Risk of Parkinson disease after organophosphate or carbamate poisoning

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Aims: Parkinson disease (PD) is a common neurodegenerative disease. The aim of this study was to evaluate the risk of PD in patients with organophosphate (OP) or carbamate (CM) poisoning by using the Taiwan National Health Insurance Research Database.

Methods: We conducted a retrospective study involving a cohort of 45,594 patients (9,128 patients with a history of OP or CM poisoning and 36,466 control patients) who were selected from the Taiwan National Health Insurance Research Database. The patients were observed for a maximum of 12 years to determine the rates of new-onset PD, and a Poisson regression model was used to identify the predictors of PD. The cumulative incidence of PD between the two cohorts was plotted through Kaplan-Meier analysis.

Results: During the study period, the incidence rate ratio (IRR) of PD in the OP or CM poisoning patients was 1.36-fold [95% confidence interval (CI)=1.26-1.47] higher than that in the control patients in the multivariable model. The absolute incidence of PD was the highest for the group aged ≥75 years in both cohorts (77.4 vs 43.7 per 10,000 person-years). However, the age-specific relative risk was higher for the group aged <50 years (adjusted IRR=3.88; 95% CI=3.44-4.39).

Conclusion: Our results suggest that the likelihood of developing PD is greater in patients with OP or CM poisoning than in those without poisoning. OP or CM poisoning may be an independent risk factor for PD.

Keywords: carbamate, National Health Insurance Research Database, organophosphate, Parkinson disease

1 INTRODUCTION

Parkinson disease is the second most common neurodegenerative disorder after Alzheimer’s disease.1,2 PD develops as a consequence of degeneration of the dopaminergic neurons within the basal ganglia. This degenerative disease becomes clinically apparent after 70% of the dopaminergic neurons of the substantia nigra are lost. The etiology of PD is diverse and complex. Some cases can be attributed to genetic
factors or environmental toxins. Well-water consumption and manga-
nese, copper and pesticide exposure have been associated with the
environmental risk factors for PD.3,6

Several case-control studies have shown the pesticides rote-
none and paraquat to have selective dopaminergic toxicity and to
be associated with an increased risk of PD.7,8 Organophosphate
(OP) and carbamate (CM) pesticides are commonly used in mod-
ern agriculture to eliminate insects. They are associated with severe
toxic injuries and high mortality rates.9−11 These pesticides damage
nerve function by acting as acetylcholinesterase inhibitors in the
nervous system, resulting in the accumulation of a neurotransmit-
ter, namely acetylcholine. The chemicals can be inhaled if people
are in an area where they were recently applied, or be ingested with
foods that are contaminated. Although most patients with OP and
CM poisoning have a positive prognosis, severe poisoning is poten-
tially lethal.

Several studies describe cases of possible OP-induced parkinson-
ism, with symptoms including resting tremors, akinesia, lack of blinking,
impairment of speech and swallowing, cogwheel rigidity, and stooped
posture.12,13 Two previous reports showed irreversible extrapyra-
midal syndromes and MRI abnormalities after severe OP poisoning,
supporting the possible role of these environmental toxins in causing
parkinsonism.14,15 However, no systematic study involved long-term
follow-up of patients after OP or CM poisoning or addressed the rate
of Parkinson disease development.

In this report, we used representative Taiwan National Health
Insurance (NHI) data sets to form a cohort for examining whether pa-
tients with OP or CM poisoning have an increased risk of PD after
several years of follow-up. To date, this is the largest cohort used to
investigate such an association.

2 | METHODS

2.1 | Data source

The Taiwan NHI program is a single-payer system established on
March 1, 1995, by the Bureau of National Health Insurance (BNHI).
The BNHI entrusted the National Health Research Institutes (NHRI)
to construct the National Health Insurance Research Database (NHIRD)
as part of this program. The NHI program covers approximately 99%
.aspx). We conducted a longitudinal cohort study by collecting data
on hospital admissions of the entire insured population of Taiwan
from the NHIRD; this study examined healthcare claims for the pe-
riod 1996 to 2011. Disease diagnoses were identified on the basis of
the International Classification of Diseases, Ninth Revision, Clinical
Modification (ICD-9-CM) codes in the NHIRD. For privacy protection,
the insurants’ identities are encrypted before being sent to research-
ers. All insurance claims are scrutinized by medical reimbursement
specialists and peer review. PD was accurately diagnosed and coded
(ICD-9 codes) by the specialists according to the standard diagnostic
criteria, including typical symptoms and signs, laboratory data and im-
aging findings. In addition, if physicians or hospitals record incorrect
codes or diagnoses, they are punished severely by the National Health
Insurance Administration.

2.2 | Ethics statement

The NHIRD encrypts patients’ personal information to protect privacy
and provides researchers with anonymous identification numbers as-
associated with relevant claims information, including sex, date of birth,
medical services received and prescriptions. Therefore, patient con-
sent 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 (CMUH104-REC2-115). The IRB
also specifically waived the consent requirement.

2.3 | Data availability statement

All data and related metadata were deposited in an appropriate public
repository in the National Health Research Institutes (NHRI). The
data on the study population that were obtained from the NHIRD (http://
nhird.nhri.org.tw/en/index.html) are maintained in the NHIRD (http://
nhird.nhri.org.tw/). The NHRI is a nonprofit foundation established
by the government. Only citizens of the Republic of China who ful-
fill the requirements of conducting research projects are eligible to
apply for the NHIRD. The use of NHIRD is limited to research pur-
poses only. Applicants must follow the Computer-Processed Personal
Data Protection Law (http://www.winkerpartners.com/?p=987) and
related regulations of National Health Insurance Administration and
NHRI, and an agreement must be signed by the applicant and his/her
supervisor upon application submission. All applications are reviewed
for approval of data release.

2.4 | Sampled patients

From the inpatient claim data set, we identified all hospitalized pa-
tients who had a new discharge diagnosis of OP or CM poisoning
(ICD-9-CM code: 989.3) from 2000 to 2011. The index date was de-
finite as the date of diagnosis of poisoning. Patients with a history of
PD (ICD-9-CM code: 332), those aged <20 years, and those lacking
complete information were excluded.16−20 Controls were randomly
selected from all of the NHI beneficiaries aged ≥20 years without OP
or CM poisoning and a PD history before the index date. The index
date for the control patients was a randomly appointed month and
day in the same index year as that of the matched OP or CM poisoning
patients. The control patients were frequency-matched by age (every
five-year stratum) and sex with the poisoning patients at a ratio of
4:1. Figure 1 shows the selection process of the subjects in the two
study cohorts.

Taiwan is made up almost entirely of ethnic Han Chinese, with a
small proportion of the Taiwanese aborigines. A survey conducted by
the council for Hakka Affairs Executive Yuan, Taiwan, in 2002 showed
that 76.9% of the Taiwan Han was Fujian origins, 10.9% with Hakka
origins, 10% as mainlanders and 1.4% as Taiwan aborigines.
2.5 | Outcome and comorbidities

All of the patients were followed from the index date to their PD diagnosis (ICD-9-CM code: 332.0), their withdrawal from this program, or the end of 2011. On the basis of hospitalization records, a history of depression (ICD-9-CM codes: 296.2, 296.3, 296.82, 300.4, and 311), stroke (ICD-9-CM codes: 430-438), dementia (ICD-9-CM codes: 290, 294.1, and 331.0), or psychosis (ICD-9-CM code: 298) identified at the baseline was considered a comorbidity. Respiratory failure (ICD-9-CM Code 518.81) was considered and identified according to their diagnoses in the hospitalization records within 3 days of the patient’s index date.

2.6 | Variables of interest

The sociodemographic variables used in this study comprised sex, age, urbanization level, and occupation. Detailed definitions of urbanization level and occupation are provided in a previous paper.21

2.7 | Statistical analysis

The distributions of demographic characteristics and baseline comorbidities were compared between the poisoning and control cohorts. Categorical variables and continuous variables were compared using the chi-square test and Student t-test, respectively. Incidence density rates and incidence rate ratios (IRRs) with 95% confidence intervals (CIs) were estimated for the poisoning cohort relative to the control cohort according to demographic status, comorbidity, and follow-up duration (in person-years, using 1 year as the cutoff for all subsequently identified PD). The IRR was determined using Poisson regression models. Variables in the multivariable model included age and comorbidities of depression, stroke, and dementia. We tested the interactions between sex and poisoning, between age and poisoning, and between comorbidity and poisoning by including a cross-product term in the model. The cumulative incidence of PD in the two cohorts was plotted using Kaplan-Meier analysis, and the difference was tested using the log-rank test. All statistical analyses were completed using SAS Version 9.3 (SAS Institute, Inc., Cary, NC, USA). A significance level of \( P<.05 \) based on two-tailed tests was set.

3 | RESULTS

A total of 45,594 patients were enrolled in this study; 9128 were assigned to the poisoning cohort, and 36,466 were assigned to the control cohort. Most patients were aged 50-75 years (48.2%) and male (70.2%). The mean age of the poisoning cohort was 53.8 (SD=16.3) years and that of the control cohort was 53.3 (SD=16.4) years. In the poisoning cohort, most of the patients were residents of less urbanized areas (55.2%) and blue-collar parents (63.4%). The poisoning patients were likely to have more comorbidities than the patients were (all \( P<.01 \)) (Table 1). The mean follow-up duration was 5.62 (±3.77) years for the poisoning cohort and 6.78 (±3.26) years for the control cohort (data not shown).

Figure 2 shows that the cumulative incidence of PD was higher in the poisoning cohort (\( P<.001 \)) than in the control cohort by the end of follow-up. During the study period, 72 poisoning patients and 222 control patients developed PD. The poisoning patients showed a 1.57-fold higher PD incidence than that of the control cohort [14.0 (95% CI=13.1-15.0) vs 8.98 (95% CI=8.67-9.30) per 10,000 person-years], with a crude IRR of 1.57 (95% CI=1.45-1.68) in the univariable model (Table 2). After adjustment for age, urbanization level, occupation, and comorbidities of depression, stroke, and dementia, the patients with OP or CM poisoning were associated with an increased risk of PD compared with those without poisoning [adjusted IRR=1.36, 95% CI=1.26-1.47].
In the sex-specific analysis, the PD incidences in the OP poisoning cohort were higher than those in the control cohort, and the risk of PD was higher for both women (adjusted IRR=1.47, 95% CI=1.27-1.70) and men (adjusted IRR=1.32, 95% CI=1.20-1.45). In the interaction analysis, sex did not significantly modify the association between poisoning and PD (P values for interaction, .08).

The age-specific analysis showed PD incidence increasing with age in both cohorts. However, the age-specific relative risk of PD was higher in the poisoning cohort than in the control cohort for all age groups. We stratify the urbanization level by the population density of the residential area into four levels, with level 1 as the most urbanized region and level 4 as the least urbanized region. The urbanization level-specific adjusted IRR of PD for the poisoning cohort relative to the control cohort was significant for all urbanization levels, except for the second highest urbanization level. Occupation-specific analysis showed that blue-collar workers in the poisoning cohort, compared with those in the control cohort, exhibited a higher risk of PD (adjusted IRR=1.59, 95% CI=1.44-1.77).

The comorbidity-specific risk and adjusted HR of PD for the poisoning cohort and the control cohort were significant for both the subgroup without comorbidity (adjusted IRR=1.33, 95% CI=1.23-1.45) and that with comorbidity (adjusted IRR=1.71, 95% CI=1.39-2.11). The analysis was stratified by the duration of follow-up; compared with the control cohort, the poisoning cohort exhibited a significantly higher risk of developing PD in the first 1 follow-up years (adjusted IRR=3.01, 95% CI=2.77-3.26), in the 2-3 follow-up years (adjusted IRR=1.27, 95% CI=1.15-1.40), and in more than 5 follow-up years (adjusted IRR=1.39, 95% CI=1.26-1.53).

The multivariable Cox proportional hazards regression analysis further evaluated the roles of sex, age, and baseline comorbidities in PD development (Table 3). The risk of PD exhibited a 10% increment per 1 year of age. Patients whose occupation was not white collar had a higher risk of developing PD (adjusted IRR=1.30, 95% CI=1.20-1.42). In the multivariable model, patients with depression had the highest risk (adjusted IRR=3.25, 95% CI=2.91-3.64), followed by those with dementia (adjusted IRR=2.50, 95% CI=2.08-3.01).

Table 4 shows that the risk of PD increased with the severity of OP or CM poisoning. Patients with a seven-day or longer hospital stay were considered to be in the high severity group; otherwise, they were considered as low severity. The high severity cases had an adjusted IRR of 1.53 (95% CI=1.37-1.72); the low severity cases had an adjusted IRR of 1.19 (95% CI=1.09-1.30). The poisoning cases with respiratory failure had an adjusted IRR of 1.63 (95% CI=1.43-1.87); the cases without respiratory failure had an adjusted IRR of 1.21 (95% CI=1.11-1.32).
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Organophosphate or carbamate poisoning</th>
<th>Crude IRR (95% CI)</th>
<th>Adjusted IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Event</td>
<td>PY</td>
<td>Rate&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>All</td>
<td>72</td>
<td>51</td>
<td>281</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>46</td>
<td>36</td>
</tr>
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<td>P for interaction</td>
<td>.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, year</td>
<td>20-49</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>50-75</td>
<td>47</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>≥75</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td>P for interaction</td>
<td>.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urbanization level&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1 (highest)</td>
<td>6</td>
<td>395</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>10</td>
<td>883</td>
</tr>
<tr>
<td></td>
<td>4 (lowest)</td>
<td>51</td>
<td>27</td>
</tr>
<tr>
<td>P for interaction</td>
<td>.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td>White collar</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Blue collar</td>
<td>58</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Others&lt;sup&gt;e&lt;/sup&gt;</td>
<td>4</td>
<td>419</td>
</tr>
<tr>
<td>P for interaction</td>
<td>.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidity&lt;sup&gt;f&lt;/sup&gt;</td>
<td>No</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>33</td>
<td>11</td>
</tr>
<tr>
<td>P for interaction</td>
<td>.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow time, years&lt;sup&gt;g&lt;/sup&gt;</td>
<td>&lt;1</td>
<td>21</td>
<td>785</td>
</tr>
<tr>
<td></td>
<td>1-2</td>
<td>8</td>
<td>729</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>7</td>
<td>662</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>6</td>
<td>601</td>
</tr>
<tr>
<td></td>
<td>4-5</td>
<td>5</td>
<td>539</td>
</tr>
<tr>
<td></td>
<td>&gt;5</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>P for interaction</td>
<td>.75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PY, person-years.

<sup>a</sup> Rate, incidence rate per 10,000 person-years.

<sup>b</sup> IRR, relative incidence rate ratio.

<sup>c</sup> Adjusted IRR, incidence rate ratio adjusted for age, urbanization level, occupation, and comorbidities of depression, stroke, and dementia.

<sup>d</sup> The urbanization level was categorized by the population density of the residential area into four levels, with level 1 as the most urbanized region and level 4 as the least urbanized region.

<sup>e</sup> Other occupations included primarily retired, unemployed, and low-income populations.

<sup>f</sup> Comorbidity: Patients with any one of the comorbidities (depression, stroke, dementia, and psychosis) were classified into the comorbidity group.

<sup>g</sup> The follow-up time is partitioned into two segments (≤5 years and >5 years) by the median.

*P* < .05, **P** < .01, ***P*** < .001

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**TABLE 2** Incidence and incidence rate ratios of Parkinson disease in patients with organophosphate or carbamate poisoning and without poisoning.
TABLE 3 Incidence rate ratios of Parkinson’s disease in association with sex, age, and comorbidities in univariable and multivariable Poisson regression models

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude IRRa</th>
<th>Adjustedb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR (95% CI)</td>
<td>IRR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OP or CM poisoning</td>
<td>1.57 (1.45, 1.68)**</td>
<td>1.36 (1.26, 1.47)**</td>
</tr>
<tr>
<td>Gender (Women vs Men)</td>
<td>1.09 (1.01, 1.17)</td>
<td>-</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.10 (1.10, 1.11)**</td>
<td>1.10 (1.10, 1.11)**</td>
</tr>
<tr>
<td>Urbanization leveld</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td></td>
<td>1.05 (0.96, 1.15)</td>
<td>1.06 (0.75, 1.49)</td>
</tr>
<tr>
<td></td>
<td>0.98 (0.88, 1.09)</td>
<td>0.84 (0.57, 1.26)</td>
</tr>
<tr>
<td></td>
<td>1.57 (1.44, 1.71)**</td>
<td>1.03 (0.75, 1.42)</td>
</tr>
<tr>
<td>Occupation</td>
<td>White collar</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td></td>
<td>Blue collar</td>
<td>1.73 (1.61, 1.85)**</td>
</tr>
<tr>
<td></td>
<td>Othersd</td>
<td>2.94 (2.68, 3.22)**</td>
</tr>
<tr>
<td>Baseline comorbidities (yes vs no)</td>
<td>Depression</td>
<td>3.61 (3.25, 4.01)** ***</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>3.31 (2.99, 3.67)** ***</td>
</tr>
<tr>
<td></td>
<td>Dementia</td>
<td>15.0 (12.4, 18.2)** ***</td>
</tr>
<tr>
<td></td>
<td>Psychosis</td>
<td>-</td>
</tr>
</tbody>
</table>

IRR, relative incidence rate ratio.

aAdjusted IRR, incidence rate ratio adjusted for age, urbanization level, occupation, and comorbidities of depression, stroke, and dementia.

The urbanization level was categorized by the population density of the residential area into four levels, with level 1 as the most urbanized region and level 4 as the least urbanized region.

dOther occupations included primarily retired, unemployed, and low-income populations.

*P<.05, **P<.01, ***P<.001.

TABLE 4 Incidence and incidence rate ratios of Parkinson disease stratified by the severity of organophosphate or carbamate poisoning

<table>
<thead>
<tr>
<th>Organophosphate poisoning severityd</th>
<th>Event</th>
<th>PY</th>
<th>Rateb</th>
<th>Crude IRR(95% CI)</th>
<th>Adjusted IRR(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonorganophosphate poisoning</td>
<td>222</td>
<td>247343</td>
<td>8.98</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Organophosphate poisoning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low severity</td>
<td>46</td>
<td>41065</td>
<td>11.2</td>
<td>1.25 (1.14, 1.36)** ***</td>
<td>1.19 (1.09, 1.30)** ***</td>
</tr>
<tr>
<td>High severity</td>
<td>26</td>
<td>10216</td>
<td>25.5</td>
<td>2.84 (2.54, 3.17)** ***</td>
<td>1.53 (1.37, 1.72)** ***</td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>222</td>
<td>247343</td>
<td>8.98</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>56</td>
<td>45283</td>
<td>12.4</td>
<td>1.38 (1.27, 1.49)** ***</td>
<td>1.21 (1.11, 1.32)** ***</td>
</tr>
<tr>
<td>Yes</td>
<td>16</td>
<td>5998</td>
<td>26.7</td>
<td>2.97 (2.58, 3.42)** ***</td>
<td>1.63 (1.43, 1.87)** ***</td>
</tr>
</tbody>
</table>

Patients with a seven-day or longer hospital stay were considered to be in the high severity group; otherwise, they were considered as low severity.

Rate, incidence rate, per 10 000 person-years.

IRR, relative incidence rate ratio.

aAdjusted IRR, incidence rate ratio adjusted for age, urbanization level, occupation, and comorbidities of depression, stroke, and dementia.

*P<.05, **P<.01, ***P<.001.

4 | DISCUSSION

This cohort study demonstrated that, compared with the control patients, the patients with OP or CM poisoning had a 1.36-fold higher risk of PD (95% CI=1.26-1.47) after adjustment for age and medical comorbidities. The relative risk of PD was higher for the high severity group (adjusted IRR=1.53 vs 1.19, P<.001) after OP or CM poisoning.

Several compounds in pesticides have been found to cause dopaminergic degeneration in the substantia nigra. These include rotenone, parquat, and the combination of parquat with maneb. Various mechanisms of pesticide intoxication have been indicated, including oxidative stress, interference with dopamine transporters, mitochondrial dysfunction, and inflammation. Baldi et al. reported on a cohort study assessing the relationship between pesticide exposure and PD in elderly French patients from 1997 to 1999. The results evidence a significant association between PD and occupational exposure to pesticides (odds ratio=2.2, 95% CI=1.1-4.3).

Acute OP intoxication is characterized by muscarinic and nicotinic symptoms as well as multiple central nervous manifestations caused by an irreversible inhibition of acetylcholinesterase. Most of the cholinergic neurons in the human brain are located in the pontine reticular formation, striatum, and basal forebrain. The striatum contains large aspiny cholinergic neurons that stimulate different GABA projections to the globus pallidus and maintain the balance of dopamine and GABA. Acetylcholinesterase is also richly distributed within the extrapyramidal system, such as in the nucleus caudatus and globus pallidus. Therefore, reduced acetylcholinesterase activity in these cholinergic neurons may produce parkinsonian features.

A case series study determined that six patients developed extrapyramidal features following intoxication with organophosphorus pesticide, with dystonia being observed in all of the patients. The

A case series study determined that six patients developed extrapyramidal features following intoxication with organophosphorus pesticide, with dystonia being observed in all of the patients. The
age ranged from 19 to 54 years. Five of the patients had rhythmic tremors that presented at rest, and four patients exhibited cogwheel rigidity with slow movement. Two previous brain images reported irreversible extrapyramidal syndromes and MRI abnormalities after severe OP poisoning, supporting the possible role of these environmental toxins in causing parkinsonism. Shahar analyzed the outcome of basal ganglia impairment after OP poisoning in 27 patients identified in the literature. Overall, 21 (77%) patients recovered within 60 days, and half of them recovered spontaneously. In the present study, we analyzed the relative risk of PD and found that the IRR was higher after 5 years in patients with OP poisoning. This suggested that OP intoxication through pesticide at an early stage resulted in not only extrapyramidal features but also an increased incidence of PD after several years of follow-up.

Although multiple studies have evaluated potential risk factors including herbicides, pesticides, and fungicides as contributing factors for PD, the exact mechanisms are not well known. The neurotoxic effect of rotenone is excessive generation of reactive oxygen species. Rotenone has been proven to increase the formation of toxic effect of rotenone is excessive generation of reactive oxygen species. These results indicated that OP intoxication might be associated with psychiatric or mental disorders.

The strengths of our study are its population-based design, generalizability of findings, and use of population-based data and NHIRD records with a very large sample size including study and control cohorts. In addition, NHIRD covers a highly representative sample of Taiwan's general population because the reimbursement policy is universal and operated by a single buyer, the government in Taiwan. All insurance claims should be scrutinized by medical reimbursement specialists and peer review according to the standard diagnosed criteria in the study. There are limitations to this study. First, we assumed that ICD-9 code 332.0 represented correct diagnoses of Parkinson disease. We could not obtain the medical charts from the NHIRD. Therefore, we did not have data on the severity of PD and could not completely exclude the possibility of secondary parkinsonism or atypical parkinsonism in our study patients. This study extended the observation time to eliminate the possibility of secondary parkinsonism or atypical parkinsonism. Second, because the diagnosis of PD was based on the clinical symptoms of PD, PD patients could have been diagnosed at outpatient visits. Therefore, the number of patients with Parkinson disease may have been underestimated. This study extended the observation time to eliminate the bias related to case numbers differing PD between outpatient clinics and hospitals. The diagnoses of OP and CM poisoning relied on ICD-9-CM codes and discharge diagnoses. The NHIRD does not provide details on types of OP, including lipophilic and hydrophilic. Third, the NHIRD does not provide detailed patient information regarding factors such as lifestyle, smoking habits, physical activity, socioeconomic status, and family history, all of which were possible confounding factors in this study. However, the data regarding the comorbidities of depression, dementia, stroke, and chronic kidney disease were reliable. Finally, the evidence derived from an observational study is generally lower in quality than that from a randomized trial. However, the toxicity of OP and CM precludes conducting a randomized trial.

5 | CONCLUSION

This population-based retrospective cohort study showed that long-term risks of PD are higher in patients with OP and CM poisoning than in patients without poisoning and that OP and CM poisoning may be independent risk factors for PD. The finding that PD is associated with OP and CM poisoning has a clinical implication: Physicians should consider the OP and CM exposure history while making a new diagnosis.
of PD, especially in young adults. Future mechanistic investigations of the connection between OP and CM exposure and the risk of PD are necessary.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS


REFERENCES

