

Association Between Carbon Monoxide Intoxication and Incidence of Ischemic Stroke: A Retrospective Nested Case-Control Study in South Korea

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Objectives: Severe neurological sequelae occur in patients with carbon monoxide (CO) intoxication; however, whether the latter increases the long-term risk of developing ischemic stroke is unclear. We investigated the association between CO intoxication and ischemic stroke using data from the Korean National Health Information Database. **Materials and Methods:** We performed a retrospective, nested case-control study of 27,984 individuals treated for CO intoxication and 27,984 sex- and age-matched controls. Initially, we calculated the overall incidence and hazard ratio (HR) of ischemic stroke using conditional logistic regression. Thereafter, we calculated the incidences and HRs according to covariates and follow-up periods. **Results:** The CO intoxication group had a significantly higher risk of developing ischemic stroke than the control group (adjusted HR 2.31, 95% CI [confidence interval] = 2.01–2.65). Male sex (adjusted HR 2.73, 95% CI = 2.23–3.34), age <40 (adjusted HR 3.53, 95% CI = 2.15–5.82), low income (adjusted HR 2.55, 95% CI = 1.56–4.15), comorbidities (adjusted HR 2.59, 95% CI = 1.48–4.52), and current smokers (adjusted HR 3.55, 95% CI = 1.67–7.60) had a higher risk of ischemic stroke. The risk of ischemic stroke was highest within 2 years after CO intoxication (adjusted HR 7.47, 95% CI = 2.76–20.26), and even >6 years after, the risk remained significantly higher than in the control group (adjusted HR 1.84, 95% CI = 1.53–2.20). **Conclusions:** CO intoxication and the long-term risk of ischemic stroke are associated.

Key Words: Carbon monoxide—CO intoxication—CO poisoning—Ischemic stroke—Nested case-control study—Retrospective cohort—Conditional logistic regression

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Introduction

Carbon monoxide (CO) is a highly toxic gas produced by the incomplete combustion of hydrocarbons.¹ As leakages often go undetected, many people experience CO intoxication.² In the US, at least 430 people die and approximately

50,000 visit an emergency department annually due to accidental CO intoxication.³ In Korea, more than 4,000 cases of CO intoxication are recorded each year, and the number has been increasing in recent years.⁴

The clinical symptoms of CO intoxication are often non-specific and vary from mild flu-like symptoms to coma and death.⁵ Since CO binds to hemoglobin and interferes with oxygen utilization, thereby causing tissue hypoxia, the central nervous system (CNS) and cardiovascular system, which heavily depend on oxygen use, are potentially affected by CO intoxication.⁶ High levels of exposure can induce myocardial ischemia, cardiac arrhythmia, and CNS symptoms, including dizziness, confusion, seizures, and CNS depression.^{7,8} After acute CO intoxication, severe delayed neurological manifestations, including difficulties with intellectual functions, short-term memory loss, amnesia, and dementia, can occur.⁹ Delayed neurological disorders may be associated with ischemic stroke,

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and in fact, a few cases of acute ischemic stroke due to CO intoxication have been reported.¹⁰⁻¹² In Taiwan, a 12-year retrospective cohort study was conducted using the Taiwan National Health Insurance Research Database from 2000 to 2011. The study found that the hazard ratio (HR) of long-term ischemic stroke increased to 2.76 in patients with CO intoxication compared to those without.¹³ This corroborates the evidence that ischemic stroke and CO intoxication are associated. However, epidemiological studies on the association between CO intoxication and the long-term risk of ischemic stroke are limited, and further epidemiological evidence is required.

Therefore, we conducted a retrospective, nested case-control study to investigate the association between CO intoxication and ischemic stroke using data from the Korean National Health Information Database (NHID)

Methods

Data source

The NHID is a public database containing data on health-care utilization, health screenings, socio-demographic variables, and mortality for the entire Korean population, created by the National Health Insurance Service.¹⁴ The NHID was established in 2002 and includes an “eligibility database,” a “national health screening database,” and a “healthcare utilization database.” The eligibility database contains information regarding age, sex, region, income-based insurance contributions, type of insurance, job and industry category, and date of death. The national health screening database contains information on health behaviors, such as smoking, drinking, and exercise, as well as clinical laboratory results. The healthcare utilization database contains information on the medical consumption of inpatients and outpatients. All disease diagnoses were described using the International Classification of Diseases, Tenth Revision, (ICD-10) codes. We used the NHID to build the target population for our nested case-control study, using data from 2002 to 2017. In addition, we used data on the causes of death provided by Statistics Korea (KoSTAT) and linked it with the NHID data.

Study population

We selected all the patients who were treated more than once with reference to ICD-10 code T58, from 2002 to 2017, as our “cases of CO intoxication,” while controls were randomly selected among those who had not been diagnosed with CO intoxication during the same period; cases and controls were matched for sex and age at a 1:1 ratio. Our sample initially included 29,357 cases and 29,357 controls. Of these, cases involving a diagnosis of ischemic stroke (ICD-10 code I63) prior to enrollment in the study as well as their respective matched subjects were excluded (a total of 367 cases and 367 controls). The NHID was established in 2002, and no data before that date are available; thus, the year 2002 was considered a

wash-out period, and the 356 cases and 356 controls enrolled during that year were excluded. We also excluded those whose records showed an error in the date of death (medical records remained after date of death) as well as their matched subjects, leading to the exclusion of three cases and three controls. Death statistics for cases involving ICD-10 code T58 were not provided by KoSTAT because such data would disclose patient information. Instead, those who died from “toxic effects of substances chiefly nonmedicinal as to source (T51–T65)” within 3 months after CO intoxication were presumed to have died directly from CO intoxication; these patients were excluded, together with their matched controls. Similarly, if no cause of death was indicated, those who died within 2 weeks after CO intoxication were presumed to have died from CO intoxication and were excluded, together with their matched controls. This led to the exclusion of 648 cases involving suspected direct death from CO intoxication and 648 matched controls. The final study sample thus consisted of 27,984 CO intoxication cases and 27,984 matched controls (Figure 1).

Definition of outcome disease and comorbidities

Ischemic stroke was defined as treatment more than once with reference to ICD-10 code I63. We identified diabetes (DM) (E10–E14), hypertension (I10–I15), dyslipidemia (E78), atrial fibrillation (AF) (I48), and ischemic heart disease (IHD) (I20–I25) as comorbidities and defined comorbidities as conditions requiring treatment more than twice with reference to their corresponding ICD-10 codes.

Covariates

The aforementioned eligibility database contains information regarding socioeconomic factors. Age was based on the year of enrollment in the study. Residential areas were divided into Seoul, metropolitan cities outside Seoul, and other regions. Household income was classified as high (highest 30%), middle, and low (lowest 30%) based on income-based insurance contributions. Smoking status was based on information on health behaviors from the national health screening database. No-smoking status information was available for more than one-third of all subjects because they had never undergone a national health screening test or had not completed the questionnaire on health behaviors. As most of the cases involved a lack of participation in a screening test rather than missing data, we did not exclude these subjects but classified them into a separate category.

Statistical analysis

We conducted descriptive statistical analyses of sex, age, household income, residential area, comorbidities, and smoking status. We used chi-square tests to assess the differences in household income and smoking status

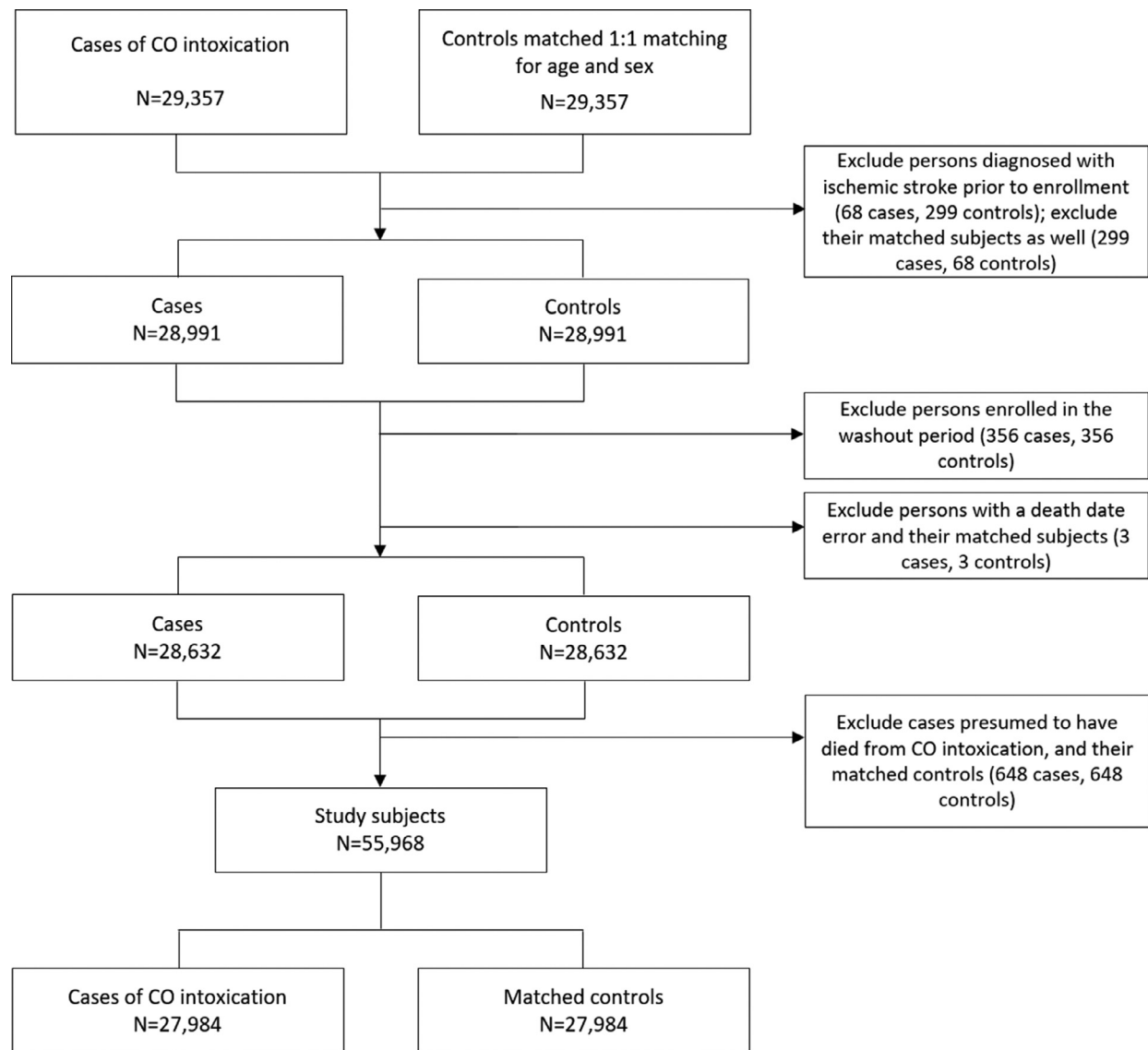


Fig. 1. Flow chart for the selection of the study population.

between the CO intoxication and control groups. We also assessed the incidence of ischemic stroke in the CO intoxication and control groups and used a chi-square test to evaluate the differences between the two groups. We evaluated the incidence rate of ischemic stroke by calculating person-years during the follow-up period in both the case and control groups. We also determined the incidence rates of ischemic stroke according to age group, sex, residential area, household income, comorbidities, and smoking status. Since the CO intoxication cases and controls were matched for sex and age at a ratio of 1:1, we used a conditional logistic regression model for analysis.¹⁵ We calculated unadjusted HRs and corresponding 95% confidence intervals (CIs) as well as HRs and 95% CIs adjusted for residence, household income, comorbidities, and smoking status. In addition, we used conditional logistic

regression to obtain unadjusted and adjusted HRs and corresponding 95% CIs for the case and control groups by stratification according to covariates and follow-up periods. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA), and $p < 0.05$ was considered statistically significant.

Ethics statement

This study was approved by the Institutional Review Board (IRB) of Gachon University Gil Medical Center (IRB No. GCIRB2019-021) and by the Korean National Health Insurance Service Medical Information Disclosure Committee (NHIS-2019-1-247), and written informed consent was waived by the IRB due to the retrospective nature of the study.

Results

Baseline characteristics of the subjects

The subjects in our study had an average age of 37.3 years. The age group of 40–64 years was the most frequent at 36.4%, followed by that of 25–39 years at 33.1%, <25 years at 23.6%, and ≥65 years at 6.9%. Men represented 55.0% of all subjects. Because cases and controls were matched for sex and age, the sex and age distributions in both groups were the same. Regarding residential area, the proportion of Seoul residents in the control group was 20.4%, which was higher than the 16.4% in the CO intoxication group. Regarding household income, subjects with high incomes represented 36.2% of all subjects in the control group and 29.1% in the CO intoxication group. The differences between the case and control groups in terms of residence and household income level were statistically significant. The proportion of patients with comorbid DM and dyslipidemia was significantly higher in the case group (DM, 8.1%; dyslipidemia, 17.6%) than in the control group (DM, 6.3%; dyslipidemia, 14.2%), whereas the proportion of patients with comorbid IHD was significantly higher in the control group (1.4%) than in the case group (1.0%). The proportions of patients with

hypertension (case group, 8.5%; control group, 8.4%) and AF (case group, 0.2%; control group, 0.3%) were not significantly different between the groups. As no national health screening data were available for 37.8% of all subjects, the smoking status of these subjects was unknown; the proportion of “no information on smoking status” was slightly higher in the CO intoxication group than in the control group. The proportion of current smokers was 22.7% in the CO intoxication group, higher than the 18.1% in the control group, while the proportion of “never smokers” was 31.7% and 36.9% in the CO intoxication and control groups, respectively; these differences were statistically significant (Table 1).

Incidence of ischemic stroke

The number of cases of ischemic stroke during the follow-up period, from 2003 to 2017, was >2 times higher in the CO intoxication group (884) than in the control group (419); this difference was statistically significant (Table 2). The follow-up person-years were 124,904.4 and 128,254.6 in the CO intoxication and control groups, respectively, and the incidence rates per 1,000 person-years were 7.08

Table 1. Baseline characteristics of the subjects.

Characteristics	All subjects N = 55,968	Carbon monoxide intoxication N = 27,984	Control N = 27,984	p-value
Mean age (years)	37.3 ± 17.5	37.3 ± 17.5	37.3 ± 17.5	1.000
Age (years)				1.000
<25	13,198 (23.6%)	6,599 (23.6%)	6,599 (23.6%)	
25–39	18,510 (33.1%)	9,255 (33.1%)	9,255 (33.1%)	
40–64	20,382 (36.4%)	10,191 (36.4%)	10,191 (36.4%)	
≥65	3,878 (6.9%)	1,939 (6.9%)	1,939 (6.9%)	
Sex				1.000
Men	30,766 (55.0%)	15,383 (55.0%)	15,383 (55.0%)	
Women	25,202 (45.0%)	12,601 (45.0%)	12,601 (45.0%)	
Residential area				<0.0001
Seoul	10,301 (18.4%)	4,596 (16.4%)	5,705 (20.4%)	
Other metropolitan cities	13,562 (24.2%)	6,726 (24.0%)	6,836 (24.4%)	
Other areas	32,105 (57.4%)	16,662 (59.5%)	15,443 (55.2%)	
Household income				<0.0001
High	18,271 (32.7%)	8,138 (29.1%)	10,133 (36.2%)	
Middle	21,598 (38.6%)	11,011 (39.4%)	10,587 (37.8%)	
Low	16,099 (28.8%)	8,835 (31.6%)	7,264 (26.0%)	
Comorbidity				
Hypertension	4,738 (8.5%)	2,376 (8.5%)	2,362 (8.4%)	0.8316
Diabetes	4,022 (7.2%)	2,267 (8.1%)	1,755 (6.3%)	<0.0001
Dyslipidemia	8,897 (15.9%)	4,930 (17.6%)	3,967 (14.2%)	<0.0001
Atrial fibrillation	132 (0.2%)	61 (0.2%)	71 (0.3%)	0.3835
Ischemic heart disease	662 (1.2%)	227 (1.0%)	385 (1.4%)	<0.0001
Smoking				<0.0001
Never smoker	19,192 (34.3%)	8,869 (31.7%)	10,323 (36.9%)	
Ex-smoker	4,176 (7.5%)	1,838 (6.6%)	2,338 (8.4%)	
Current smoker	11,424 (20.4%)	6,363 (22.7%)	5,061 (18.1%)	
Missing	21,176 (37.8%)	10,914 (39.0%)	10,262 (36.7%)	

Table 2. Incidence of ischemic stroke between 2003 and 2017.

Incidence of ischemic stroke	All subjects N = 55,968	Carbon monoxide intoxication N = 27,984	Control N = 27,984	p-value
No	54,665 (97.7%)	27,100 (96.8%)	27,565 (98.5%)	<0.0001
Yes	1,303 (2.3%)	884 (3.2%)	419 (1.5%)	

Table 3. Incidence rates and hazard ratios (HRs) of ischemic stroke according to residential area, household income, comorbidities, and smoking status.

Variables	No. of cases	Person-years	Incidence*	HR (95% CI)	
				Crude	Adjusted
Group					
Control	419	128,254.6	3.27	1	1
Carbon monoxide intoxication	884	124,904.4	7.08	2.34 (2.06-2.67)	2.31 (2.01-2.65)
Residential area					
Seoul	212	52,619.7	4.03	1	1
Other metropolitan cities	241	60,425.9	3.99	0.95 (0.73-1.25)	0.82 (0.61-1.11)
Other areas	850	140,113.5	6.07	1.55 (1.23-1.94)	1.16 (0.90-1.49)
House income					
High	422	82,152.1	5.14	1	1
Middle	429	95,894.8	4.47	1.27 (1.04-1.57)	1.15 (0.91-1.45)
Low	452	75,112.2	6.02	1.44 (1.17-1.77)	1.14 (0.91-1.44)
Comorbidity (no vs yes)					
Hypertension	201	15,983.2	12.58	0.93 (0.72-1.19)	0.99 (0.70-1.40)
Diabetes	150	13,426.1	11.17	0.89 (0.68-1.16)	0.92 (0.63-1.34)
Dyslipidemia	216	28,521.6	7.57	0.85 (0.68-1.06)	0.84 (0.60-1.18)
Atrial fibrillation	9	369.1	24.38	2.25 (0.69-7.30)	3.15 (0.86-11.50)
Ischemic heart disease	35	1,996.6	17.53	1.35 (0.79-2.31)	2.28 (1.21-4.32)
Smoking					
Never smoker	616	93,906.3	6.56	1	1
Ex-smoker	111	17,290.4	6.42	0.87 (0.63-1.19)	0.97 (0.68-1.38)
Current smoker	251	51,152.2	4.91	1.45 (1.12-1.89)	1.48 (1.10-1.98)
Missing	325	90,810.1	3.58	1.46 (1.17-1.83)	1.49 (1.16-1.91)

*Incidence rate per 1,000 person-years.

and 3.27 in the case and control groups, respectively (Table 3).

Conditional logistic regression

The risk of ischemic stroke was approximately 2.3 times higher in the CO intoxication group than in the control group, and the difference was statistically significant (crude HR 2.34, 95% CI 2.06–2.67). Accordingly, the risk of ischemic stroke was high after adjustments for residential area, household income, comorbidities, and smoking status (adjusted HR 2.31, 95% CI 2.01–2.65). As for other covariates, we observed significant increases in the risk of ischemic stroke in patients with IHD (adjusted HR 2.28, 95% CI = 1.21–4.32), current smokers (adjusted HR 1.48, 95% CI = 1.10–1.98), and subjects without available smoking information (adjusted HR 1.49, 95% CI = 1.16–1.91). Regarding residential area and household income, univariate analyses yielded significant increases in risk in those

living in non-metropolitan areas (crude HR 1.55, 95% CI 1.23–1.94) and those in the low-income group (crude HR 1.44, 95% CI 1.17–1.77); however, these differences disappeared after adjustment for other variables (Table 3).

Stratification according to socioeconomic factors, comorbidities, and smoking status revealed a stronger association between CO intoxication and ischemic stroke in men, those <40 years of age, those with low incomes, and current smokers than in women, elderly patients, those in the other household-income groups, and never smokers, respectively. Subjects living in Seoul showed a weaker association than those living in other regions; nevertheless, no statistically significant differences were observed (Table 4).

Stratification according to follow-up periods revealed a 3.7 times higher (unadjusted) risk of ischemic stroke within 2 years of CO intoxication, which further increased to a >7 times higher risk after adjustment for

Table 4. Incidence rates and hazard ratios (HRs) of ischemic stroke stratified by sex, age, residential area, household income, comorbidity, and smoking status.

Variables	Carbon monoxide intoxication			Control			HR (95% CI)*	
	No. of cases	Person-years	Incidence**	No. of cases	Person-years	Incidence**	Unadjusted	Adjusted
Sex								
Women	419	59,696.9	7.02	232	60,791.2	3.82	1.98 (1.66-2.37)	1.98 (1.63-2.39)
Men	465	65,207.5	7.13	187	67,463.4	2.77	2.79 (2.31-3.37)	2.73 (2.23-3.34)
Age (years)								
<40	108	71,063.3	1.52	39	72,273.6	0.54	2.83 (1.95-4.13)	3.53 (2.15-5.82)
40-64	432	44,199.7	9.77	164	45,749.6	3.58	2.92 (2.41-3.54)	2.73 (2.23-3.34)
≥65	344	9,641.5	35.68	216	10,231.4	21.11	1.70 (1.38-2.06)	1.67 (1.35-2.08)
Residential area								
Seoul	121	21,731.8	5.57	91	30,887.9	2.95	1.41 (0.76-2.63)	1.81 (0.71-4.59)
Other metropolitan cities	150	28,041.1	5.35	91	32,384.8	2.81	2.53 (1.39-4.61)	2.17 (1.02-4.96)
Other areas	613	75,131.5	8.16	237	64,982	3.65	2.02 (1.63-2.49)	2.16 (1.72-2.70)
House income								
Low	325	39,972.4	8.13	127	35,139.8	3.61	2.50 (1.61-3.88)	2.55 (1.56-4.15)
Middle	300	48,786.6	6.15	129	47,108.2	2.74	2.31 (1.59-3.36)	2.27 (1.52-3.39)
High	259	36,145.5	7.17	163	46,006.6	3.54	1.82 (1.27-2.62)	2.03 (1.34-3.08)
Comorbidity								
No	684	105,692.4	6.47	332	111,247.7	2.98	2.19 (1.85-2.58)	2.11 (1.77-2.52)
Yes	200	19,212	10.41	87	17,006.9	5.12	2.09 (1.39-3.14)	2.59 (1.48-4.52)
Smoking								
Never smoker	411	44,858	9.16	205	49,048.4	4.18	2.11 (1.66-2.67)	2.08 (1.61-2.68)
Ex-smoker	77	7,578.9	10.16	34	9,711.5	3.50	3.50 (1.15-10.63)	2.73 (0.67-11.06)
Current smoker	190	27,696.6	6.86	61	23,455.7	2.60	2.69 (1.51-4.77)	3.55 (1.67-7.60)
Missing	206	44,771	4.60	119	46,039.1	2.58	2.11 (1.22-3.64)	2.22 (1.24-3.95)

*HR is the risk in the CO intoxication group with reference to that in the control group.

**Incidence rate per 1,000 person-years.

Table 5. Incidence and hazard ratios (HRs) of ischemic stroke stratified by follow-up period.

Follow-up periods	Carbon monoxide intoxication				Control		HR (95% CI)*		
	Incidence**		Incidence**		No. of cases	Person-years	Incidence**	Unadjusted	Adjusted
	No. of cases	Person-years	No. of cases	Person-years					
≤2	107	7,695.3	13.90	7,325.5	17	7,325.5	2.32	3.73 (2.11-6.60)	7.47 (2.76-20.26)
2-4	131	22,111.5	5.92	22,215.6	45	22,215.6	2.03	3.16 (2.12-4.70)	3.64 (2.17-6.12)
4-6	152	24,999.3	6.08	25,898.7	76	25,898.7	2.93	2.42 (1.74-3.36)	2.29 (1.60-3.27)
>6	494	70,098.3	7.05	72,814.8	281	72,814.8	3.86	1.87 (1.58-2.21)	1.84 (1.53-2.20)

*HR is the risk of CO intoxication group with reference to control group.

**Incidence rate per 1,000 person-years.

other covariates. The risk decreased over time but remained significantly higher (1.8 times) than that in the control group 6 years after the CO intoxication event (Table 5).

Discussion

We used a national health database, the NHID, to analyze the incidence of ischemic stroke in individuals who had experienced CO intoxication and in a group of age- and sex-matched controls. We found that people who had experienced CO intoxication had a significantly higher risk of developing ischemic stroke, more than twice that of those who had not experienced CO intoxication. In particular, male sex, those younger than 40 years, those in the low-income group, subjects with comorbidities, and current smokers had a higher risk of ischemic stroke. The risk of ischemic stroke was the highest within 2 years after CO intoxication, and even >6 years after, the risk remained significantly higher than that in the control group.

These long-term, significant increases in the risk of ischemic stroke after CO intoxication are consistent with the findings of a previous study¹² that used the National Health Insurance Research Database of Taiwan. The adjusted HR for ischemic stroke after CO intoxication in the Taiwanese study was 2.6 (95% CI = 2.15–3.15), similar to the effect magnitude of risk observed in our study. The Taiwanese study also showed a higher risk of ischemic stroke in men and younger age groups. However, contrary to that in our study, the risk of ischemic stroke was higher in the high-income group as well as in subjects without comorbidities, in the Taiwanese study.

The increased risk of ischemic stroke after CO intoxication can be explained by oxidative injury.¹⁶ Oxidative stress caused by CO intoxication can induce cerebrovascular endothelial dysfunction or endothelial cell death, thereby causing brain injury, which leads to ischemic stroke.¹⁷⁻¹⁹ Moreover, increased fibrinogen function and hypercoagulability are induced during exposure to CO, leading to thromboembolism.^{20,21} This can accelerate the occurrence of ischemic stroke. Although the risk of stroke in the early stages decreases with time, chronic effects of CO-related brain injury persist, potentially increasing the long-term risk of ischemic stroke.

Another mechanism that might explain how CO intoxication increases the long-term risk of ischemic stroke is the induction of cardiac arrhythmia. Hypoxic stress due to CO intoxication is related to cardiac rhythm disturbances including sinus tachycardia, atrial flutter and fibrillation, premature ventricular contractions, and ventricular tachycardia and fibrillation,²² which are known to increase the risk of ischemic stroke.^{23,24} In our study, the risk of stroke increased by >3 times in individuals with AF as an underlying disease; however, the increase was not statistically significant. As the number of individuals with comorbid AF in our sample was <10, this

comparison presumably did not have enough statistical power to yield meaningful results.

The average age at CO intoxication in our sample was 37.3 years, with more than half of the cases occurring in individuals aged <40 years. The risk of ischemic stroke after CO intoxication was higher in this age group than in elderly individuals. Similarly, in a Taiwanese study, the 20–34 age group had the highest risk of CO intoxication.¹² The risk of developing ischemic stroke increases with age, and other risk factors, such as comorbidities and socioeconomic status, also affect the incidence of ischemic stroke in elderly people. In younger age groups, not only is ischemic stroke rare, but the prevalence of comorbidities is also low; thus, CO exposure may have a stronger effect. Although we did not identify the prevalence of comorbidities and other risk factors in the younger age group, the effect of CO intoxication in younger people can be considered greater than that in the elderly.

Regarding household income, the CO intoxication group contained fewer individuals with high incomes and more subjects with low incomes than the control group did. Lower socioeconomic groups have a greater risk of CO exposure due to leakage,^{25,26} and this can lead to greater CO intoxication, which was consistent with the results of our study. The prevalence of risk factors such as comorbidities and smoking is high in low-income demographics,²⁷ indicating that a low income is indeed related to the observed increase in the incidence of ischemic stroke. A study that used the Korean NHID in 2014 found that the lower the household income, the higher the incidence of ischemic stroke.²⁸ Hospital-based observational studies in Italy also showed the same results.²⁹ However, the risk of ischemic stroke in the low-income group was not significantly different from that in higher-income groups when other covariates were taken into account. When we stratified cases according to income levels in the current study, the increase in the risk of ischemic stroke in the CO intoxication group was greater in the low-income group than that in higher-income groups; however, the difference was not large compared with that in other income groups.

Regarding comorbidities, DM and dyslipidemia were significantly more prevalent in the CO intoxication group, whereas IHD was significantly more prevalent in the control group at the baseline. However, the only comorbidity that increased the risk of ischemic stroke was IHD. As mentioned earlier, AF increased the risk of ischemic stroke by more than 3 times, nonetheless, the difference was not statistically significant in comparison with groups with other comorbidities. Although there was a significant difference in the underlying prevalence of some comorbidities between the case and control groups, it was corrected through multivariate analysis. Furthermore, we attempted to minimize the bias due to these differences through stratified analysis according to comorbidities. When stratified according to the presence of comorbid

diseases, the risk of ischemic stroke after CO intoxication increased in the group with comorbidities. One might assume that thrombosis, embolism, and systemic hypoperfusion, which may be caused by CO intoxication, are more likely to occur in groups with underlying diseases. However, compared to the group without comorbidities, the group with comorbidities showed a small difference in risk magnitude, and our findings contradict those of the Taiwanese study in this respect. Therefore, further research is needed to elucidate this point.

As regards smoking, the proportion of current smokers was significantly higher than that of never smokers in the CO-intoxication group at baseline. Smoking is a well-known major risk factor for ischemic stroke, and in our study, current smokers had a high risk of ischemic stroke, accordingly. Since the proportion of current smokers differed between the case and control groups, the analysis results might have been affected; however, as with the comorbidities, it was corrected through multivariate analysis, and the risk of bias was minimized by stratified analysis according to smoking status. The increase in the risk of ischemic stroke after CO intoxication was much greater in current smokers than in never smokers. This suggests that smoking can further increase the risk of ischemic stroke due to the effect of its synergy with CO intoxication.

On investigating how the risk of ischemic stroke developed over time after CO intoxication, we found that it was highest within the first 2 years and then gradually decreased thereafter. However, even >6 years after, although the effect magnitude had decreased, the risk of ischemic stroke after CO intoxication remained statistically significant. This suggests that CO intoxication increases the risk of developing ischemic stroke in the long term as well as in the early stage.

This study has several limitations. First, there might have been a validation problem regarding the diagnoses of ischemic stroke and comorbidities. While the diagnosis of CO intoxication is relatively accurate, discrepancies may exist between the diagnoses listed in the NHID and the diseases patients had in reality, stemming from the inherent nature of claims data that are designed for reimbursement rather than research purposes. Reimbursement policies could also contribute to such discrepancies.³⁰ Second, the NHID lacked some information. We did not have access to laboratory records and radiographic data, and information on smoking behavior in the health examination database was incomplete because nearly 30% of subjects had never undergone a national health check-up. Furthermore, although controls were randomly selected by matching individuals for sex and age, selection biases might have occurred because other factors were not considered. In fact, the number of ischemic strokes that occurred before enrollment in the control group was much higher than that before CO intoxication in the case group. However, because this bias is expected to weaken

the association between CO intoxication and ischemic stroke, the actual association can thus be expected to be even stronger. In addition, whereas we suggest mechanisms related to thrombosis, microvascular injury, and cardiac arrhythmia to explain the increased risk of ischemic stroke caused by CO intoxication, our data do not allow us to compare the occurrence of stroke according to etiology. Finally, since the number of CO intoxication cases diagnosed before 2010 was much smaller than the number diagnosed later, it is likely that many undiagnosed cases were not included in the NHID. We cannot rule out the possibility that these missing cases affected our results.

Despite these limitations, our study was a well-designed retrospective study that comprehensively analyzed the total number of CO intoxication cases in Korea within a certain period. Our study included more cases and assessed a longer follow-up period than the earlier Taiwanese study. In addition, we adjusted and stratified our analyses according to smoking status, which is an important risk factor for ischemic stroke. Moreover, we linked data from KoSTAT on causes of death to the NHID to estimate the long-term health effects of CO intoxication more accurately by excluding individuals who might have died from CO intoxication.

Conclusions

Our analyses using the NHID show that individuals who have experienced CO intoxication are consistently at a higher risk of ischemic stroke. Although our results should be interpreted with caution because of the limitations of the NHID, our findings corroborate that CO intoxication and ischemic stroke are associated and that CO intoxication increases the long-term risk of ischemic stroke. Appropriate management and follow-up assessments are necessary for people who have experienced CO intoxication to prevent the occurrence of ischemic stroke.

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Declaration of Competing Interest

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