

Prevalence of Severe Acetylcholinesterase (AChE) Inhibition and High Blood Pressure in Pesticide Applicators: A Cross-sectional Study in Central Java, Indonesia

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ABSTRACT

Background. Regardless of the unclear mechanism pathway of Organophosphates (OP) exposure and hypertension, a study in Madagascar reported that the prevalence of hypertension in agricultural villages was very high. Nevertheless, OPs disrupt cellular protein metabolism, leading to cardiovascular, reproductive, and thyroid disorders, hormonal systems, and hypertension.

Objective. This study is aimed at exploring the prevalence of severe AChE inhibition and high blood pressure in pesticide applicators in vegetable farming areas in Central Java, Indonesia.

Methods. This study used a cross-sectional design and recruited 151 participants consecutively from two vegetable farming areas in Central Java who were aged 18–65 years and actively using pesticides for at least one year. The participants' sociodemographic and occupational characteristics were obtained using the structured interviewer-administered questionnaire. This study quantitatively validated the pesticide exposure intensity level (IL) by calculating the lifetime years of pesticide use and the number of days spraying per year to estimate the cumulative exposure level (CEL). Blood pressure was measured with an upper arm digital blood pressure monitor. Acetylcholinesterase (AChE) activity was measured using a spectrophotometer.

Results. The determinant variables of severe AChE inhibition were age ≤ 50 years, two or more last spraying days, high cumulative exposure level, frequent re-entering of the sprayed farming area, and low educational level. The high cumulative exposure level of pesticides and age of >50 years of study participants are the determinant variables of high blood pressure among the pesticide applicators, with the OR (95% CI) being 1.81 (0.91;3.60) and 3.95 (1.94;7.65), respectively.

Conclusion. Severe AChE inhibition was found in 54% of participants, while the prevalence of high blood pressure (HBP) was approximately 47%. Pesticide cumulative exposure level and applicator's age are the determining factors for both severe AChE inhibition and high blood pressure.

Keywords: *acetylcholinesterase, acetylcholinesterase inhibition, agrochemicals, pesticides, farmers, hypertension, occupational exposure, rural health, toxicity*



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INTRODUCTION

Agriculture is a major economic sector in Indonesia and many other countries in the world; however, in Indonesia the majority of agricultural workers are smallholders. Smallholding, or small-scale farming, is often characterized by high levels of pesticide use and poor pesticide handling practices, as demonstrated by the use of a wide variety of pesticides, complex mixtures, higher doses and frequency of use, and inappropriate use of personal protective equipment (PPE).¹⁻³

Health problems due to exposure to pesticides are influenced by the interaction of several factors, especially the type of active pesticide ingredient that determines pesticide toxicity, dose, route and duration of exposure, preventive measures, and can also be influenced by an individual's genetic susceptibility, which affects the ability to metabolize xenobiotics.⁴⁻⁶

Organophosphates (OP), which include malathion, parathion, dimethoate, and chlorpyrifos (CPF), are among the most widely used pesticides in the agricultural sector. The main organ target of OP is the central and peripheral nervous system, through inhibition of cholinesterase enzyme activity.⁷ OP toxicity occurs through a series of metabolic processes, including bioactivation to the active '-oxon' metabolites and detoxification to form the inactive metabolites. Upon bioactivation, '-oxon' may inhibit acetylcholinesterase (AChE), making it one of the biomarkers of OP exposure.⁸ In addition, it may also disrupt cellular protein metabolism, cardiovascular, reproductive, hormonal systems, thyroid disorders, and hypertension.⁹⁻¹² Inhibition of red blood cell acetylcholinesterase (AChE) and related neurologic symptoms were reported in several studies. A study in Benin reported an inhibition of AChE in approximately 60% of the farmworkers.¹³ Similarly, a recent study in Central Java, Indonesia reported a 59% prevalence of neuropathy symptoms among farmers exposed to acetylcholinesterase inhibitor pesticides.¹⁴

Another health concern in this smallholder population is general diseases such as hypertension, which may also be related to agricultural activities. Hypertension was found among approximately one out of three Indonesian adult populations, according to the 2018 Indonesian Basic Health Research (RISKESDAS) report. One study reported the prevalence of hypertension in agricultural villages in Madagascar was 49%.¹⁵ However, it is unclear whether hypertension is more prevalent in the agricultural community than in the general population or whether any occupational characteristics may contribute to the development of hypertension in pesticide applicators.

This study aimed to evaluate the prevalence of severe AChE inhibition and high blood pressure in pesticide applicators in vegetable farming areas in Central Java, Indonesia.

MATERIALS AND METHODS

Study Design and Participants

This cross-sectional study was conducted in 2020. The study population was pesticide applicators aged 18 – 65 who had been actively using pesticides for at least one year, located in two vegetable farming areas in Central Java, Indonesia. The minimum sample size was calculated using the sample size formula for comparison of two independent population means with a 95% confidence interval and a precision error of 10%. Therefore, a total of 151 eligible participants were recruited consecutively. The sociodemographic characteristics, e.g., age, sex, educational level, smoking habits, and occupational characteristics of the participants, consisting of several agricultural work-related and pesticide-handling activities, were obtained through the structured interviewer-administered questionnaire as described previously.^{1,11}

The pesticide exposure intensity level (IL), the lifetime years of pesticide use, and the number of days spraying per year were used to estimate the cumulative exposure level (CEL) according to a validated quantitative method from the Agricultural Health Study.¹⁶ The IL reflects several factors including personal hygiene practices, the use of personal protective equipment (PPE), and mixing and application methods. Using the estimation results, participants were then classified into high CEL and low CEL groups based on the median CEL value.

The study protocol was approved by the Ethical Committee of the Faculty of Medicine Universitas Indonesia on March 23, 2020 (No. KET-339/UN2.F1/ETIK/PPM.00.02/2020). Informed consent was confirmed by the Ethical Committee. Written informed consent was obtained from all participants.

Blood Pressure Measurement

Participants were required to rest before measurement. Participants' blood pressure was measured using an upper arm digital blood pressure monitor in a sitting position. Blood pressure was measured twice, and the mean of systolic and diastolic blood pressure was used in the analysis. High blood pressure (BP) was defined as a systolic BP ≥ 140 mmHg and/or a diastolic BP ≥ 90 mmHg according to The Seventh Report Joint National Committee Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).¹⁷

Red Blood Cell Acetylcholinesterase Activity

Red blood cell acetylcholinesterase (AChE) activity was determined photometrically using the principles of enzymatic kinetics.¹⁰ In brief, AChE activity was analyzed by an industrial toxicology laboratory (Prodia Industrial Toxicology Laboratory) using the Ellmann method with minor adjustments. After isolation, washing, and hemolysis of erythrocytes, they were mixed with acetylcholine iodide as the substrate to determine AChE activity. Acetylcholine iodide will be converted into acetate and thiocholine in the

presence of AChE. The resulting thiocholine will react with Ellman's reagent to produce a yellow pigment that can be measured photometrically. Enzyme activity is proportional to the rate of color formation, which is measured as the extinction coefficient at 405 nm for 4 measurements after adding the substrate; then the average extinction coefficient is calculated. Enzyme activity is obtained from differences in extinction. Detectable AChE activity levels were adjusted by hemoglobin so that the AChE activity was expressed as U/g hemoglobin to describe the inhibition levels. The AChE inhibition levels were divided into severe inhibition (AChE <24.5 U/g Hb) and mild/not inhibited (AChE ≥24.5 U/g Hb) as recommended in the guidelines by Tropical Pesticides Research Institute (TPRI) and used in a previous study.¹⁸

Statistical Analysis

Statistical analysis was performed using SPSS 20 for Windows. The characteristics of the study participants were described using frequency distribution and percentage for categorical variables, while the mean (SD) or median (minimum-maximum) was used to report continuous variables.

There are two distinct dependent variables in our study: severe AChE inhibition and high blood pressure. Severe AChE inhibition is an indicator of biological effect directly related to organophosphate exposure, and high blood pressure is a clinical health outcome with multifactorial determinants, not limited to pesticide exposure. These two dependent variables were analyzed separately to explore their respective determinants independently and provide a clearer and more accurate interpretation of the available data.

The chi-square test was used to analyze the difference in the characteristics of the study population according to severe AChE inhibition and HBP groups. Multiple logistic regression analysis was performed to examine the possible association between severe AChE inhibition and high BP and its contributing factors. Occupational and non-occupational characteristics associated with severe AChE inhibition or HBP at a significance level of $p \leq 0.20$ in the bivariate analysis were included in the multiple logistic regression analysis. All p -values are two-sided, with significance being considered at $p < 0.05$ for these tests.

RESULTS

The mean age of the study participants was 50 (SD 9.4) years. Most of them were men with low levels of education (≤ 9 years of formal education). They spent about 6 hours a day farming, including 3 hours a week spraying pesticides (Table 1). The practice of using multiple pesticides was common among our participants, as about 94% of them used multiple pesticides in their routine use. Regarding the utilization of personal protective equipment (PPE), 1 out of 4 participants work without PPE, while only 2% use proper PPE during their pesticide handling activities.

Table 1. Characteristics of the Study Participants

Characteristics (n =151)	Description	
	Mean (SD)	Median (1 st – 3 rd quartile)
Age (years)	49.8 (9.4)	
RBC AChE (U/g Hb)	23.8 (5.9)	
Post-spraying days		1 (1 – 3) days
Daily duration of agricultural activities		6.0 (6.0 – 7.0) hours/day
Weekly duration of spraying pesticide		3.0 (2.0 – 5.8) hours/week
Lifetime years of pesticide use		25 (18 – 30) years
Number of days spraying per year		104 (61 – 146) days
Cumulative exposure level (CEL)		24.5 (14.8 – 40.4) $\times 10^3$

Severe AChE inhibition was found in 54% of participants, while the prevalence of high blood pressure (HBP) was approximately 47%. Non-occupational characteristics and the characteristics of pesticide handling activities among study participants were grouped according to severe AChE inhibition and HBP (Tables 2 and 3).

Age, smoking, CEL, and several occupational characteristics were found to be associated with severe AChE inhibition in the bivariate analysis. Using multiple logistic regression analysis, those aged ≤ 50 years, grouped as high CEL, and frequently entering the sprayed area are at risk for having severe AChE inhibition (Table 4). For blood pressure, those aged >50 years were at risk for HBP, but high CEL was also retained in the final model (Table 5), assuming that it is an important determinant of HBP in this study population.

DISCUSSION

The high prevalence of severe AChE inhibition in our study was in agreement with a previous study among horticultural farmers in Tanzania.¹⁸ This result also suggests that participants were exposed to substances with inhibitory properties of AChE activity.¹⁹ Inhibition of AChE leads to accumulation of ACh, and subsequent excessive stimulation of cholinergic receptors interferes with neurotransmitters.^{20,21} While the high levels of exposure and acute toxicity of OPs in humans have clinical relevance as they can cause life-threatening conditions, chronic exposure to low OP doses is associated with several health effects and nervous system pathologies such as oxidative stress, cognitive impairment, and neurological and behavioral disorders.²²⁻²⁵

The determinant variables of the severe AChE inhibition in this study were age ≤ 50 years, 2 (two) or more last spraying days, high cumulative exposure level, frequently re-entering a sprayed farming area, and low educational level.

Table 2. Non-occupational Characteristics of the Study Population Grouped according to Severe AChE Inhibition and High Blood Pressure

Variables	n (%)	Severe AChE inhibition		p ^{cs}	High blood pressure		p ^{cs}
		Yes	No		Yes	No	
<i>Age</i>							
≤50 years	76 (50.3)	50 (61.0)	26 (37.7)	0.004	23 (32.4)	53 (66.2)	<0.001
>50 years	75 (49.7)	32 (39.0)	43 (62.3)		48 (67.6)	27 (33.8)	
<i>Sex</i>							
Male	137 (90.7)	74 (90.2)	63 (91.3)	0.823	63 (88.7)	74 (92.5)	0.426
Female	14 (9.3)	8 (9.8)	6 (8.7)		8 (11.3)	6 (7.4)	
<i>Educational level</i>							
Low (≤9 years)	131 (86.8)	75 (91.5)	56 (81.2)	0.063	67 (94.4)	64 (80.0)	0.009
High (>9 years)	20 (13.2)	7 (8.5)	13 (18.8)		4 (5.6)	16 (20.0)	
<i>Smoking habit</i>							
Smoking	73 (48.3)	46 (56.1)	27 (39.1)	0.038	36 (50.7)	37 (46.2)	0.585
Not smoking	78 (51.7)	36 (43.9)	42 (60.9)		35 (49.3)	43 (53.8)	
<i>Body mass index</i>							
≥25 kg/m ²	32 (21.2)	17 (20.7)	15 (21.7)	0.880	16 (22.5)	16 (20.0)	0.704
<25 kg/m ²	119 (78.8)	65 (79.3)	54 (78.3)		55 (77.5)	64 (80.0)	

cs: chi-square

Table 3. Characteristics of Pesticide Handling Activities Grouped according to Severe AChE Inhibition and High Blood Pressure

Variables	n (%)	Severe AChE inhibition		p ^{cs}	High blood pressure		p ^{cs}
		Yes	No		Yes	No	
<i>Time of application</i>							
Other than morning time	60 (39.7)	24 (29.3)	36 (52.2)	0.004	25 (35.2)	35 (43.8)	0.285
Morning time	91 (60.3)	58 (70.7)	33 (47.8)		46 (64.8)	45 (56.2)	
<i>Type of knapsack sprayer</i>							
Motorized	116 (76.8)	68 (82.9)	48 (69.6)	0.053	55 (77.5)	61 (76.2)	0.860
Manual	35 (23.2)	14 (17.1)	21 (30.4)		16 (22.5)	19 (23.8)	
<i>Number of pesticides used</i>							
≤3 types	107 (70.9)	67 (81.7)	40 (58.0)	0.001	55 (77.5)	52 (65.0)	0.092
>3 types	44 (29.1)	15 (18.3)	29 (42.0)		16 (22.5)	28 (35.0)	
<i>Direct contact with the concentrate</i>							
Frequent	110 (72.8)	62 (75.6)	48 (69.6)	0.405	53 (74.6)	57 (71.2)	0.639
Rare/never	41 (27.2)	20 (24.4)	21 (30.4)		18 (25.4)	23 (28.8)	
<i>Re-enter the sprayed farm area</i>							
Frequent	33 (21.9)	24 (29.3)	9 (13.0)	0.016	19 (26.8)	14 (17.5)	0.169
Rare/never	118 (78.1)	58 (70.7)	60 (87.0)		52 (73.2)	66 (82.5)	
<i>Use long sleeves and long pants</i>							
Rare/never	24 (15.9)	13 (15.9)	11 (15.9)	0.988	10 (14.1)	14 (17.5)	0.567
Frequent	127 (84.1)	69 (84.1)	58 (84.1)		61 (85.9)	66 (82.5)	
<i>Last spraying days</i>							
≥2 days	73 (48.3)	52 (63.4)	21 (30.4)	<0.001	33 (46.5)	40 (50.0)	0.666
1 day	78 (51.7)	30 (36.6)	48 (69.6)		38 (53.5)	40 (50.0)	
<i>Cumulative exposure level</i>							
High	77 (51.0)	49 (59.8)	28 (40.6)	0.019	43 (60.6)	34 (42.5)	0.027
Low	74 (49.0)	33 (40.2)	41 (59.4)		28 (39.4)	46 (57.5)	

cs: chi-square

Table 4. Logistic Regression Analysis of the Association between Severe AChE Inhibition and the Potential Determinants

Predictor	B	SE (B)	p	cOR	aOR	95% CI for aOR (Lower; Upper)
(Constant)	-3.15	0.66	<0.001			
Age ≤50 years	1.38	0.409	0.001	2.58	3.96	1.78; 8.84
Two or more last spraying day	1.36	0.38	<0.001	3.96	3.90	1.84; 8.27
High cumulative exposure level	1.10	0.40	0.006	2.17	3.00	1.38; 6.52
Frequently re-enter a sprayed farming area	1.06	0.50	0.035	2.76	2.90	1.08; 7.78
Low educational level	1.05	0.58	0.071	2.49	2.84	0.91; 8.86

B = Parameter estimate

SE (B) = Standard error for B

cOR = crude odds ratio

aOR = adjusted odds ratio

Table 5. Logistic Regression Analysis of the Association between High Blood Pressure and the potential determinants

Predictor	B	SE (B)	P	cOR	aOR	95% CI for aOR (Lower; Upper)
(Constant)	-0.83	0.29	0.004			
Age >50 years	1.35	0.35	<0.001	4.10	3.95	1.94; 7.65
High cumulative exposure level	0.59	0.35	0.090	2.08	1.81	0.91; 3.60

B = Parameter estimate

SE (B) = Standard error for B

cOR = crude odds ratio

aOR = adjusted odds ratio

There is growing evidence to suggest that aging can influence AChE activity levels, although the results are inconclusive. Among our participants, those in the younger age group are more active in farming activities, which is indicated by higher daily intensity levels; therefore, higher exposure is expected. Considering there is no information about symptoms of OP intoxication and the fact that those who sprayed in the last 2 (two) or more days had a higher risk of experiencing severe AChE inhibition, we suggest that our participants were exposed to chronic, low-level pesticide exposure. 1 out of 5 study participants frequently re-entered the sprayed farming area. The re-entry interval applies to anyone entering agricultural areas that have been sprayed. This interval is implemented to protect the farmers from exposure to pesticides, which can occur through inhalation or contact with the skin. Given the limited personal protective equipment used by participants, it can be assumed that this frequently performed hazardous activity may result in higher levels of exposure. Since most of our study participants had a low level of education, it is possible that the level of knowledge regarding proper pesticide handling practices was also poor. Therefore, poor knowledge leads to poor health and pesticide-handling behaviors.^{26,27}

Higher exposure intensity, more frequent application, and a longer period of exposure to pesticides over many years will result in a high CEL score, thus being grouped as high CEL. We found in this study that those grouped as high CEL were at higher risk for developing severe AChE inhibition. Several OPs are weak inhibitors of AChE activity, and through activation into the active-oxon form, the inhibitory potential of AChE becomes greater.²⁸ Therefore, higher

levels of inhibition may indicate larger forms of -oxon and higher exposure. Ideally, it is necessary to determine a personal AChE baseline measurement before the exposed period due to high interindividual variability in AChE activities.²⁹ In this study, each participant only underwent 1 AChE test. The lack of baseline data on individual subjects makes it impossible to assess the decline in AChE activity before and after exposure. However, due to the relatively constant nature of agricultural activities in Indonesia throughout the year, the measured AChE activity indicates a level of toxicity upon current and repeated exposure.

The prevalence of hypertension in our study was much higher than what was reported in the 2018 RISKESDAS and pooled South East Asia countries.³⁰ However, it was in agreement with the previous study in an agricultural village in Madagascar, Indonesia, and another study in the US that also reported a high prevalence of hypertension in agricultural workers.^{15,31,32}

While aging is a physiological condition, inflammation is the most common feature of aging, which is believed to contribute to intracellular oxidative stress associated with hypertension.³³ Older age was a non-modifiable risk factor for hypertension in our study. Our finding was supported by the fact that in a previous study, hypertension was highly prevalent among the older group.^{33,34}

Previous studies concluded that some metabolic dysregulation caused by chronic exposure to OPs may be associated with metabolic syndrome and other chronic diseases.^{35,36} However, in this study, we only found that those grouped in the high CEL group are susceptible to having HBP, suggesting the possible association between pesticide

exposure and HBP; therefore, it warrants further studies to confirm the causal relationship between pesticide exposure and hypertension.

Our study has some limitations. First, the exact amount of pesticide or mixture was not measured directly. Second, there is no available information regarding exposure to contaminated food, water, or the environment. Both limitations may introduce random misclassification in exposure estimates. Despite the limitation described above, one of the strengths of this study is that the number of participants is considered large for a study of its kind.

CONCLUSION

Severe AChE inhibition was found in 54% of participants, while the prevalence of high blood pressure (HBP) was approximately 47%. Pesticide cumulative exposure level and applicator's age are the determining factors for both severe AChE inhibition and high blood pressure. The high prevalence of severe AChE inhibition suggests the presence of exposure-dependent AChE inhibition among pesticide applicators. Furthermore, the prevalence of high blood pressure was higher than the Indonesian or Southeast Asia average. Our findings provide evidence of the potential health impacts of long-term pesticide use; however, it warrants further study to confirm the causal relationship. Therefore, the need for primary and secondary prevention activities, i.e., campaigns on proper pesticide handling practices through a multisectoral approach and collaboration, is essential.

Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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