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Increased Risk of Parkinson Disease in Patients With Carbon Monoxide Intoxication

A Population-Based Cohort Study

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Abstract: The present study evaluated the association of carbon monoxide intoxication (COI) with Parkinson disease (PD).

A total of 9012 adults newly diagnosed with COI were enrolled in this study as the COI cohort. The control (non-COI) cohort, comprising 36,048 participants, was matched for each COI patient according to age, sex, and the year of hospitalization. We calculated the hazard ratios (HR) and 95% confidence intervals by using a Cox proportional hazards regression model.

The overall incidence of PD (per 10,000 person-year) in the COI and non-COI cohorts was 27.4 and 2.53, respectively. After adjustment for age, sex, and comorbidities, the COI patients exhibited a 9.08-fold increased risk for PD. The COI patients without comorbidity exhibited a significantly higher risk of PD (adjusted HR = 15.8) than did the COI patients without comorbidity (adjusted HR = 4.15). Patients with COI and receiving hyperbaric oxygen therapy exhibited a 14.3-fold increased risk of PD; the adjusted HR of patients who did not receive hyperbaric oxygen treatment was increased 7.97-fold.

The risk of PD increased in the COI patients and the significance increased in young people. COI is a crucial factor leading to PD.

(*Medicine* 94(19):e869)

Abbreviations: CI = confidence interval, COI = carbon monoxide intoxication, HR = hazard ratio, ICD-9 = International Classification of Diseases, Ninth Revision, NHIRD = National Health Insurance Research Database, PD = Parkinson disease.

INTRODUCTION

Parkinson disease (PD) is a progressive neurodegenerative disorder of the central nervous system. PD affects between 100 and 200 per 100,000 people over 40 years, and over 1 million people in North America alone.[1] Initially, patients with PD exhibit tremor, bradykinesia, and rigidity.[2–5] Subsequently, approximately 25% of patients become severely disabled or die within 5 years of PD onset.[6] The condition of most patients shifts from impairment to disability within 3 to 7 years of PD onset.[7] Approximately 77% of patients exhibit a poor outcome 10 years after diagnosis.[8,9] The pathogenesis of PD is unknown. Oxidative stress is only one of the proposed pathogenic mechanisms. The cause of PD is unknown; however, the underlying mechanisms of PD have been determined.[10] The oxidative stress hypothesis postulates that inappropriate production of reactive oxygen species leads to neurodegeneration.[11,12]

Carbon monoxide intoxication (COI) occurs after inhalation of excessive amounts of carbon monoxide (CO), a toxic gas. However, because CO is colorless, odorless, tasteless, and initially nonirritating, detecting CO is difficult for humans. COI leads to approximately 40,000 emergency department consultations, and between 5000 and 6000 deaths per year in the United States.[13–15] Approximately 40% of patients with considerable COI develop delayed neurologic sequelae (DNS).[16–19] These include variable degrees of cognitive deficits, personality changes, movement disorders, and focal neurologic deficits. The mechanism of DNS has not been entirely determined; however, it probably involves lipid peroxidation through oxidative stress and damaged endothelial cells.[20–23] Ischemia-reperfusion injury and exposure to high oxygen may exacerbate the initial oxidative damage in those who recover from COI.[24,25]

Both diseases related to oxidative stress have been rarely discussed together. Therefore, this study evaluated the association of COI with PD.

METHODS

Data Source

The study was based on data from the National Health Insurance Research Database (NHIRD) in Taiwan. The National Health Research Institute (NHRI), which maintains

Editor: Thomas Mueller.
Received: March 14, 2015; revised: April 15, 2015; accepted: April 16, 2015.
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This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW104-TDU-B-212–113002); China Medical University Hospital, Academia Sinica Taiwan Biobank, Stroke Biosignature Project (BM104010092); NRPB Stroke Clinical Trial Consortium (MOST 103–2325-B-039 -006); Tseng-Lien Lin Foundation, Taichung, Taiwan; Taiwan Brain Disease Foundation, Taipei, Taiwan; Katsuzo and Kiyo Aoshima Memorial Funds, Japan; and Health, and welfare surcharge of tobacco products, China Medical University Hospital Cancer Research Center of Excellence (MOHW104-TDU-B-212–124–002, Taiwan).
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding received for this study.
C-YL and M-CC are contributed equally to this work.
The authors have no conflicts of interest to declare.
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ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000869

and updates the NHIRD, provided the medical claims data and approved this study. We used scrambled patient identification numbers to link files, including inpatient care claims and the registry for beneficiaries. This study was approved by the Institutional Review Board of China Medical University, Central Taiwan (CMU-REC-101–012). According to the National Health Insurance (NHI) annual statistics report, the coverage of the NHI in 2007 was nearly 99% of the entire population of Taiwan; in total, more than 25 million people were enrolled in this program (http://www.nhi.gov.tw/english/index.aspx). The diagnosis codes in this study were derived from the International Classification of Diseases, Ninth Revision (ICD-9). The NHIRD covers a highly representative sample of Taiwan's general population, because the reimbursement policy is universal and operated by a single buyer, the government in Taiwan. All insurance claims should be scrutinized by medical reimbursement specialists and peer review. COI and PD were accurately diagnosed and coded (ICD-9 codes) by the specialists according to the standard diagnosed criteria including typical symptoms/signs, laboratory data, and imaging findings. In addition, if the doctors or hospitals make the wrong codes or diagnoses will be punished by the National Health Insurance Administration with a lot of penalty. Therefore, the diagnoses of COI and PD in this study were highly reliable. In addition, we have published related studies according to the same diagnoses and ICD-9 codes.[26–29]

Sampled Participants

We conducted a retrospective cohort study of patients who were newly hospitalized for COI (ICD-9 code 986) between January 1, 2000 and December 31, 2011. The date of the first hospitalization for COI was identified as the index date. We excluded patients who had exhibited PD (ICD-9 code 332) before the index date and those with incomplete age or sex information. For each identified COI patient, four comparison person was randomly identified frequency-matched with age (at 5-years interval), sex,, year of index date and using the same exclusion criteria for the non-COI cohort.

Outcome and Comorbidities

All subjects were followed for the period beginning at the index date until the end of 2011, loss to follow-up, the date of withdraw from the NHI, or until the occurrence of PD. We used inpatient diagnosis files to ascertain the existence of comorbidities, including diabetes (ICD-9 code 250), hypertension (ICD-9 codes 401–405), head injury (ICD-9 codes 310.2, 800, 801, 803, 804, 850, 851, 853, 854), depression (ICD-9 codes 296.2, 296.3, 296.82, 300.4, 311), stroke (ICD-9 codes 430–438), dementia (ICD-9 codes 290, 294.1, 331.0), and chronic kidney disease (ICD-9 code 585). Acute respiratory failure (ICD-9 code 518.81) was also considered and identified according to diagnoses in the hospitalization records within 3 days of the patient's index date. We also evaluated the risks of PD for the COI patients who received hyperbaric oxygen (HBO) therapy (Procedure Code 93.95).

Statistical Analysis

The differences in demographic variables between COI and non-COI cohorts were analyzed using a chi-square test for categorical variables and a *t* test for continuous variables. We assessed the cumulative incidence of PD by using the Kaplan–Meier method between the COI cohort and the non-COI cohort and estimated their differences using a log-rank test. The incidence for PD was calculated in both cohorts. Univariate and multivariate Cox proportional hazards regression was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for PD. The multivariate model was simultaneously adjusted for sex, age, and the comorbidities of diabetes, hypertension, head injury, depression, stroke, dementia, and chronic kidney disease. A 2-tailed P value < 0.05 was considered statistically significant. All analyses were performed using SAS statistical software (Version 9.2 for Windows; SAS Institute, Inc., Cary, NC).

RESULTS

Table 1 contains the baseline characteristics of the patients with and without COI. Most patients were aged <34 years (42.9%) and the mean ages of the COI cohort and non-COI cohort were 39.8 (±13.9) and 39.7 (±14.3) years, respectively. Comorbidities at the baseline were more prevalent in the COI cohort than in the non-COI cohort (all $P < 0.01$). The mean follow-up was 4.50 years for the COI cohort and 4.94 years for the non-COI cohort. After 12 years of follow-up, the cumulative incidence of PD in the COI cohort was approximately 1.47% higher than that in the non-COI cohort ($P < 0.001$; Figure 1). The overall incidence of PD was 10.6-fold higher in the COI cohort than in the non-COI cohort (27.4 and 2.53 per 10,000 person-year, respectively; Table 2). After adjustments for age, sex, and the comorbidities of diabetes, hypertension, head injury, depression, stroke, dementia, and chronic kidney disease, the COI patients exhibited a 9.08-fold higher risk of developing PD (95% CI = 6.21–13.3) than did the non-COI patients. The sex-specific relative risk of PD in the COI cohort

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

	Carbon Monoxide Poisoning				
	Yes (N = 9012)		No (N = 36,048)		
	n	%	n	%	*P*-value
Age, year					0.99
20–34	3867	(42.9)	15,468	(42.9)	
35–49	3343	(37.1)	13,372	(37.1)	
50–64	1263	(14.0)	5052	(14.0)	
≥65	539	(5.98)	2156	(5.98)	
Mean (SD)*	39.8	(13.9)	39.7	(14.3)	0.48
Sex					0.99
Female	4270	(47.4)	17,080	(47.4)	
Male	4742	(52.6)	18,968	(52.6)	
Comorbidity					
Diabetes	589	(6.54)	792	(2.20)	<0.001
Hypertension	847	(9.40)	1295	(3.59)	<0.001
Hyperlipidemia	321	(3.56)	439	(1.22)	<0.001
Head injury	713	(7.91)	1029	(2.85)	<0.001
Depression	2540	(28.2)	147	(0.41)	<0.001
Stroke	352	(3.91)	527	(1.46)	<0.001
Dementia	23	(0.26)	34	(0.09)	<0.001
Chronic kidney disease	44	(0.49)	102	(0.28)	0.002

* Chi-square test, *t* test.

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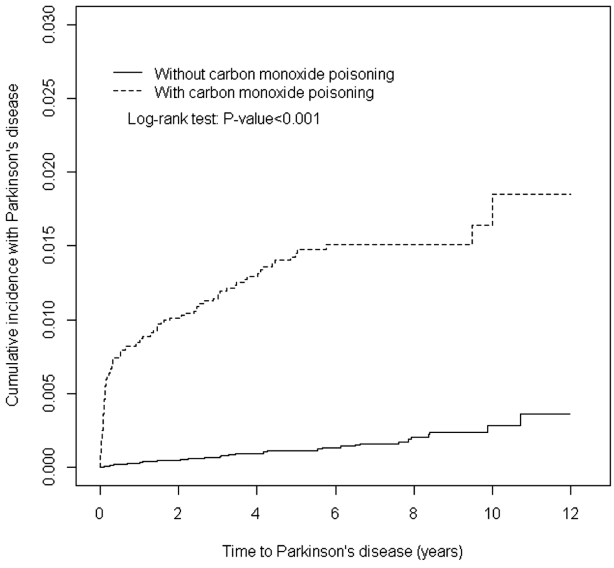

FIGURE 1. Cumulative incidence of Parkinson disease compared between with and without carbon monoxide poisoning.

compared with that in the non-COI cohort was significant for both women (adjusted HR = 14.1; 95% CI = 7.20–27.7) and men (adjusted HR = 7.48; 95% CI = 4.66–12.0). The incidence of PD increased with age and in the presence of comorbidities. The age-specific relative risk of PD in the COI patients compared with that in the control patients was higher in all age groups, particularly in patients between 20 and 49 years of age (adjusted HR = 39.4; 95% CI = 16.7–93.0). The risk of PD stratified by comorbidity exhibited a 15.8-fold risk and was observed in patients without comorbidity (95% CI = 9.80–24.8). Table 3 lists the joint effects of COI and depression or respiratory failure on the risk of PD. A higher risk of PD was observed in patients with both COI and depression (adjusted HR = 20.3; 95% CI = 13.1–31.2) or both COI and respiratory failure (adjusted HR = 15.9; 95% CI = 10.2–24.8), compared with patients without COI, depression, or respiratory failure. Patients with COI and receiving HBO therapy were 14.3-fold more likely to develop PD (95% CI = 8.80–23.2) than were patients without COI and not receiving HBO therapy, followed by patients with COI and not receiving HBO (HR = 7.97; 95% CI = 5.35–11.9).

A stratified analysis of the follow-up duration revealed that the adjusted HR of PD decreased with the follow-up length (Table 4). The adjusted HR of PD was significantly higher in the first 2 follow-up years (adjusted HR = 19.4; 95% CI = 11.0–34.2) than after the first 2 years (adjusted HR = 4.20; 95% CI = 1.76–9.99: within 3 to 4 follow-up years; adjusted HR = 2.89; 95% CI = 1.18–7.07: >4 follow-up years).

DISCUSSION

The COI cohort group comprised mostly younger people and people with more comorbidities than those present in the general population (Table 1). Whether young age and comorbidities increased the likelihood of people consciously or accidentally poisoning themselves with CO requires further research.

In the present study, the COI patients exhibited a 9.08-fold higher risk of PD (95% CI = 6.21–13.3) than did the non-COI patients. This suggests a stronger association between COI and PD than previous subjects with a family history of PD (odds ratio [OR] from 4.45 to 3.25; 95% CI = 2.43–4.35),[30] exposure to pesticides (adjusted relative risk = 1.7; 95% CI = 1.2–2.3; $P = .002$),[31–37] brain concussion (OR = 1.57; 95% CI = 1.35–1.83),[38] midlife migraine (OR = 3.6; 95% CI = 2.7–4.8),[39] exposure to environmental toxins (high manganese release,

TABLE 2. Incidence and Hazard Ratio of Parkinson Disease Between Patients With Carbon Monoxide Poisoning and Without Carbon Monoxide Poisoning

	Carbon Monoxide Poisoning							
	Yes			No				
Outcome	Event	PY	Rate†	Event	PY	Rate†	Crude HR‡ (95% CI)	Adjusted HR§ (95% CI)
All	111	40,579	27.4	45	177,987	2.53	10.6 (7.48, 15.0)***	9.08 (6.21, 13.3)***
Sex								
Female	57	20,210	28.2	12	85,600	1.40	19.9 (10.7, 37.2)***	14.1 (7.20, 27.7)***
Male	54	20,369	26.5	33	92,387	3.57	7.19 (4.67, 11.1)***	7.48 (4.66, 12.0)***
Age, year								
20–49	68	34,135	19.9	6	146,068	0.41	45.7 (20.6, 109.5)***	39.4 (16.7, 93.0)***
50–64	17	4791	35.5	11	22,891	4.81	7.14 (3.34, 15.3)***	5.75 (2.42, 13.7)***
≥65	26	1652	157.3	28	9028	31.0	4.83 (2.83, 8.25)***	3.55 (1.92, 6.54)***
Comorbidity‖								
No	54	25,144	21.5	27	165,925	1.63	13.3 (8.38, 21.1)***	15.8 (9.80, 24.8)***
Yes	57	15,435	36.9	18	12,062	14.9	2.48 (1.46, 4.21)***	4.15 (2.38, 7.23)***

CI = confidence interval, HR = hazard ratio, PY = person-years; ***$P < 0.001$.

† Incidence rate per 10,000 person-years.

‡ Relative hazard ratio.

§ Hazard ratio adjusted for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, head injury, depression, stroke, dementia, and chronic kidney disease.

‖ Patients with any one of the comorbidities (including diabetes, hypertension, hyperlipidemia, head injury, depression, stroke, dementia, and chronic kidney disease) were classified as the comorbidity group.

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TABLE 3. Cox Proportional Hazard Regression Analysis for the Risk of Parkinson Disease-Associated Carbon Monoxide Poisoning With Interaction of Depression and Respiratory Failure

Variables		Crude HR[†] (95% CI)	Adjusted HR[‡] (95% CI)
Carbon monoxide poisoning	Depression		
No	No	1 (Reference)	1 (Reference)
No	Yes	6.36 (0.88, 46.1)	4.55 (0.62, 33.5)
Yes	No	8.97 (6.14, 13.1)***	9.27 (6.30, 13.6)***
Yes	Yes	15.9 (10.4, 24.2)***	20.3 (13.1, 31.2)***
Carbon monoxide poisoning	Respiratory failure		
No	No	1 (Reference)	1 (Reference)
Yes	No	6.84 (5.03, 9.30)***	5.35 (3.79, 7.55)***
Yes	Yes	19.2 (12.6, 29.5)***	15.9 (10.2, 24.8)***
Carbon monoxide poisoning	Hyperbaric oxygen therapy		
No	No	1 (Reference)	1 (Reference)
Yes	No	9.58 (6.64, 13.8)***	7.97 (5.35, 11.9)***
Yes	Yes	14.0 (8.95, 22.0)***	14.3 (8.80, 23.2)***

CI = confidence interval, HR = hazard ratio, *** $P < 0.001$.
[†] Relative hazard ratio.
[‡] Hazard ratio adjusted for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, head injury, depression, stroke, dementia, and chronic kidney disease.

relative risk = 1.78; 95% CI = 1.54, 2.07; high copper release, relative risk = 1.1; 95% CI = 0.94, 1.31),[40,41] milk consumption (2.3-fold excess of PD; 95% CI = 1.3–4.1),[42] high dietary intake of iron (increased risk of PD; OR = 1.7; 95% CI = 1.0, 2.7),[43] excess body weight,[44] higher levels of education,[45] and a history of anemia[46] (Table 2).

Compared with patients in the non-COI cohort, the incidence of PD was as much as 39.4-fold higher in young COI patients, 5.75-fold higher in the middle-age patients, and 3.55-fold higher in the elderly patients, higher than in those in the same age group (Table 2). PD is uncommon in people younger than 40.[47]

In addition, we observed that the COI patients with no comorbidity were more likely to develop PD than were the non-COI patients. The incidence of PD was as much as 15.8-fold higher in the patients with no comorbidity, and 4.15-fold higher in COI patients with comorbidities. This suggests that PD is caused mainly by COI itself, not relative to comorbidity factors (Table 2).

Depression is the most common psychiatric symptom of PD.[48] A higher risk of PD was observed for patients with both COI and depression (adjusted HR = 20.3; 95% CI = 13.1–31.2; Table 3). COI combined with depression amounted for 28.2%; however, COI without depression leading to PD seemed to be a more prominent cause than depression without COI. Previous studies have reported that COI with respiratory failure was a strong aggravating factor for PD (adjusted HR = 15.9; 95% CI = 10.2–24.8; Table 3). The results of the current study suggest that oxidative stress damage to the brain plays a major role in the development of PD.

HBO treatment has been recommended as a therapy for COI patients.[13,14,49,50] Compared with patients without COI who did not receive HBO therapy in our study, patients with COI who received HBO therapy were 14.3-fold more likely to develop PD (95% CI = 8.80–23.2), followed by patients with COI who did not receive HBO therapy (adjusted HR = 7.97; 95% CI = 5.35–11.9; Table 3). HBO treatment did not appear to be an effective preventative measure for PD. In addition, HBO treatment seemed unable to prevent reperfusion injury for neurodegeneration. There may be a severe degree of COI in patients who received HBO treatment, leading to less favorable results. The treatments with hyperbaric oxygen were received

TABLE 4. Trends of Parkinson Disease Event Risks by Stratified Follow-Up Years

	Carbon Monoxide Poisoning							
	Yes			No				
Follow Time, years	Event	PY	Rate	Event	PY	Rate	Crude HR[†] (95% CI)	Adjusted HR[‡] (95% CI)
≤2	84	15021	55.9	16	64625	2.48	22.1 (12.9, 37.7)***	19.4 (11.0, 34.2)***
3–4	16	11102	14.4	12	49263	2.44	5.92 (2.80, 12.5)***	4.20 (1.76, 9.99)**
>4	11	14455	7.61	17	64098	2.65	2.87 (1.34, 6.12)**	2.89 (1.18, 7.07)*

CI = confidence interval, HR = hazard ratio, PY = person-years; Rate = incidence rate per 10,000 person-years. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.
[†] Relative hazard ratio.
[‡] Hazard ratio adjusted for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, head injury, depression, stroke, dementia, and chronic kidney disease.

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by the patients with more severe symptoms of COI. Therefore, we found influence of the severity of COI in the development of PD (Table 3). Certain aspects of COI possibly cause irreversible oxidative damage and neurodegeneration. Moreover, additional randomized controlled trials are required to determine the efficacy and differences between the methods for treating PD with and without COI. A stratified analysis according to follow-up durations revealed that the adjusted HR of PD decreased with the follow-up length (Table 4), and harmful COI effects rapidly developed.

LIMITATIONS

In the present cohort study, the degree of COI could not be determined. The NHI database provides no detailed information regarding the frequency of CO exposure (ie, whether acute or chronic poisoning had occurred) or the level of CO exposure. Therefore, further analysis is required to facilitate a deeper understanding.

The strengths of our study are the population-based design, the generalizability of findings, and the use of population-based data and NHIRD records with a large sample size including study and control cohorts. In addition, the NHIRD comprises a highly representative sample of Taiwan's general population, because the reimbursement policy is universal and operated by a single buyer, the government of Taiwan. All insurance claims are typically scrutinized by medical reimbursement specialists and peer reviewed.

Nevertheless, this study was subject to limitations. First, the NHIRD provides no detailed information on factors such as patient lifestyle, habits, body mass index, physical activity level, socioeconomic status, or family history, all of which are possible confounding factors in this study. Second, the evidence derived from a cohort study is generally of lower methodological quality than that obtained from randomized trials, because a cohort study is subject to numerous biases related to the necessary adjustments for confounding factors. Despite the meticulous design of this study and adequate control of confounding factors, biases could remain because of possibly unmeasured and unknown confounding factors. Third, the registries in the NHI claims are primarily used for administrative billing and are not verified for scientific purposes. Because of the anonymity of the identification numbers, obtaining additional information by directly contacting the patients was not possible. The accuracy of medical coding in the claims data may affect the data validity. However, the data on the diagnoses in the NHIRD are highly reliable. The insurance system has mechanisms to monitor the insurance claims.

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