Effect of Carbon Monoxide Poisoning on Epilepsy Development: A Nationwide Population-Based Cohort Study

Yu-Hsiang Meng, MD; Ming-Shun Hsieh, MD, PhD; Yu-Chi Chi, BS; Chorng-Kuang How, MD, PhD; Pau-Chung Chen, MD, PhD; Chia-Ming Chang, MD*

*Corresponding Author. E-mail: cmchang5@vghtpe.gov.tw.

Study objective: Carbon monoxide (CO) poisoning causes central nervous system toxicity resulting in delayed neurologic sequelae. This study aims to evaluate the risk of epilepsy in patients with a history of CO intoxication.

Methods: We conducted a retrospective population-based cohort study using the Taiwan National Health Insurance Research Database and enrolled patients with and without CO poisoning matched for age, sex, and index year in a 1:5 ratio, between 2000 and 2010. Multivariable survival models were used to assess the risk of epilepsy. The primary outcome was newly developed epilepsy after the index date. All patients were followed until a new diagnosis of epilepsy, death, or December 31, 2013. Stratification analyses by age and sex were also conducted.

Results: This study included 8,264 patients with CO poisoning and 41,320 without. Patients with a history of CO poisoning were strongly associated with subsequent epilepsy (adjusted hazard ratio [HR] 8.40; 95% confidence interval [CI], 6.48 to 10.88). In the age-stratified analysis, intoxicated patients aged 20 to 39 years had the highest HR (adjusted HR 11.06; 95% CI, 7.17 to 17.08). In the sex-stratified analysis, adjusted HRs for male and female patients were 8.00 (95% CI, 5.86 to 10.92) and 9.53 (95% CI, 5.95 to 15.26), respectively.

Conclusion: Patients with CO poisoning were associated with an increased risk of developing epilepsy compared with those without CO poisoning. This association was more prominent in the young population. [Ann Emerg Med. 2023;82:145-151.]

Please see page 146 for the Editor's Capsule Summary of this article.

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2022.11.021

INTRODUCTION

Carbon monoxide (CO) is a common cause of poisoning encountered in the emergency department that gives rise to a worldwide cumulative incidence of 137 per million people and a mortality of 4.6 per million person-years.[1,2] The affinity of CO for hemoglobin is 250 times higher that of oxygen, thereby, interfering with cellular respiration and causing damage to major oxygen-consuming organs.[2,3] Several hypotheses have also been proposed to explain the injury involved in CO poisoning, including myocardial stunning because of mitochondrial dysfunction and synergistic effects of inflammation apart from ischemia.[2,4-11]

Delayed neurologic sequelae refer to neurologic, cognitive, and psychiatric impairments after CO poisoning; the reported onset and recovery rates vary among studies.[6,10,12] A few brain regions that are correlated with seizures in neonatal hypoxic ischemic encephalopathy have been identified in CO-intoxicated patients.[12,13] These include basal ganglia and hippocampus, both of which are known for seizure initiation.[14,15]

We examined the relationship between CO poisoning and subsequent epilepsy, given that the frequently involved brain locations coincide with those mentioned. No study, to our knowledge, has specifically assessed the relationship between them. We performed a nationwide population-based study to investigate this association.

METHODS

Study Design and Data Source

This retrospective cohort study was conducted using the National Health Insurance Research Database, deidentified claims data derived from Taiwan's single-payer system that

Editor's Capsule Summary

What is already known on this topic

Carbon monoxide (CO) is a central nervous system toxin, but the impact of serious exposure on triggering epilepsy is not clear.

What question this study addressed

Does epilepsy develop often following CO poisoning?

What this study adds to our knowledge

Using a population-based retrospective cohort, patients admitted after CO poisoning had higher rates of subsequent epilepsy (adjusted hazard ratio [HR] 8.40; 95% confidence interval [CI] 6.48 to 10.88), seen in men and women (8.00, 95% CI 5.86 to 10.92 and 9.53, 95% CI 5.95 to 15.26, respectively).

How this is relevant to clinical practice

If confirmed, educating patients with CO exposure resulting in hospitalization that they have increased risk of developing epilepsy will prepare each for this possibility.

provides mandatory universal coverage. It was approved by the Institutional Review Board of China Medical University (CMUH104-REC2-115) and exempted from the informed consent of participants. This study is reported according to the Reporting of Studies Conducted Using Observational Routinely Collected Health Data statement.[16]

Selection of Participants

We included patients aged 20 years and above admitted to all hospitals in Taiwan from January 1, 2000, to December 31, 2010, identified from the inpatient claims during this timeframe, and matched each patient to five patients without CO poisoning randomly on age (divided into multiple 5-year strata), sex, and index years. The admission date was regarded as the index date for cohort entry. The earliest admission date was used if the patient without CO poisoning had multiple hospitalizations within the matched year. We excluded patients aged above 100 years of age, with epilepsy before the index date, or with missing information on either sex or age.

Exposure, Covariates, and Outcome

The primary exposure was CO poisoning, which was identified by the coded discharge diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 986) of the hospitalized patients in the claims data. We included the common comorbidities to reflect the patient's baseline health status in the analysis. These covariates were hypertension (ICD-9-CM codes 401-405), hyperlipidemia (272), diabetes mellitus (250, 357.2, 362.01, 362.02, 366.41), coronary artery disease (411-414), heart failure (428), stroke (430-438), chronic kidney disease (581-588, 403-404, 285.21, 250.4), and chronic obstructive pulmonary disease (490-492, 494, 496). The primary outcome of this study was the development of epilepsy during the follow-up period, defined as ICD-9-CM code 345 (except for 345.6) (Table E1, available at http://www.annemergmed.com).

Analysis

We used Cox proportional hazards regression and adjusted for age, sex, history of CO poisoning, and the above comorbidities to compare differences in developing epilepsy for each variable. The incidence rates of subsequent epilepsy in the cohorts with and without CO poisoning were estimated using the Kaplan-Meier method and tested by the log-rank test. Patients were followed up until the earliest date of either new diagnosis of epilepsy, death, or December 31, 2013. Stratification analyses of the entire population by sex and age to estimate the hazards of epilepsy in CO-poisoned patients were further performed. In the sex-stratified analysis, age and comorbidities were adjusted in the models, and in the age-stratified analysis, age, sex, and comorbidities were included. Statistical analyses were conducted by SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Two-sided *P* values less than .05 were considered statistically significant.

RESULTS

Our study included 8,264 patients with CO poisoning and 41,320 without CO poisoning (Figure 1). The mean age of the study population was 39 years, with 58% (28,746/49,584) and 36% (17,886/49,584) in the 20 to 39 and 40 to 64 age groups, respectively. Men accounted for 52% (25,932/49,584) of these subjects. The exposed group had greater proportions of comorbidities than the control group (Table 1). Hypertension, diabetes, coronary artery disease, and stroke were the most common comorbidities. The mean follow-up intervals were 6.5 years in the exposed cohort and 7.2 years in the unexposed. Figure 2 depicts a greater cumulative incidence of epilepsy for the CO poisoning cohort in the 13-year follow-up period.

All the covariates were associated with an increased risk of epilepsy in the univariate analyses (Table 2). After adjustment, CO-poisoned patients exhibited a greater hazard

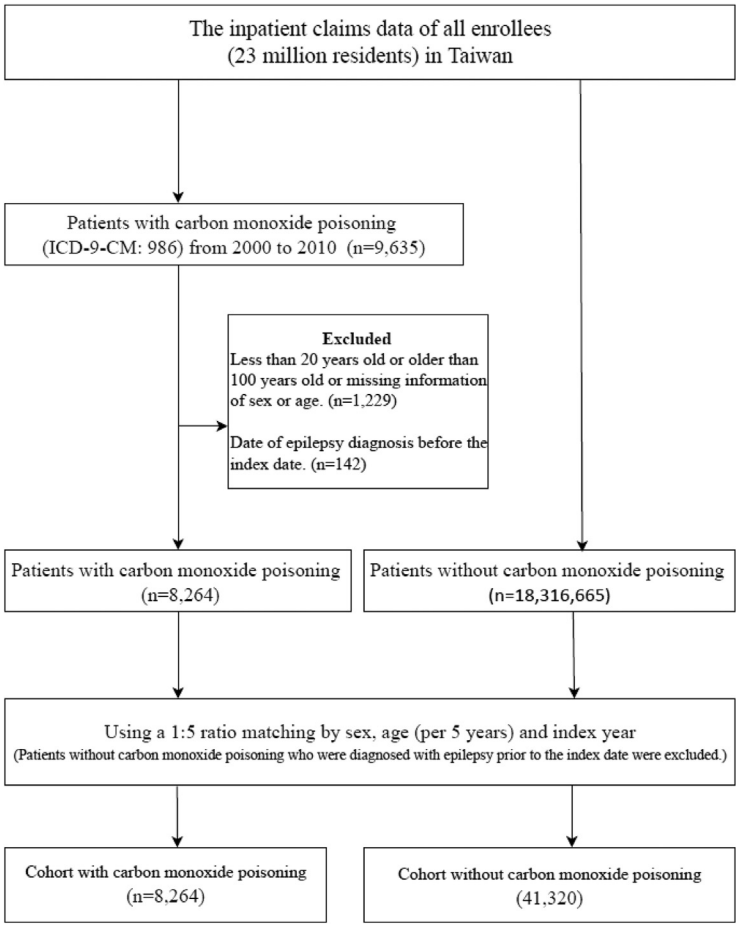

Figure 1. Flowchart of the patient selection process in the exposed (CO-poisoned patients) and unexposed (non-CO-poisoned patients) cohorts.

of subsequent epilepsy (adjusted HR 8.40; 95% confidence interval [CI], 6.48 to 10.88; unadjusted HR 8.79, 95% CI, 6.80 to 11.36) (Table 2). Compared with their female counterparts, the risk of epilepsy was higher in male patients (adjusted HR 1.98; 95% CI, 1.51 to 2.60; unadjusted HR 2.07; 95% CI, 1.58 to 2.71). The adjusted hazard ratio (HR) for epilepsy in the elder and middle-aged patients were 2.77 (95% CI, 1.77 to 4.32) and 1.67 (95% CI, 1.27 to 2.21), respectively, compared with the 20 to 39 age group. Hypertension, stroke, and chronic kidney disease remained associated with subsequent epilepsy in multivariate analysis (hypertension: adjusted HR 1.80; 95% CI, 1.09 to 2.98; stroke: adjusted HR 2.49; 95% CI, 1.48 to 4.21; chronic kidney disease: adjusted HR 2.67; 95% CI, 1.51 to 4.71).

The results of stratification analyses are listed in Table 3. When stratified by sex, both men and women with a history of CO poisoning displayed higher incidence rates and HRs for epilepsy (men: adjusted HR 8.00; 95% CI, 5.86 to 10.92; women: adjusted HR 9.53; 95% CI, 5.95 to 15.26). In the age-specific analysis, CO poisoning was associated with epilepsy in all age groups. Though the incidence rates of epilepsy rose with age, the 20 to 39 age group had the greatest HR (adjusted HR 11.06; 95% CI, 7.17 to 17.08), followed by the 40-64 and 65-100 age groups (aged 40-64: adjusted HR 8.53, 95% CI [5.76-12.63]; aged 65 to 100 years: adjusted HR 4.16; 95% CI, 2.15 to 8.07).

LIMITATIONS

One limitation of the database we used was the inability to obtain some important risk factors that might confound the results, such as socioeconomic status, smoking, substance use, alcohol consumption, and suicide attempts.[17] Also, depression could be a confounder in the relationship between CO poisoning and epilepsy. For one, depressive patients are more likely to attempt suicide, which may result in CO poisoning. For another, an association between depression and epilepsy was identified in a cohort study.[18] Nonetheless, given that depression is underdiagnosed and that only severe cases would be hospitalized, its diagnosis is not well documented in the

Table 1. Demographic characteristics and baseline comorbidities in patients with and without carbon monoxide poisoning diagnosis.

	Carbon monoxide poisoning			
	No (n=41320)		Yes (n=8264)	
Variables	**n**	**%**	**n**	**%**
Sex				
Female	19710	47.7	3942	47.7
Male	21610	52.3	4322	52.3
Age group, y				
20-39	23955	58.0	4791	58.0
40-64	14905	36.1	2981	36.1
65-100	2460	6.0	492	6.0
Mean (SD)	40 (13.9)		40 (13.8)	
Baseline comorbidity				
Hypertension	1269	3.1	478	5.8
Hyperlipidemia	465	1.1	224	2.7
Diabetes mellitus	803	1.9	336	4.1
Coronary artery disease	565	1.4	241	2.9
Congestive heart failure	177	0.4	68	0.8
Stroke	486	1.2	232	2.8
Chronic kidney disease	318	0.8	149	1.8
COPD	344	0.8	156	1.9

COPD, chronic obstructive pulmonary disease.

inpatient claims.[19] Therefore, not including depression in the model is considered one of the limitations. In addition, factors related to disease severity, including initial carboxyhemoglobin levels and initial intubation status, were unavailable. We did not assess the association between hyperbaric oxygen therapy and epilepsy in CO-poisoned patients to avoid biased results.[9] Moreover, because we only used inpatient claims, patients treated and released after an ED visit without subsequent inpatient admissions were not included. Consequently, extrapolating our findings to those with CO poisoning not requiring hospitalization is potentially biased. Lastly, we did not locate central nervous lesions because of no imaging exams available for analysis. Hence, we can only infer the possible mechanism from previous epidemiological findings.

DISCUSSION

In this population-based cohort, we demonstrated that CO-intoxicated patients were more likely to develop epilepsy after CO exposure. The adjusted HR of patients with a history of CO poisoning aged between 20 and 39 years was approximately three times higher than that of patients aged 65 years and over. Male and female patients

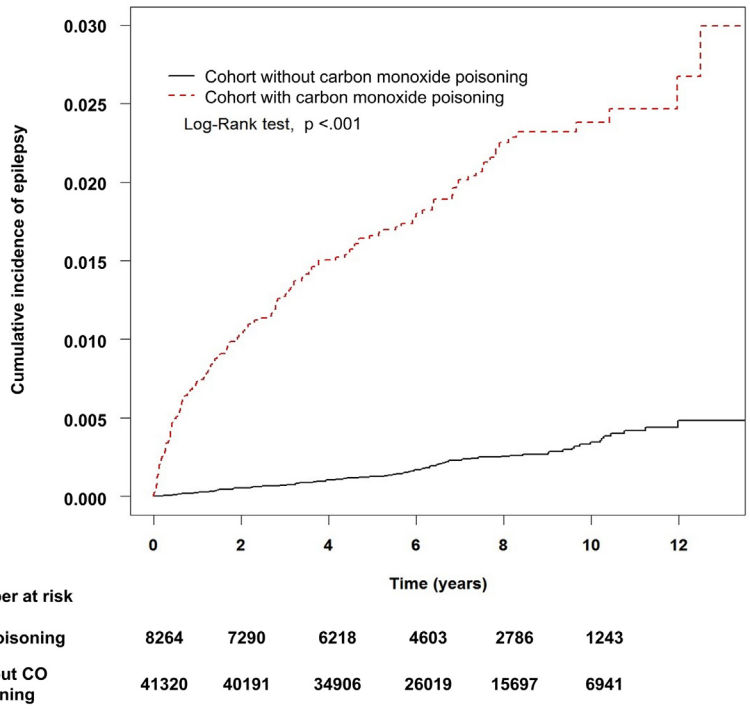

Figure 2. Cumulative incidence of epilepsy between the two cohorts during the follow-up period.

Table 2. Cox model measured HR and 95% CIs of epilepsy associated with carbon monoxide poisoning, sex, age, and comorbidities.

		Crude		Adjusted	
Characteristics	**Epilepsy no. (n=247)**	**HR**	**(95% CI)**	**HR**	**(95% CI)**
Carbon monoxide poisoning					
No	95	1.00	reference	1.00	reference
Yes	152	8.79	(6.80-11.36)	8.40	(6.48-10.88)
Sex					
Female	77	1.00	reference	1.00	reference
Male	170	2.07	(1.58-2.71)	1.98	(1.51-2.60)
Age group, ys					
20-39	99	1.00	reference	1.00	reference
40-64	109	1.82	(1.39-2.40)	1.67	(1.27-2.21)
65-100	39	4.70	(3.24-6.81)	2.77	(1.77-4.32)
Baseline comorbidity (reference=non)					
Hypertension	41	7.08	(5.06-9.91)	1.80	(1.09-2.98)
Hyperlipidemia	13	4.76	(2.72-8.32)	0.98	(0.52-1.83)
Diabetes mellitus	24	6.00	(3.93-9.15)	1.31	(0.79-2.19)
Coronary artery disease	15	4.96	(2.94-8.36)	0.72	(0.38-1.34)
Congestive heart failure	4	4.94	(1.84-13.28)	0.80	(0.28-2.34)
Stroke	26	10.81	(7.19-16.25)	2.49	(1.48-4.21)
Chronic kidney disease	17	10.78	(6.58-17.65)	2.67	(1.51-4.71)
COPD	12	6.98	(3.91-12.48)	1.59	(0.84-3.01)

Adjusted HR: adjusted for carbon monoxide poisoning, age, sex, and comorbidities in Cox proportional hazards regression.

shared similar risks of developing epilepsy after CO poisoning.

The pathophysiology of delayed neurologic sequelae in CO poisoning remains to be elucidated. It generally occurs within six weeks after the incident with various presentations ranging from headache, anxiety, and memory impairment, to inability to ambulate.[2] A popular explanation is that the sequelae arise from hypoxic brain insults, resulting in the accumulation of reactive oxygen species that destroy neurons.[20] Additionally, CO also induces inflammatory responses that eventually cause harm to the nervous system.[5] Moreover, a new mechanism involving catecholamine transmission has been proposed.[21] In all, diverse pathways are implicated in its toxic effect, which warrants further investigation.

Table 3. Incidence rates, hazard ratios, and confidence intervals of epilepsy for patients with versus without carbon monoxide poisoning in the stratification of sex and age.

	Carbon monoxide poisoning							
	No (n=41320)			**Yes (n=8264)**			**Crude HR**	**Adjusted HR**
Variables	**Event**	**Person-years**	**IR**	**Event**	**Person-years**	**IR**	**(95%CI)**	**(95%CI)**
Sex								
Female	27	143786	0.19	50	26999	1.85	9.84(6.16-15.71)	9.53(5.95-15.26)
Male	68	154261	0.44	102	26878	3.79	8.53(6.27-11.59)	8.00(5.86-10.92)
Age group, y								
20-39	30	175798	0.17	69	33371	2.07	12.07(7.86-18.52)	11.06(7.17-17.08)
40-64	41	107401	0.38	68	18360	3.70	9.63(6.53-14.19)	8.53(5.76-12.63)
65-100y	24	14848	1.62	15	2147	6.99	4.36(2.29-8.32)	4.16(2.15-8.07)

IR, incidence rate, per 1,000 person-years;
Adjusted HR: adjusted for age, sex, and comorbidities in Cox proportional hazards regression.

Though some acutely CO-intoxicated patients presenting with seizures have been reported, few studies have examined the relationship between CO poisoning and epilepsy.[22-25] We identified a significantly larger proportion of patients who developed epilepsy within a decade after CO poisoning. Basal ganglia are frequently involved in CO poisoning and are among the brain regions responsible for seizure initiation.[12,26-29] A study indicated that basal ganglia volume decreased during the six months after CO poisoning.[29] Several studies found in children with epilepsy after neonatal encephalopathy, usually attributed to asphyxia, that most of them had basal ganglia injury on magnetic resonance imaging.[13,30,31] The same phenomenon is described for the hippocampus, a part of the limbic system related to temporal lobe epilepsy.[14,15,26,28,32] It could potentially explain why some CO-poisoned patients suffer psychiatric sequelae such as depression and anxiety as well.[33] Still, other brain lesions, including generalized white matter demyelination, can also account for subsequent seizures.[12,26]

The risks of epilepsy after CO poisoning in young and middle-aged patients increased considerably compared with older subjects. Several factors may contribute to the age-stratified differences in HRs. First, as the incidence of epilepsy peaks in childhood and the elderly years, it was likely that senior epileptic patients who had CO poisoning afterward were excluded from the analysis.[34,35] Namely, the effect of CO intoxication on epilepsy might be attenuated by age, which itself is an independent risk factor.[36] Furthermore, the aged population might not survive long enough to develop CO poisoning-induced epilepsy because of shorter life expectancy. Still another explanation is that a larger proportion of the younger patients could be intoxicated by intentional exposure that led to more severe sequelae. Collectively, the risks of subsequent epilepsy remained significantly high in all age groups despite different intensities.

We believe this is the first research to delineate the relationship between CO poisoning and subsequent epilepsy. We used a population-based design that provides adequate power rendered by the sample size. Finally, we found that younger patients are at higher risk of developing epilepsy after CO poisoning. This may ultimately assist risk stratification in intoxicated patients.

In conclusion, CO poisoning is a significant risk factor for subsequent epilepsy in a large nationwide cohort. It influences the neurologic outcome in all age groups with the highest HR in patients aged 20 to 39 years. Future research may identify the relationship between brain lesion locations and epilepsy and investigate the mechanism of epilepsy in CO-poisoned patients.

We appreciate Yen-Ting Kuo's assistance in proofreading the manuscript.

Supervising editor: Richard C. Dart, MD, PhD. Specific detailed information about a possible conflict of interest for individual editors is available at https://www.annemergmed.com/editors.

Author affiliations: From the Department of Emergency Medicine (Meng, Chi, Chang, How), Taipei Veterans General Hospital, Taipei, Taiwan; Department of Emergency Medicine (Meng, Hsieh, Chang, How), College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan; the Institute of Environmental and Occupational Health Sciences (Chang, Chen), College of Public Health, National Taiwan University, Taipei, Taiwan; the Institute of Emergency and Critical Care Medicine (How), College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan; Department of Nursing (Chi), Taipei Veterans General Hospital, Taipei, Taiwan; Department of Emergency Medicine (Hsie), Taipei Veterans General Hospital Taoyuan Branch, Taoyuan, Taiwan.

Author contributions: CMC and CKH conceived the study. CMC and MSH designed the study, and MSH conducted statistical analysis. YHM and CKH validated the results and provided statistical advice on the design. YHM drafted the manuscript, and all authors contributed substantially to its revision. CMC takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors deny having such relationships.

Publication dates: Received for publication May 10, 2022. Revisions received September 16, 2022; October 17, 2022, and November 10, 2022. Accepted for publication November 22, 2022.

Meetings: An abstract was accepted for poster presentation at the American College of Emergency Physicians (ACEP) 2017 *Scientific Assembly* in Washington D.C., October 29 to November 1, 2017.

REFERENCES

1. Mattiuzzi C, Lippi G. Worldwide epidemiology of carbon monoxide poisoning. *Hum Exp Toxicol*. 2020;39:387-392.
2. Rose JJ, Wang L, Xu Q, et al. Carbon monoxide poisoning: pathogenesis, management, and future directions of therapy. *Am J Respir Crit Care Med*. 2017;195:596-606.
3. Alonso JR, Cardellach F, López S, et al. Carbon monoxide specifically inhibits cytochrome c oxidase of human mitochondrial respiratory chain. *Pharmacol Toxicol*. 2003;93:142-146.

4. Tritapepe L, Macchiarelli G, Rocco M, et al. Functional and ultrastructural evidence of myocardial stunning after acute carbon monoxide poisoning. *Crit Care Med*. 1998;26:797-801.
5. Thom SR, Bhopale VM, Fisher D, et al. Delayed neuropathology after carbon monoxide poisoning is immune-mediated. *Proc Natl Acad Sci U S A*. 2004;101:13660-13665.
6. Weaver LK, Hopkins RO, Chan KJ, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. *N Engl J Med*. 2002;347:1057-1067.
7. Scheinkestel CD, Bailey M, Myles PS, et al. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial. *Med J Aust*. 1999;170:203-210.
8. Buckley NA, Juurlink DN, Isbister G, et al. Hyperbaric oxygen for carbon monoxide poisoning. *Cochrane Database Syst Rev*. 2011:CD002041.
9. Weaver LK, Valentine KJ, Hopkins RO. Carbon monoxide poisoning: risk factors for cognitive sequelae and the role of hyperbaric oxygen. *Am J Respir Crit Care Med*. 2007;176:491-497.
10. Annane D, Chadda K, Gajdos P, et al. Hyperbaric oxygen therapy for acute domestic carbon monoxide poisoning: two randomized controlled trials. *Intensive Care Med*. 2011;37:486-492.
11. Raphael J-C, Elkharrat D, Jars-Guincestre M-C, et al. Trial of normobaric and hyperbaric oxygen for acute carbon monoxide intoxication. *Lancet*. 1989;334:414-419.
12. Hsiao CL, Kuo HC, Huang CC. Delayed encephalopathy after carbon monoxide intoxication–long-term prognosis and correlation of clinical manifestations and neuroimages. *Acta Neurol Taiwan*. 2004;13:64-70.
13. Lin YK, Hwang-Bo S, Seo YM, et al. Clinical seizures and unfavorable brain MRI patterns in neonates with hypoxic ischemic encephalopathy. *Medicine (Baltimore)*. 2021;100:e25118.
14. Furman M. Seizure initiation and propagation in the pilocarpine rat model of temporal lobe epilepsy. *J Neurosci*. 2013;33:16409-16411.
15. Tatum WO 4th. Mesial temporal lobe epilepsy. *J Clin Neurophysiol*. 2012;29:356-365.
16. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med*. 2015;12:e1001885.
17. Dworetzky BA, Bromfield EB, Townsend MK, et al. A prospective study of smoking, caffeine, and alcohol as risk factors for seizures or epilepsy in young adult women: data from the Nurses' Health Study II. *Epilepsia*. 2010;51:198-205.
18. Josephson CB, Lowerison M, Vallerand I, et al. Association of depression and treated depression with epilepsy and seizure outcomes: a multicohort analysis. *JAMA Neurol*. 2017;74:533-539.
19. Williams SZ, Chung GS, Muennig PA. Undiagnosed depression: a community diagnosis. *SSM Popul Health*. 2017;3:633-638.
20. Cronje FJ, Carraway MS, Freiberger JJ, et al. Carbon monoxide actuates O(2)-limited heme degradation in the rat brain. *Free Radic Biol Med*. 2004;37:1802-1812.
21. Oh S, Choi SC. Acute carbon monoxide poisoning and delayed neurological sequelae: a potential neuroprotection bundle therapy. *Neural Regen Res*. 2015;10:36-38.
22. Mori T, Nagai K. Carbon-monoxide poisoning presenting as an afebrile seizure. *Pediatr Neurol*. 2000;22:330-331.
23. Marziali S, Di Giuliano F, Picchi E, et al. Non-convulsive status epilepticus in a patient with carbon-monoxide poisoning treated with hyperbaric oxygen therapy. *Neuroradiol J*. 2016;29:431-435.
24. Durnin C. Carbon monoxide poisoning presenting with focal epileptiform seizures. *Lancet*. 1987;1:1319.
25. Herman LY. Carbon monoxide poisoning presenting as an isolated seizure. *J Emerg Med*. 1998;16:429-432.
26. Lo CP, Chen SY, Lee KW, et al. Brain injury after acute carbon monoxide poisoning: early and late complications. *AJR Am J Roentgenol*. 2007;189:W205-211.
27. Kim DM, Lee IH, Park JY, et al. Acute carbon monoxide poisoning: MR imaging findings with clinical correlation. *Diagn Interv Imaging*. 2017;98:299-306.
28. O'Donnell P, Buxton PJ, Pitkin A, et al. The magnetic resonance imaging appearances of the brain in acute carbon monoxide poisoning. *Clin Radiol*. 2000;55:273-280.
29. Pulsipher DT, Hopkins RO, Weaver LK. Basal ganglia volumes following CO poisoning: a prospective longitudinal study. *Undersea Hyperb Med*. 2006;33:245-256.
30. Glass HC, Hong KJ, Rogers EE, et al. Risk factors for epilepsy in children with neonatal encephalopathy. *Pediatr Res*. 2011;70:535-540.
31. Xu Q, Chau V, Sanguansermsri C, et al. Pattern of brain injury predicts long-term epilepsy following neonatal encephalopathy. *J Child Neurol*. 2019;34:199-209.
32. Gale SD, Hopkins RO, Weaver LK, et al. MRI, quantitative MRI, SPECT, and neuropsychological findings following carbon monoxide poisoning. *Brain Inj*. 1999;13:229-243.
33. Jasper BW, Hopkins RO, Duker HV, et al. Affective outcome following carbon monoxide poisoning: a prospective longitudinal study. *Cogn Behav Neurol*. 2005;18:127-134.
34. Cross JH. Epilepsy in the WHO European region: fostering epilepsy care in Europe. *Epilepsia*. 2011;52:187-188.
35. Beghi E, Giussani G, Nichols E, et al. Global, regional, and national burden of epilepsy, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurol*. 2019;18:357-375.
36. Hauser WA. Seizure disorders: the changes with age. *Epilepsia*. 1992;33(Suppl 4):S6-14.