Increased Long-Term Risk of Dementia in Patients With Carbon Monoxide Poisoning: A Systematic Review and Meta-Analysis of Cohort Studies

Meixian Zhang1*, Zhu Liduzi Jiesisibie1*, Ho-Shan Wei2, Pei-En Chen3,4, Ching-Wen Chien5, Ping Tao6, and Tao-Hsin Tung1

1Enze Medical Research Center, Taizhou Hospital of Zhejiang Province, Wenzhou Medical University, Linhai, China
2Department of Public Health, Kaohsiung Medical University, Kaohsiung, Taiwan
3Institute of Health Policy and Management, National Taiwan University, Taipei, Taiwan
4Taiwan Association of Health Industry Management and Development, Taipei, Taiwan
5Institute for Hospital Management, Tsing Hua University, Shenzhen Campus, Shenzhen, China
6Department of Medical Affairs and Planning, Section of Medical Fees Kaohsiung Veterans General Hospital, Kaohsiung City, Taiwan

Objective To assess whether carbon monoxide (CO) poisoning increases the incidence of dementia.

Methods We searched the Cochrane Library, PubMed, and EMBASE from inception to 14 August 2022. Two authors independently selected studies, assessed the quality of included studies, and extracted data. Any disagreement was resolved by discussion with a third author. Only cohort study with an enough follow-up period was included for systematic reviews and meta-analysis.

Results Thirty-three full texts were initially searched, but only three studies met our inclusion criteria, and they were comprised of 134,563 participants who were initially free of dementia. The follow-up period ranged from 9 to 12 years. We found that CO poisoning increased the risk of dementia incidence (adjusted hazard ratio 2.61, 95% confidence interval 1.56 to 4.36, p=0.0003). Subgroup analysis showed that the increased dementia risk was significant in males but not in females, and the highest risk was in young age group, followed by in middle age group, but not in the old one.

Conclusion Overall the evidence from prospective cohort studies supported a link between CO exposure and an increased dementia risk, although all the included studies were limited to Taiwanese population.

Keywords Carbon monoxide poisoning; Cohort study; Dementia; Meta-analysis.
even death. In addition, about 30% of CO poisoning patients would exhibit chronic neuropsychiatric symptoms several months later, such as mental deterioration, gait disturbance, incontinence, mutism, and Parkinsonism. Several studies have reported that CO poisoning increased the risk of dementia. It is estimated that the cumulative incidence rate and mortality rate of CO poisoning worldwide are 137 and 4.6 cases per million person-years in 2017, respectively. In Taiwan, the mortality rate of unintentional CO poisoning continued to rise from 1.6 to 3.5 per million person-years during the period 1997–2003, and the most common events of CO poisoning are using heating appliances in enclosed space or suicide. Furthermore, the incidence of intentional CO poisoning including suicide by charcoal burning has also increased. 

In this study, we performed a systematic literature review and meta-analysis of cohort studies to assess the long-term risk of dementia, Alzheimer's disease, and cognitive disorder in people with experience of CO poisoning.

METHODS

Literature search

We conducted and reported this study according to MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines. The search was carried out without language restriction on the electronic databases Cochrane, PubMed, and EMBASE up to 14 August 2022. The search strategy contained two components: 1) Charcoal-burning OR Carbon monoxide poisoning OR Carbasyhemoglobinemia OR Carboxyhemoglobin OR Charcoal-burning suicide, and 2) Neurodegenerative Disease OR Alzheimer OR Dementia OR Cognitive Decline OR Chronic traumatic encephalopathy. These components were combined using the Boolean “AND” operator to obtain any link between them. The search strategy was modified when searching other databases. No hand-searching was worked.

Study selection

Studies were included for meta-analysis if they met the following criteria: 1) cohort study design was used, 2) the exposure was CO poisoning, 3) the end point was incidence of dementia, Alzheimer, and cognitive disorder, 4) the study reported quantitative estimates of hazard ratio (HR), or relative risk with 95% confidence intervals (CIs) or sufficient data for determination of dementia related to CO poisoning, and 5) the cohort had an adequate follow-up interval. We excluded cross-sectional or case-control studies, as well as conference abstracts that provided limited information. We scrutinized the relevant studies using their titles and abstracts first and then reviewed all relevant articles, with confusion resolved by discussion with a third author.

Data extraction and quality assessment

The following information was extracted from each study using a standardized data-extraction form: the first author’s name, year of publication, country, study design, study duration, participants’ characteristics, sample size, database, and risk estimates. Two authors (H-S W and ZL J) independently performed the quality assessment of included studies using the Newcastle-Ottawa Scale (NOS) for cohort studies. The scale assesses aspects regarding population/sampling methods, exposure/outcome collections, as well as statistical matching/adjustments of the data. A maximum of nine quality scores were assigned for each study. Studies with seven or more scores were awarded high quality. Discrepancies were resolved by the third investigator.

Statistical analysis

We synthesized all available association estimates between exposure to CO poisoning and risk of dementia in Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The estimate risk of outcome as HRs and 95% CIs were pooled under a random-effects model because of considerable clinical heterogeneity. We assessed heterogeneity using the I² statistic, which evaluates the degree of variation across studies that is due to heterogeneity rather than chance alone. An I² value of ≥50% indicates substantial heterogeneity.

RESULTS

Results of literature search

A total of 218 unique citations were identified by our search strategy (137 from PubMed, 106 from Embase, and 11 from the Cochrane Library, with 36 duplicates), of which 33 were accepted for full text review after screening by titles and abstracts. From the remaining 33 articles, we excluded papers with irrelevant content (n=9), different outcome (n=7), case report (n=11), animal experiment (n=2), and conference abstracts (n=1). Ultimately, three articles were eligible and included in our meta-analysis, and two studies have the stratified data. A detailed screening flow is shown in Figure 1.

Study characteristics

The primary characteristics of the included studies are summarized in Table 1. These studies were published between 2016 and 2018, based on the National Health Insurance Re-
All three selected studies were assessed to have high quality with a mean score of 9. The level of agreement between reviewers was 100%. Figure 2 shows a forest plot presenting the association between CO poisoning and dementia.

**Table 1. Characteristics of studies included in the meta-analysis**

| Study, year, database used | Inclusion criteria | Subjects | Outcome measures | Study endpoint | NOS score | Effect size |
|---------------------------|--------------------|----------|------------------|---------------|-----------|-------------|
| Lai et al., 2016 Taiwan's NHIRD 2000–2011 | New inpatient patients diagnosed with CO poisoning (ICD-9-CM 986) | 4,103 patients with newly diagnosed charcoal-burning suicide attempts, 12,309 controls individual-matched by sex, age, and index year without charcoal-burning suicide attempts in a ratio of 1:3. | Dementia | Diagnosis of dementia, death, withdrawal from the insurance program, or December 31, 2011 | S | HR: 1.50, 95% CI: 1.11–2.04 |
| Wong et al., 2016 Taiwan's NHIRD 2005–2010 | Inpatient and outpatient patients diagnosed with CO poisoning (ICD-9-CM 986, E868.8) | 14,590 patients with CO poisoning, 58,360 controls individual-matched by sex, age (+1 year), and index date without CO exposure in a ratio of 1:4 | Dementia | Diagnosis of dementia, death, or December 31, 2013 | S | HR: 2.75, 95% CI: 2.26–3.35 |
| Chang et al., 2018 Taiwan's NHIRD 2000–2010 | ≥20 years of age Diagnosis of charcoal-burning suicide attempts (ICD-9-CM code: E952) | 9,041 adults newly diagnosed with CO poisoning, 36,160 controls frequency-matched by sex, age (every 5 years), and hospitalization year with non-CO poisoning in a ratio of 1:4 | Dementia | Diagnosis of dementia, withdrawal from the insurance program, or December 31, 2010 | S | HR: 4.220, 95% CI: 3.188–5.586 |

Scale domains: S, selection of study groups; C, comparability; O, outcome assessment. NHIRD, National Health Insurance Research Database; CO, carbon monoxide; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes; NOS, Newcastle-Ottawa Scale; HR, hazard ratio; CI, confidence interval.
association between CO poisoning and the risk for dementia. The adjusted effect estimates of all three studies were shown after adjustment for age, sex and comorbidities including hypertension, diabetes and cerebrovascular disease. However, three studies were different with adjustment for other comorbidities, and only one study adjusted for geographic area and urbanization level of residence, and monthly insured premium. Heterogeneity across studies was also found to be statistically significant ($I^2=92\%$, $p<0.001$). The random effect model suggested significant increased risk for dementia in those who were exposed to CO poisoning compared with those who were not (overall HR=2.61, 95% CI 1.56–4.36). The quality of evidence for this outcome was rated as high.

### Subgroup analyses

Two published studies by Lai et al.\textsuperscript{13} and Wong et al.\textsuperscript{14} provided detailed data on the stratified analysis based on the sex of CO poisoning patients. Overall, 23,631 patients with CO poisoning and 94,520 controls were included, with 49.4% (n=11,681) female. As illustrated in Figure 3, there was substantial heterogeneity across the studies ($I^2=79\%$ in males and 85% in females), indicating a very high degree of variation. A random-effects model meta-analysis found no increase in the risk of dementia in subjects with female patients (HR 1.78; 95% CI 0.80–3.97). The quality of evidence for this outcome was rated as very low. The risk of dementia was increased in male patients with CO poisoning (HR 2.31; 95% CI 1.39–3.85). We interpreted the quality of evidence for this outcome as high.

Although the boundary values of age groups between the two studies are different, they can be divided into three groups according to the young, middle and old groups. Figure 4 shows the adjusted HRs for the association between CO exposure and incident dementia were 5.18 (95% CI 1.30–20.59) in young group, 3.74 (95% CI 1.11–12.60) in middle age group and 1.70 (95% CI 0.69–4.17) in old group, respectively. We judged the quality of evidence for this outcome as high.

### Sensitivity analyses

In this study, the results of sensitivity analyses show that the pooled positive effect estimate was no longer statistically significant after omitting one of selected studies, which indi-
cated that there was a significant trend that the overall result was influenced by an individual study.\textsuperscript{14}

\textbf{DISCUSSION}

\textbf{Clinical implications}

To the best of our knowledge, this is the first systematic review and meta-analysis focusing on the contribution of CO poisoning on the incident dementia. The results indicate that the risk of dementia in the CO exposed cohorts was more than twofold higher than that in reference population. Subgroup analysis based on sex and age of participants find most of subgroups of CO poisoning to be associated with an increased risk of dementia. The present study is robust because of high quality of the prospective study design and minimized the selection and recall bias. Nonetheless, it is important to note that the heterogeneity of selected studies might attenuate the strength of the result to some degree.

The neurobiological mechanism underlying the association between CO poisoning and dementia has to be elucidated. CO poisoning causes impaired oxygen delivery and mitochondrial oxygen utilization as well as generation of reactive oxygen species. Because of the strong binding to Hb facilitated by the high affinity for the iron ions, high levels of CO exposure diminishes the oxygen-carrying and delivery capacity of the blood. CO poisoning causes brain hypoxia, which may lead to inflammation and subsequent injury. An earlier study found from 63 suspected patients that CO poisoning could cause acute inflammatory responses, even for patients with short-term exposure.\textsuperscript{22} Extravascular CO is bound to molecules such as myoglobin, cytochromes, and nicotinamide adenine dinucleotide phosphate reductase, resulting in impairment of oxidative phosphorylation at the mitochondrial level. Besides, subsequent oxidative stress, and inflammatory responses induced by many hypoxia-independent pathways also contribute to cause nerve damage.\textsuperscript{12} Much evidence suggests that CO toxicity may result in increased reactive oxygen species, free radical, or neuronal nitric oxide, which likely contributes to lipid peroxidation and neuronal and/or cellular injury. Oxidative stress is usually caused by an increase in the production of reactive oxygen species, or an inefficient antioxidant defense system, or a combination of both. Oxidative stress can trigger a series of pathophysiological processes leading to cellular injury and toxicity.\textsuperscript{23}

A randomized clinical trial has found CO poisoning can induce apolipoprotein E (APOE) epsilon4 carriers suffer greater morbidity,\textsuperscript{24} and the APOE epsilon4 allele was a well known genetic risk factor for dementia\textsuperscript{25,26} and Alzheimer’s disease,\textsuperscript{27} the primary cause of dementia in the elderly. Currently, we realized that CO poisoning could cause neurological and neuropsychological problems, but the incidence of sequelae after poisoning was unclear. A registry-based observational study in Korea showed that 26.1\% of patients with acute CO poisoning developed delayed neurological sequelae within 6 weeks of discharge.\textsuperscript{28} According to the Weaver’s reported, 46\% of patients with CO poisoning had abnormal neuropsychological findings and symptoms at 6 weeks,\textsuperscript{30} 19\% had cognitive impairment,\textsuperscript{30} and 37\% had abnormal neurologic findings on exami-
nation during 6-year follow up. The studies included in this meta-analysis reported that the incidence rate of dementia was from 15.2 ranging to 23.33 per 10,000 person-years in patients with CO poisoning.

In this study, HRs for the association of CO exposure with incident dementia were highest in young age, followed by middle-aged group. And it was also higher in male than in female. It implied that young and male CO-poisoning patients are more prone to suffer from dementia and need exclusive clinical care. The increasing incidence of mental disorders and intentional or suicide attempt by CO poisoning in the young may be a potential cause for the association of CO poisoning with increased risk of dementia, but further research is needed to confirm this possibility. Due to the difference in alveolar ventilation and total Hb mass between genders, women had a shorter CO clearance compared to men, even after adjusting for ventilation rate. This could explain for the greater likelihood of dementia related CO poisoning in the young and middle-aged males. Therefore, we should focus on preventing CO poisoning accidents occurred at home and in the workplace and public areas. In addition, charcoal-burning suicides became popular in some East Asian countries in the first decade of the 21st century. Taiwan and Hong Kong were the epicenter of the charcoal burning suicide epidemic. Suicides by CO poisoning were more likely to be males and ages 18 to 64 years, and least likely to have a previously identified mental disorder. But they had the highest risk of dementia after CO poisoning according to this meta-analysis. This has important public health implications given that the young- and middle-aged males, as a group, are known to be less likely to be cared. It highlights that they are worthy to be more concern.

There have been no recent new options for therapy. The standard treatment for CO poisoning includes the administration of oxygen and general supportive care. Hyperbaric oxygen (HBO) treatment significantly reduces the half-life of COHb. Several evidences have showed the benefits from HBO therapy on memory, delayed neuropsychological sequelae and lowing mortality, but evidences supporting the use of HBO in patients with CO poisoning come from randomized trials with significant limitations and observational studies. So, identifying patients who will benefit from HBO treatment remains uncertain. In addition, some discordant findings were noted in a randomized trial of 191 patients with CO poisoning, which failed to document benefit, but found more delayed neurologic sequelae for HBO-treated patients. The risk for poisoning-related cognitive sequelae was influenced by various factors such as age, CO exposure interval, poisoning severity and genetic predisposition. Thus, whether the benefits outweigh the potential harms of using HBO to treat CO poisoning remains unclear.

Methodological considerations
There are several limitations to this study. Firstly, only limited cohort studies were identified, and the subjects were based on Taiwanese population. Whether the risk of dementia differs in patients with CO poisoning elsewhere in the world is unclear. Secondly, all studies included in this systematic review based on the same database. Thus, the same patient may have been included repeatedly 1 to 3 times in this systematic review, and this database's disadvantages would similarly present in this meta-analysis. For instance, dementia diagnosis based on International Classification of Diseases, Ninth Revision, Clinical Modification codes may be less accurate than that obtained through a complete interview and neurological examination. Furthermore, the generalizability of the results to populations in other countries is limited. Thirdly, we were unable to conduct subgroup analyses based on the severity level of CO poisoning because the included studies did not provide adequate data. Fourthly, patients who attempted charcoal burning suicide might have suffered more severe brain damage than patients of occupationally related CO poisoning. However, none of the three studies reported the rate of CO poisoning after charcoal-burning suicide.

Conclusion
These findings support a link between CO poisoning and dementia. This evidence implied that we should not only pay attention to the acute symptom in patients with CO poisoning, but also the long-term impact. Further studies that provide data for different ethnic groups are needed to clarify whether a subgroup of patients with CO exposure has an elevated risk of dementia.

Availability of Data and Material
All data generated or analyzed during the study are included in this published article (and its supplementary information files).

Conflicts of Interest
The authors have no potential conflicts of interest to disclose.

Author Contributions
Conceptualization: Tao-Hsin Tung, Ching-Wen Chien, Ping Tao. Data curation: Zhu Liduzi Jiesisibieke, Ho-Shan Wei, Pei-En Chen. Formal analysis: Zhu Liduzi Jiesisibieke, Ho-Shan Wei. Methodology: Tao-Hsin Tung. Supervision: Tao-Hsin Tung. Writing—original draft: Meixian Zhang, Zhu Liduzi Jiesisibieke, Writing—review & editing: Meixian Zhang, Tao-Hsin Tung.

ORCID iDs
Meixian Zhang https://orcid.org/0000-0002-6538-7037
Zhu Liduzi Jiesisibieke https://orcid.org/0000-0002-4986-653X
Ho-Shan Wei https://orcid.org/0009-0003-2710-6817
Pei-En Chen https://orcid.org/0000-0002-0982-3703
Ching-Wen Chien https://orcid.org/0000-0002-0601-4994
Ping Tao https://orcid.org/0000-0002-6590-7311
Tao-Hsin Tung https://orcid.org/0000-0003-2097-8375
REFERENCES

1. Prince MJ, Wu F, Guo Y, Robledo LMG, O'Donnell M, Sullivan R, et al. The burden of disease in older people and implications for health policy and practice. Lancet 2015;385:549-562.

2. Albanese E, Launer LJ, Egger M, Prince MJ, Giannakopoulos P, Wolters FJ, et al. Body mass index in midlife and dementia: systematic review and meta-regression analysis of 589,649 men and women followed in longitudinal studies. Alzheimers Dement (Amst) 2017;8:165-178.

3. Bowman K, Thambisetty M, Kuchel GA, Ferrucci L, Melzer D. Obesity and longer term risks of dementia in 65-74 year olds. Age Ageing 2019;48:367-373.

4. Choi D, Choi S, Park SM. Effect of smoking cessation on the risk of dementia: a longitudinal study. Ann Clin Transl Neurol 2018;5:1192-1199.

5. Doherty S, Marseglia A, Xu W, Darin-Mattsson A, Wang HX, Fratiglioni L. Genetic risk of dementia mitigated by cognitive reserve: a cohort study. Ann Neurol 2019;86:68-78.

6. Livingston G, Sommerlad A, Ortega V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet 2017;390:2673-2734.

7. Ott A, Slooter AJ, Hofman A, van der Hart O, Bos I, van Harskamp F, Witteman JC, Van de Ven BE, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000;283:2008-2012.

18. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses [Internet]. Available at: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed March 21, 2023.

19. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-1558.

20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-560.

21. Thom SR, Bhopale VM, Milovanova TM, Hardy KG, Loque CJ, Lambert DS, et al. Plasma biomarkers in carbon monoxide poisoning. Clin Toxicol 2010;48:47-56.

22. Aksel S, Erdogan S, Idiz N, Celik S, Kaya M, Ucar F, et al. The role of reactive oxygen species and oxidative stress in carbon monoxide toxicity: an in-depth analysis. Redox Rep 2014;19:180-189.

23. Weaver LK. Carbon monoxide poisoning. Undersea Hyperb Med 2020;47:151-169.

24. Hopkins RO, Weaver LK, Valentine KJ, Mower C, Churchill S, Carquist J. Apolipoprotein E genotype and response of carbon monoxide poisoning to hyperbaric oxygen treatment. Am J Respir Crit Care Med 2007;176:1001-1006.

25. Rodrigues JI, Cepero AV, Gil IYS, Medina AMI, Llibre-Guerra JC, Llibre-Guerra JJ, et al. Incidence of dementia and association with APOE genotype in older Cubans. Dementia Neurocogn 2014;8:356-363.

26. Saunders AM, Straitmatter WJ, Schmechel D, George-Hyslop PH, Pericak-Vance MA, Joo SH, et al. Association of apolipoprotein E allele ε4 with late-onset familial and sporadic Alzheimer's disease. Neurology 1993;43:1467-1472.

27. Jeon SB, Sohn CH, Seo DW, Oh BJ, Lim KS, Kang DW, et al. Acute brain lesions on magnetic resonance imaging and delayed neurological sequelae in carbon monoxide poisoning. JAMA Neurol 2018;75:436-443.

28. Weaver LK, Hopkins RO, Chan KJ, Churchill S, Elliott CG, Clemmer TP, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med 2002;347:1057-1067.

29. Hopkins RO, Weaver LK. Cognitive outcomes 6 years after acute carbon monoxide poisoning. In: Undersea and Hyperbaric Medical Society; Inc., editor. Undersea and Hyperbaric Medical Society Annual Scientific Meeting; 2008 Jun 18-27; Salt Lake City, USA. Salt Lake City: Undersea Hyperb Med; 2008. p. 258.

30. Weaver LK, Hopkins RO, Churchill SK, Deru K. Neurological outcomes 6 years after acute carbon monoxide poisoning. In: Undersea and Hyperbaric Medical Society; Inc., editor. Undersea and Hyperbaric Medical Society Annual Scientific Meeting; 2008 Jun 18-27; Salt Lake City, USA. Salt Lake City: Undersea Hyperb Med; 2008. p. 258.

31. Hopkins RO, Weaver LK, Stratman E, Walker EL. Acceleration of carbon monoxide elimination in man by high pressure oxygen. Science 1950;111:652-654.
Carbon Monoxide Poisoning and Dementia Incidence

39. Liu WC, Yang SN, Wu CWJ, Chen IW, Chan JY. Hyperbaric oxygen therapy alleviates carbon monoxide poisoning-induced delayed memory impairment by preserving brain-derived neurotrophic factor-dependent hippocampal neurogenesis. Crit Care Med 2016;44:e25-e39.

40. Lin CH, Su WH, Chen YC, Feng PH, Shen WC, Ong JR, et al. Treatment with normobaric or hyperbaric oxygen and its effect on neuropsychometric dysfunction after carbon monoxide poisoning: a systematic review and meta-analysis of randomized controlled trials. Medicine 2018;97:e12456.

41. Nakajima M, Aso S, Matsui H, Fushimi K, Yasunaga H. Hyperbaric oxygen therapy and mortality from carbon monoxide poisoning: a nationwide observational study. Am J Emerg Med 2020;38:225-230.

42. Huang CC, Ho CH, Chen YC, Lin HJ, Hsu CC, Wang JJ, et al. Hyperbaric oxygen therapy is associated with lower short- and long-term mortality in patients with carbon monoxide poisoning. Chest 2017;152:943-953.

43. Scheinkestel CD, Myles PS, Cooper DJ, Millar IL, Tuxen DV, Bailey M, et al. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial. Med J Aust 1999;170:203-210.

44. 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.