Increased Risk of Dementia in Patients With Acute Organophosphate and Carbamate Poisoning

A Nationwide Population-Based Cohort Study

Jiun-Nong Lin, MD, PhD, Cheng-Li Lin, MSc, Ming-Chia Lin, PhD, Chung-Hsu Lai, MD, PhD, Hsi-Hsun Lin, MD, Chih-Hui Yang, PhD, and Chia-Hung Kao, MD

Abstract: Organophosphate (OP) and carbamate (CM) are the most commonly used pesticides against insects. Little is known regarding the relationship between dementia and acute OP and CM poisoning.

A nationwide population-based cohort study was conducted from the National Health Insurance Research Database in Taiwan. The incidence and relative risk of dementia were assessed in patients hospitalized for acute OP and CM poisoning from 2000 to 2011. The comparison cohort was matched with the poisoned cohort at a 4:1 ratio based on age, sex, and the year of hospitalization.

During the follow-up period, the incidence of dementia was 29.4 per 10,000 person-years in the poisoned group, and represented a 1.98-fold increased risk of dementia compared with the control cohort (95% confidence interval, 1.59–2.47).

This study provides evidence on the association between dementia and acute OP and CM poisoning. Regular follow-up of poisoned patients for dementia is suggested.

INTRODUCTION

Organophosphate (OP) and carbamate (CM) are the most widely used pesticides against insects in agriculture and the household. These compounds are common causes of poisoning and poison-related deaths worldwide, either resulting from occupational, accidental, or intentional exposure. An estimated 300,000 deaths occur each year from intentional pesticide poisoning in rural Asia, and two-thirds of these deaths are caused by OP pesticide.1,2

Both OP and CM inhibit acetylcholinesterase activity, prevent hydrolysis of acetylcholine, and result in acetylcholine accumulation at the cholinergic synapses of the nervous system and neuromuscular junctions.1,3 Although both of these compounds possess similar poisoning mechanisms, OPs irreversibly bind to acetylcholinesterase, whereas CMs reversibly bind to the enzyme.4 Acute poisoning with OP and CM leads to over-stimulation of muscarinic and nicotinic receptors, and results in bronchorrhea, bronchospasm, miosis, bradycardia, salivation, lacrimation, urination, diarrhea, muscle fasciculations, weakness, confusion, agitation, and coma.3

Dementia is a major health problem that strongly influences quality of life in affected patients. The prevalence of dementia is approximately 7% of people aged older than 65 years, and patients with dementia are expected to double every 20 years.4 Alzheimer disease is the most common cause of dementia, followed by vascular dementia.5 Several diseases or factors are associated with dementia, including susceptible genes, environmental factors, diabetes mellitus, hypertension, obesity, smoking, lack of exercise, hyperlipidemia, malnutrition, depression, drugs, and toxins.6–10 Both OP and CM are neurotoxins, and several studies have revealed an association between chronic pesticide exposure and an increased prevalence of cognitive dysfunction and dementia.11–16 How- ever, data on whether acute OP and CM poisoning have long-term effects on dementia are limited. Therefore, we conducted a nationwide population-based retrospective cohort study to
explore the association between dementia and acute OP and CM poisoning requiring hospitalization by analyzing the database of the National Health Insurance Research Database (NHIRD) of Taiwan.

**METHODS**

**Data Source**

The Taiwan National Health Insurance (NHI) is a government-operated, mandatory enrollment health insurance that includes a single-payer system launched since March 1, 1995. According to the NHI annual statistical report, more than 25 million people were enrolled in this program in 2007, representing nearly 99% of the entire population of Taiwan (http://www.nhi.gov.tw/english/index.aspx). The National Health Research Institutes (NHRI) stores all reimbursement claim data to establish and maintain the NHIRD. All personal information is encoded with surrogated identification to protect personal privacy before being released for research. Diseases were defined according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM).

**Ethics Statement**

The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMU-REC-101-012). The IRB also specifically waived the consent requirement.

**Sampled Patients**

Patients aged more than 20 years who were hospitalized for acute OP and CM poisoning (ICD-9-CM 989.3) between 2000 and 2011 were recruited in this study. The index date was defined as the date for diagnosis of OP and CM poisoning. A non-OP and non-CM poisoning cohort was randomly selected from all NHI beneficiaries for comparison. This control cohort was matched with the poisoned cohort at a 4:1 ratio based on age and sex. The follow-up duration was determined from the index date to occurrence of dementia, loss to follow-up, withdrawal from NHI, or until December 31, 2011. The incidence of dementia was 29.4 per 10,000 person-years (mean ± standard deviation [SD]), and a male predominance (approximately 70%) was discerned. In the acute OP and CM poisoning cohort, approximately 63.3% of patients were labors. Underlying comorbidities were more prevalent among patients with acute OP and CM poisoning compared with the control patients ($P < 0.001$).

**Outcome**

The follow-up duration was determined from the index date to occurrence of dementia, loss to follow-up, withdrawal from NHI, or until December 31, 2011.

**Covariates of Interest**

Occupations and comorbidities were involved for data analysis. The occupations were categorized into public servants, labors (farmers, fishermen, and industry workers), business-men/businesswomen, low-income earners, and others. Patients were defined as low-income earners if their insured income was lower than the level required for charging premium. Underlying comorbidities were analyzed, including diabetes mellitus (ICD-9-CM 250), hypertension (ICD-9-CM 401–405), head injury (ICD-9-CM 310.2, 800, 801, 803, 804, 850, 851, 853, and 854), depression (ICD-9-CM 296.2, 296.3, 296.82, 300.4, and 311), stroke (ICD-9-CM 430–438), chronic obstructive pulmonary disease (COPD; ICD-9-CM 490–492, 494, and 496), coronary artery disease (ICD-9-CM 410–414), congestive heart failure (ICD-9-CM 428), atrial fibrillation (ICD-9-CM 427.31), cancer (ICD-9-CM 140–208), and chronic kidney disease (ICD-9-CM 585, 586, 588.8, and 588.9).

**Statistical Analysis**

All data were analyzed using SAS statistical software (Version 9.3; SAS Institute Inc., Cary, NC). Student $t$ test and the Chi-square test were used to examine the differences in continuous variables and categorical variables, respectively. The cumulative incidence of dementia was calculated using the Kaplan–Meier method and the difference between the 2 cohorts was tested using the log-rank test. The incidence rates (per 10,000 person-year) were estimated for both the cohorts, stratified by associated demographic variables, occupations, comorbidity, and follow-up duration. Univariate and multivariate Cox proportion hazard regression models were used to examine the effect of OP and CM poisoning on the risk of dementia, shown as hazard ratios (HRs) with 95% confidence intervals (CIs). The multivariable models were adjusted for age, sex, occupation, and comorbidities listed previously and also considered the multiplicative interaction of age and sex. All $P$ values were 2-tailed, and $P < 0.05$ was considered statistically significant.

**RESULTS**

This study consisted of 9616 patients with acute OP and CM poisoning and 38,510 control patients without OP and CM poisoning. Table 1 shows the demographics and comorbidities of the poisoned and control groups. The age of patients with OP and CM poisoning was $53.6 ± 16.4$ years (mean ± standard deviation [SD]), and a male predominance (approximately 70%) was discerned. In the acute OP and CM poisoning cohort, approximately 63.3% of patients were labors. Underlying comorbidities were more prevalent among patients with acute OP and CM poisoning compared with the control patients ($P < 0.001$).

The follow-up durations were $5.39 ± 3.85$ and $6.51 ± 3.44$ years (mean ± SD) for the poisoned cohort and the control group, respectively. The overall prevalence of dementia among poisoned patients was $3.17\%$ during 12 years of follow-up. The cumulative incidence of dementia among patients with OP and CM poisoning was significantly higher than that among the nonpoisoned cohort ($P < 0.001$, Figure 1).

The incidence of dementia was $29.4$ per $10,000$ person-years among patients with OP and CM poisoning; this was significantly higher than that among the control group ($14.2$ per $10,000$ person-years) (Table 2). The adjusted HRs for dementia associated with acute OP and CM poisoning were $1.98$ (95% CI, 1.59–2.47). Women had a higher prevalence rate of dementia than men, but the risk of dementia following acute OP and CM poisoning was slightly higher in men than in women (adjusted HRs $2.06$ vs. $1.86$). The incidence of dementia increased with age in both cohorts. The age-specific adjusted HRs of dementia associated with OP and CM poisoning peaked among patients $50–64$ years of age (adjusted HR, $2.74$; 95% CI, $1.54–4.86$). The occupation-specific risks of dementia following acute OP and CM poisoning were significantly high in labors (adjusted HR, $2.21$; 95% CI, $1.69–2.9$) and businessmen/businesswomen (adjusted HR, $2.52$; 95% CI, $1.46–4.34$). Comorbidity-specific
analysis showed that the incidence of dementia associated with OP and CM poisoning increased independent of underlying diseases. The relative risk for dementia was highest during the first year following acute OP and CM poisoning (adjusted HR, 2.95; 95% CI, 2.02–4.31), hypertension (adjusted HR, 2.43; 95% CI, 1.79–3.31), depression (adjusted HR, 3.99; 95% CI, 2.81–5.67), stroke (adjusted HR, 2.69; 95% CI, 1.81–3.99), COPD (adjusted HR; 2.23; 95% CI, 1.4–3.54), coronary artery disease (adjusted HR, 2.17; 95% CI, 1.49–3.18), congestive heart failure (adjusted HR, 2.17; 95% CI, 1.16–4.08), and atrial fibrillation (adjusted HR, 3.34; 95% CI, 1.63–6.85) enhanced the risk of dementia in patients with acute OP and CM poisoning. The analysis of interaction between acute OP and CM poisoning and each comorbidity showed that diabetes mellitus (P = 0.03), depression (P < 0.001), stroke (P = 0.03), and COPD (P = 0.008) exhibited significant interactions with acute OP and CM poisoning in the development of dementia.

Table 4 shows the combined effects of acute OP and CM poisoning and comorbidities on the risk of dementia. Coexistence with diabetes mellitus (adjusted HR, 2.95; 95% CI, 2.02–4.31), hypertension (adjusted HR, 2.43; 95% CI, 1.79–3.31), depression (adjusted HR, 3.99; 95% CI, 2.81–5.67), stroke (adjusted HR, 2.69; 95% CI, 1.81–3.99), COPD (adjusted HR; 2.23; 95% CI, 1.4–3.54), coronary artery disease (adjusted HR, 2.17; 95% CI, 1.49–3.18), congestive heart failure (adjusted HR, 2.17; 95% CI, 1.16–4.08), and atrial fibrillation (adjusted HR, 3.34; 95% CI, 1.63–6.85) enhanced the risk of dementia in patients with acute OP and CM poisoning. The analysis of interaction between acute OP and CM poisoning and each comorbidity showed that diabetes mellitus (P = 0.03), depression (P < 0.001), stroke (P = 0.03), and COPD (P = 0.008) exhibited significant interactions with acute OP and CM poisoning in the development of dementia.

**DISCUSSION**

In this nationwide population-based cohort study, we disclosed the increased risk of dementia in patients hospitalized for acute OP and CM poisoning.

The primary response mechanism for acute OP and CM toxicity is acetylcholinesterase inhibition. However, the pathogenesis for cognitive and neurobehavioral impairment associated with pesticide intoxication remains unclear. The possible mechanisms include synaptic dysfunction caused by acetylcholine accumulation, affecting lipid, carbohydrate, and protein metabolism, genetic factors among vulnerable people, increased oxidative stress, and the effects of non-specific brain anoxia.

Several studies have recognized that chronic or occupational pesticide exposure is a possible factor for dementia. The Canadian Study of Health and Aging showed a 2-fold increased risk of developing vascular dementia in people with occupational exposure to pesticides or fertilizers.

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**TABLE 1. Characteristics of Patients With and Without Organophosphate and Carbamate Poisoning**

| Factor                                  | Yes (n = 9616) | No (n = 38,510) | P-Value  |
|-----------------------------------------|----------------|----------------|----------|
| Age (years)                             |                |                | 0.99     |
| 20–34                                   | 1369 (14.2)    | 5488 (14.3)    |          |
| 35–49                                   | 2626 (27.3)    | 10,526 (27.3)  |          |
| 50–64                                   | 2849 (29.6)    | 11,409 (29.6)  |          |
| ≥65                                     | 2772 (28.8)    | 11,087 (28.8)  |          |
| Sex                                     |                |                | 0.95     |
| Male                                    | 6742 (70.1)    | 27,014 (70.2)  |          |
| Female                                  | 2874 (29.9)    | 11,496 (29.9)  |          |
| Occupation status                       |                |                | <0.001   |
| Public servant                          | 387 (4.02)     | 4364 (11.3)    |          |
| Laborb                                  | 6084 (63.3)    | 14,222 (36.9)  |          |
| Businessman/businesswoman               | 2337 (24.3)    | 15,689 (40.7)  |          |
| Low-income earnerb                      | 49 (0.51)      | 147 (0.38)     |          |
| Others                                  | 759 (7.89)     | 4088 (10.6)    |          |
| Comorbidity                             |                |                |          |
| Diabetes mellitus                       | 1337 (13.9)    | 2117 (5.5)     | <0.001   |
| Hypertension                            | 2144 (22.3)    | 3660 (9.5)     | <0.001   |
| Head injury                             | 1054 (11)      | 1196 (3.1)     | <0.001   |
| Depression                              | 1599 (16.6)    | 204 (0.53)     | <0.001   |
| Stroke                                  | 877 (9.12)     | 1622 (4.21)    | <0.001   |
| COPD                                    | 684 (7.11)     | 1058 (2.75)    | <0.001   |
| Coronary artery disease                 | 897 (9.33)     | 1740 (4.52)    | <0.001   |
| Congestive heart failure                | 318 (3.31)     | 524 (1.36)     | <0.001   |
| Atrial fibrillation                     | 166 (1.73)     | 298 (0.77)     | <0.001   |
| Cancer                                  | 399 (4.15)     | 1030 (2.67)    | <0.001   |
| Chronic kidney disease                  | 186 (1.93)     | 315 (0.82)     | <0.001   |

COPD = chronic obstructive pulmonary disease.
Chi-square test.
bIncluding farmer, fishermen, and industry.
COPD is a specific brain anoxia.

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**FIGURE 1. Cumulative incidence of dementia among patients with and without organophosphate and carbamate poisoning.** A significantly increased risk of dementia was found in patients with organophosphate and carbamate poisoning (log-rank test, P < 0.001).
studies have also revealed pesticide exposure to be a risk factor for Alzheimer disease.\textsuperscript{12–14} For example, one of the largest studies, the Cache County study, has shown that patients with occupational exposure to pesticides were at a higher risk for Alzheimer disease (HR, 1.42; 95% CI, 1.06–1.91) than were those who were not exposed to pesticides.\textsuperscript{12} Although several studies have discussed the link between cognitive decline and pesticide exposure, only case reports or small case-series studies have investigated the association between acute pesticide poisoning and dementia.\textsuperscript{22–26} Patients with acute OP intoxication requiring hospitalization were found to have a persistent decline in neuropsychological functions or neurobehavioral impairment, but not overt dementia during their follow-up periods.\textsuperscript{22–26} We found a 1.98-fold increased risk of dementia in hospitalized patients with acute OP and CM poisoning compared with the control population. This is the first large nationwide population-based cohort study to evaluate the association between dementia and patients with acute OP and CM poisoning.

In the present study, OP and CM poisoning was more prevalent in male patients (70.1%) than in female patients; this is consistent with previous reports.\textsuperscript{12,16} This may be because most patients with OP and CM poisoning were farmers, of which most were men.\textsuperscript{12,16} Our study revealed that women exhibited a higher risk of dementia than men,\textsuperscript{27,28} whereas other studies have shown no sex difference.\textsuperscript{29,30} Studies have suggested that women are at higher risk of dementia than men,\textsuperscript{27,28} whereas other studies have shown no sex difference.\textsuperscript{29,30} In the present study, we only analyzed the influence of occupations on the risk of dementia and the prevalence of comorbidities among patients with OP and CM poisoning.

### TABLE 2. Incidence and Hazard Ratios of Dementia in Patients With and Without Organophosphate and Carbamate Poisoning

| Factor                          | Yes                        | No                        | Crude HR (95% CI) | Adjusted HR\textsuperscript{*} (95% CI) |
|---------------------------------|-----------------------------|---------------------------|-------------------|----------------------------------------|
|                                 | Event Person-Year Rate\textsuperscript{a} | Event Person-Year Rate\textsuperscript{a} |                   |                                        |
| All                             | 152                         | 355                       | 2.07 (1.71–2.5)*** | 1.98 (1.59–2.47)***                    |
| Sex                             |                             |                           |                   |                                        |
| Male                            | 92                          | 230                       | 1.92 (1.51–2.45)***| 2.06 (1.44–2.95)***                    |
| Female                          | 60                          | 125                       | 2.35 (1.73–3.2)*** | 1.86 (1.42–2.43)***                    |
| Age (years)                     |                             |                           |                   |                                        |
| 20–49                           | 6                           | 6                         | 4.54 (1.46–14.1)** | 1.87 (0.44–7.99)                      |
| 50–64                           | 30                          | 30                        | 4.9 (2.95–8.13)*** | 2.74 (1.54–4.86)***                    |
| ≥65                             | 116                         | 319                       | 2.02 (1.63–2.5)*** | 1.7 (1.34–2.15)***                     |
| Occupational status             |                             |                           |                   |                                        |
| Public servant\textsuperscript{1} | 9                         | 58                        | 2.29 (1.13–4.61)\textsuperscript{*} | 1.04 (0.43–2.52)                      |
| Labor\textsuperscript{3}        | 114                         | 134                       | 2.46 (1.92–3.15)***| 2.21 (1.69–2.9)***                     |
| Businessman/businesswoman       |                             |                           |                   |                                        |
| Low-income earner\textsuperscript{8} | 0                        | 3                         | 6.63 (0.32–1.24)  | 1.32 (0.59–2.92)                      |
| Others                          | 9                           | 89                        | 1.04 (0.43–2.52)  | 2.74 (1.54–4.86)***                    |
| Comorbidity\textsuperscript{4}  |                             |                           |                   |                                        |
| Yes                             | 111                         | 165                       | 1.03 (0.81, 1.31)  | 2.32 (1.62–3.32)***                    |
| No                              | 41                          | 190                       | 1.66 (1.18, 2.32)**| 2.09 (1.61–2.71)**                     |
| Year of follow-up               |                             |                           |                   |                                        |
| ≤1                              | 41                          | 46                        | 4.08 (2.68–6.22)***| 3.65 (2.29–5.81)***                    |
| 2–5                             | 61                          | 163                       | 1.79 (1.33–2.4)*** | 1.44 (1.02–2.03)                      |
| >5                              | 50                          | 146                       | 1.72 (1.25–2.37)***| 1.88 (1.32–2.66)***                    |

CI = confidence interval, HR = hazard ratio.
\textsuperscript{a}Incidence rate per 10,000 person-years.
\textsuperscript{b}Adjusted for age, occupation, multiplicative interaction of age and sex, and comorbidities of diabetes mellitus, hypertension, head injury, depression, stroke, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, atrial fibrillation, cancer, and chronic kidney disease.

Including government, education, and military.

Including farmer, fishermen, and industry.

Insured income is lower than the level required for charging premium.

Including diabetes mellitus, hypertension, head injury, depression, stroke, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, atrial fibrillation, cancer, and chronic kidney disease.

\textsuperscript{1}P < 0.05.

\textsuperscript{*}P < 0.01.

\textsuperscript{**}P < 0.001.


| Factor                                           | Crude HR (95% CI)      | Adjusted HR (95% CI)  |
|--------------------------------------------------|------------------------|-----------------------|
| Age (years)                                      | 1.13 (1.12–1.14)***    | 1.13 (1.11–1.15)***   |
| Sex                                              |                        |                       |
| Male                                             | 1 (Reference)          | 1 (Reference)         |
| Female                                           | 1.33 (1.11–1.59)**     | 1.97 (0.52–7.51)      |
| Multiplicative interaction of age and sex         | 1.02 (1.01–1.02)**     | 0.99 (0.97–1.01)      |
| Occupation                                       |                        |                       |
| Public servant†                                   | 2.74 (2–3.76)***       | 1.36 (0.99–1.86)      |
| Labor†                                           | 2.49 (1.96–3.17)***    | 1.06 (0.83–1.36)      |
| Businessman/businesswoman                         | 1 (Reference)          | 1 (Reference)         |
| Low-income earner§†                               | 3.52 (1.11–11.1)†      | 1.04 (0.33–3.3)       |
| Others                                           | 4.31 (3.24–5.74)***    | 1.48 (1.1–1.99)‡      |
| Comorbidities                                    |                        |                       |
| Organophosphate and carbamate poisoning          |                        |                       |
| Yes                                              | 2.07 (1.71–2.50)***    | 1.98 (1.59–2.47)***   |
| No                                               | 1 (Reference)          | 1 (Reference)         |
| Diabetes mellitus                                |                        |                       |
| Yes                                              | 4.16 (3.3–5.24)***     | 1.5 (1.17–1.91)†      |
| No                                               | 1 (Reference)          | 1 (Reference)         |
| Hypertension                                     |                        |                       |
| Yes                                              | 5.59 (4.64–6.73)***    | 1.26 (1–1.57)‡        |
| No                                               | 1 (Reference)          | 1 (Reference)         |
| Head injury                                      |                        |                       |
| Yes                                              | 1.3 (0.88–1.93)        | –                     |
| No                                               | 1 (Reference)          | 1 (Reference)         |
| Depression                                       |                        |                       |
| Yes                                              | 3.47 (2.58–4.67)***    | 2.33 (1.68–3.24)***   |
| No                                               | 1 (Reference)          | 1 (Reference)         |
| Stroke                                           |                        |                       |
| Yes                                              | 6.8 (5.46–8.49)***     | 1.63 (1.27–2.1)***    |
| No                                               | 1 (Reference)          | 1 (Reference)         |
| COPD                                             |                        |                       |
| Yes                                              | 5.57 (4.26–7.29)***    | 1.34 (1.01–1.79)†     |
| No                                               | 1 (Reference)          | 1 (Reference)         |
| Coronary artery disease                          |                        |                       |
| Yes                                              | 4.41 (3.46–5.63)***    | 0.97 (0.74–1.27)      |
| No                                               | 1 (Reference)          | 1 (Reference)         |
| Congestive heart failure                         |                        |                       |
| Yes                                              | 5.34 (3.57–8)***       | 0.93 (0.6–1.43)       |
| No                                               | 1 (Reference)          | 1 (Reference)         |
| Atrial fibrillation                              |                        |                       |
| Yes                                              | 5.49 (3.34–9.04)***    | 1.17 (0.69–1.96)      |
| No                                               | 1 (Reference)          | 1 (Reference)         |
| Cancer                                           |                        |                       |
| Yes                                              | 1.23 (0.68–2.23)       | –                     |
| No                                               | 1 (Reference)          | 1 (Reference)         |
| Chronic kidney disease                           |                        |                       |
| Yes                                              | 3.52 (1.88–6.58)***    | 1.16 (0.61–2.18)      |
| No                                               | 1 (Reference)          | 1 (Reference)         |

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio.

† Multivariable analysis including age, occupation, multiplicative interaction of age and sex, and comorbidities of diabetes mellitus, hypertension, head injury, depression, stroke, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, atrial fibrillation, cancer, and chronic kidney disease.

Including government, education, and military.

† Including farmer, fishermen, and industry.

§ Insured income is lower than the level required for charging premium.

* P < 0.05.

** P < 0.01.

*** P < 0.001.
dementia. Our study revealed that labors and businessmen/businesswomen who had acute OP and CM poisoning increased the risk of dementia. This effect was not found in public servants, low income and others.

As mentioned previously, several factors contribute to dementia. In this study, diabetes mellitus, depression, stroke, and COPD showed significant interactions with acute OP and CM poisoning in the development of dementia. Vascular dementia, also known as multiinfarct dementia, is the second most common form of dementia. A positive link between dementia and stroke can be expected. Diabetes mellitus is a well-known risk factor for dementia. Population-based studies suggest that COPD is independently associated with increased risk of

| Variables | Adjusted HR (95% CI) | P-Value |
|-----------|----------------------|---------|
| Organophosphate and carbamate poisoning Diabetes mellitus | 1.48 (1.08–2.02)*** | 0.03 |
| Organophosphate and carbamate poisoning Hypertension | 1.29 (0.99–1.69)*** | 0.15 |
| Organophosphate and carbamate poisoning Depression | 1.91 (1.46–2.49)*** | <0.001 |
| Organophosphate and carbamate poisoning Stroke | 2.95 (2.02–4.31)*** | 0.03 |
| Organophosphate and carbamate poisoning COPD | 1.5 (1.06–2.13)*** | 0.008 |
| Organophosphate and carbamate poisoning Coronary artery disease | 1.81 (1.34–2.44)*** | 0.83 |
| Organophosphate and carbamate poisoning Congestive heart failure | 1.98 (1.57–2.48)*** | 0.92 |
| Organophosphate and carbamate poisoning Atrial fibrillation | 2.03 (1.61–2.57)*** | 0.96 |
| Organophosphate and carbamate poisoning Chronic kidney disease | 2.43 (1.79–3.31)*** | 0.17 |

COPD = chronic obstructive pulmonary disease.

* P < 0.05.

*** P < 0.001.

Multivariable analysis including age, occupation, multiplicative interaction of age and sex, and other comorbidities.
cognitive impairment or dementia. Among these underlying diseases, depression was the most pronounced disease (adjusted HR, 3.99; 95% CI, 2.81–5.67) associated with dementia. This comorbidity is also an important factor for cognitive decline and dementia. Besides the influence of these diseases themselves on the development of dementia, our study further showed the additional interactions of these comorbidities with acute OP and CM poisoning in the development of dementia.

A primary strength of this study is its large nationwide population-based investigation, including a collection of comprehensive demographic characteristics and complete follow-up histories. However, several limitations remain in this study. First, OP and CM poisoning share the same ICD-9-CM code 989.3. According to the ICD-9-CM-based study, we cannot differentiate the type of pesticide intoxication. Second, we investigated patients hospitalized for acute OP and CM poisoning. Although these patients were heavily poisoned, we could not categorize the precise intensity of intoxication. Certain studies have shown severe neurobehavioral impairment in patients with severe poisoning. Those with mild OP and CM poisoning could be omitted from our study. Third, the present study is a retrospective cohort study. Despite the meticulous design and control of some confounding factors, biases could remain because of possibly unmeasured or unknown confounding factors. In addition, the NHIRD lacks information on the lifestyle, physical activity, habits, body mass index, educational level, and family history of patients, all of which were possible confounding factors in this study. Fourth, there are no laboratory data and imaging reports in the NHIRD. This information is important for the diagnosis of OP and CM poisoning and dementia. Finally, the registries in the NHI claims are primarily used for administrative billing of health care and are not provided for the purpose of scientific research. The accuracy of coding in the claims data may have the potentially bias. It is impossible to validate the data by inspecting the medical records or contacting the patients because of the anonymity of the personally identifiable information. However, the data on the diagnoses in the NHIRD are highly reliable. The NHIRD is a universal and mandatory enrolled health insurance with a single payer, the government of Taiwan. The insurance system has mechanisms to monitor the insurance claims. All insurance claims should be scrutinized by medical reimbursement specialists and peer review. Incorrect coding of diagnoses or treatments will result in no reimbursement, and the institutions will be punished with a lot of penalty. Moreover, several studies have proven the accuracy of NHIRD.

In conclusion, our study recognized the epidemiological link between dementia and acute OP and CM poisoning. These compounds are still extensively used worldwide. Because of the substantially increased prevalence of dementia, the public health effect of pesticide exposure is immense. We suggest minimizing pesticide exposure and conducting regular follow-ups of patients with OP and CM poisoning.

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