–85538.66)	79,337.19	76,357.40 (71,533.38–81506.74)	↑**85,535.37**	76,620.60 (71,546.91–82,059.42)
Overall primary care visits	45,761.40	45,729.83 (42,787.47–48874.53)	↓**43975.48**	48,139.30 (45,041.90–51449.69)	48,261.52	46,270.24 (43,293.11–49452.10)	↑**50,765.80**	46,415.54 (43,303.85–49753.31)
Overall specialist visits	31,161.92	29,960.56 (28,338.30–31675.68)	↓**27287.23**	32,630.78 (30,423.56–35001.12)	31,076.01	31,138.68 (28,856.00–33601.93)	↑**34769.57**	31,288.92 (28,923.82–33848.76)
Outpatient virtual visits	2095.12	1951.95 (1808.70–2095.20)	↑**40590.38**	2154.37 (2006.51–2302.23)	↑**46017.95**	2227.40 (2037.05–2417.74)	↑**48091.56**	2357.71 (2110.30–2605.13)
All-cause ED visits	10,100.69	10,068.26 (9784.08–10360.69)	↓**7493.03**	10,732.22 (10,424.83–11048.68)	↓**9521.78**	11,212.29 (10,891.15–11542.90)	↓**8665.09**	10,421.43 (10,119.82–10732.04)
All-cause hospitalizations	2286.45	2272.71 (2141.90–2411.51)	↓**1754.93**	2302.32 (2169.81–2442.93)	2130.06	2243.01 (2113.91–2380.00)	2190.15	2279.70 (2145.83–2421.94)
All-cause mortality	332.72	327.38 (292.97–365.83)	↑**355.78**	308.78 (276.33–345.05)	301.28	276.44 (247.39–308.91)	342.71	320.15 (286.50–357.75)
Sleep Studies	207.16	210.28 (181.88–243.11)	↓**52.92**	216.05 (186.21–250.67)	↓**114.38**	214.09 (184.10–248.97)	184.11	208.15 (179.03–242.00)
Electroencephalography (EEG)	1808.74	1825.91 (1688.09–1975.00)	↓**700.13**	1922.09 (1771.35–2085.68)	↓**1199.39**	1798.59 (1649.30–1961.39)	↓**1347.96**	1792.12 (1636.33–1962.76)
Magnetic resonance imaging (MRI)	2024.73	2006.34 (1912.39–2104.90)	↓**1353.05**	2068.11 (1969.86–2171.26)	↓**1870.51**	1998.60 (1903.66–2098.29)	2112.39	2040.84 (1942.85–2143.77)
Computed Tomography (CT)	3884.55	3879.68 (3647.37–4126.78)	↓**2926.87**	4199.82 (3948.34–4467.31)	↓**3875.36**	4140.35 (3892.43–4404.06)	4096.44	4130.12 (3878.41–4398.19)

In bold: observed rates outside the projected 95% confidence intervals of projected rates were considered as significantly different.

Table 3: Observed and projected costs (total and by subgroups) with 95% confidence intervals (CIs) estimated by ARIMA models in individuals with a prior diagnosis of epilepsy: in millions, 2021 adjusted dollars. Similar periods in previous years (2016–2019) were used to calculate projected cost

	Observed	Projected (95% CI)	Observed	Projected (95% CI)	Observed	Projected (95% CI)	Observed	Projected (95% CI)
Type of cost	Pre-COVID Jan–Feb 2020		Wave I Mar–May 2020		Summer Lull Jun–Aug 2020		Wave II Sep 2020 – Mar 2021	
Total costs	121.30	119.52 (115.06–124.16)	**111.76**	127.14 (122.29–132.18)	126.30	125.97 (120.00–132.23)	131.10	127.98 (120.51–135.92)
Physician costs	16.89	16.69 (15.85–17.57)	**13.82**	17.61 (16.72–18.55)	16.92	17.07 (16.18–18.00)	17.92	17.10 (16.17–18.09)
Hospital costs	58.69	57.72 (54.71–60.89)	**55.98**	60.18 (56.87–63.69)	**64.40**	59.72 (55.94–63.75)	**66.73**	61.14 (56.47–66.20)
Drug costs	14.13	13.99 (12.96–15.10)	**13.62**	14.89 (13.79–16.09)	14.69	14.50 (13.40–15.70)	14.84	14.93 (13.71–16.27)
Home–care costs	25.99	25.71 (25.15–26.28)	**24.93**	27.62 (27.01–28.23)	**25.14**	27.86 (26.97–28.75)	**25.64**	28.08 (26.80–29.37)
Laboratory costs	0.71	0.71 (0.60–0.83)	**0.42**	0.70 (0.58–0.85)	0.59	0.64 (0.48–0.84)	0.62	0.63 (0.43–0.92)

All-cause outpatient visits

Compared to similar pre-pandemic periods, both all-cause primary care and specialist visits significantly decreased during *Wave I*, returned to projected during the *Summer Lull,* and increased during *Wave II*: observed rate of all-cause outpatient visit rates (per 100,000 people at risk) 85,535.4 vs projected 76,620.6, 95% CI 71,546.9–82,059.4 (Table 2; Supplementary Figure 1). Virtual care visit rates significantly increased and remained well above projected throughout the first year of the pandemic (Table 2). Sex and age did not influence this pattern (Supplementary Tables 1–3).

Relevant Diagnostic Tests (Supplementary Figure 2)

EEG testing rates significantly decreased during the first year of the pandemic (Table 2) and remained significantly lower than projected during *Wave II* (observed rate per 100,000 people of 1,348.0 vs projected 1,792.1, 95% CI 1,636.3–1,962.8) overall, but not for individuals at age 25–34 years old for whom rates returned to projected during *Summer Lull* and *Wave II* (Supplementary Table 6). Sex did not influence this pattern. Following the same trend, observed rates for *sleep studies* during *Wave I* and Summer Lull were significantly lower than projected, but returned to projected during *Wave II* (observed rate of 184.1 vs projected 208.15, 95% CI: 179.03–242.00) for all, but not for individuals at age 50–64 years old for whom rates remained significantly lower than projected throughout all periods studied (Table 2, Supplementary Table 5). Sex did not influence this pattern.

During *Wave I* and *Summer Lull*, rates for *MRI* significantly decreased and returned to projected during *Wave II* (observed rate per 100,000 people of 2,112.4 vs projected of 2,040.8, 95%: 1,942.9–2,143.8), except for females and those in the age group 65 years and older, for whom rates remained lower than projected (Table 2, Supplementary Table 7). Similarly, observed rates remained lower than projected during *Wave I* and *Summer Lull* for *CT* and returned to projected during *Wave II*: observed rate of 4,096.4 vs. projected of 4,130.1, 95%: 3,878.4–4,398.2 (Table 2). This pattern was similar by age and sex subgroups (Supplementary Table 8).

ED Visits and Hospitalizations

During the first year of the pandemic, all-cause ED visits rates remained significantly lower than projected: during *Wave II*, the observed rate was 8,665.1 vs. projected of 10,421.4 (10,119.8–10,732.0) (Table 2, Fig. 1). During the first year of the pandemic, all-cause hospitalization rates remained significantly lower than projected during *Wave I* and returned to projected during *Summer Lull* and *Wave II* (Table 2, Fig. 1). Sex and age did not influence this pattern (Supplementary Tables 9–10).

All-Cause Mortality

Compared to projected, observed all-cause mortality rates significantly increased during *Wave I* (observed rate of 355.8 vs projected of 308.8, 95% CI: 276.3–345.1) and returned to the projected during *Summer Lull* and *Wave II* (Table 2, Supplementary Figure 3). During *Wave I*, all-cause mortality was increased only among individuals 65 years old and older: observed rates of 950.5 vs. projected 809.4, 95% CI: 700.5–935.2. Sex did not influence this pattern (Supplementary Table 11).

Health System Costs

The observed total health system cost was significantly reduced only during *Wave I* and then returned to the projected (Table 3). A similar pattern was noted for physician-, medication-, and laboratory-related costs. While the observed cost of hospitalizations reduced during *Wave I*, it increased above projected since June 2020 and remained elevated above projected during *Wave II*: 66.73 million vs 61.14, 95%: 56.47–66.20 (Figure 1).

Changes in Non-Urgent Healthcare Services Since the Pandemic and Adverse Health Outcomes

The primary care visits and COVID period interaction terms were significantly related to the rates of all-cause ED visits and hospitalizations (interaction p-values<0.008) (Table 4). The interaction p-values indicate one or more significant differences between these RRs, suggesting that the decrease in the rate of ED visits and hospitalizations with the pandemic, compared to pre-pandemic, was greater during those months with a lower frequency of primary care visits than those with a higher frequency. The increase in the rate of all-cause mortality during the pandemic, compared to pre-pandemic, was greater during those months with a higher frequency of primary care visits than those with a lower frequency (interaction p-value < 0.0001).

The EEG tests and COVID period interaction terms were not significantly related to the rates of all-cause ED visits and hospitalizations (interaction p-values > 0.6) (Table 4). The increase in the rate of all-cause mortality during the pandemic, compared to pre-pandemic, was greater during those months with the lower frequency of EEG rates than those with higher frequency (interaction p-value $< .0001$). The decrease in the rate of ED visits and hospitalizations with the pandemic, compared to pre-pandemic, was greater during those months with a lower frequency of sleep study tests than those with a higher frequency (interaction p-values $< .004$) (Table 4). The effect on all-cause mortality was not significant (interaction p-value $= 0.54$). The decrease in the rate of ED visits and hospitalizations with the pandemic, compared to pre-pandemic, was greater during those months with a lower frequency of MRI tests than those with a higher frequency (interaction p-values < 0.03) (Table 4). The increase in the rate of all-cause mortality during the pandemic, compared to pre-pandemic, was greater during those months with the lower frequency of MRI rates than months with higher frequency (interaction p-value < 0.001). Similarly, the decrease in the rate of ED visits and hospitalizations with the pandemic, compared to pre-pandemic, was greater during those months with a lower frequency of CT scans than those with a higher frequency (p values for interactions $< .0001$) (Table 4). The increase in the rate of all-cause mortality during the pandemic, compared to pre-pandemic, was greater during those months with the lowest frequency of CT scan rates than months with higher frequency (interaction p-value $= 0.04$).

Restricted to the pandemic period and compared to months with the lowest proportion of virtual care visits (reference = Quantile I), more virtual care visits were generally associated with increased ED visit rates, but not hospitalization (other than Quantile III) or all-cause mortality rates (Table 5).

Discussion

Our population-based, retrospective study is one of the first to describe the impact of the COVID-19 pandemic on healthcare utilization and mortality rates in adults with epilepsy during the

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Table 4: Adjusted rate ratios (RR)* comparing hospitalization, emergency department (ED) visit, and mortality rates during COVID (March 2020 to February 2021) to the pre-COVID period (March 2019 to February 2020) by quantiles# of non-urgent service use visits

Monthly frequency of non-urgent health services	All-cause ED visits	Interaction	All-cause Hospitalizations	Interaction	All-cause Mortality	Interaction
	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
All outpatient visits						
Quantile I	0.76 (0.73–0.79)	0.0083	0.84 (0.80–0.89)	0.0027	0.97 (0.85–1.11)	<0.0001
Quantile II	0.79 (0.77–0.81)		0.89 (0.86–0.92)		0.99 (0.94–1.06)	
Quantile III	0.82 (0.80–0.84)		0.93 (0.90–0.96)		1.21 (1.15–1.28)	
Primary care visits						
Quantile I	0.76 (0.73–0.79)	0.0002	0.86 (0.82–0.91)	0.0078	0.99 (0.87–1.13)	<0.0001
Quantile II	0.79 (0.77–0.81)		0.88 (0.86–0.91)		0.97 (0.92–1.03)	
Quantile III	0.83 (0.81–0.86)		0.93 (0.91–0.96)		1.22 (1.16–1.29)	
Other specialist care visits						
Quantile I	0.79 (0.74–0.83)	0.4736	0.84 (0.77–0.91)	0.0832	1.15 (0.92–1.43)	0.0259
Quantile II	0.79 (0.77–0.81)		0.90 (0.87–0.93)		1.00 (0.93–1.07)	
Quantile III	0.81 (0.79–0.82)		0.92 (0.90–0.94)		1.12 (1.07–1.17)	
Electroencephalography						
Quantile I	0.80 (0.72–0.89)	0.9971	0.87 (0.75–1.00)	0.6429	1.98 (1.45–2.72)	<0.0001
Quantile II	0.80 (0.79–0.82)		0.90 (0.88–0.92)		1.07 (1.03–1.11)	
Computed Tomography scan						
Quantile I	0.73 (0.62–0.87)	<0.0001	0.70 (0.53–0.94)	<0.0001	1.86 (1.01–3.45)	0.0368
Quantile II	0.77 (0.75–0.79)		0.86 (0.83–0.89)		1.01 (0.92–1.10)	
Quantile III	0.84 (0.82–0.85)		0.94 (0.92–0.96)		1.11 (1.06–1.15)	
Magnetic resonance imaging						
Quantile I	0.82 (0.71–0.95)	0.0270	0.88 (0.73–1.06)	<0.0001	2.13 (1.41–3.22)	0.0011
Quantile II	0.78 (0.76–0.81)		0.84 (0.81–0.87)		1.11 (1.03–1.20)	
Quantile III	0.82 (0.81–0.84)		0.94 (0.92–0.96)		1.06 (1.01–1.11)	
Sleep studies						
Quantile I	0.74 (0.71–0.77)	<0.0001	0.84 (0.80–0.89)	0.0044	1.09 (0.97–1.22)	0.5445
Quantile II	0.82 (0.81–0.84)		0.92 (0.90–0.94)		1.05 (1.01–1.10)	

All models were adjusted for sex, age, rurality, income, and mental health status.
*Reference group: pre-COVID period. Healthcare service use frequency and COVID-19 period interaction were explored using categorical variables. Interactions were unpacked by calculating RRs for the COVID period (post vs. pre) at each level of quantile. Significant interaction p–values indicate one or more significant differences between RRs.
#Exposure frequency was organized into quantiles. The number of quantile groups was dependent on the available variability in exposure rates (exposures with higher variability were allocated more groups up to a maximum of five).

Table 5: Adjusted rate ratios (RR) comparing hospitalization, emergency department (ED) visit, and mortality rates by quantiles* of virtual care visits since the beginning of the COVID-19 pandemic

Monthly frequency of virtual care visits	All-cause ED visits		All-cause hospitalizations		All-cause mortality	
	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
Quantile I	Reference		Reference		Reference	
Quantile II	1.43 (1.09–1.86)	0.0092	1.19 (0.90–1.56)	0.2137	1.17 (0.83–1.66)	0.3762
Quantile III	1.71 (1.31–2.23)	<0.0001	1.37 (1.04–1.80)	0.0259	1.09 (0.77–1.56)	0.6197
Quantile IV	1.61 (1.23–2.11)	0.0005	1.22 (0.93–1.61)	0.1580	1.05 (0.73–1.50)	0.7911
Quantile V	1.34 (1.02–1.76)	0.0335	0.98 (0.74–1.30)	0.8868	1.03 (0.71–1.50)	0.8842

All models were adjusted for sex, age, rurality, income, and mental health status.
*Exposure frequency was organized into quantiles. The number of quantile groups was dependent on the available variability in exposure rates (exposures with higher variability were allocated more groups up to a maximum of five).

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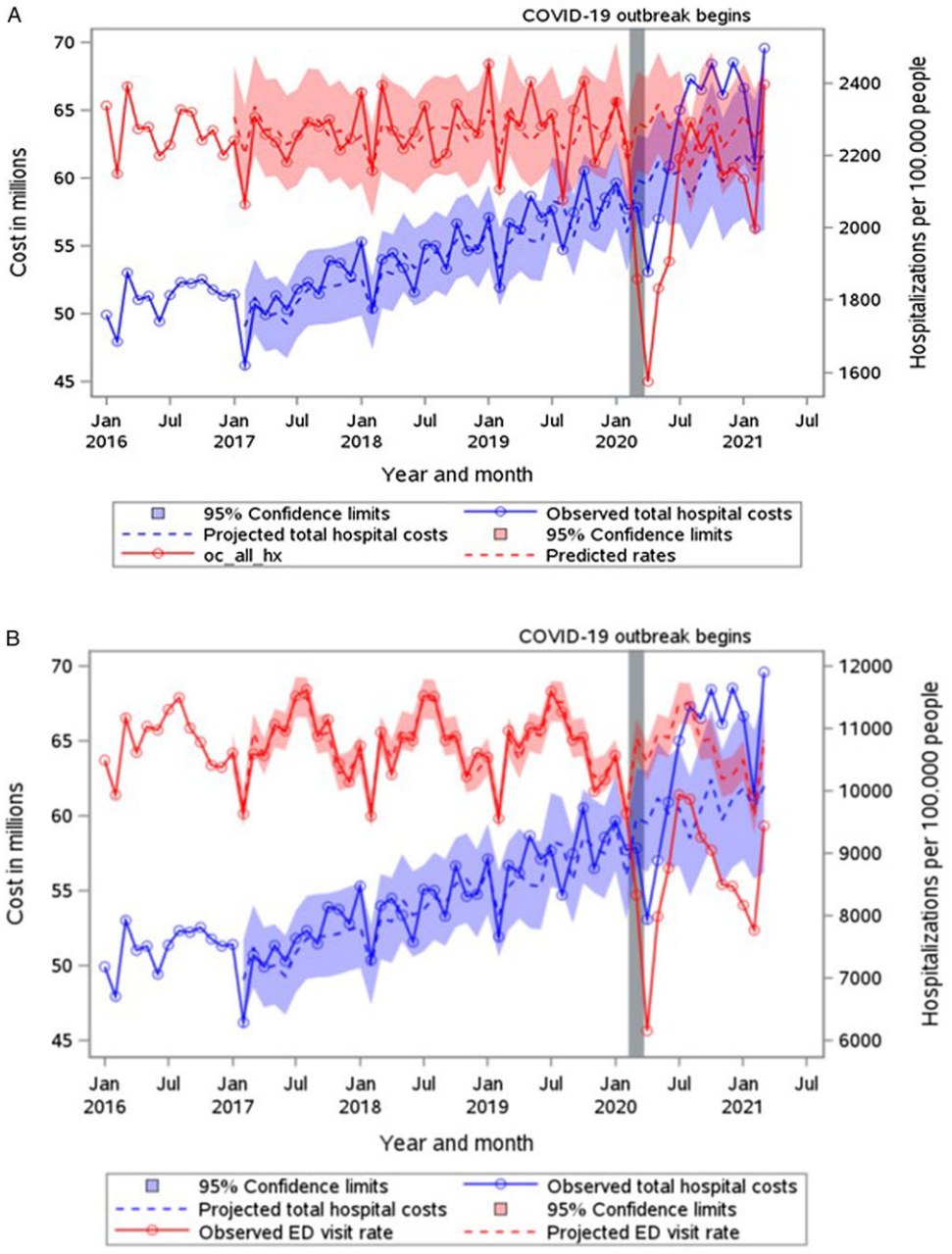

Figure 1: Observed versus projected monthly hospital costs and inpatient visit rates per 100,000 people at-risk in adults with a previous diagnosis of epilepsy: (***a***) hospitalizations; and (***b***) emergency department (ED) visits.

first year of the pandemic. During the first quarter of the pandemic, in adults with epilepsy, we demonstrated an overall reduction in outpatient visits, relevant diagnostic testing, ED visits, and hospitalizations, as well as an important shift to virtual care and a temporary increase in mortality. Both primary care and specialist visits significantly increased by the end of the first year of the pandemic compared to pre-pandemic years. Most of the diagnostic test rates returned to projected by the end of the first year of the pandemic. Although inpatient visit rates returned to projected by the end of the first year of the pandemic, the observed cost of hospitalizations increased above projected since June 2020 and remained elevated by the end of the first year of the pandemic, suggesting a more complex patient population. The increase in the rate of all-cause mortality during the pandemic, as compared to pre-pandemic, was greater during those months with the lower frequency of EEG, MRI, and CT scan rates as compared to months with higher frequency, suggesting that access to those diagnostic tests is likely important for individuals with epilepsy while planning restrictions on non-urgent health services. More virtual care visits were generally associated with increased ED visit rates, but not hospitalization or all-cause mortality rates, suggesting better discretion in referring people to the ED and/or the need for further enhancement of the quality of virtual care delivery.[26]

These results largely support those of existing literature on the topic. Previous studies have shown that during the early phase of the pandemic, there was a temporary reduction in non-emergency healthcare services and a rapid increase in telemedicine.[27] In addition, our findings are consistent with many survey-based studies that reported that individuals with epilepsy and their caregivers perceived that the pandemic posed challenges to access

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healthcare professionals during the beginning of the pandemic.[2,3,7,9,28,29] Our results also support those of recent literature that describes a decrease in ambulatory testing specific for the diagnosis of epilepsy, like EEG, and discontinuation or limited availability of epilepsy surgeries.[4] The diagnosis of epilepsy, in certain cases, may rely on detecting epileptiform abnormalities on EEG or a localizing structural epileptogenic lesion on neuroimaging. Such findings on ancillary testing increase the risk of seizure recurrence and justify the initiation of ASM.[18,30] A delay in diagnosis leads to a delay in treatment with ASMs, which leaves individuals with undiagnosed epilepsy exposed to the risk of future seizures and the life-threatening complications that can result from seizure recurrence (including status epilepticus, brain damage, musculoskeletal injuries, aspiration pneumonia, and rhabdomyolysis).[31–33] There have also been reports of individuals with COVID-19 who presented with seizures, although recent data has shown that the incidence of new epilepsy following COVID-19 infection is low (0.30%).[33] On the other hand, an increased risk of severe complications with COVID-19 has been shown in individuals with epilepsy,[34] which may contribute to increased all-cause mortality. Further, COVID-19 may lower the seizure threshold, leading to provoked seizures in the epilepsy population, similar to other systemic infections. A winter seasonality (a respiratory virus season) of increased mortality rates shown in our study even before the pandemic supports this hypothesis. Finally, drug interactions of ASMs (especially hepatic inducers, such as phenytoin and carbamazepine) with antiviral medications may reduce the efficacy of antiviral medications. Antiviral medications may also lower the seizure threshold.[35,36] All of these factors combined, as well as social and behavioral factors (for example, avoiding visiting the emergency room, despite a medical emergency, due to perceived risk of COVID-19 exposure),[37] could have produced a temporary increase in mortality during *Wave I*, as seen in other publications.[5] The correlation of increased primary care visits with increased mortality in the epilepsy population may be a reflection of more complex/severe patients requiring closer follow-up (supported by increased healthcare costs); the same population is also at risk of seizure breakthrough via lowering of the seizure threshold in the setting of infection,[38] which has the potential to lead to serious complications and death.[35]

Our study has several strengths, such as the ability to analyze data from a sizable population during the entire first year of the pandemic and the use of the ARIMA analytic approach that provided us with projected rates that allowed us to take into account baseline trends prior to the pandemic for more accurate analysis and its monthly analysis design. While an open-cohort sampling strategy does not allow to follow the same group of individuals over the entire time period and estimate cumulative incidences (risks), this approach represents the reality more accurately as patients enter and leave the Ontario health system through immigration/emigration.

Our study, however, has several limitations. This study was not designed to infer causation and was limited to adults only. We lack data on the cause of death; therefore, we cannot completely rule out that a temporary increase in all-cause mortality during the early phase of the pandemic was not directly related to COVID-19 complications as the primary factor. Our study is limited to a part of North America and may not necessarily reflect the impact of the pandemic in other countries with different healthcare systems. While EEG, MRI, and CT are often done as part of initial diagnostic work in individuals with epilepsy, repeat relevant diagnostic testing can still be considered for different populations and clinical scenarios.[39] Thus, access to relevant diagnostic tests should be applicable to individuals with known epilepsy as well. We have not considered in our analyses the duration or severity of epilepsy (for example, we did not distinguish between well-controlled versus refractory epilepsy) and prior comorbidities other than mental health, which should be addressed in future studies. Although our study focused only on the first year since the pandemic, this year was critical for individuals with chronic conditions, given the significant restrictions in health care services in this population and the rapid shift from in-person to virtual care. It is unclear whether longer follow-up would be helpful, given that most services returned to projected at the end of the first year of the pandemic.

Conclusion

In this population-based, retrospective cohort study, in adults with epilepsy, during the first quarter of the pandemic, we demonstrated an overall reduction in all-cause outpatient visits, epilepsy-related diagnostic testing, inpatient visits, and a temporary increase in mortality, as well as a significant shift to virtual care. All-cause primary care and specialist visits significantly increased by the end of the first year of the pandemic compared to pre-pandemic years. Most of the diagnostic tests returned to projected by the end of the first year of the pandemic. Although inpatient visits returned to projected by the end of the first year of the pandemic, the observed hospitalization cost remained above projected by the end of the first year of the pandemic, suggesting a more complex patient population. We demonstrated that access to epilepsy-relevant diagnostic testing (such as EEG, MRI, and CT) is likely important for patients with epilepsy while planning restrictions on non-urgent health services. Virtual care visits associated with increased ED visit rates suggest a better discretion in referring people to the ED and/or the need for further enhancement of the quality of virtual care delivery.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2023.316.

Data availability & sharing statement. In Ontario, the dataset from this study is held securely in coded form at ICES. While data-sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are, therefore, either inaccessible or may require modification.

Author contribution. All coauthors were involved in the following: study conception and design, interpretation of the data, critically revising the manuscript for accuracy and important intellectual content, and final approval of the version to be published.

Tetyana Kendzerska and Andrea Gershon were also involved in obtaining administrative data. Espinoza Vargas Maria and Tetyana Kendzerska were also involved in drafting the manuscript.

Michael Pugliese was additionally involved in data analyses, visual data presentation, and drafting of the manuscript.

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of this material are based on data and information compiled and provided by the Canadian Institute for Health Information (CIHI). The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. The analyses, conclusions, opinions, and statements expressed herein are those of the author and not necessarily those of CIHI. No endorsement by the OHDP, its partners, the Province of Ontario, and ICES, CIHI, or the Ontario MOH and/or MLTC is intended or should be inferred.

Competing interests. All authors declare they have no potential conflict of interest. Tetyana Kendzerska and Andrea Gershon are supported by the PSI (Physicians' Services Incorporated) foundation. Teresa To is supported by the Canadian Institutes of Health Research, Tier 1 Canada Research Chair in Asthma. Claire Kendall is supported by a Faculty of Medicine Clinical Chair Award. The funding sponsors had no role in the study design, data collection and analysis, or preparation of the manuscript. No other relationships or activities could appear to have influenced the submitted work.

Guarantor statement. Together, Tetyana Kendzerska and Michael Pugliese had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. They affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; any discrepancies from the study as planned have been explained. All authors had full access to statistical reports and tables.

Ethical statement. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ICES is a prescribed entity under Ontario's Personal Health Information Protection Act (PHIPA). Section 45 of PHIPA authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation, or monitoring of the allocation of resources to or planning for all or part of the health system. Projects that use data collected by ICES under section 45 of PHIPA, and use no other data, are exempt from REB review. The use of the data in this project is authorized under section 45 and approved by ICES' Privacy and Legal Office.

All methods were carried out in accordance with relevant guidelines and regulations. The study datasets were linked using unique encoded identifiers and analyzed in the secure environment at ICES following Ontario privacy standards.

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