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ORIGINAL STUDY

The Relationship of Organophosphate Pesticide Exposure and Cognitive Decline Among Residents of an Agricultural Area in Northern Thailand

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Abstract

Background: **Organophosphate pesticide (OP) exposure may be associated with the subsequent development of cognitive decline, which is used to assess the early stage of Alzheimer's disease. We investigated the correlations between biomarkers of OP exposure and cognitive decline among farmers and nonfarmers.**

Methods: **Blood samples were collected from 98 participants. Biomarkers of OP exposure were analyzed, including acetylcholinesterase enzyme (AChE) and butyrylcholinesterase enzyme (BChE) activity. Cognitive decline was measured using the Thai Mental State Examination.**

Results: **The average AChE and BChE activity levels were 3.94 ± 0.93 units/ml (mean ± SD) and 3.13 ± 0.88 units/ml, respectively. Being employed in agricultural occupations were positively correlated with cognitive decline, even after adjustment for sex, age, and educational level (odds ratio: 5.469, 95% CI 1.012−29.55). There was significantly lower AChE activity in participants who had used pesticides for more than 10 years. There was also a positive correlation between low AChE activity and cognitive decline in the study population.**

Conclusion: **The monitoring of exposure biomarkers may be useful in investigating the risk of cognitive decline in at-risk groups.**

Keywords: Organophosphate pesticides, Cognitive decline, Pesticide exposure biomarkers, Thailand

1. Introduction

Pesticides are commonly used to eliminate pests or other organisms that are harmful to crops or animals. In 2020, approximately 3.5 million tons of pesticides were applied to crops from seed to harvest worldwide. Thailand is Asia's fifth largest pesticide user, with 21,800 tons used per year [1]. The United States Environmental Protection Agency and other related organizations have reported numerous health effects associated with widespread, uncontrolled pesticide use [1−4]. Organophosphate pesticides (OPs) are among the most commonly used pesticides by Thai farmers. The

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toxic effects of OPs have been linked to Alzheimer's disease (AD) [5,6].

Alzheimer's disease is the most common form of dementia. Furthermore, its prevalence is increasing worldwide. According to a report by the Alzheimer's Association in 2020, an estimated 5.8 million Americans aged 65 years and older are living with AD. This number is expected to increase by at least 6.7% between 2020 and 2025. The increasing number of patients is a growing public health crisis owing to the concomitant rise in medical costs, as well as social costs including long-term care services and caregiver costs [7,8]. AD is pathologically characterized by the presence of senile plaques composed of aggregated amyloid, neurofibrillary tangles, and consequent neuronal cell death [9,10].

A significant correlation between pesticide exposure and the prevalence of AD was found in several earlier investigations. Pesticide exposure has also been linked with hypertension, high cholesterol levels in middle age, smoking, traumatic brain injury, and depression. These conditions and health behaviors may occur as a result of pesticide use. They can result in oxidative stress, neuroinflammation, microtubule alterations, the accumulation of beta-amyloid, increased levels of intracellular calcium, and mitochondrial dysfunction, which are all contributing factors in organophosphate-induced neurological diseases and lead to AD [11–13].

The data from the WHO showed that 16,278 people died in Thailand from Alzheimer's disease and dementia in 2019, accounting for 3.29% of all deaths. The death rate due to Alzheimer's disease and dementia was 24.8 per 100,000 people. The rate is increasing every year [14]. Agriculture is the top industry in Thailand, which employed about 31.9% of total employed people in 2021 (about 12, 001, 900 people) [15]. Thai farmers commonly use OPs on their crops, which may lead to increased risk of AD. OPs may cause AD by increasing free radical formation, apoptotic proteins imbalance (Bax, anti-apoptotic Bcl-2, and Bcl-xL), altering the ability of mitochondrial membranes to release cytochrome-C, activation of ceramide production, expression of JNK, ERK1/2, MAP kinases, altering and increasing the levels of intracellular calcium levels, and activation of the calpains and CKD5. All of these processes can lead to neuronal apoptosis and neurodegenerative diseases as AD [10]. The consequence is that large numbers of farmers are in the high-risk group for AD.

In occupational and environmental medicine, the two main types of ChE measured in the blood are: 1) erythrocyte AChE, and 2) plasma or serum BChE. The potential for AChE and BChE inhibition varies greatly between organophosphorus compounds. Some organophosphate pesticides have a stronger inhibitory effect on BChE than on AChE. Higher exposure to a large group of organophosphate and carbamate pesticides, when quantified by intensity and duration, are highly correlated with BChE inhibition. However, the inhibition of BChE does not directly correspond to the biological effects of organophosphates on the nervous system. In the case of chronic organophosphate exposure, AChE inhibition is more sensitive than BChE inhibition [16].

The Thai Mental State Examination (TMSE) is the most commonly used questionnaire for cognitive decline assessment in Thailand. It is a 30-point questionnaire that measures a patient's orientation, registration, attention, calculation, language, and recall. The TMSE is used to assess cognitive impairment in clinical and research settings. It is also typically used by medical and allied health professionals to screen for dementia. The TMSE can be used to estimate the severity and progression of cognitive impairment, as well as to track the course of cognitive changes in an individual over time. Thus, the TMSE is an effective tool for documenting a person's response to treatment for dementia as well [17]. The Thai Ministry of Public Health confirmed that there is a significant correlation between the TMSE and the Thai Mini-Mental State Examination 2002 [18].

The aim of the present study was to investigate the correlation between the biomarkers of OP exposure and cognitive decline by using the TMSE among farmers and non-farmers in an agricultural area of northern Thailand.

2. Materials and methods

2.1. Study population

The study location was San Pa Thong District, Chiang Mai Province, Thailand, which is predominantly agricultural. The economically important crops include longan, onion, and rice in the Mae Ka subdistrict, Ban Mae subdistrict, and Thung Sa Toke subdistrict, respectively. Ninety-eight participants were voluntarily enrolled in our study from August to October 2017. Since the target area was agricultural, participants who used pesticides for less than 20% of their working time were classified as non-farmers. Participants who used pesticides on their farms and spent at least 70% of their time working in agriculture were classified as farmers. Potential participants who had conditions that may be linked to exposure to organophosphate and carbamate substances, such as liver disease and anemia, were excluded.

Data on demographic characteristics were collected using questionnaires. The questions included general information, health conditions, and pesticide exposure practices.

2.2. Blood sample collection

Blood samples were collected by venipuncture into sodium-heparinized tubes. The blood was spun and separated to collect plasma. Phosphate buffered saline, with a pH of 7.4, was used to wash the red blood cells (RBCs). The samples were aliquoted and frozen at −20 °C prior to measuring cholinesterase enzyme activity.

2.3. Measurement of cholinesterase activity

Cholinesterase activity has been used as a biomarker of OP exposure because OPs can inhibit the activity of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). This study used a modified version of the methods described by Ellman et al. [19]. Cholinesterase activity was measured by using acetylthiocholine iodide and butyrylthiocholine iodide as substrates for measuring AChE activity in RBCs and BChE activity in plasma, respectively. Cholinesterase activity was reported as units per milliliter (units/ml).

2.4. Cognitive decline assessment

The Thai Mental State Examination was used to assess cognitive decline. The score was the total number of correctly completed items out of 30 items. The questionnaire included measures for orientation, registration, attention, calculation, language, and recall, with score distributions of 6, 3, 5, 3, 3, and 10, respectively. A score equal to or less than 23 indicated cognitive decline. Lower scores indicated poorer brain function and increased cognitive decline [18].

2.5. Statistical analysis

Descriptive statistics (numbers and percentages) were used to represent the characteristics of the study participants. Study participants' characteristics among farmers and nonfarmers were compared using the Chi-square test. The distribution of the study results was determined, and the appropriate statistics were calculated. The independent t-test and one-way ANOVA were used to compare AChE and BChE activity across study participant characteristics. The Mann−Whitney U test and Kruskal−Wallis tests were used to compare TMSE scores across different groups defined by study participants' characteristics. The odds ratio (OR) of cognitive decline associated with agricultural occupation status (farmers versus nonfarmers) was calculated using a logistic regression model. The outcomes are presented as odds ratios (ORs) with 95% confidence intervals (95% CIs). The independent t-test was used to calculate associations between cholinesterase activity and cognitive decline. The statistical tests were two-sided, with a significance level of 0.05. The SPSS statistical program, version 17 was used for the analyses.

2.6. Ethical issues

The study was approved by the Chiang Mai University Human Experimentation Committee (HEC) (Document no. 1/2017, Project no. 23/59).

3. Results

There were 98 participants ranging in age from 25 to 70 years, including 67 men (68.4%) and 31 women (31.6%). The mean age of all participants was 55.9 years old. There were 66 participants under 60 years old (67.3%) and 32 participants over 60 years old (32.7%). The majority of participants (N = 77, 78.6%) earned a monthly salary of less than 20,000 Thai baht. Slightly over half of the participants (N = 54, 55.1%) had completed primary school. Sixty-seven and 31 participants identified themselves as farmers and nonfarmers, respectively. The majority of participants (N = 55, 56.1%) had used pesticides for more than ten years. The comparison of demographic characteristics showed differences in sex, age, educational level, and years of pesticide use between the nonfarmer and farmer groups. However, salaries did not differ between the groups (Table 1).

The mean cholinesterase activity results for OP exposure biomarkers AChE and BChE were 3.94 ± 0.93 units/ml and 3.13 ± 0.88 units/ml, respectively (Table 2). There was a significant difference in AChE activity levels between participants who had not used pesticides (4.34 ± 8.50 units/ml) and those who had used pesticides for more than ten years (3.74 ± 0.95 units/ml); while the other characteristics between these two groups were all the same. There were no differences in the levels of BChE between farmers and nonfarmers in the present study.

Table 1. Demographic characteristics of nonfarmers (n = 31) and farmers (n = 67) in San Pa Thong District, Chiang Mai Province, Thailand.

Variable	Category	Total frequency n (%)	Nonfarmer n (%)	Farmer n (%)	*p-value*
Sex	Male	67 (68.4)	12 (38.7)	55 (82.1)	<0.001*
	Female	31 (31.6)	19 (61.3)	12 (38.7)	
Age range (years)	≤60	66 (67.3)	26 (83.9)	40 (59.7)	0.018**
	>60	32 (32.7)	5 (16.1)	27 (40.3)	
Education level	Primary school	54 (55.1)	15 (48.4)	39 (58.2)	0.020**
	Secondary school	32 (32.7)	8 (25.8)	24 (35.8)	
	Higher than secondary school	12 (12.2)	8 (25.8)	4 (6.00)	
Total monthly salary (Thai baht)	≤10,000	34 (34.7)	11 (35.5)	23 (34.3)	0.412
	10,001–20,000	43 (43.9)	10 (32.3)	33 (49.3)	
	20,001–30,000	10 (10.2)	5 (16.1)	5 (7.50)	
	30,001–40,000	6 (6.1)	3 (9.7)	3 (4.50)	
	≥40,001	5 (5.1)	2 (6.5)	3 (4.50)	
Number of years of pesticide use	None	22 (22.4)	22 (71.0)	0 (0.00)	<0.001*
	1–10	21 (21.4)	2 (6.5)	19 (28.4)	
	>10	55 (56.1)	7 (22.6)	48 (71.6)	

Abbreviations: Significantly different at * $p < 0.001$ and ** $p < 0.05$ for Chi-square test.

Table 3 displays the results for the participants' TMSE scores. Males (25.0 ± 3.47) scored lower than females (26.9 ± 3.01). Participants with lower education level also had lower scores; there was a difference in scores between participants with a primary school (24.1 ± 3.26) compared to a secondary school (26.8 ± 2.90) education and those with an education higher than secondary school (28.9 ± 1.44). Yet, there was no difference in scores between people with a secondary school education and an education higher than secondary school. Furthermore, farmers (25.0 ± 3.70) had lower scores than nonfarmers (26.9 ± 2.25). However, there were no differences between people who were 60 years old (25.9 ± 3.36) or under and those who were over 60 years old (24.9 ± 3.52), in groups with different monthly salaries, or by differing years of pesticide use in this study.

Farmers had more than five-fold higher odds of cognitive decline (as measured by the TMSE) when compared to nonfarmers (crude OR; 5.372, 95% CI; 1.152–24.63). After adjusting for sex, age, and educational level, similar results were obtained. The adjusted OR was 5.469 (95% CI: 1.012–29.55, Table 4).

Table 2. Comparison of mean acetylcholinesterase enzyme (AChE) and butyrylcholinesterase enzyme (BChE) activity levels by participant study characteristics.

Variable	Category	AChE Mean ± SD (units/ml)	*p-value*	BChE Mean ± SD (units/ml)	*p-value*
Sex	Male	3.84 ± 0.99	0.139	3.16 ± 0.97	0.549
	Female	4.14 ± 0.77		3.05 ± 0.67	
Age range (years)	≤60	3.98 ± 0.91	0.490	3.20 ± 0.90	0.256
	>60	3.85 ± 0.98		2.98 ± 0.84	
Education level	Primary school	3.78 ± 0.93	0.090	3.00 ± 0.91	0.264
	Secondary school	4.03 ± 0.88		3.26 ± 0.89	
	Higher than secondary school	4.39 ± 0.96		3.36 ± 0.70	
Total monthly salary (Thai baht)	≤10,000	3.99 ± 0.98	0.224	3.04 ± 1.07	0.516
	10,001–20,000	3.81 ± 0.93		3.09 ± 0.79	
	20,001–30,000	3.85 ± 0.64		3.07 ± 0.54	
	30,001–40,000	3.97 ± 1.00		3.48 ± 0.96	
	≥40,001	4.83 ± 0.76		3.68 ± 0.67	
Farming occupation status	Nonfarmer	4.12 ± 0.82	0.181	3.13 ± 0.71	1.000
	Farmer	3.85 ± 0.97		3.13 ± 0.96	
Number of years of pesticide use	None	4.34 ± 0.84[a]	0.030*	3.23 ± 0.74	0.520
	1–10	4.04 ± 0.85		3.25 ± 0.77	
	>10	3.74 ± 0.95[a]		3.03 ± 0.98	
Total		3.94 ± 0.93		3.13 ± 0.88	

Abbreviations: AChE; acetylcholinesterase and BChE; butyrylcholinesterase. Values followed by the same letters (a) in the same column are significantly different at * $p < 0.05$ for one-way ANOVA test; post-hoc p-value; p-value adjusted with the Bonferroni method.

Table 3. Comparison of mean and median Thai Mental State Examination (TMSE) scores by study participant characteristics.

Variables	Category	TMSE score		*p value*
		Mean ± SD	Median (IQR)	
Sex	Male	25.0 ± 3.47	26.0 (22.0–28.0)	0.010*
	Female	26.9 ± 3.01	27.0 (25.0–30.0)	
Age range (years)	≤60	25.9 ± 3.36	26.0 (24.0–29.0)	0.181
	>60	24.9 ± 3.52	25.5 (22.0–28.0)	
Education level	Primary school	24.1 ± 3.26	25.0 (21.0–26.3)[a,b]	≤0.001**
	Secondary school	26.8 ± 2.90	27.0 (25.0–29.0)[a]	
	Higher than secondary school	28.9 ± 1.44	29.0 (28.3–30.0)[b]	
Total monthly salary (Thai baht)	≤10,000	25.3 ± 3.17	25.0 (22.8–28.3)	0.191
	10,001–20,000	25.5 ± 3.38	26.0 (24.0–28.0)	
	20,001–30,000	25.7 ± 4.24	26.5 (22.8–30.0)	
	30,001–40,000	25.2 ± 4.54	26.0 (20.5–29.3)	
	≥40,001	28.8 ± 1.30	29.0 (27.5–30.0)	
Farming occupation status	Nonfarmer	26.9 ± 2.25	27.0 (25.0–29.0)	0.017*
	Farmer	25.0 ± 3.70	25.0 (22.0–28.0)	
Number of years of pesticide use	None	26.7 ± 2.25	27.0 (25.0–29.0)	0.072
	1–10	25.9 ± 4.33	28.0 (21.5–29.5)	
	>10	25.0 ± 3.33	25.0 (23.0–27.0)	

Abbreviations: Interquartile range (IQR); 1st quartile - 3rd quartile, $p < 0.05$. * Mann–Whitney U test; Values followed by the same letters (a, b) in the same column are significantly different at p < 0.001 ** Kruskal–Wallis test; post hoc p-value; p-value adjusted with the Bonferroni method.

Table 4. Association between farming occupation status and cognitive decline using logistic regression analysis (n = 98).

Variable	Category	Cognitive decline	
		Crude OR (95% CI)	Adjusted OR (95% CI)#
Farming occupation status	Nonfarmer	(ref)	(ref)
	Farmer	5.372 (1.152–24.63)*	5.469 (1.012–29.55)*

Abbreviations: OR; Odds ratio, #adjusted for sex, age, and education level, CI; confidence interval, *$p < 0.05$.

Table 5. Mean and median cholinesterase activity levels and association of cholinesterase activity levels with cognitive decline (n = 98).

Variable	Category	AchE	*p-value*	BchE	*p-value*
		Mean ± SD (units/ml)		Mean ± SD (units/ml)	
Cognitive decline	No	4.03 ± 0.93	0.046*	3.13 ± 0.88	0.840
	Yes	3.57 ± 0.86		3.10 ± 0.93	

Abbreviations: AChE; acetylcholinesterase and BChE; butyrylcholinesterase, *$p < 0.05$ by independent t-test.

Furthermore, people with cognitive decline had significantly lower AChE activity in their blood samples (3.57 ± 0.86 units/ml) than those with no cognitive decline (4.03 ± 0.93 units/ml). However, BChE activity was not related to cognitive decline in our results (Table 5).

4. Discussion

The findings from 98 participants in our study revealed that people who had used pesticides for more than ten years had significantly lower AChE activity than those who had not. Sex, age, education level, salary, and farming occupation were not associated with AChE or BChE activity. However, there were differences in the cognitive decline results based on sex, education level, and farming occupation. There were also differences in demographic characteristics between the nonfarmer and farmer groups. However, even after adjusting for sex, age, and educational level, farmers had a higher risk of cognitive decline than nonfarmers. The results from the OP exposure biomarkers revealed a positive correlation between low acetylcholinesterase enzyme activity and cognitive decline in the study population.

Most of the study participant characteristics were not associated with cholinesterase activity, except for having more than 10 years of pesticide exposure. We found that having more than 10 years of pesticide exposure was associated with lower AChE levels, but not with BChE levels. Our finding is supported by a previous study by Lionetto et al., which found that AChE inhibition is more sensitive than BChE inhibition in the case of chronic organophosphate exposure. However, BChE inhibition is strongly related to the intensity and duration of higher exposure to a wide range of organophosphate and carbamate pesticides [16]. Our results were also similar to a previous study in Thailand, which found no differences in cholinesterase activity in participants by specific participant characteristics, including sex and age. This previous study also found that subjects who had been exposed to pesticides for ten years had significant differences in cholinesterase levels in their plasma samples compared to nonexposed subjects [20]. However, a different study found that body weight, height, age, and sex influenced BChE activity in nonexposed people. In this study, the researchers attributed differences in cholinesterase activity to differences in personal characteristics of participants such as race/ethnicity [21].

In this study, there were significant differences in TMSE scores based on sex and education level; males scored lower than females, and higher scores were found among those with higher education level. The relationship of social characteristics with cognition has been studied in the past few years. Each cognitive test has distinct performance differences. One study found that females scored better than males in some cognitive domains, while males scored better in other domains [22]. There was also a study suggesting that females have a slightly steeper global cognitive decline than males during aging. Subjects with higher education levels had better scores on the cognitive test [23]. A brain atrophy study reported that males showed more intensity in brain atrophy than females during aging. This could be the cause of a greater decrease in cognitive function for males [24]. However, a systematic review of sex and cognitive decline reported that most of the studies concluded that the rate of decline was not related to sex [25]. Education was reported to be the primary influence on late-life cognitive function [26]. In addition, it was also suggested that education reduces the risk of Alzheimer's disease and related dementias [27].

Farmers showed lower TMSE scores than nonfarmers in this study. This indicated that cognitive decline was positively correlated with being employed as a farmer versus nonfarmer, after adjustment for sex, age, and educational level. This result is similar to the results of several studies about the correlation between pesticide exposure and cognitive decline, which included AD. In a study of rural South Koreans, there was a significantly increased number of people with cognitive decline in the group of older people, the lower educational level group, and the pesticide-exposed group [28]. Another study in Costa Rica found that pesticide-exposed subjects performed worse on the MMSE test (Mini-Mental State Examination) than nonexposed subjects, with means of 24.5 versus 25.9 ($p = 0.01$) after controlling for age, sex, and education level [29].

Cholinesterase activity was used as a biomarker of OP exposure in this study. We evaluated the correlation of AChE and BChE activity with cognitive decline. In this study, the subjects with cognitive decline showed a significant correlation with lower AChE activity, but not BChE activity. This finding is similar to the result of a study in Indonesia in which school-age children exposed to pesticides were analyzed for AChE activity using Ellman's method and cognitive function using the Modified Mini-Mental State Examination for Children (MMMSEC). Their findings revealed that lower AChE levels were significantly associated with poorer cognitive function [30]. In addition, a study of occupational exposure (OE) and environmental exposure (EE) groups in Chile found that AChE and BChE activity was correlated with cognitive decline among the EE group. However, only BChE activity was correlated with OE [31].

This study had some limitations. Our study had a smaller sample size than expected because the study was conducted during the cultivation season. During this season, most of the target subjects were unable to participate. Information from study participants about the amount of pesticide they used and the size of their farm was not complete because most of our participants did not own the farms that they worked at. The large differences in the distribution of sex, age, and education level between farmers and nonfarmers occurred because a majority of nonfarmers were government officers who were younger and female and had higher education levels compared to farmers. As a result, the odds ratio for the association between farming occupation status comparing farmers to nonfarmers with cognitive decline in our study may not reflect the true OR. Another aspect to note is that a follow-up assessment of cholinesterase biomarkers and TMSE should be performed to confirm the results.

5. Conclusions

This study observed an association between increased OP exposure using pesticides for over 10 years compared to less than 10 years. In addition, our study found that farmers had increased odds of cognitive decline. We found a positive correlation between cognitive decline and low AChE activity in

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the study participants. The findings suggest that continued monitoring of OP exposure biomarkers may be useful in investigating the risk of cognitive decline in at-risk groups. Further studies about the risks of cognitive decline should be performed and reported to raise awareness of avoiding pesticide use.

Data availability statement

All data were included in this paper.

Funding statement

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Conflict of interest

The authors declare that there are no conflicts of interest.

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