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RESEARCH ARTICLE

REVISED Association between pesticide exposure and obesity: A cross-sectional study of 20,295 farmers in Thailand [version 3; peer review: 2 approved, 1 not approved]

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v3 **First published:** 04 Jun 2021, **10**:445
https://doi.org/10.12688/f1000research.53261.1

Second version: 02 Feb 2022, **10**:445
https://doi.org/10.12688/f1000research.53261.2

Latest published: 17 May 2022, **10**:445
https://doi.org/10.12688/f1000research.53261.3

Abstract

Background: Obesity is a serious condition because it is associated with other chronic diseases which affect the quality of life. In addition to problems associated with diet and exercise, recent research has found that pesticide exposure might be another important risk factor. The objective of this study was to determine the association between pesticide exposure and obesity among farmers in Nakhon Sawan and Phitsanulok province, Thailand.

Methods: This study was a population-based cross-sectional study. Data on pesticide use and obesity prevalence from 20,295 farmers aged 20 years and older were collected using an in-person interview questionnaire. The association was analysed using multivariable logistic regression, adjusted for its potential confounding factors.

Results: Obesity was found to be associated with pesticide use in the past. The risk of obesity was significantly predicted by types of pesticides, including insecticides (OR = 2.10, 95% CI 1.00-4.38), herbicides (OR = 4.56, 95% CI 1.11-18.62), fungicides (OR = 2.12, 95% CI 1.34-3.36), rodenticides (OR = 2.55, 95% CI 1.61-4.05), and molluscicides (OR = 3.40, 95% CI 2.15-5.40). Among 35 surveyed individual pesticides, 22 were significantly associated with higher obesity prevalence (OR = 1.78, 95% CI 1.10-2.88 to OR = 8.30, 95% CI 2.54-27.19), including herbicide butachlor, 15 insecticides (two carbamate insecticides, five organochlorine insecticides, and eight organophosphate insecticides), and six fungicides.

Conclusion: This study found obesity in farmers in Nakhon Sawan and Phitsanulok province, Thailand, to be associated with the long-term use of several types of pesticides. The issue should receive more public attention, and pesticide use should be strictly controlled.

Open Peer Review

Approval Status ✓ ✗ ✓

	1	2	3
version 3 (revision) 17 May 2022			✓ view
version 2 (revision) 02 Feb 2022	✓ view		? view
version 1 04 Jun 2021	? view	✗ view	

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Any reports and responses or comments on the article can be found at the end of the article.

Keywords
Pesticide exposure, obesity, farmer health, insecticide exposure, herbicide exposure, fungicide exposure

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Author roles: Noppakun K: Conceptualization, Formal Analysis, Investigation, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Juntarawijit C**: Conceptualization, Data Curation, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This project received grant support from the Thailand Science Research and Innovation (SRI)
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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How to cite this article: Noppakun K and Juntarawijit C. **Association between pesticide exposure and obesity: A cross-sectional study of 20,295 farmers in Thailand [version 3; peer review: 2 approved, 1 not approved]** F1000Research 2022, **10**:445 https://doi.org/10.12688/f1000research.53261.3

First published: 04 Jun 2021, **10**:445 https://doi.org/10.12688/f1000research.53261.1

REVISED **Amendments from Version 2**

The data on the association between pesticides and obesity have been reanalyzed with the addition of education and income variables as a covariate. In Tables 2-3, the presentation of the data has been revised to show the percentage use of pesticides between the obese and non-obese groups. The action had a minor effect on the observed odds ratio, but the overall findings and directions of the associations remained the same. Therefore, there was no need to modify the discussion and conclusion sections.

The first paragraph of the discussion has been revised to clarify the difference between the prevalence of obesity among this study group and the public.

Any further responses from the reviewers can be found at the end of the article

Abbreviations

BMI: body mass index
CM: carbamate pesticide
CVD: cardiovascular diseases
2,5-DCP: 2,5-dichlorophenol
DDT: dichlorodiphenyltrichloroethane
EDC: endocrine-disrupting chemicals
ICD-10: International Classification of Diseases 10th
OC: organochlorine pesticide
OPs: organophosphate pesticide
PCBs: polychlorinated biphenyl
p,p'-DDE: dichlorodiphenyldichloroethylene
VHV: village health volunteers

Background

Obesity is a global public health problem. In 2016, the World Health Organization (WHO) reported that there were approximately two billion people aged 18 years and older who were overweight, of which 650 million were obese, with this number expected to rise.[1] In Thailand, the latest national survey reported obesity prevalence among adults aged 18 years and older, to be 4.0% class I obesity (body mass index (BMI) 30.0-34.9 kg/m^2), 0.8% class II obesity (BMI 35.0-39.9 kg/m^2), and 0.1% class III obesity (BMI $\geq$40.0 kg/m^2).[2] Obesity is not just an image problem, it can also affect health and well-being. Obesity has been linked with various health problems, including cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), cancer, and other health problems including liver and kidney disease, sleep apnea, and depression, which can eventually lead to mortality.[3] Many factors can affect obesity, including age, genes, diet, a sedentary lifestyle, certain diseases, and medications, as well as other health conditions including sleeping habits, stress, and depression.[4]

Recent studies have found that pesticide exposure may be associated with metabolic disorders such as obesity.[5] Mice studies have reported that chlorpyrifos, an organophosphate pesticide, has interfered with mucus-bacterial interactions in the gut, leading to increased lipopolysaccharide entry into the body resulting in excess fat storage.[6] A study in Korea found women with *Methanobacteriales, a* bacteria in the gut that is linked to obesity, have higher body weight and waist circumference.[7] This finding was consistent with a study in the United States of America (U.S.A) that with the use of the National Health and Nutrition Examination Survey (NHANES), found that obesity in adults was associated with the fumigant insecticide paradichlorobenzene,[8] and 2,5-dichlorophenol (2,5-DCP) exposure.[9] In a cohort study, dichlorodiphenyldichloroethylene (p,p'-DDE), and polychlorinated biphenyl (PCBs) were associated with higher BMI, high triglyceride levels, and insulin resistance.[10] Not only pesticides, a recent study also linked a simultaneous exposure to bisphenol A (BPA), bisphenol S (BPS), and mono (carboxyoctyl) phthalate (MCOP), to an elevated risk of obesity.[11]

As far as we know, to date, this issue has not been investigated in Thailand. This cross-sectional study aimed to determine the association between pesticide exposure and obesity among farmers in Nakhon Sawan and Phitsanulok province, Thailand. The main interest was to associate obesity to pesticides, either by group or individual chemicals. The results will be useful for verification of previous results and prevention of obesity.

Methods

Study design and setting

Data in this cross-sectional study was collected from farmers in Nakhon Sawan and Phitsanulok province, Thailand. Nakhon Sawan province is located about 250 km north of Bangkok, Thailand, with a population of 1,066,455 people and

401,432 households, from 15 districts (data for the year 2016). The majority of people are farmers, and the main crops are rice, sugarcane, and cassava. In 2017, the province had a gross domestic product (GDP) of 21,852 THB (716 USD).[12] In 2019, Phitsanulok province, located 377 km north of Bangkok, had a population of 865,368 people from nine districts and 342,787 households. Agriculture is the biggest sector of the economy, generating about 28% of GDP with an employment rate of 41.9%. The major crops in the province are rice, sugar cane, cassava, and vegetables.[13,14]

Study participants and sampling procedure

Study participants were farmers aged 20 years and older, who had worked as farmers for at least five years. Participants were selected using multistage sampling. Firstly, three districts from each province were randomly selected. In each district, three sub-districts were further randomly selected. In each sub-district, we selected 2,100-4,500 farmer families, accounting for about 30-100% of all farmer families in each sub-district. Using data from the local authority and personal contact, village health volunteers (VHV) identified farmer families, who were contacted for data collection. In each family, one adult who met the inclusion criteria was interviewed.

All local hospitals inside the selected subdistrict were contacted and public health staff and its membership VHV were invited to participate in the study. VHV who had mobile phone and internet access to the online questionnaires were recruited. These volunteers also had to attend a one-day training session to be informed about the project and to be trained on interviewing the participants, along with the correct use of online questionnaires. Most of the interviews took place in the participant's home, however sometimes in other places, e.g. local temple or hospital. Data was collected between October 2020 and February 2021. Data from all 20,295 participants were included in the data analysis.

The minimum sample size was calculated to be 18,772, based on the following assumptions: significance level = 95%; power of detection = 80%; ratio of unexposed/exposed = 1; percent of unexposed with outcome = 5%; odds ratio = 1.2. Exposed refers to exposure group, or those who used pesticides. Unexposed refers to unexposed group or those who do not use pesticides.

Study questionnaire and data collection

Data was collected using an in-person interview questionnaire and an online version. The questionnaire had three major parts (provided as *Extended data*[15]). Part I, contained demographic information, including gender, age, marital status and education. Information on cigarette smoking and alcohol consumption were also collected.

In part II, there were questions regarding the long-term use of pesticides. This question was modified from the questionnaire used in our previous study.[16] Data on both types and individual pesticides were collected. Pesticides were categorized into insecticides, herbicides, fungicides, rodenticides, and molluscicides. Insecticides were further subdivided into four classes: organochlorine, organophosphate, carbamate, and pyrethroid. For individual pesticides, we collected data on 35 pesticides that were commonly used in Thailand and have been reported in previous literatures to affect obesity.[16] Study participants were asked whether they have ever used the pesticides, using a 'yes' or 'no' question. Pesticide use was defined as a mixture or spray pesticides for agriculture purposes. Household pest control was excluded in this study.

In part III, participants were asked whether they had been medically diagnosed with obesity by using a "yes" or "no" question. This information was later confirmed by the disease record ICD-10 of the local hospitals. The confirmed cases were included in the data analysis, while the missing data was excluded. In Thailand, the Ministry of Public Health follows The World Health Organization obesity criteria for the Asia Pacific Region in which the body mass index over 25.0 kg/m^2 was identified as obesity.[17]

Statistical analysis

Demographic data were analysed using descriptive statistics (frequency, percentage, mean, and standard deviation). An association between pesticides and obesity was determined using multivariable logistic regression, adjusted for gender (male, female), age (20-30, 31-40, 41-50, 51-60, 60>), smoking (non-smoker, ex-smoker, smoker) and alcohol consumption (non-drinker (or abstainer), ex-drinker, regular drinker), education (not attend school, primary school, secondary school, college degree or higher), and income per month (THB) (<5000, 5001-10000, 10001-30000, >30000), presented in odds ratio (OR), 95% confidence intervals.

P-values <0.05 were statistically significant. All data analysis was performed using IBM SPSS Statistics (version 26) and OpenEpi online version 3.5.1.

Table 1. Characteristics of not obese, and obese participants.

	Not obese N (%)	Obese N (%)	P value **
Obesity	20217 (99.6)	78 (0.4)	
Having other related diseases			<0.001*
-Hypertension	5402 (26.7)	43 (55.1)	
-Diabetes mellitus	2208 (10.9)	23 (29.5)	
-Dyslipidemia	1871 (9.3)	11 (14.1)	
-Heart disease	243 (1.2)	2 (2.6)	
-Sleep disorder	14 (0.1)	2 (2.6)	
-Stroke	331 (1.6)	1 (1.3)	
Gender			0.173
Male	9072 (44.9)	29 (37.2)	
Female	11145 (55.1)	49 (62.8)	
Age, yr			0.030 *
20-30	722 (3.6)	4 (5.1)	
31-40	1830 (9.1)	11 (14.1)	
41-50	4238 (21.0)	24 (30.8)	
51-60	6518 (32.2)	23 (29.5)	
61+	6909 (34.2)	16 (20.5)	
Mean $\pm$ SD = 55 $\pm$ 12			
Min-Max = 20-98			
District			<0.001*
PH-WB	4518 (22.3)	0 (0)	
PH-BK	2106 (10.4)	25 (32.1)	
PH-BR	2991 (14.8)	9 (11.5)	
NS-LY	3364 (16.6)	15 (19.2)	
NS-MW	3662 (18.1)	9 (11.5)	
NS-TT	3576 (17.7)	20 (25.6)	
Marital status			0.657
Married	15476 (76.5)	63 (80.8)	
Single	1727 (8.5)	6 (7.7)	
Divorced/widowed/separated	3014 (14.9)	9 (11.5)	
Education level			<0.001*
Not attend school	838 (4.1)	1 (1.3)	
Primary school	14915 (73.8)	40 (51.3)	
Secondary school	4158 (20.6)	32 (41.0)	
College degree or higher	306 (1.5)	5 (6.4)	
Income per month (THB)			0.021*
<5000	7317 (36.2)	30 (38.5)	
5001-10000	10887 (63.9)	36 (46.2)	
10001-30000	1844 (9.1)	9 (11.5)	
>30000	169 (0.8)	3 (3.8)	
Cigarette smoke (n = 20217)			0.040 *
Non- smoke	17043 (84.3)	64 (82.1)	
Ex-smoker	918 (4.5)	8 (10.3)	
Current smoker	2256 (11.2)	6 (7.7)	

Table 1. *Continued*

	Not obese N (%)	Obese N (%)	P value **
Alcohol consumption (n = 20217)			0.557
Non-drinker	15553 (76.9)	57 (73.1)	
Ex-drinker	1461 (7.2)	8 (10.3)	
Regular drinker	3203 (15.8)	13 (16.7)	

*Statistically significant difference with p-value <0.05.
**Chi-square test.

Ethical considerations

The study was approved by the Ethical Committee of Naresuan University (COA No. 657/2019). Before the interviews, all the study participants gave informed consent to participate in the study, and they had the right to stop the interview at any time.

Results

Out of the 20,295 participants, 78 were medically diagnosed to be obese (0.4%) (Table 1 and the *Underlying Data*[18]). The case group also had other chronic diseases, e.g., hypertension (55.1%), diabetes mellitus (29.5%), and dyslipidaemia (14.1%). Only a small number of the cases currently smoke (7.7%) or drink alcohol (16.7%). Among other demographic characteristics, only age, having other related diseases, district, education level, income per month, and cigarette smoking status were significantly associated with obesity ($p < 0.05$).

It was found that all types of pesticides, including insecticides, herbicides, fungicides, rodenticides, and molluscicides, were significantly associated with obesity prevalence (Table 2). The associations were also found in many of the surveyed individual pesticides (Table 3). Those pesticides were from various types of pesticide, including herbicides butachlor, 15 insecticides (two carbamate (CM) insecticide, five organochlorine pesticides (OC) insecticide, and eight organophosphate pesticides (OP) insecticide), and six fungicides.

Table 2. Association (OR) between different types of pesticide and obesity.

	Not obese (N = 20217) N (%)	Obese (N = 78) N (%)	OR (crude)	OR (adjusted)*
Any pesticide				
No	1092 (5.4)	8 (10.3)	1.0	1.0
Yes	19125 (94.6)	70 (89.7)	0.50 (0.24-1.04)	0.46 (0.22-0.97)
Insecticide				
No	4248 (21.0)	8 (10.3)	1.0	1.0
Yes	15969 (79.0)	70 (89.7)	**2.33 (1.12-4.84)****	**2.10 (1.00-4.38)**
Herbicide				
No	2293 (11.3)	2 (2.6)	1.0	1.0
Yes	17924 (88.7)	76 (97.4)	**4.86 (1.19-19.81)**	**4.56 (1.11-18.62)**
Fungicide				
No	12076 (59.7)	31 (39.7)	1.0	1.0
Yes	8141 (40.34)	47 (60.3)	**2.25 (1.43-3.54)**	**2.12 (1.34-3.36)**
Rodenticide				
No	15809 (78.2)	46 (59.0)	1.0	1.0
Yes	4408 (21.8)	32 (41.0)	**2.50 (1.59-3.92)**	**2.55 (1.61-4.05)**
Molluscicide				
No	15364 (76.0)	38 (48.7)	1.0	1.0
Yes	4853 (24.0)	40 (51.3)	**3.33 (2.14-5.20)**	**3.40 (2.15-5.40)**

*Adjusted variables: Gender (male, female), age (20-30, 31-40, 41-50, 51-60, 60+), smoking (never, ex-smoker, current smoker), alcohol consumption (never, used to drink, currently drink), education (not attend school, primary school, secondary school, college degree or higher), income per month (THB) (<5000, 5001-10000, 10001-30000, >30000).
**Significant OR were indicated in bold numbers.

Table 3. **Association (OR) between individual pesticide and obesity.**

Pesticide	Not obese (N = 20217) N (%)	Obese (N = 78) N (%)	OR crude	OR adjusted
Herbicide				
Glyphosate				
No	5716 (28.3)	17 (21.8)	1.0	1.0
Yes	14501 (71.7)	61 (78.2)	1.42 (0.83-2.43)	1.32 (0.77-2.26)
Paraquat				
No	10622 (52.5)	37 (47.4)	1.0	1.0
Yes	9594 (47.5)	41 (52.6)	1.23 (0.79-1.92)	1.12 (0.71-1.75)
2,4-D				
No	10531 (52.1)	35 (44.9)	1.0	1.0
Yes	9686 (47.9)	43 (55.1)	1.34 (0.86-2.10)	1.25 (0.80-1.95)
Butachlor				
No	16033 (79.3)	43 (55.1)	1.0	1.0
Yes	4184 (20.7)	35 (44.9)	**3.12 (2.00-4.88)****	**2.98 (1.90-4.69)**
Alachlor				
No	18669 (92.3)	68 (87.2)	1.0	1.0
Yes	1547 (7.7)	10 (12.8)	1.78 (0.91-3.46)	1.63 (0.83-3.17)
Diuron				
No	19810 (98.0)	74 (94.9)	1.0	1.0
Yes	407 (2.0)	4 (5.1)	2.63 (0.96-7.23)	2.64 (0.95-7.32)
Organophosphate insecticide				
Abamectin				
No	9577 (47.7)	25 (32.1)	1.0	1.0
Yes	10640 (52.6)	53 (67.9)	**1.91 (1.19-3.07)**	**1.78 (1.10-2.88)**
Chlorpyrifos				
No	15466 (76.5)	40 (51.3)	1.0	1.0
Yes	4751 (23.5)	38 (48.7)	***3.09 (1.98-4.83)***	***2.86 (1.82-4.49)***
Folidol (parathion)				
No	17675 (87.4)	62 (79.5)	1.0	1.0
Yes	2542 (12.6)	16 (20.5)	**1.80 (1.03-3.11)**	1.73 (0.99-3.03)
Methamidophos				
No	19439 (96.2)	71 (91.0)	1.0	1.0
Yes	778 (3.8)	7 (9.0)	**2.47 (1.13-5.39)**	**2.25 (1.02-4.95)**
Monocrotophos				
No	19754 (97.7)	72 (92.3)	1.0	1.0
Yes	463 (2.3)	6 (7.7)	**3.56 (1.54-8.23)**	**3.26 (1.40-7.58)**
Mevinphos				
No	19977 (98.8)	74 (94.9)	1.0	1.0
Yes	240 (1.2)	4 (5.1)	**4.50 (1.63-12.40)**	**4.37 (1.57-12.20)**
Dicrotophos				
No	19756 (97.7)	72 (92.3)	1.0	1.0
Yes	460 (2.3)	6 (7.7)	**3.59 (1.55-8.51)**	**3.35 (1.44-7.80)**

Table 3. *Continued*

Pesticide	Not obese (N = 20217) N (%)	Obese (N = 78) N (%)	OR crude	OR adjusted
Dichlorvos				
No	19998 (98.9)	75 (96.2)	1.0	1.0
Yes	219 (1.1)	3 (3.8)	**3.67 (1.15-11.72)**	**3.63 (1.13-11.68)**
EPN				
No	19631 (97.1)	75 (96.2)	1.0	1.0
Yes	586 (2.9)	3 (3.8)	1.34 (0.42-4.27)	1.25 (0.39-3.99)
Imidacloprid				
No	19524 (99.6)	73 (0.4)	1.0	1.0
Yes	681 (99.3)	5 (0.7)	1.96 (0.79-4.88)	1.82 (0.73-4.53)
Profenofos				
No	19730 (97.6)	72 (92.3)	1.0	1.0
Yes	487 (2.4)	6 (7.7)	**3.38 (1.46-7.81)**	**2.99 (1.28-6.97)**
Carbamate insecticide				
Carbaryl				
No	18958 (93.8)	64 (82.1)	1.0	1.0
Yes	1259 (6.2)	14 (17.9)	**3.30 (1.84-5.90)**	**3.24 (1.80-5.82)**
Methomyl				
No	18889 (93.4)	68 (87.2)	1.0	1.0
Yes	1328 (6.6)	10 (12.8)	**2.09 (1.08-4.08)**	1.95 (0.99-3.84)
Carbosulfan				
No	17722 (87.7)	56 (71.8)	1.0	1.0
Yes	2495 (12.3)	22 (28.2)	**2.79 (1.70-4.58)**	**2.53 (1.54-4.18)**
Carbofuran				
No	18098 (89.5)	64 (82.1)	1.0	1.0
Yes	2119 (10.5)	14 (17.9)	1.87 (1.05-3.34)	1.68 (0.92-3.05)
Pyrethroid insecticide				
Permethrin				
No	17780 (87.9)	67 (85.9)	1.0	1.0
Yes	2437 (12.1)	11 (14.1)	1.20 (0.63-2.27)	1.09 (0.57-2.07)
Organochlorine insecticide				
Endosulfan				
No	17135 (84.8)	53 (67.9)	1.0	1.0
Yes	3082 (15.2)	25 (32.1)	**2.63 (1.63-4.23)**	**2.46 (1.50-4.02)**
Dieldrin				
No	20038 (99.1)	75 (96.2)	1.0	1.0
Yes	179 (0.9)	3 (3.8)	**4.48 (1.40-14.33)**	**4.78 (1.48-15.42)**
Aldrin				
No	20120 (99.5)	75 (96.2)	1.0	1.0
Yes	97 (0.5)	3 (3.8)	**8.29 (2.57-26.75)**	**8.30 (2.54-27.19)**

Table 3. *Continued*

Pesticide	Not obese (N = 20217) N (%)	Obese (N = 78) N (%)	OR crude	OR adjusted
DDT				
No	19297 (95.4)	69 (88.5)	1.0	1.0
Yes	920 (4.6)	9 (11.5)	**2.73 (1.36-5.49)**	**2.76 (1.36-5.57)**
Chlordane				
No	19940 (98.6)	70 (89.7)	1.0	1.0
Yes	277 (1.4)	8 (10.3)	**8.25 (3.93-17.31)**	**8.12 (3.84-17.17)**
Heptachlor				
No	17058 (84.4)	62 (79.5)	1.0	1.0
Yes	3158 (15.6)	16 (20.5)	1.39 (0.80-2.42)	1.29 (0.74-2.24)
Fungicide				
Metalaxyl				
No	18649 (92.2)	63 (80.8)	1.0	1.0
Yes	1568 (7.8)	15 (19.2)	**2.83 (1.61-4.99)**	**2.61 (1.47-4.63)**
Mancozeb				
No	18854 (93.3)	70 (89.7)	1.0	1.0
Yes	1363 (6.7)	8 (10.3)	1.58 (0.76-3.29)	1.37 (0.66-2.88)
Maneb				
No	19291 (95.4)	71 (91.0)	1.0	1.0
Yes	926 (4.6)	7 (9.0)	2.06 (0.94-4.48)	1.88 (0.86-4.11)
Propineb				
No	19272 (95.3)	68 (87.2)	1.0	1.0
Yes	945 (4.7)	10 (12.8)	**3.00 (1.54-5.85)**	**2.75 (1.40-5.38)**
carbendazim				
No	17913 (88.6)	57 (73.1)	1.0	1.0
Yes	2304 (11.4)	21 (26.9)	**2.87 (1.74-4.74)**	**2.60 (1.57-4.32)**
	<0.001*			
Thiophanate				
No	19842 (98.1)	73 (93.6)	1.0	1.0
Yes	375 (1.9)	5 (6.4)	**3.63 (1.46-9.04)**	**3.55 (1.42-8.91)**
Benomyl				
No	19976 (98.8)	74 (94.9)	1.0	1.0
Yes	241 (1.2)	4 (5.1)	**4.50 (1.63-12.40)**	**4.61 (1.66-12.80)**
Bordeaux mixture				
No	20108 (99.5)	76 (97.4)	1.0	1.0
Yes	109 (0.5)	2 (2.6)	**4.85 (1.18-20.00)**	**5.40 (1.30-22.48)**

*Adjusted variables: Gender (male, female), age (20-30, 31-40, 41-50, 51-60, 60+), smoking (never, ex-smoker, current smoker), alcohol consumption (never, used to drink, currently drink), education (not attend school, primary school, secondary school, college degree or higher), income per month (THB) (<5000, 5001-10000, 10001-30000, >30000).
**Significant OR were indicated in bold numbers.

Discussion

In this study, the prevalence rate of obesity among the study group (0.4%) was lower than that of the general population (4.0%), which referred to those with class I to class III obesity.[2] However, if we consider 0.8% for class II, and 0.1% for class III, the prevalence was similar to those among the study group. In this study, the obese group are those who went to see the doctor and were registered in the ICD-10 of the hospital. Therefore, this group was more likely to suffer from severe obesity. In further analysis, this study also found that many of the obesity cases have other health problems (hypertension (55%), T2DM (30%)) (Table 1).

This results of this study also found that many pesticides are strongly associated with the prevalence of obesity. The risk of obesity was significantly predicted by various types of pesticides, including insecticides (OR = 2.10, 95% CI 1.00-4.38), herbicides (OR = 4.56, 95% CI 1.11-18.62), fungicides (OR = 2.12, 95% CI 1.34-3.36), rodenticides (OR = 2.55, 95% CI 1.61-4.05), and molluscicides (OR = 3.40, 95% CI 2.15-5.40) (Table 2). Among 35 surveyed individual pesticides 22 were significantly associated with obesity (OR = 1.78, 95% CI 1.10-2.88 to OR = 8.30, 95% CI 2.54-27.19), including herbicide butachlor, 15 insecticides (two CMs-carbaryl, carbosulfan, five organochlorine insecticides- endosulfan, dieldrin, aldrin, DDT, chlordane, and eight organophosphate insecticides- abamectin, chlorpyrifos, methamidophos, monocrotophos, mevinphos, dicrotophos, dichlorvos, profenofos), and six fungicides- metalaxyl, propineb, carbendazim, thiophanate, benomyl, bordeaux mixture (Table 3). Turnbaugh et al,[19] found pesticides affect the gut microbiome that controls the energy harvest, which may lead to obesity. This finding was supported by a recent study that found long-term exposure to chlorpyrifos affects gut microbiota homeostasis and induces inflammation, resulting in excess fat accumulation in the body.[6] Additionally, a Korean study reported on the Methanobacteriales in the gut being associated with increased waist circumference, and bodyweight.[7]

Some pesticides are endocrine-disrupting chemicals (EDC). These are exogenous chemicals that interfere with the action of hormones, and/or obesogens, that inappropriately regulate lipid metabolism and adipogenesis to promote obesity.[20] At present, there are 105 pesticides listed as EDC, insecticides (46%) e.g. OCs DDT, 2,4-D, aldrin, endosulfan, chlorpyrifos, herbicide (21%) e.g. alachlor, diuron, glyphosate, and fungicides (31%) e.g., benomyl, carbendazim. A study found EDCs affect weight gain by altering lipid metabolism, fat cell size and number, and hormones involved in appetite, food preference, and energy metabolism.[21]

Epidemiological studies on the association between pesticide exposure and obesity are rare. U.S.A National Health and Nutrition Examination Survey (NHANES) from 2005-2008, indicated that obesity of the general population was associated with environmental exposure to some pesticides, e.g. 2,4-dichlorophenol (2,4-DCP), and 2,5-dichlorophenol (2,5-DCP).[8] Among non-diabetic individuals, a study found that exposure to OC pesticides, especially p,p'-DDE, increased the risk of higher BMI, triglycerides, and decreased HDL cholesterol.[10] Another study using NHANES survey from 2003-2006, also found exposure to environmental pesticides increased obesity in children aged 6-19 years.[22] In this study, a dose-dependency was observed between the quartile of exposure to 2,5-DCP and the prevalence of obesity. These results were supported by a follow-up study which found 2,5-DCP exposure to be significantly associated with obesity (OR = 1.09, 95% CI 1.1-1.19) among children and adolescents aged 6-18 years.[9] A follow-up cohort study has found that middle-aged obese women were associated with mothers that used DDT, while pregnant with these women. (OR = 1.26, 95% CI 6-49 to OR = 1.31, 95% CI 6-62).[23]

There were several limitations to the study that need to be mentioned. By using a cross-sectional design, the study was limited in explaining the causality since both disease and exposure data were examined at the same time. Though a large sample size was used, the number of obese participants was still small. This limited the power of detection and control of confounding factors. Data on other risk factors, such as diet, exercise, or genetics were not collected. These confounding factors might have a different impact on the results. However, the problem may not have much effect on the study results since the case and control groups were from the same community and having the same occupation. For family history, to be a real confounding factor, the family history must be associated with both obesity and the use of pesticides. In this case the family's histories are strongly linked to obesity, but not to the use of pesticides. Due to their health, the obese people tended to avoid using chemicals whenever possible. Therefore, family history was unlikely to affect the observed association of our study. Small sample sizes also caused high values on the odds ratio with wide confidence intervals, therefore the result should be interpreted with caution. More study to confirm causal relationships between pesticide exposure and obesity was surely needed and the results should be used as a hypothesis generation. Another concern was that the obesity cases from ICD-10 records may not have been valid or represent the prevalence of the disease in the study. Currently, data on the validity of ICD-10 diagnosis coding for overweight/obesity in Thailand is not available. However, studies in Europe e.g., Sweden and Denmark, reported that the data is accurate and suitable to be used in epidemiological research.[24]

In this study, information on pesticides exposure was solely based on the questionnaire method instead of biomarker or other individual quantitative measurement. This might cause concern over the information bias due to poor reliability and accuracy of the questionnaire data. However, for a large-scale study of long-term exposure to pesticides, this method may be the only option. Measurement of a biomarker in blood or urine is costly and may only represent short-term exposure.[25] For long-term exposure, using a questionnaire collecting data on the duration and intensity of pesticide use was accepted and has been used in many large-scale studies under the Agricultural Health Study in the United State for other diseases.[26] Also, by using a large number of individual pesticides to predict risk of obesity, it is very likely that the problem of co-exposure or the joint effect of mixed exposure to pesticides will occur.[11] This could distort the study result. Further study should try to do a dose-response analysis and study the effect of multiple pesticide exposure.

Conclusion

In Nakhon Sawan and Phitsanulok province of Thailand, obesity in farmers was associated with the long-term use of several types of pesticides, including insecticides, herbicides, fungicides, rodenticides, and molluscicides. The study additionally found 22 individual pesticides was significantly associated with obesity. This finding was consistent with the literature and studies done in other countries. The information should be publicized, and pesticide use should be controlled. Further studies should be done to confirm the results, and to determine a safe limit of pesticide exposure for obesity risk.

Data availability

Underlying data

Figshare: Dataset for study on pesticide exposure and obesity, among farmers in Nakhon Sawan and Phitsanulok province, Thailand.

https://doi.org/10.6084/m9.figshare.14524983.v2.[18]

This project contains the following underlying data:

- Dataset Pesticide and obesity (SAV and CSV). (All underlying data gathered in this study)
- Data Dictionary (DOCX).

Extended data

Figshare: Dataset for study on pesticide exposure and obesity, among farmers in Nakhon Sawan and Phitsanulok province, Thailand.

https://doi.org/10.6084/m9.figshare.14524980.v1.[15]

This project contains the following extended data:

- Questionnaire-pesticide and obesity-English (DOCX). (Study questionnaire in English)
- Questionnaire-pesticide and obesity-Thai (DOCX). (Study questionnaire in Thai)

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Acknowledgments

The author is grateful to all the study participants who took the time to participate in this study and provided valuable information. Thank you very much to local hospital staff from Nakhon Sawan, and Phitsanulok province, and the village health volunteers for collecting data. Thank you also to Mr. Kevin Mark Roebl of Naresuan University’s Writing Clinic (DIALD) for editing assistance.

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Open Peer Review

Current Peer Review Status: ✓ ✗ ✓

Version 3

Reviewer Report 23 May 2022

https://doi.org/10.5256/f1000research.134032.r138054

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Erik Jors
Clinic of Occupational Medicine, Clinical Institute, University of Southern Denmark, Odense, Denmark

I find that the paper with the changes in this third version can be indexed.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pesticide poisonings

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 07 April 2022

https://doi.org/10.5256/f1000research.79778.r128600

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Erik Jors
Clinic of Occupational Medicine, Clinical Institute, University of Southern Denmark, Odense, Denmark

Dear Authors and Editors,

I have read this interesting article on pesticide exposure and obesity among Thailand farmers. The research describes the association between obesity and the use of pesticides among farmers. It shows that there might be an association, but results have to be further analyzed before indexing, especially for relevant confounders like education and income and if possible for amounts of pesticides used. I, therefore, cannot approve the article for indexing but urge the authors to improve it before indexing can be reconsidered.

I have the following comments and suggestions for revision:

Major corrections:

1. In your analysis, you control for sex, age, smoking, and alcohol consumption which is fine, but you miss some important confounders of which you have data presented in Table 1 - income and educational level. Both might influence the use of pesticides and/or obesity, so I suggest you take them into your multivariate analysis.

2. You should have included the amounts and/or frequency of pesticide use. As it is now, one spraying per year counts equal to 100 sprayings per year, or 100 grams per year equals 1 kg per year. Please include this in your limitations if you do not have the data to include in your analysis as it is a major shortcoming.

3. Obesity often runs in families, you have no data on this but it should be discussed in the article.

4. In Table 2 you present results I do not understand - please discuss why the 'use of any pesticide' seems to be protective against obesity while the 'use of each of the specific pesticides' seems to be associated with obesity. This has to be discussed and explained.

Minor corrections:

1. The literature included could have been more comprehensive, please try to include more of the relevant literature.

2. In Tables 2-3, it would have been more illustrative to have the percentages among the not obese, like xx% uses pesticides, yy% do not, and the same for the obese.

3. It is interesting why this group of farmers has so less obesity than the general population - this must be discussed in the article.

When these issues are addressed I will be happy to review the article again.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pesticide poisonings

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 13 May 2022

Chudchawal Juntarawijit, Naresuan University, Phitsanulok, Thailand

Comment and response

Comment
I have read this interesting article on pesticide exposure and obesity among Thailand farmers. The research describes the association between obesity and the use of pesticides among farmers. It shows that there might be an association, but results have to be further analyzed before indexing, especially for relevant confounders like education and income and if possible for amounts of pesticides used. I, therefore, cannot approve the article for indexing but urge the authors to improve it before indexing can be reconsidered.

Response
We would like to thank you so much for your time and effort in reviewing our paper. Your comments are very useful in helping to improve the quality of the paper.

Major corrections:
Comment
In your analysis, you control for sex, age, smoking, and alcohol consumption which is fine, but you miss some important confounders of which you have data presented in Table 1 - income and educational level. Both might influence the use of pesticides and/or obesity, so I suggest you take them into your multivariate analysis.

Response
As suggested, the data has been reanalyzed with two variables (income and education levels) added to the model. However, only minor changes to the OR were observed, but the overall levels and direction of the associations remain intact. The data in Tables 2-3 and in other related texts have been updated.

Comment
You should have included the amounts and/or frequency of pesticide use. As it is now, one spraying per year counts equal to 100 sprayings per year, or 100 grams per year equals 1 kg per year. Please include this in your limitations if you do not have the data to include in your analysis as it is a major shortcoming.

Response
Yes, we agree that the major limitation of this study was exposure assessment, but it might be the best available method for this type of study. The problem was also raised by other reviewers and the issue was already discussed and presented in the last paragraph of the discussion. Please see also the response to reviewer #1 and reviewer #2.

Comment
Obesity often runs in families, you have no data on this but it should be discussed in the article.

Response
To be a real confounding factor, the family history must be associated with both obesity and the use of pesticides. In this case, the family's histories are strongly linked to obesity, but may not be to the use of pesticides. Due to their health, obese people tended to avoid using chemicals whenever possible. Therefore, family history was unlikely to affect the observed association of our study.

Comment
In Table 2 you present results I do not understand - please discuss why the 'use of any pesticide' seems to be protective against obesity while the 'use of each of the specific pesticides' seems to be associated with obesity. This has to be discussed and explained.

Response
The problem may come from the fact that there were many individual pesticides, while only some of them were associated with obesity. Therefore, the overall effect of any pesticides may or may not be the same as those of individual ones. In this study, only 22 out of the 35 individual pesticides were found to be significantly associated with obesity. In fact, there are more than 35 individual pesticides used in Thailand, and the term "pesticides" may be confusing to the participants. In addition, the data were from two different questions, the first was "have you ever used any pesticides?", and the other one was "have you ever used, for instance, glyphosate?

The problem may also stem from the inaccuracy of the exposure assessment of the chemicals when the questionnaire method is used. The issue has already been discussed and presented in the last paragraph of the Discussion.

Minor corrections:
Comment
The literature included could have been more comprehensive, please try to include more of the relevant literature.

Response
This issue is rather new, and so far there have only been a few studies on it carried out. To the best of our knowledge, all the relevant studies have already been reviewed.

Comment
In Tables 2-3, it would have been more illustrative to have the percentages among the not obese, like xx% uses pesticides, yy% do not, and the same for the obese.

Response
In Tables 2-3, the data on the use of pesticides among the obese and non-obese groups have been edited as you suggested. Thank you very much for your insightful advice.

Comment
It is interesting why this group of farmers has so less obesity than the general population - this must be discussed in the article.

Response
Although the prevalence rate of obesity among the study group (0.4%) was lower than that of the general population (4.0%), which referred to those with class I to class III obesity, if we consider 0.8% for class II, and 0.1% for class III, the prevalence was similar to those among the study group. In this study, the obese group is those who went to see the doctor and were registered in the ICD-10 of the hospital. Therefore, this group was more likely to suffer from severe obesity.

This issue has already been mentioned in the first paragraph of the discussion. Sorry for the confusion, and to make it clearer, the paragraph has been revised.

Competing Interests: No competing interests were disclosed.

Reviewer Report 07 February 2022

https://doi.org/10.5256/f1000research.79778.r122025

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Yankai Xia
State Key Laboratory of Reproductive Medicine, Center for Global Health, School of Public Health, Nanjing Medical University, Nanjing, China

The authors addressed most of my comments and I recommend acceptance.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Exposure to pesticides and health effects

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 15 October 2021

https://doi.org/10.5256/f1000research.56626.r95935

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❌ **Yuki Ito**
Department of Occupational and Environmental Health, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

The authors have investigated the relationships of pesticides used by farmers and obesity following the Thailand Ministry of Public Health definitions. They found a positive association between pesticide use and obesity. However, there are major points to be concerned as mentioned below. Also, the paper may benefit from an English language edit.

Abstract:

- Background in the Abstract should be specified by demonstrating the relationships between pesticides exposure and obesity.

- The authors should write the objective in the background section, not in the method section.

Background:
- The background should address the rationale of the study.
- In the last line of the first paragraph of the background section, the authors have stated lots of factors associated with obesity. Unfortunately, they cited only one article. More corresponding references should be added in this section.
- In the second paragraph, the authors described the association of PCBs, bisphenols, and one phthalate with obesity. Instead of these descriptions, the authors should cite other epidemiological studies examining the relationship between pesticide exposure and obesity.
- Authors stated that "identifications of individual pesticides to predict the risk of obesity was the main interest". However, they did not assess the risk of pesticide exposure. They only investigated the observational relationships between the groups of pesticide use and obesity. The last line has no basis to write in this section.

Methods:
- The authors should remove the duplicate statement such as, "the major crops in the province are rice, sugar cane, casava and vegetables" from the study settings and design section.
- Please clarify the last two lines of "study participants and sampling procedure". Define the term exposed and unexposed.
- A major concern is the definition of obesity. The authors investigated the relationship between pesticide use and obesity following the definition of the Thailand Ministry of Public Health. However, the definition of obesity is not clear. Based on the author's statement, it seems like the definition of a metabolic syndrome but not obesity (see the article by Engin, 2017[1]). The authors should clarify it. They can consider BMI, WC, and/or other anthropometric indices of overweight and obesity if data is available.

Results:
- Out of 20,295, only 78 study participants were obese. The overall prevalence of obesity was very low, although the authors did not calculate prevalence both in males and females.
- Tables 1 and 2 were not prepared carefully. These two tables should merge and put data in each column and row carefully.
- If possible, please provide all the demographic data (collected by questionnaires), including socio-economic status, education, ethnicity, etc.
- For investigating the OR, they have adjusted the results only by gender, age, smoking, and alcohol consumption. They have no data about diet, physical activity, socioeconomic status or income that may affect the results.

Discussion:

- This section should be written based on results deeply and sharply. They should explain their findings, e.g. why and how by comparing other studies.
- Additionally, this study is only based on questionnaire data and did not monitor the individual exposure levels of pesticides. This is another major limitation of this study.

Conclusion:

- The conclusion should be short and specific based on the results.
- The authors should not use “increased the risk of obesity”.

References

1. Engin A: The Definition and Prevalence of Obesity and Metabolic Syndrome.*Adv Exp Med Biol*. 2017; **960**: 1-17 PubMed Abstract | Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Exposure assessment of pesticides and their association with health effects.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 24 Nov 2021

Chudchawal Juntarawijit, Naresuan University, Phitsanulok, Thailand

Comment
The authors have investigated the relationships of pesticides used by farmers and obesity

following the Thailand Ministry of Public Health definitions. They found a positive association between pesticide use and obesity. However, there are major points to be concerned as mentioned below. Also, the paper may benefit from an English language edit.

Response
Thank you, we really appreciate your time and effort to review the manuscript.

We admitted that this study may be far from perfect. By using a descriptive cross-sectional study, this study has several limitations. As compared to an analytical cross-sectional study, a better study design with a control group is often found in medical studies. With the descriptive design, this study had some limitations and could not be compared with the analytical one. This study lacks data on some confounding variables and relies only on the questionnaire method for pesticide exposure data. However, the results supported the usefulness of ICD-10 data for studying obesity. We hope that the result could be useful as a small piece of information to the relatively rare literature on the association of pesticides and obesity.

The English language was edited by Mr. Kevin.

Abstract:
Comment
Background in the Abstract should be specified by demonstrating the relationships between pesticides exposure and obesity.

Response
Currently, there was not enough evidence demonstrating the relationship between pesticides exposure and obesity. With 250 words as the maximum word count limited by F1000Research, the issue, therefore, was only briefly described here.

Comment
The authors should write the objective in the background section, not in the method section.

Response
We agree and the objective has been revised and moved to the background section, as follows:

Background: ...The objective of this study was to determine the association between pesticide exposure and obesity among farmers in Nakhon Sawan and Phitsanulok province, Thailand.

Methods: This study was a population-based cross-sectional study.

Background:
Comment
The background should address the rationale of the study.

Response

The main reason why this study is needed was that obesity is an important public health problem and exposure to pesticides might be one of its causes. However, currently, there was only limited evidence. This study was among a few studies trying to investigate the association between obesity and pesticide exposure using a large cross-sectional study design.

Comment
In the last line of the first paragraph of the background section, the authors have stated lots of factors associated with obesity. Unfortunately, they cited only one article. More corresponding references should be added in this section.

Response
The reference was a systematic review that mentioned various factors associated with obesity.

Comment
In the second paragraph, the authors described the association of PCBs, bisphenols, and one phthalate with obesity. Instead of these descriptions, the authors should cite other epidemiological studies examining the relationship between pesticide exposure and obesity.

Response
In this section, we try to present information on pesticides and obesity. To our knowledge, all of the epidemiological studies on pesticides and obesity were already included. In the last statement, we just want to mention that not only pesticides but also some other compounds, e.g., PCBs, bisphenols, and one phthalate might also cause obesity.

To make it clear, the statement has been revised.

Comment
Authors stated that “identifications of individual pesticides to predict the risk of obesity was the main interest”. However, they did not assess the risk of pesticide exposure. They only investigated the observational relationships between the groups of pesticide use and obesity. The last line has no basis to write in this section.

Response
To be more precise, the statement “*identifications of individual pesticides to predict the risk of obesity was the main interest*” has been revised as follows:

"The main interest was to associate obesity to pesticides, either by group or individual chemical.”

Methods:
Comment
The authors should remove the duplicate statement such as, “the major crops in the province are rice, sugar cane, cassava and vegetables” from the study settings and design section.

Response
Actually, that statement was not duplicated but they described major crops of the two different provinces, Nakhon Sawan and Phitsanulok.

Comment
Please clarify the last two lines of “study participants and sampling procedure”. Define the term exposed and unexposed.

Response
Exposed refers to the exposure group or those who used pesticides. Unexposed refers to the unexposed group or those who do not use pesticides.

This information has been added to the paper.

Comment
A major concern is the definition of obesity. The authors investigated the relationship between pesticide use and obesity following the definition of the Thailand Ministry of Public Health. However, the definition of obesity is not clear. Based on the author’s statement, it seems like the definition of a metabolic syndrome but not obesity (see the article by Engin, 2017[1]). The authors should clarify it. They can consider BMI, WC, and/or other anthropometric indices of overweight and obesity if data is available.

Response
We thank you the reviewer for making a very important point and agreeing to revise our manuscript as we picked up the case with obesity using a diagnosis in ICD-10. We have deleted the statement “*In Thailand, the Ministry of Public Health follows the International Diabetes Federation’s definition (2005), which defines obesity as a waist circumference of no more than 90 cm for men and 80 cm for women, plus two out of the following four criteria:..*” and replaced with the following, “*In Thailand, the Ministry of Public Health follows The World Health Organization obesity criteria for Asia Pacific Region in which body mass index over 25.0 kg/m2 was identified as obesity.*".

Results:
Comment
Out of 20,295, only 78 study participants were obese. The overall prevalence of obesity was very low, although the authors did not calculate prevalence both in males and females.

Response
Prevalence of obesity was very low since the study use data from ICD-10 records, instead of survey data on BMI or waist circumstance. The issue was already discussed in the manuscript.

Comment
Tables 1 and 2 were not prepared carefully. These two tables should merge and put data in each column and row carefully.

Response

The two tables have been merged. An error in the table head has been corrected.

Comment
If possible, please provide all the demographic data (collected by questionnaires), including socioeconomic status, education, ethnicity, etc.

Response
In this survey, we collected data from respondents who are farmers living in a rural area of six districts but found obesity cases in five districts (Table 1).

For socioeconomic data, only the district location of participants, and their education, and monthly income were collected. However, these factors were not included in the model because of several reasons. For district location, most of the participants were farmers from rural areas, thus there was no reason to believe district location to associate with obesity. Moreover, the district was closely related to pesticide use and will cause multicollinearity problems, if included in the model (Bhandari, 2020). For income, there was no relationship with obesity in middle-income countries, e.g. Thailand (Ameye and Swinnen, 2019). For education, previous research found a higher risk of obesity to be inversely associated with education (Anyanwu, 2010). However, in this study more obesity was found among those with higher education (Table 1). In addition, when these two variables were included in the model, not much effects on OR were found. For example, for molluscicide the OR was changed from 2.28 (1.48-3.64) to 2.37 (1.48-3.79) when added education and to 2.39 (1.49-3.83) when added income (Table 2-1). For baseline diseases, most of them should be considered as the so-called 'downstream outcome' closely related to obesity and thus, should not be included in the model (DVL, 2020).
More demographic information has been added to Table 1.

For ethnicity, in Thailand, we did not have ethnic groups.

Comment
For investigating the OR, they have adjusted the results only by gender, age, smoking, and alcohol consumption. They have no data about diet, physical activity, socioeconomic status or income that may affect the results.

Response
Yes, we agree that that information on diet and physical activity would be useful and should be used for the adjustment. It is a study limitation and the issue was already discussed in the study limitation. The problem should not seriously affect study results since all of the participants were farmers from rural areas.

For data on socioeconomic, actually, we also collected data on district location, education, and monthly income. However, these factors were not included in the model because of several reasons. For district location, most of the participants were farmers from rural areas, thus there was no reason to believe district location to associate with obesity. However, the district was closely related to pesticide use and caused a multicollinearity problem, therefore, it was not be included in the model (Bhandari, 2020). For education and income, previous research found a higher risk of obesity to inversely associate with education (Anyanwu, 2010). For income, there was no relationship with obesity in middle-income countries, e.g. Thailand (Ameye and Swinnen, 2019). When the model included these two variables, the OR was not much changed. For example, for Molluscicide the OR was changed from 2.28 (1.48-3.64) to 2.37 (1.48-3.79) when added education and to 2.39 (1.49-3.83) when added income (Table 2-1). For baseline diseases, most of them should be considered as the so called 'downstream outcome' closely related to obesity but not confounding and thus, should not be included in the model as well (DVL, 2020).

Discussion:
Comment
This section should be written based on results deeply and sharply. They should explain their findings, e.g. why and how by comparing other studies.

Response
Thank you for the suggestion. We agree and try to comply with your suggestion as much as we can.

Comment
Additionally, this study is only based on questionnaire data and did not monitor the individual exposure levels of pesticides. This is another major limitation of this study.

Response
For a large study of long-term effects of pesticides, a questionnaire might be the only option. Since pesticide dose is a good marker for short-term pesticide exposure. However, it was costly and may not be suitable for a large survey study. The questionnaire method is probably the best alternative to collect data on long-term pesticide exposure. The method is commonly used in epidemiological studies e.g., Agricultural Health Study in the United State. For studies using a large group of participants, the method has been proved to be useful without any serious bias (Coble *et al*., 2011) (Hoppin *et al*., 2002).

The limitation was further discussed as suggested.

Conclusion:
Comment
The conclusion should be short and specific based on the results.

Response
Thank you for the suggestion. We agree and try to comply with your suggestion as much as we can.

Comment
The authors should not use "increased the risk of obesity".

Response
The statement has been changed to "*The study additionally found exposure to 24 individual pesticides was significantly associated with obesity*."

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Anyanwu, G. E., Ekezie, J., Danborno, B., & Ugochukwu, A. I. (2010). Impact of education on obesity and blood pressure in developing countries: A study on the Ibos of Nigeria. North American Journal of Medical Sciences, 2(7), 320–324. https://doi.org/10.4297/najms.2010.2320

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Coble *et al*., (2011). An updated algorithm for estimation of pesticide exposure intensity in the agricultural health study, Int. J. Environ. Res. Public Health; 8(12), 4608–4622. doi: 10.3390/ijerph8124608.

Hannah Ameye and Johan Swinnen, (2019). Obesity, income and gender: The changing global relationship, Global Food Security, 23, 267-281. https://doi.org/10.1016/j.gfs.2019.09.003.

Hoppin, F. Yucel, M. Dosemeci, and D. P. Sandler, (2002). Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study, J. Expo. Anal. Environ. Epidemiol.; 12(5), 313–318. doi: 10.1038/sj.jea.7500232.

Table 2-1 Odds ratio when more variables were added to the model.

Pesticide: Molluscicide
OR (in the table 2) 3.36 (2.13-5.31)
OR (when add baseline disease) 3.30 (2.08-5.22)
OR (add district location) 2.28 (1.43-3.64)
OR (add education) 2.37 (1.48-3.79)
OR (add income) 2.39 (1.49-3.83)

Competing Interests: No competing interests were disclosed.

Reviewer Report 01 October 2021

https://doi.org/10.5256/f1000research.56626.r94404

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Yankai Xia
State Key Laboratory of Reproductive Medicine, Center for Global Health, School of Public Health,

Nanjing Medical University, Nanjing, China

This study used questionnaire-based pesticide exposure data of 20,295 farmers to determine the association between pesticide use and obesity in Thailand. With the large-scale cross-sectional epidemiological data, the study determined that regional obesity in farmers could be associated with pesticide use. The study displayed novelty and value in public health on Thailand regional health. However, I thought there were several questions in this manuscript. Therefore, I thought major revision was necessary. The detailed review points were listed below.

1. In the abstract, the authors declared that they collected the long-term pesticide exposure data. However, I thought the term ‘long-term’ should be considered carefully as the questionnaire did not collect the frequencies of pesticides use (only yes or no). Also, the nature of the cross-sectional study (without follow-up) could poorly support the conclusion.

2. In the farmer population, pesticide-attributed obesity may be associated with the living conditions or geographical location of these individuals. Therefore, I thought it would be helpful if the authors provided the related data of these individuals.

3. Methods: Since there is a great difference between genders on obesity diagnosis, I recommended the authors perform stratified analysis to determine the gender-specific associations.

4. Results: The authors checked the relations between pesticide exposure and obesity. Is there any interaction between the different pesticides?

5. Results: The authors should clarify the demographic characteristics in detail.

6. Results: It will be helpful to display the C-index of each model to validate the reliability.

7. Discussion: I noticed that the OR for pesticides is from 1.75 to 8.37, while the OR over 3 may be overestimated and lead to unnecessary panic for public health. I thought the authors should discuss their results more carefully.

8. Discussion: I thought the authors should declare the nature of the cross-sectional study and tell the readers that the study was limited in explaining the causality.

9. Discussion: The strengthen part only replicates the conclusion.

10. One of the most limited parts of this study was the lack of dose or level data of pesticides use, which may cause serious bias. The authors should make a discussion about this.

11. The authors should explain the reliability and validity of their questionnaire as there may be information bias that exists with the questionnaire method.

12. I recommended the authors list the data on body measure index or waist circumstances in Table 1.

13. Waist circumferences and baseline diseases should be adjusted as covariates.

14. According to the previous literature, there is a great difference between populations in different age groups. Therefore, I thought age-specific associations between pesticides use and obesity should be considered.

15. As the authors declared, the limited data on dietary patterns, physical activities, and genetic variants may lead to potential bias. However, I thought the authors should be concerned about whether their adjusted models could explain the variance.

16. Could the authors list the blood pressure, glucose, triglyceride, and HDL value in the tables? Also, I think adjusting them in the model should be considered.

17. The effects of pesticides exposure may have co-exposure patterns, the authors should notice that.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Exposure to pesticides and health effects

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 24 Nov 2021

Chudchawal Juntarawijit, Naresuan University, Phitsanulok, Thailand

Comment

This study used questionnaire-based pesticide exposure data of 20,295 farmers to determine the association between pesticide use and obesity in Thailand. With the large-scale cross-sectional epidemiological data, the study determined that regional obesity in farmers could be associated with pesticide use. The study displayed novelty and value in public health on Thailand regional health. However, I thought there were several questions in this manuscript. Therefore, I thought major revision was necessary. The detailed review points were listed below.

Response
Thank you very much for your time and effort to review this manuscript and for providing valuable suggestions.

Comment
1. In the abstract, the authors declared that they collected the long-term pesticide exposure data. However, I thought the term 'long-term' should be considered carefully as the questionnaire did not collect the frequencies of pesticides use (only yes or no). Also, the nature of the cross-sectional study (without follow-up) could poorly support the conclusion.

Response
The term '*long-term use*' has been replaced with '*historical use*'.

In this study, actually, we also collected data on the frequency and duration of pesticides use and calculated cumulative days of exposure. Unfortunately, there was only a small number of cases with obesity, therefore the association between quartile days of exposure and obesity could not be performed.

Comment
2. In the farmer population, pesticide-attributed obesity may be associated with the living conditions or geographical location of these individuals. Therefore, I thought it would be helpful if the authors provided the related data of these individuals.

Response
In this survey, we collected data from respondents who are farmers living in a rural area of six districts but found obesity cases in five districts (Table 1).

For socioeconomic data, only the district location of participants, and their education, and monthly income were collected. However, these factors were not included in the model because of several reasons. For district location, most of the participants were farmers from rural areas. Moreover, the district was closely related to pesticide use and will cause multicollinearity problems, if included in the model (Bhandari, 2020). For income, there was no relationship with obesity in middle-income countries, e.g. Thailand (Ameye and Swinnen, 2019). For education, previous research found a higher risk of obesity to be inversely associated with education (Anyanwu, 2010). However, in this study more obesity was found among those with higher education (Table 1). In addition, when these two variables were included in the model, not many effects on OR were found. For example, for molluscicide, the OR was changed from 2.28 (1.48-3.64) to 2.37 (1.48-3.79) when added education and to 2.39 (1.49-3.83) when added income (Table 2-1). For baseline diseases, most of them should be considered as the so-called 'downstream outcome' closely related to obesity and thus, should not be included in the model (DVL, 2020).

More demographic information has been added to Table 1.

Comment
3. Methods: Since there is a great difference between genders on obesity diagnosis, I recommended the authors perform stratified analysis to determine the gender-specific associations.

Response
Thank you for bringing up a good point. Though, there is a great difference between genders on obesity diagnosis, the prevalence of obesity between gender was not different (p=0.173) (Table 1). In addition, we already added gender as a covariate in the analysis of the adjusted odds ratio as shown in Table 2 and Table 3. Moreover, the number of subjects with obesity diagnosed was too small to do stratification.

Comment
4. Results: The authors checked the relations between pesticide exposure and obesity. Is there any interaction between the different pesticides?

Response
That is a good point. Yes, we also believed that there might be some interaction between the different pesticides. However, due to limitations on small cases, the problem could not be further investigated. The issue has been added to the discussion section.

Comment
5. Results: The authors should clarify the demographic characteristics in detail.

Response
The results and Table 1 have been revised.

Comment
6. Results: It will be helpful to display the C-index of each model to validate the reliability.

Response
According to Austin and Steyerberg (2012), there are three primary reasons to develop a logistic regression model. The first one is to determine the independent predictors of a binary outcome. The second one is to define the association between a predictive variable and the outcome after adjusting for confounding factors. The third reason is to predict the probability of the occurrence of a binary outcome given a specific vector of covariates. The third reason often occurs in biomedical research, where researchers are interested in predicting the prognosis of individual patients. And the C-statistic is an indicator of assessing the prediction of the logistic regression model. However, the main objective was to find the association between obesity and pesticide exposure.

Comment

7. Discussion: I noticed that the OR for pesticides is from 1.75 to 8.37, while the OR over 3 may be overestimated and lead to unnecessary panic for public health. I thought the authors should discuss their results more carefully.

Response
Yes, we agree with you and the statement '*Some results were with high OR and wide confidence intervals, and thus should be interpreted with caution.*' has been added to the study limitation section.

Comment
8. Discussion: I thought the authors should declare the nature of the cross-sectional study and tell the readers that the study was limited in explaining the causality.

Response
Thank you for your suggestion. The following statements have been added to the study limitation:

'There were several limitations to the study that need to be mentioned. By using a cross-sectional design, the study was limited in explaining the causality since both disease and exposure data were examined at the same time.'

Comment
9. Discussion: The strengthen part only replicates the conclusion.

Response
The statement has been deleted.

Comment
10. One of the most limited parts of this study was the lack of dose or level data of pesticides use, which may cause serious bias. The authors should make a discussion about this.

Response
Pesticide dose is a good marker for short-term pesticide exposure. However, it was costly and may not be suitable for a large survey study. The questionnaire method is probably the best alternative to collect data on long-term pesticide exposure. The method is commonly used in epidemiological studies e.g., Agricultural Health Study in the United State. For studies using a large group of participants, the method has been proved to be useful without any serious bias (Coble et al., 2011) (Hoppin et al., 2002). The limitation on the issue was further discussed as suggested.

Comment
11. The authors should explain the reliability and validity of their questionnaire as there may be information bias that exists with the questionnaire method.

Response

The limitation of questionnaire use was further discussed. As mentioned before, the questionnaire method might be the only option for the study of long-term exposure to pesticides among a large population. Since the technique was used in both case and control groups, information bias if occur might be non-differential.

Comment
12. I recommended the authors list the data on body measure index or waist circumstances in Table 1.

Response
In this study, data on BMI and WC were not collected as most previous studies did. The study was designed to be a descriptive cross-sectional study to explore the prevalence of medical-diagnosed obesity using ICD-10 records and to identify its associated risk factors. The usefulness and limitation of the ICD-10 data were already discussed in the manuscript.

Comment
13. Waist circumferences and baseline diseases should be adjusted as covariates.

Response
As mentioned before, we did not have waist circumference data since the study used a medical diagnosis of obesity (ICD-10), which is also based on BMI and waist circumferences data.

For baseline diseases, they should be considered as a so-called ‘downstream outcome’ variable. According to Dan VanLunen (2020), this type of variable should not be used as a covariate.

Comment
14. According to the previous literature, there is a great difference between populations in different age groups. Therefore, I thought age-specific associations between pesticides use and obesity should be considered.

Response
We agree that age-specific association could improve study quality. This study uses a different study design from those in the literature. In this study, we use a descriptive cross-sectional design, whereas, most of the literature uses analytical cross-sectional with a control group. The analytical study might be better in control of confounding variables but not suitable for a large-scale study.

In this study, the age-specific association was also not possible because the number of cases with obesity was small.

Comment
15. As the authors declared, the limited data on dietary patterns, physical activities, and genetic variants may lead to potential bias. However, I thought the authors should be concerned about whether their adjusted models could explain the variance.

Response
Yes, we agree. More information has been added to the study limitation as follows:

'*Data on other risk factors, such as diet, exercise, or genetics were not collected. These confounding factors might have a different impact on the results. However, the problem may not have much effect on the study results since the case and control groups were from the same community and had the same occupation.*'

Comment
16. Could the authors list the blood pressure, glucose, triglyceride, and HDL value in the tables? Also, I think adjusting them in the model should be considered.

Response
As mentioned before, the study was designed as a simple descriptive cross-sectional survey to try to find a prevalence of obesity using ICD-10 data.

Among the two types of a cross-sectional study, descriptive and analytical, each one has its own strength and limitations. The descriptive studies, which could be conducted in a large-scale study, are often used for prevalence studies. For the analytical study, a study with a control group, often found in a medical study, and has better control for confounding.

Comment
17. The effects of pesticides exposure may have co-exposure patterns, the authors should notice that.

Response
Thank you for raising this good point. Yes, co-exposure was an interesting issue. However, with the study design and the small number of cases, this study could not evaluate the problem. The issue has been added in the discussion as a study limitation.

References

Anyanwu, G. E., Ekezie, J., Danborno, B., & Ugochukwu, A. I. (2010). Impact of education on obesity and blood pressure in developing countries: A study on the Ibos of Nigeria. North American journal of medical sciences, 2(7), 320–324.
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Competing Interests: No competing interests were disclosed.

Author Response 24 Nov 2021

Chudchawal Juntarawijit, Naresuan University, Phitsanulok, Thailand

Table 2-2 OR after adding more variables to the model.

Pesticide: Molluscicide
OR (as shown in Table2) 3.36 (2.13-5.31)
OR (after add baseline diseases) 3.30 (2.08-5.22)
OR (add district location) 2.28 (1.43-3.64)
OR (add education) 2.37 (1.48-3.79)
OR (add income) 2.39 (1.49-3.83)

Competing Interests: No competing interests were disclosed.

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