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

A Nationwide Population-Based Cohort Study

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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.

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Abbreviations: CI = confidence interval, CM = carbamate, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes, OP = organophosphate, SD = standard deviation.

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.[1] Acute poisoning with OP and CM leads to overstimulated muscarinic and nicotinic receptors, and results in bronchorrhea, bronchospasm, miosis, bradycardia, salivation, lacrimation, urination, diarrhea, muscle fasciculations, weakness, confusion, agitation, and coma.[1,3]

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] However, 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

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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 (each 5-year span), sex, and the year of OP and CM poisoning. Patients with incomplete age or sex information and who were diagnosed with dementia (ICD-9-CM 290, 294.1, and 331.0), syphilitic dementia (ICD-9-CM 094.1), or human immunodeficiency virus infection (ICD-9-CM 042, V08, V01.79, 795.71, and 079.53) before the index date were excluded from the study.

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), businessmen/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 $\pm$ 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 $\pm$ 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

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

	Organophosphate and Carbamate Poisoning				
	Yes (n = 9616)		No (n = 38,510)		
Factor	**n**	**%**	**n**	**%**	***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	
Labor†	6084	63.3	14,222	36.9	
Businessman/ businesswoman	2337	24.3	15,689	40.7	
Low-income earner‡	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	3.11	<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.
* Including government, education, and military.
† Including farmer, fishermen, and industry.
‡ Insured income is lower than the level required for charging premium.

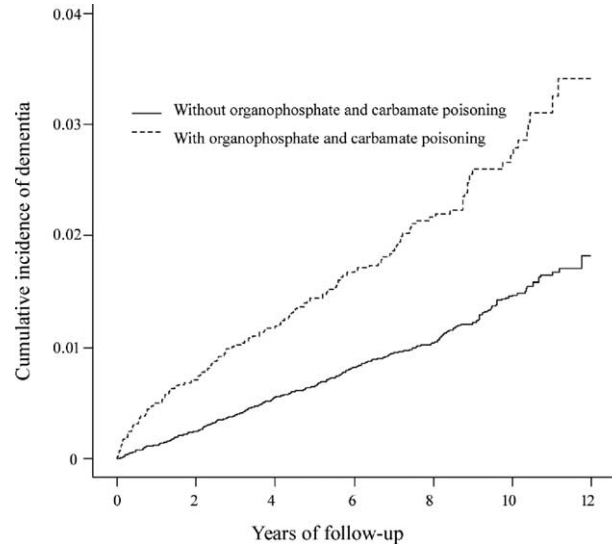

FIGURE 1. Cumulative incidence of dementia among patients with and without organophosphate and carbamate poisoning. A significantly increased risk of dementia was found in patients with organophosphate and carbamate poisoning (log-rank test, $P < 0.001$).

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, 3.65; 95% CI, 2.29–5.81).

We further analyzed the influence of demographics, occupations, and underlying comorbidities on dementia (Table 3). The risk of dementia increased with age (adjusted HR, 1.13; 95% CI, 1.11–1.15, per year), as well as diabetes mellitus, hypertension, depression, stroke, and COPD. Among these comorbidities, depression was identified to be the highest risk factor (adjusted HR, 2.33; 95% CI, 1.68–3.24). Compared occupation with businessmen/businesswomen, occupation with public servants, labors, and low-income earners were no difference in the risk of dementia. Other factors including sex, coronary artery disease, congestive heart failure, atrial fibrillation, and chronic kidney disease did not further intensify the association with 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.[1,3] However, the pathogenesis for cognitive and neurobehavioral impairment associated with pesticide intoxication remains unclear. The possible mechanisms include synaptic dysfunction caused by acetylcholine accumulation,[17] affecting lipid, carbohydrate, and protein metabolism,[17] genetic factors among vulnerable people,[18] increased oxidative stress,[19] and the effects of nonspecific brain anoxia.[20]

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.[5,21] Other

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

	Organophosphate and Carbamate Poisoning							
	Yes			No				
Factor	Event	Person-Year	Rate[#]	Event	Person-Year	Rate[#]	Crude HR (95% CI)	Adjusted HR[¶] (95% CI)
All	152	51,795	29.4	355	250,510	14.2	2.07 (1.71–2.5)***	1.98 (1.59–2.47)***
Sex								
Male	92	36,394	25.3	230	174,612	13.2	1.92 (1.51–2.45)***	2.06 (1.44–2.95)***
Female	60	15,401	39.0	125	75,899	16.5	2.35 (1.73–3.2)***	1.86 (1.42–2.43)***
Age (years)								
20–49	6	24,859	2.41	6	113,386	0.53	4.54 (1.46–14.1)**	1.87 (0.44–7.99)
50–64	30	16,065	18.7	30	77,163	3.89	4.9 (2.95–8.13)***	2.74 (1.54–4.86)***
≥65	116	10,871	106.7	319	59,962	53.2	2.02 (1.63–2.5)***	1.7 (1.34–2.15)***
Occupational status								
Public servant[†]	9	1974	45.6	58	29,012	20.0	2.29 (1.13–4.61)*	1.04 (0.43–2.52)
Labor[‡]	114	32,493	35.1	134	93,740	14.3	2.46 (1.92–3.15)***	2.21 (1.69–2.9)***
Businessman/ businesswoman	20	13,107	15.3	71	102,040	6.96	2.2 (1.34–3.61)**	2.52 (1.46–4.34)***
Low-income earner[§]	0	215	0.00	3	863	34.8	—	—
Others	9	4007	22.5	89	24,855	35.8	0.63 (0.32–1.24)	1.32 (0.59–2.92)
Comorbidity[‖]								
Yes	111	24,177	45.9	165	36,826	44.8	1.03 (0.81, 1.31)	2.32 (1.62–3.32)***
No	41	27,618	14.9	190	213,685	8.89	1.66 (1.18, 2.32)**	2.09 (1.61–2.71)***
Year of follow-up								
≤1	41	8075	50.8	46	37,174	12.4	4.08 (2.68–6.22)***	3.65 (2.29–5.81)***
2–5	61	25,480	23.9	163	121,953	13.4	1.79 (1.33–2.4)***	1.44 (1.02–2.03)*
>5	50	18,240	27.4	146	91,384	16.0	1.72 (1.25–2.37)***	1.88 (1.32–2.66)***

CI = confidence interval, HR = hazard ratio.

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

[¶] 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.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

studies have also revealed pesticide exposure to be a risk factor for Alzheimer disease.[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.[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.[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.[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.[12,16] This may be because most patients with OP and CM poisoning were farmers, of which most were men.[12,16] Our study revealed that women exhibited a higher incidence of dementia both in the poisoned cohort and in the control group. However, we observed no significant difference in the risk of dementia between men and women patients with acute OP and CM poisoning. The risk of dementia among men and women is inconsistent in literature. Certain studies have suggested that women are at higher risk of dementia than are men,[27,28] whereas other studies have shown no sex difference.[29,30]

Educational level and occupational status have been reported to be associated with dementia.[9,31] Low educational level, low occupational status, and low job complexity increase the risk of dementia.[9] Occupational attainment and educational level are closely linked to each other. However, educational levels were not available in the NHIRD. In the present study, we only analyzed the influence of occupations on the risk of

TABLE 3. Hazard Ratios of ACS in Association With Age, Sex, Occupation and Comorbidities in Univariable and Multivariable Cox Regression Models

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.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

TABLE 4. Cox Proportional Hazard Regression Analysis for the Risk of Dementia Stratified by the Interaction of Comorbidity and Organophosphate and Carbamate Poisoning

Variables		Adjusted HR[†] (95% CI)	*P*-Value
Organophosphate and carbamate poisoning	Diabetes mellitus		0.03
No	No	1 (Reference)	
No	Yes	1.48 (1.08–2.02)*	
Yes	No	1.88 (1.48–2.37)***	
Yes	Yes	2.95 (2.02–4.31)***	
Organophosphate and carbamate poisoning	Hypertension		0.15
No	No	1 (Reference)	
No	Yes	1.29 (0.99–1.69)	
Yes	No	1.91 (1.46–2.49)***	
Yes	Yes	2.43 (1.79–3.31)***	
Organophosphate and carbamate poisoning	Depression		<0.001
No	No	1 (Reference)	
No	Yes	4.94 (2.74–8.9)***	
Yes	No	2.05 (1.65–2.55)***	
Yes	Yes	3.99 (2.81–5.67)***	
Organophosphate and carbamate poisoning	Stroke		0.03
No	No	1 (Reference)	
No	Yes	1.81 (1.34–2.44)***	
Yes	No	2.03 (1.61–2.57)***	
Yes	Yes	2.69 (1.81–3.99)***	
Organophosphate and carbamate poisoning	COPD		0.008
No	No	1 (Reference)	
No	Yes	1.5 (1.06–2.13)*	
Yes	No	1.98 (1.57–2.48)***	
Yes	Yes	2.23 (1.4–3.54)***	
Organophosphate and carbamate poisoning	Coronary artery disease		0.83
No	No	1 (Reference)	
No	Yes	0.86 (0.61–1.23)	
Yes	No	1.79 (1.41–2.27)***	
Yes	Yes	2.17 (1.49–3.18)***	
Organophosphate and carbamate poisoning	Congestive heart failure		0.92
No	No	1 (Reference)	
No	Yes	0.82 (0.47–1.45)	
Yes	No	1.91 (1.53–2.38)***	
Yes	Yes	2.17 (1.16–4.08)***	
Organophosphate and carbamate poisoning	Atrial fibrillation		0.96
No	No	1 (Reference)	
No	Yes	0.98 (0.48–2.01)	
Yes	No	2.19 (1.79–2.68)***	
Yes	Yes	3.34 (1.63–6.85)*	
Organophosphate and carbamate poisoning	Chronic kidney disease		0.17
No	No	1 (Reference)	
No	Yes	1.44 (0.71–2.93)	
Yes	No	1.93 (1.55–2.4)	
Yes	Yes	1.28 (0.32–5.16)	

COPD = chronic obstructive pulmonary disease.
[†] Multivariable analysis including age, occupation, multiplicative interaction of age and sex, and other comorbidities.
* $P < 0.05$.
*** $P < 0.001$.

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.[5] A positive link between dementia and stroke can be expected. Diabetes mellitus is a well-known risk factor for dementia.[6,31] Diabetes mellitus may increase risk of dementia through several mechanisms.[6] Population-based studies suggest that COPD is independently associated with increased risk of

cognitive impairment or dementia.[32,33] 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.[5,31] 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.[24] 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 lack 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 NHI 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 diseases 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.[34,35]

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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