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Patients With Carbon Monoxide Poisoning and Subsequent Dementia

A Population-Based Cohort Study

Ching-Yuan Lai, MD, Yu-Wei Huang, MD, Chun-Hung Tseng, MD, Cheng-Li Lin, MSc, Fung-Chang Sung, PhD, MPH, and Chia-Hung Kao, MD

Abstract: The present study evaluated the dementia risk after carbon monoxide poisoning (CO poisoning).

Using the National Health Insurance Research Database of Taiwan, a total of 9041 adults newly diagnosed with CO poisoning from 2000 to 2011 were identified as the CO poisoning cohort. Four-fold (N=36,160) of non-CO poisoning insured people were randomly selected as controls, frequency-matched by age, sex, and hospitalization year. Incidence and hazard ratio (HR) of dementia were measured by the end 2011.

The dementia incidence was 1.6-fold higher in the CO exposed cohort than in the non-exposed cohort (15.2 vs 9.76 per 10,000 person-years; n = 62 vs 174) with an adjusted HR of 1.50 (95% CI = 1.11–2.04). The sex- and age-specific hazards were higher in male patients (adjusted HR = 1.74, 95% CI = 1.20–2.54), and those aged <=49 years (adjusted HR = 2.62, 95% CI = 1.38–4.99). CO exposed patients with 7-day or longer hospital stay had an adjusted HR of 2.18 (95%

CI = 1.42, 3.36). The CO poisoning patients on hyperbaric oxygen (HBO2) therapy had an adjusted HR of 1.80 (95% CI = 0.96–3.37).

This study suggests that CO poisoning may have association with the risk of developing dementia, which is significant for severe cases. The effectiveness of HBO2 therapy remains unclear in preventing dementia. Patients with CO poisoning are more prevalent with depression.

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Abbreviations: CI = confidence interval, CO = carbon monoxide, HR = hazard ratio.

INTRODUCTION

The Global Burden of Disease Study has ranked dementia the 5th common chronic disease.¹ The Institute for Health Metrics and Evaluation (IHME) has estimated that there was a 112.8% increase in the disability-adjusted life-year cost for dementia in 2010 compared that in 1990. It was anticipated that the cost would increase further for more than 80% by 2030.¹ The Alzheimer Disease International (ADI) Report has also estimated that approximately 44.4 million people were affected by dementia in 2010, and this number would increase to 75.6 million by 2030 and 135.5 million by 2050. In 2010, the Global total social costs for dementia were estimated to be US \$ 604 billion, corresponding to 1.0% of the global GDP.^{2–4} Dementia is more important than Alzheimer disease alone in causing a huge economic burden.^{5–7} Dementia is the brain disease characterized by impaired memory and loss of thinking and reasoning, which severely affect the patient's daily functioning.⁸

The risk of developing dementia has been associated with several conditions, including alcohol abuse (alcohol-related dementia), chronic traumatic encephalopathy, drug side effects, depression, and other central nervous system disorders.^{9–15} Establishing a link between associated risk factors and dementia may provide appropriate means of treatment and counseling, thereby reducing the risk of dementia and costs of treatment.

Carbon monoxide (CO) poisoning is a common and important cause of death among populations, including populations in the United States, and England and Wales.¹⁶ Approximately 15,000 unintentional nonfire related episodes of CO poisoning have been reported annually in England and Wales, leading to 50,000 emergency department visits and 500 deaths.¹⁷ The memory difficulty and confusion are initial neurological symptoms of acute CO poisoning in addition to headache, weakness, dizziness, nausea, and vomiting.¹⁵ Furthermore, unconsciousness, respiratory arrest, and even death could develop for the CO poisoning victims.¹⁷ Previous studies have reported that up to 30% of patients result in the sequelae of neurologic complications after the poisoning.^{18,19}

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From the Department of Emergency Medicine, China Medical University Hospital, Taichung (C-YL); Department of Critical Care Medicine, E-DA Hospital, Department of Community Medicine, E-DA Hospital and I-Shou University Kaohsiung (Y-WH), Department of Neurology, China Medical University Hospital (C-HT), Management Office for Health Data China Medical University Hospital (C-LL), College of Medicine (C-LL), Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine (C-HK), Department of Health Services Administration (F-CS); and Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan (C-HK).

Correspondence: Chia-Hung Kao, Graduate Institute of Clinical Medicine Science, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 40447, Taiwan (e-mail: d10040@mail.cmuh.org.tw).

C-Y L and Y-W H contributed equally to this work.

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Intellectual function impairments, short-term memory loss, dementia, amnesia, psychosis, irritability, dysfunctional gait, speech disorders, Parkinson disease-like syndrome, cortical blindness, and depression are among the poisoning sequelae.^{20,21} Victims of CO poisoning may suffer from brain hypoxia, inflammation, and subsequent injuries.²² Patients with ischemia-reperfusion injury exposing to high oxygen may aggravate the oxidative damage after recovery from CO poisoning.^{23,24} Encephalopathy and other neuropsychiatric disorders are other sequelae in victims. It remains unclear whether such abnormalities increase the risk of dementia.^{25–28} In an earlier Japanese study, Mimura et al²⁸ found considerable sequelae in CO poisoning patients after follow-up for 33 years. No large-scale long-term follow-up study has ever evaluated this relationship. The present study was conducted to evaluate whether patients with CO poisoning are at an elevated risk of developing dementia.

METHODS

Data Source

We conducted this study using the National Health Insurance Research Database obtained from the National Health Insurance program of Taiwan, which was initiated in 1995 to provide comprehensive medical care to the general population. This insurance system has covered approximately 99% of the entire 23 million population of Taiwan (<http://www.nhi.gov.tw/english/index.aspx>). The Taiwan National Health Research Institutes is responsible to manage the claims data and secure the confidentiality of the insured individuals according to the directives of the insurance authority. The diagnostic codes were determined based on the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). To assure the accuracy of diagnosis, the Bureau of National Health Insurance sifted and validated medical records review that including clinical manifestations, physical examination, and laboratory and image studies. Because patient identifications were scrambled into surrogate numbers to protect patient privacy, no patients consent was required for this study, which has been approved by the Research Ethics Committee at China Medical University and Hospital (CMUH104-REC2-115).

Study Population

We identified 9041 new patients diagnosed with CO poisoning (ICD-9 code 986) from the inpatient claims data in 2000 to 2011. The date of the first hospitalization for CO poisoning was designated as the index date. Patients with a history of dementia (ICD-9-CM 290, 294.1, and 331.0–331.2) before the index date or those with incomplete age or sex information were excluded from the study. From inpatient individuals without the history of CO poisoning and/or dementia, we randomly selected 36,160 persons as the non-CO poisoning cohort frequency-matched against CO poisoning patients by age (every 5 years), sex, and the year of hospitalization.

Outcome and Comorbidities

Individuals in both study cohorts were followed up until the date of diagnosis of dementia, loss to follow-up, death, withdrawal from the insurance program, or the end of 2011, whichever occurred earlier. We identified the baseline information on comorbidity and health care utilizations as covariates including diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM code 401–405), head injury (ICD-9-CM code 310.2, 800,

801, 803, 804, 850, 851, 853, and 854), depression (ICD-9-CM code 296.2, 296.3, 296.82, 300.4, and 311), cerebrovascular diseases (ICD-9-CM code 430–438), chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 490–492, 494, and 496), cognitive impairment (ICD-9-CM codes 31.83, 438.0, 310.8, and 294.9), urinary tract infection (ICD-9-CM code 599.0), and pneumonia (ICD-9-CM codes 480–487).²⁹

Statistical Analysis

The Chi-square test was used to examine the differences in the categorical demographic variables and comorbidities between CO poisoning and non-CO poisoning cohorts, whereas the Student's *t*-test was used to examine mean ages between the 2 cohorts. Comorbidities included diabetes, hypertension, head injury, depression, stroke, COPD, cognitive impairment, urinary tract infection, and pneumonia. The overall sex, age, and comorbidity specific incidence rates (per 10,000 person-years) were calculated for each cohort. The Kaplan–Meier method plotted cumulative incidences of dementia for both CO poisoning and non-CO poisoning cohorts and the proportions were examined using the log-rank test. Univariate and multivariate Cox proportional hazards regression analyses were performed to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of dementia for patients of the CO poisoning, compared with the non-CO poisoning subjects. The multivariable Cox model, in addition to age and gender, included comorbidities of head injury, depression, COPD, and cognitive impairment, which were significantly different in distributions at the baseline between the 2 cohorts. We further evaluated whether sex, age, and comorbidity interacted with CO poisoning for the dementia risk. The effect of hyperbaric oxygen (HBO2) therapy (Procedure Code 93.95) on the risk of dementia was evaluated for CO poisoning patients who had received the treatment within 3 days after the hospital admission. We further evaluated the dementia risk by the severity of CO poisoning using 7 days of hospital stay as a cut-off to distinct severity. The SAS software (Version 9.3 for Windows; SAS Institute Inc., Cary, NC) was used to perform all the data analyses. Kaplan–Meier curves were plotted using the R software (Version 2.14.1; R Development Core Team, Vienna, Austria). *P* values < 0.05 were considered statistically significant.

RESULTS

The CO poisoning and non-CO poisoning cohorts were similar in distributions of sex and age (Table 1). Near 80% of study subjects in both cohort aged less than 50 years old, with a mean age of 39.8 years (standard deviation = 13.8). The CO poisoning cohort exhibited higher comorbidities of depression and COPD, but lower head injury and cognitive impairment than did the non-CO poisoning cohort (all *P*-values < 0.05). After a 12-year follow-up period, the CO poisoning cohort revealed a higher cumulative incidence of dementia than did the non-CO poisoning cohort (*P* = 0.008, Figure 1). The mean follow-up years for the CO poisoning and non-CO poisoning cohorts were 4.53 and 4.93 years, respectively.

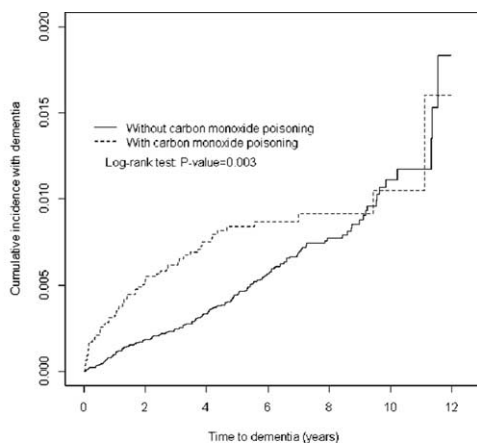
The overall incidence rate of dementia was 1.56-fold higher in the CO poisoning cohort than in the non-CO poisoning cohort (15.2–9.76 per 10,000 person-years; *n* = 62 vs 174), with an adjusted HR of 1.50 (95% CI = 1.11–2.04) (Table 2). In both cohorts, men exhibited a higher incidence of dementia than did women; moreover, the incidence increased with age and was higher for patients with comorbidity than for those without comorbidity. The sex-specific hazards showed a higher in male

TABLE 1. Characteristics of Patients With Carbon Monoxide Poisoning and Frequency Matched Patients Without Carbon Monoxide Poisoning

	Carbon Monoxide Poisoning				P-Value
	Yes (N = 9042)		No (N = 36,160)		
	n	%	n	%	
Age, year					0.99
20–34	3875	42.9	15,500	42.9	
35–49	3365	37.2	13,454	37.2	
50–64	1268	14.0	5071	14.0	
≥65	534	5.91	2135	5.90	
Mean (SD)*	39.8	13.8	40.0	14.2	0.40
Gender					0.99
Female	4291	47.5	17,163	47.5	
Male	4751	52.5	18,997	52.5	
Comorbidity					
Diabetes	592	6.55	2548	7.05	0.09
Hypertension	841	9.30	3598	9.95	0.06
Head injury	714	7.90	3537	9.78	<0.001
Depression	2558	28.3	1306	3.61	<0.001
CVD	353	3.90	1451	4.01	0.64
COPD	1170	3.23	240	2.65	0.005
Cognitive impairment	43	0.48	292	0.81	0.001
Urinary tract infection	587	6.49	2483	6.87	0.21
Pneumonia	696	7.70	2651	7.33	0.23

Chi-square test. COPD=chronic obstructive pulmonary disease, CVD=cerebrovascular disease, SD=standard deviation.
* t-Test.

patients (adjusted HR = 1.74, 95% CI = 1.20–2.54), and the age-specific hazards showed a higher for those aged <49 years (adjusted HR = 2.62, 95% CI = 1.38–4.99). Among study population without comorbidities, patients with CO poisoning



CO poisoning, No.		Control, No.				
At risk	9042	6518	4754	3049	1415	453
dementia events	0	42	12	5	1	1
At risk	36160	28705	21140	13385	6230	1927
dementia events	0	61	36	40	21	12

FIGURE 1. Cumulative incidence of dementia in patients with and without carbon monoxide poisoning.

had a higher risk of dementia compared to the non-CO poisoning cohort.

Table 3 summarizes the HRs of dementia associated with the interaction between CO poisoning and sex, age, comorbidity, and HBO2 therapy. Compared with women in the control cohort, men with CO poisoning patients exhibited an adjusted HR of 2.33 developing dementia (95% CI = 1.57–3.46). The HR of dementia increased with age, higher for those with CO poisoning than those without poisoning, but not for the elderly. The CO poisoning patients with a comorbidity had an adjusted HR of 1.75 (95% CI = 1.08–2.83) for dementia, compared with persons without poisoning and comorbidity. Compared with the non-CO poisoning cohort, the CO poisoning patients without HBO2 therapy had an adjusted HR of 1.45 (95% CI = 1.05–2.01) to develop dementia. CO poisoning patients receiving HBO2 therapy had an adjusted HR of 1.80, but not significant. Table 4 shows the risk of dementia increased with the severity of the poisoning. The severe cases had an adjusted HR of 2.18 (95% CI = 1.42–3.36).

DISCUSSION

An earlier study has reported that the mortality from intentional CO poisoning was 1.5-fold higher than that from accidental poisoning³⁰ and the suicide rate was higher in young men.^{31,32} Particularly, charcoal-burning suicides increased markedly in Taiwan in the first decade of the 21st century.^{33,34} Our study shows that the majority patients of CO poisoning are young, more men than women, and prevalent with depression at baseline (Table 1). Whether the younger and men are at the increased likelihood of voluntarily poisoning requires further research. Prevention strategies are needed to avoid the exposure to CO.^{35,36}

A previous large, multicenter, long-term population-based study on the dementia risk showed that self-perceived poor health increased the risk of dementia for near 4 folds.⁹ The risk can be typically aggravated by alcohol, drugs, smoking, infection, brain trauma, stroke, and chronic diseases.^{9–15} A recent prospective cohort study revealed that patients receiving general anesthesia and surgery developed dementia in a short period with an HR of 1.99.¹⁴ Another study shows that patients with trauma brain injury are also at an increased risk of dementia with an adjusted HR of 3.26 (95% CI = 2.69–3.94).¹⁵ In the present study, the adjusted HR of dementia was 1.75 (95% CI = 1.08, 2.83) for CO poisoning patients with comorbidities, compared with the non-CO poisoning cohort without comorbidity (Table 3). We found the dementia risk was 2.4-fold greater for men than for women (21.5 vs 8.80 per 100,000 person-years) in the CO exposed cohort (Table 2). The age-specific analysis shows a 2.6-fold greater hazard of developing dementia for young poisoned patients than controls. There are more men and much larger number of young people suffer from CO poisoning, representing a proportion loss of healthy life.

CO poisoning may increase the risk of subsequent morbidity and mortality. A recent study found the mortality was 5.24 times higher in patients with CO poisoning than the non-CO poisoning cohort.³⁵ Information on subsequent neurological and cognitive sequelae after the poisoning is limited.^{20,21,36} CO poisoning causes brain hypoxia which may contribute inflammation and subsequent injury.²² An American study found from 63 suspected cases that CO poisoning could cause considerable inflammation responses, even for patients with brief exposure.³⁷ Studies have hypothesized that reactive oxygen species, free radicals, and neuronal nitric oxide induce oxidative injury³⁸ and

TABLE 2. Incidence and Hazard Ratio of Dementia in Patients With and Without Carbon Monoxide Poisoning

Outcome	Carbon Monoxide Poisoning						Crude HR [‡] (95% CI)	Adjusted HR [§] (95% CI)
	Yes			No				
	Event	PY	Rate [†]	Event	PY	Rate [†]		
All	62	40,937	15.2	174	178,311	9.76	1.54(1.15, 2.06)**	1.50(1.11, 2.04)**
Gender								
Female	18	20,446	8.80	68	87,115	7.81	1.12(0.67, 1.89)	1.14(0.66, 1.96)
Male	44	20,491	21.5	106	91,196	11.6	1.83(1.29, 2.61)***	1.74(1.20, 2.54)**
Age, year								
20–49	20	34,473	5.80	27	148,693	1.82	3.17(1.78, 5.65)***	2.62(1.38, 4.99)**
50–64	19	4808	39.5	40	21,402	18.7	2.11(1.22, 3.64)**	1.99(1.10, 3.61)*
≥65	23	1656	138.9	107	8216	130.2	1.05(0.67, 1.65)	1.05(0.66, 1.66)
Comorbidity								
Diabetes								
No	54	38,965	13.9	143	168,607	8.48	1.62(1.19, 2.22)**	1.56(1.12, 2.17)**
Yes	8	1972	40.6	31	9704	32.0	1.26(0.58, 2.75)	1.37(0.61, 3.10)
Hypertension								
No	44	38,069	11.6	108	165,054	6.54	1.76(1.24, 2.49)**	1.75(1.20, 2.55)**
Yes	18	2868	62.8	66	13,257	49.8	1.25(0.74, 2.11)	1.13(0.66, 1.93)
Head injury								
No	59	37,933	15.6	157	162,593	9.66	1.60(1.19, 2.16)**	1.62(1.18, 2.22)**
Yes	3	3004	9.99	17	15,718	10.8	0.85(0.25, 2.90)	0.62(0.17, 2.31)
Depression								
No	46	30,722	15.0	162	173,240	9.35	1.58(1.14, 2.20)**	1.55(1.12, 2.16)**
Yes	16	10,215	15.7	12	5071	23.7	0.68(0.32, 1.43)	1.07(0.47, 2.42)
Cerebrovascular disease								
No	53	39,815	13.3	138	173,063	7.97	1.66(1.21, 2.28)**	1.66(1.19, 2.31)**
Yes	9	1122	80.2	36	5247	68.6	1.15(0.55, 2.39)	1.04(0.49, 2.22)
COPD								
No	57	40,146	14.2	158	173,765	9.09	1.55(1.15, 2.10)**	1.55(1.13, 2.13)**
Yes	5	792	63.2	16	4545	35.2	1.75(0.64, 4.79)	1.31(0.45, 3.80)
Cognitive impairment								
No	62	40,776	15.2	169	177,193	9.54	1.59(1.19, 2.12)***	1.53(1.12, 2.08)**
Yes	0	161	0.00	5	1117	44.8	–	–
Urinary tract infection								
No	55	38,781	14.2	136	168,767	8.06	1.75(1.28, 2.39)***	1.51(1.08, 2.11)*
Yes	7	2156	32.5	38	9544	39.8	0.81(0.36, 1.82)	1.16(0.50, 2.68)
Pneumonia								
No	53	38,632	13.7	142	168,761	8.41	1.62(1.18, 2.22)**	1.54(1.10, 2.15)*
Yes	9	2305	39.1	32	9549	33.5	1.17(0.56, 2.45)	1.24(0.57, 2.69)

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, PY = person-years.

† Incidence rate per 10,000 person-years.

‡ Relative hazard ratio.

§ Hazard ratio after adjustment for age, sex, and comorbidity of head injury, depression, COPD, and cognitive impairment.

lead to neuropathologic effects post-CO poisoning.³⁹ A recent retrospective cohort study showed that victims of CO poisoning exhibited a 9.08-fold increased risk for Parkinsonism.⁴⁰ Other studies also found patients with CO poisoning are at a higher risk of developing cardiovascular complications.^{33,41} However, there are conflicting findings about the risk of cardiovascular deaths after CO poisoning.^{42,43} More evidences are needed to evaluate whether CO poisoning affects small vessel diseases leading to dementia.

HBO2 therapy is the primary treatment for CO poisoning to restore the oxygen level in the blood and to prevent the

neuropsychiatric syndrome^{44–46} and hypoxic encephalopathy.^{26,46–48} HBO2 does much more in CO poisoning than just treat hypoxia, by preventing the inflammatory cascade and later complications.⁴⁹ However, the beneficial effects of HBO2 therapy for CO poisoning remain debatable.⁴⁹ Our study showed an increased HR of dementia on HBO2 therapy in patients with CO poisoning, but not significant. Our further data analysis showed severe CO poisoned patients with longer hospital stay are at higher HR of developing dementia. It is possible that patients receiving HBO2 therapy are sicker and the risk of dementia may be less likely associated with the CO

TABLE 3. Cox Proportional Hazards Regression Analysis for Hazard Ratio of Dementia-Associated Carbon Monoxide Poisoning With Interaction of Gender, Age, and Comorbidity

Variables		Adjusted HR [†] (95% CI)	P-Value [‡]			
Carbon monoxide poisoning	Gender		0.12			
	No	Female		1(Reference)		
	No	Male		1.28(0.94, 1.75)		
	Yes	Female		1.05(0.62, 1.79)		
Carbon monoxide poisoning	Age, year	Male	2.33(1.57, 3.46) ^{***}	0.002		
		No	20–34		1(Reference)	
		No	35–49		2.75(1.20, 6.28) [*]	
		No	50–64		17.8(8.30, 38.3) ^{***}	
		No	≥65		114.2(54.7, 238.3) ^{***}	
		Yes	20–34		2.38(0.77, 7.31)	
	Yes	35–49	8.32(3.48, 19.9) ^{***}			
	Yes	50–64	32.5(14.0, 75.3) ^{***}			
	Yes	≥65	112.4(49.3, 256.1) ^{***}			
	Carbon monoxide poisoning	Comorbidity [§]			0.03	
		No	No			1(Reference)
		No	Yes			1.16(0.82, 1.66)
Yes		No	1.72(1.22, 2.42) ^{**}			
Carbon monoxide poisoning	Hyperbaric oxygen therapy	Yes	1.75(1.08, 2.83) [*]			
		No	1(Reference)			
		Yes	1.45(1.05, 2.01) [*]			
		Yes	1.80(0.96, 3.37)			

*P < 0.05, **P < 0.01, ***P < 0.001. CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, PY = person-years.

[†] Hazard ratio after adjustment for age, sex, and comorbidity of head injury, depression, COPD, and cognitive impairment.

[‡] p for interaction.

[§] Patients with any one of the comorbidities (i.e., head injury, depression, COPD, and cognitive impairment) were classified as the comorbidity group.

exposure. Studies that have investigated the epidemiological relationship between CO poisoning and dementia are scarce. The CO-poisoning related sequelae needs much more studies.⁵⁰

LIMITATIONS

This study was subject to limitations. First, this study used retrospective cohort study design, which relies on the data available. Information on lifestyle, body mass index, physical activity, and family health history were not available to measure their potential confounding effects in this study. COPD is a

disorder associated with lifestyles. We therefore used COPD in the data analysis as controlling variable to substituting lifestyles. Second, this study used ICD-9-CM coding system to identify disorders. To avoid coding errors, we excluded data with the diagnosis appeared only once. An ad hoc committee established by the insurance authority could monitor claims data to insure the accuracy. Therefore, coding errors have been minimized. Third, patients with CO poisoning may have association with other late neuropsychiatric disorders other than dementia. We did not have enough power to measure other disorders as we were able to identify only 62 cases of dementia.

TABLE 4. Incidence and Hazard Ratio for Dementia Stratified by the Severity of Carbon Monoxide Poisoning

Carbon Monoxide Poisoning Severity [†]	Event	PY	Rate [‡]	Adjusted HR [§] (95% CI)
Non-CO poisoning	174	178,311	9.76	1(Reference)
CO poisoning				
Low severity	36	32,424	11.1	1.23(0.85, 1.79)
High severity	26	8513	30.5	2.18(1.42, 3.36) ^{***}
P for trend				<0.001

***P < 0.001. CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio.

[†] Patients with 7-day or longer hospital stay were identified in high severity group, otherwise were considered as low severity.

[‡] Incidence rate, per 10,000 person-years.

[§] Hazard ratio after adjustment for age, sex, and comorbidity of head injury, depression, COPD, and cognitive impairment.

We therefore did not differentiate between Alzheimer disease, vascular dementia, and dementia related to other causes. Forth, laboratory data were unavailable in our database. We, therefore, are unable to evaluate whether amyloid and TAU formation, and alpha-synuclein are associated in the CO-related dementia. Finally, in the present cohort study, the severity of CO poisoning was not coded in the claims record. No detailed information was available in the claims data to clarify whether the events were voluntarily or accidentally, acute or chronic poisoning, and co-ingestions. The level of CO exposure was unknown. Patients who were cared at outpatient clinics could be less severe cases and were not included in this study. HBO2 therapy is available at medical centers and large community hospitals. However, reasons of choosing and not choosing HBO2 therapy might somewhat reflect the severity of CO poisoning. We therefore are unable to make any robust conclusion about the effectiveness of the HBO2 therapy for dementia patients.

In conclusion, this study suggests that CO poisoned patients may associate with an increased risk of dementia. It is important to note there is a large number of CO poisoning events, which occur to mainly young populations. Further data analysis showed the cumulative mortality over 12 years (2000–2011) was approximate 10.2% (922/9041) in the CO poisoning cohort and 32.3% (20/62) in those with dementia developed. People suffering from depression may need more medical attention, particularly for the young population. Further study needs to differentiate between late neuropsychiatric effects of CO poisoning and dementia. The limitations left many unanswered questions. Different dementias are associated with other etiological factors. These would take future investigators a great amount of research efforts to study.

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