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Pesticides as a risk factor for metabolic syndrome: Population-based longitudinal study in Korea

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Pesticides as a risk factor for metabolic syndrome: Population-based longitudinal study in Korea

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ABSTRACT

Pesticides as a risk factor for metabolic syndrome: Population-based longitudinal study in Korea

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Background and purpose

Metabolic syndrome (MetS) is an adverse health effect that can be associated with pesticide exposure. However, there are few epidemiologic studies on the relationship between pesticide use and MetS incidence. The present study examined the relationship between pesticide exposure and incidence of MetS in a rural population in Korea.

Methods

We examined the causal relationship between pesticide use and MetS incidence in a rural population. We used Data from the Korea Farmers Cohort study of 1,162 participants. Poisson regression with a robust error variance was used to calculate relative risks (RRs) and 95% confidence intervals (CIs) to estimate the relationship between pesticide exposure and MetS.

Results

The incidence of MetS was 20.7%. Pesticide use increased the RR of MetS incidence. In women, we observed a low–dose effect related to MetS and pesticide exposure.

Conclusion

Pesticide exposure is related to the incidence of MetS; the causal relationship differs in men and women.

Keywords: Pesticide exposure, Metabolic syndrome, Longitudinal study, Incidence, South Korean adults, Rural

I. Introduction

The prevalence of metabolic syndrome (MetS) is growing worldwide[1]. This syndrome is related to an increased risk of cardiovascular diseases, and specific cancers, such as Non–Hodgkin's lymphoma, and leukaemia[3–5]. MetS is the primary cause of mortality and morbidity in developed countries[6].

Pesticides have been linked to MetS[7,8]. Oxidative stress plays a key role in the pathophysiology of MetS and can lead to its major clinical manifestations[9]. Exposure to pesticides is known to be related to increased oxidative stress in the human body by the generation of reactive oxygen species, such as hydrogen peroxide, superoxide, and hydroxyl radicals[10–13]. Meanwhile, the global use of pesticides, estimated to be approximately 2.72 million tons in 2012[14], has increased steadily in developing countries[15]. It is well known that the agricultural use of pesticides in South Korea is among the most intensive in the world[16]. The types of pesticides, their target organs, and their mechanisms of action on human body are described in Table 1[5,10,51-53]. Although pesticides are used to control insects, fungi, and weeds to attain higher quality products, and to increase production rate, especially in agriculture[13,17,18], they are also toxic chemicals. Therefore, the wide use of various pesticides has increased concerns about the potential relationship of pesticide exposure and MetS.

Although correlation between pesticide exposure and MetS in was found in a cross–sectional study[7] and animal research[8], no studies have investigated the relationship between pesticide exposure and MetS incidence. The present study analysed the relationship between the incidence of MetS and pesticide exposure by using cohort data from a rural population in South Korea.

Table 1. Toxicological characteristics of pesticide poisoning.

Chemical Basis	Types	Examples	Site of toxicity	Mechanisms of toxicity
Organochlorines	Insecticides	DDT, methoxychlor, hexachloro-cyclohexane, cyclodienes	CNS, kidney, liver, male reproductive system	Oxidative stress and lipid peroxidation, inhibition of gamma-aminobutyric acid
Organo-phosphates	Insecticides, herbicides	Diazinon, malathion, parathion, chlorpyrifos, dichlorvos, glyphosate	CNS, kidney, erythrocytes	Irreversible inhibition of erythrocytes cholinesterase, acetylcholinesterase, plasma cholinesterase, oxidative stress
Carbamates	Insecticides, fungicides	Aldicarb, carbaryl, carbofuran	Erythrocytes	Reversible inhibition of erythrocytes acetylcholinesterase, plasma cholinesterase
Pyrethroids	Insecticides	Allethrin, bifenthrin, Permethrin	Liver, CNS, kidney, erythrocytes	Modification of the gating characteristics of sodium channels, oxidative stress
Phosphines	Fumigants	Aluminum or zinc, phosphide	Lungs, CNS, liver, kidney	Inhibition of cellular oxidative respiration
Chlorophenoxy derivatives	Herbicides	2,4-D and 2,4,5-T	Skin, eyes, respiratory, GI tracts	Uncoupling of oxidative phosphorylation, disruption of acetylcoenzyme A metabolism
Bipyridyls	Herbicides	Diquat, paraquat	Epithelium, cornea, liver, kidney, GI and respiratory tract	Hydroxyl free radicals that lead to cell death

II. Backgrounds

1. Definition of metabolic syndrome

MetS is defined as metabolic abnormalities comprising at least three of five of the following conditions: central obesity, high blood pressure, high fasting plasma glucose, elevated serum triglycerides, and low high–density cholesterol (HDL) level[2].

2. Criteria of metabolic syndrome

MetS was defined as the presence of at least three of the following conditions: 1) waist circumference ≥ 90 cm in men or ≥ 80 cm in women; 2) a serum triglyceride(TG) concentration ≥ 150 mg/dL; 3) a serum HDL cholesterol(HDL-C) concentration < 40 mg/dL for men or < 50 mg/dL in women; 4) systolic blood pressure (SBP) ≥ 130 mmHg, or diastolic blood pressure (DBP) ≥ 85 mmHg; and 5) serum glucose concentration ≥ 100 mg/dL in fasting[25].

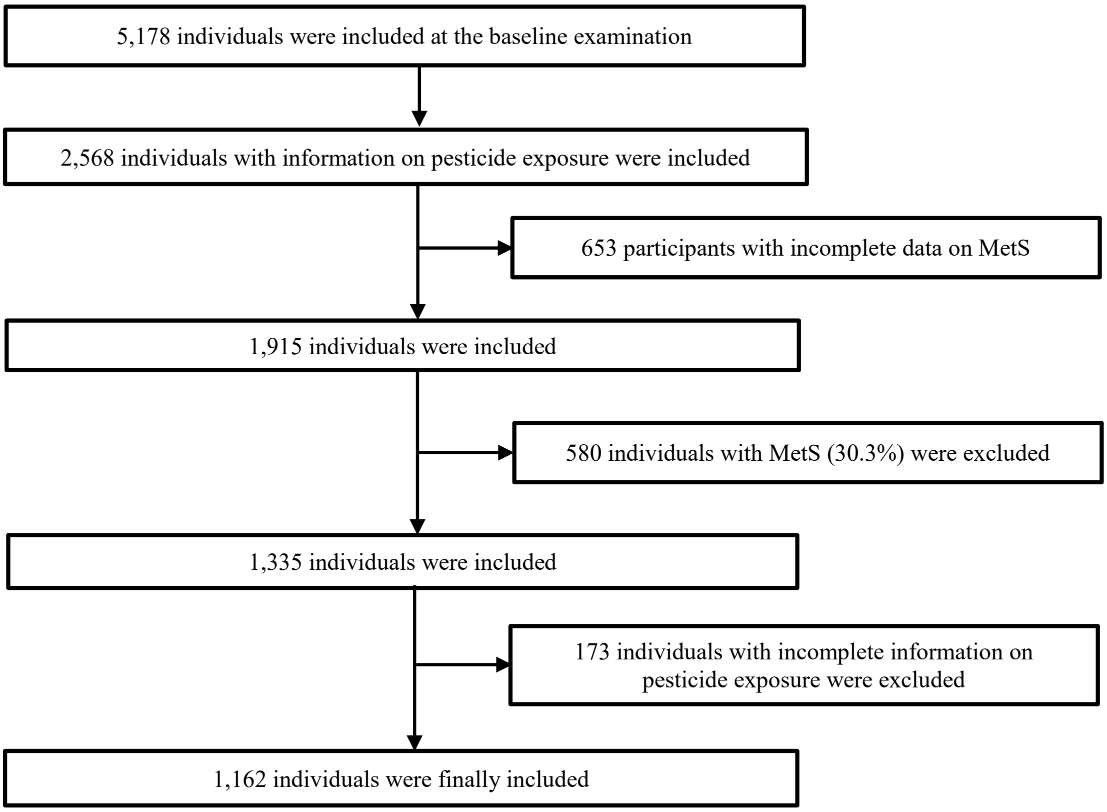
III. Methods

1. Study population

This study used data from the applicants of the Korea Farmers Cohort study. It was the aim of this population-based prospective cohort study to reveal the prevalence, incidence, and risk factors of common and preventable chronic diseases, such as hypertension, diabetes mellitus, MetS, and cardiovascular disease. The applicants were living in the rural areas of Wonju and Pyeongchang, South Korea, and were between 39 and 72 years of age. The study commenced after each subject had provided written informed consent, the study was begun. Each participant was asked to answer the questionnaires in a face–to–face interview. The study was permitted by the Institutional Review Board (IRB) of Yonsei University Wonju Severance Christian Hospital.

The baseline and follow-up surveys were conducted between November 2005 and January 2008 and April 2008 and August 2012, respectively. A total of 5,178 adults were screened; of these, 2,568 individuals participated in the additional survey about pesticide exposure at baseline to find associations between pesticide exposure and MetS. In this study, ‘pesticide exposure’ or ‘pesticide use’ was limited to the use of occupational pesticides, and indirect exposure to the environment and pesticide ingestion from food or water were not included. We excluded 653 subjects with incomplete data on MetS, 580 subjects with MetS, and 173 subjects with incomplete data on pesticide exposure; finally, 1,162 subjects were included (Figure 1). The average number of follow-up years was 2.64.

Fig. 1. The study population of the Korean Farmers Cohort Study



2. Data collection

To collect information on pesticide exposure and its clinical features, we gathered data by using a standardised modified questionnaire developed in the Agricultural Health Study (AHS) in baseline survey[19,20]. Information, including age, gender, BMI, alcohol consumption, smoking status, physical activity level, and educational level was obtained through self–reporting. Study subjects also offered information about their medical history and pesticide exposure.

3. Covariates

Baseline characteristics for continuous variables are summarised as the mean ±1 standard deviation (±SD) and categorical variables as count with percentage (%). Age was considered as a continuous variable. Smoking status was categorised into three groups (non-smoker, ex-smoker, and current smoker). Alcohol use was categorised into two groups according to current alcohol consumption (no, yes). Physical activity was categorised into two groups according to regular exercise (no, yes). Educational level was grouped into two groups (completion of primary school or lower, completion of middle school or higher. Marital status was divided into two groups (married, other status). BMI was categorised into two categories (<25, ≥25 kg/m^2)

4. Exposure assessment

Participants were asked to finish the questionnaires with reasonable reliability and validity and to provide thorough information on their use of pesticides[21,22]. They were asked to state if they had ever used any pesticides, and if they had ever mixed or applied any pesticides. The sum of the years of pesticide use and the average number of days per year of pesticide use were also asked.

Exposure to pesticides may occur during transporting, mixing, or applying pesticides, or cleaning and repairing equipment. We included information about these factors in the analysis. Based on these factors, the intensity level of pesticide exposure and cumulative exposure index (CEI) were calculated as follows[23]:

*Intensity level = (mixing status + application method + repair status) × PPE

*CEI = intensity level × duration (number of years) × frequency (average days per year)

The mixing status of pesticide was divided into three groups (never mixed, <50% of time mixed, and 50%+ of time mixed, which were assigned 0, 3, and 9, respectively), and the application methods were divided into six groups (does not apply, seed treatment or tablet distribution, in furrow/banded, boom on tractor, backpack, hand spray or mist blower/fogger or air–blast, which were allocated 0, 1, 2, 3, 8, and 9, respectively). For PPE use, subjects were scored according to the use of protective equipment and divided into 8 groups (allocated 1.0, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, and 0.1, respectively). The pesticide exposure assessment is described elsewhere[20]. The PPE score of pesticide use was categorised into the three groups based on their medians (0, lower than 1, and 1).

Both the duration (0, 1–12, and >12 years) and frequency (0, 1–25, and >25 days average per year) of pesticide use were categorised into three groups based on their medians. The intensity level of pesticide exposure was categorised into three groups based on their medians (0, 0 to lower than the lower than the median (9.0) was classified as the "lower group", higher than the median was classified as the "higher group"). The CEI of pesticide exposure was categorised into three groups based on their medians (0, 0 to lower than the median (2,241) was classified as the "lower group", higher than the median was classified as the "higher group").

5. Outcome variable

The outcome was the incidence of MetS.

6. Statistical analysis

To analyse the relationship between pesticide exposure and MetS, we counted the numbers and percentiles of participants at first based on each continuous variable by using t–test. The t-test, as a parametric statistic, was used for normally distributed variables. Chi–square test was performed to estimate differences in the incidence of MetS according to covariates and to calculate p–values. The chi–square test, as a non-parametric statistic, was used for categorical variables. For common events, such as occurrence of MetS, odds ratios may overestimate relative risks (RRs)24. Poisson regression with a robust error variance is widely used to directly estimate RRs for both common and rare outcomes[36]. Therefore, in this study, Poisson regression with a robust error variance was used to calculate RRs and 95% confidence intervals (CIs) to estimate the relationship between pesticide exposure and MetS. For the analysis of supplementary data at baseline, the odds ratios(ORs) for MetS were calculated by multiple logistic regression analysis. ORs and RRs were adjusted for age, gender, smoking status, alcohol use, regular exercise, education, and marital status. In addition, a stratified analysis by gender was conducted in calculating RRs for MetS. All two sided p–values of <0.05 were considered statistically significant. All analyses were computed by using the SPSS statistical software package (v21.0; IBM Co., Armonk, NY, USA).

IV. Results

1. Descriptive statistics of variables

The descriptive and baseline information of the study population at enrolment is listed in Table 2. At enrolment, the average number of diagnostic criteria for MetS was 1.2 (SD ±0.7) in pesticide not–using group and 1.3 (SD ±0.7) in the pesticide–using group, respectively (p–value <0.01). There were statistically significant differences in fasting glucose, HDL–C, TG, and waist circumference between pesticide in the not–using group and the pesticide–using group. In addition, age, gender, smoking status, alcohol use, regular exercise, education, and marital status were significantly different between each group.

Table 2. Baseline demographic characteristics of subjects according to the use of pesticides (n=1,162)

	Pesticide use		
	No (n=660)	Yes (n=502)	
Demographic characteristics	Mean (±SD)* or Frequency (%)**		p-value
Sex			
Male	187 (28.3%)	471 (66.9%)	<.0001
Female	473 (71.7%)	394 (45.6%)	
Age (years)	53.2 (±8.0)	55.2 (±7.9)	<.0001
SBP (mmHg)	124.7 (±16.9)	124.2 (±17.5)	0.63
DBP (mmHg)	80.0 (±11.1)	80.5 (±11.6)	0.47
Fasting glucose (mg/dL)	89.0 (±11.0)	91.7 (±15.4)	<.001
HDL–C (mg/dL)	47.4 (±10.5)	48.7 (±10.9)	0.05
TG (mg/dL)	111.8 (±57.2)	128.9 (±77.6)	<.0001
Waist circumference (cm)	79.1 (±7.7)	82.5 (±7.6)	<.0001
MetS criterion (n)	1.2 (±0.7)	1.3 (±0.7)	<.0001
Smoking status			
Non–smoker	531 (80.5%)	318 (64%)	<.0001
Ex–smoker	51 (7.7%)	77 (15.5%)	
Current smoker	78 (11.8%)	102 (20.5%)	
Alcohol use			
No	422 (64.2%)	251 (50.4%)	<.0001
Yes	235 (35.8%)	247 (49.6%)	
Regular exercise			
No	402 (61.2%)	429 (86.3%)	<.0001
Yes	255 (38.8%)	68 (13.7%)	
BMI (kg/m^2)			
<25	477 (72.3%)	345 (68.7%)	0.19
≥25	183 (27.7%)	157 (31.3%)	
Education			
Primary school or below	248 (37.8%)	329 (65.5%)	<.0001
Middle school or above	409 (62.3%)	173 (34.5%)	
Marital status			
Married	574 (87.4%)	458 (92.9%)	<.01
Others	83 (12.6%)	35 (7.1%)	

*p–value from t-test

**p–value from chi-square test

2. Gender differences in pesticide exposure

In table 3, The pesticide using subjects were 59.1% male and 32.9% female, respectively (p–value <0.001). Other variables related to high pesticide exposure were much higher in men than in women (p–value <0.001).

Table 3. Sex differences in pesticide exposure (n=1162)

Pesticide--related variables	Male, n (%)	Female, n (%)	p–-value*
Pesticide use			<.0001
No	187 (40.9%)	473 (67.1%)	
Yes	270 (59.1%)	232 (32.9%)	
Mixing status of pesticide			<.0001
No	216 (47.3%)	547 (77.6%)	
<50% of time mixed	83 (18.2%)	61 (8.7%)	
50%+ of time mixed	158 (34.6%)	97 (13.8%)	
Application method			<.0001
No	197 (43.1%)	543 (77%)	
Seed treatment or tablet distribution	43 (9.4%)	15 (2.1%)	
Backpack	130 (28.5%)	71 (10.1%)	
Mist blower/fogger or air--blaster	87 (19%)	76 (10.8%)	
Years of pesticide use			<.0001
0	187 (40.9%)	473 (67.1%)	
≤12	133 (29.1%)	139 (19.7%)	
>12	137 (30%)	93 (13.2%)	
Frequency of pesticide use (per year)			<.0001
0	187 (40.9%)	473 (67.1%)	
1–-25	132 (28.9%)	120 (17%)	
>25	138 (30.2%)	112 (15.9%)	
Scores for PPE			<.0001
0	187 (40.9%)	473 (67.1%)	
0.1–-0.8	144 (31.5%)	87 (12.3%)	
1	126 (27.6%)	145 (20.6%)	
Intensity level of pesticide exposure			<.0001
0	188 (41.1%)	507 (71.9%)	
Lower group	123 (26.9%)	119 (16.9%)	
Higher group	146 (32%)	79 (11.2%)	
CEI of pesticide use			<.0001
0	188 (41.1%)	507 (71.9%)	
Lower group	111 (24.3%)	105 (14.9%)	
Higher group	158 (34.6%)	93 (13.2%)	

*p–-value from chi–-square test

3. Incidence of MetS according to pesticide exposure

The incidence of MetS was significantly elevated in study subjects who had ever used any pesticides than in those who had not (Table 4). The incidence of MetS was 20.7% and 12.1% in the pesticide exposure group and non-pesticide exposure group respectively (p–value <0.01). The incidence of MetS significantly elevated in study subjects who had ever used mixed pesticides or had ever used a mist blower/fogger or air blaster; these differences were statistically significant. All variables related to pesticide exposure were association with the incidence of MetS significantly

Table 4. Incidence of MetS according to pesticide exposure (n=1,162)

Pesticide-related variables	Incidence of MetS, n (%)	p-value*
Pesticide use		<.0001
No	80 (12.1%)	
Yes	104 (20.7%)	
Mixing status of pesticide		<.001
No	102 (13.4%)	
<50% of time mixed	38 (26.4%)	
50%+ of time mixed	44 (17.3%)	
Application method		0.04
No	100 (13.5%)	
Seed treatment or tablet distribution	12 (20.7%)	
Backpack	38 (18.9%)	
Mist blower/fogger or air–blaster	34 (20.9%)	
Years of pesticide use		<.001
0	80 (12.1%)	
≤12	61 (22.4%)	
>12	43 (18.7%)	
Frequency of pesticide use (per year)		<.001
0	80 (12.1%)	
1–25	53 (21%)	
>25	51 (20.4%)	
Scores for PPE		<.001
0	80 (12.1%)	
0.1–0.8	52 (22.5%)	
1	52 (19.2%)	
Intensity level of pesticide exposure		<.01
0	89 (12.8%)	
Lower group	52 (21.5%)	
Higher group	43 (19.1%)	
CEI of pesticide use		<.01
0	89 (12.8%)	
Lower group	45 (20.8%)	
Higher group	50 (19.9%)	

*p–value from chi–square test

4. RRs of MetS incidence by variables related to pesticide exposure

The RRs of MetS incidence by variables related to pesticide exposure are shown in Table 5. The RR of MetS incidence were significantly elevated in the “ever used pesticides” group than in the reference (RR 1.71, 95% CI 1.31–2.23), after adjustment for age, sex, smoking status, alcohol use, regular exercise, education, and marital status (RR 1.96, 95% CI 1.43–2.70). The “<50% of time mixed” group (RR 2.18, 95% CI 1.52–3.12), mist blower/fogger or air–blast application (RR 1.67, 95% CI 1.13–2.46), ≤12 years of pesticide use (RR 2.21, 95% CI 1.55–3.17), 1–25 days of pesticide use per year (RR 2.22, 95% CI 1.59–3.08), lower score group of PPE (RR 1.74, 95% CI 1.27–2.38), pesticide exposure at a higher intensity (RR 1.83, 95% CI 1.32–2.54), pesticide exposure at a lower CEI (RR 1.84, 95% CI 1.29–2.62) increased the RRs of MetS incidence most significantly in each category of variables related to pesticide exposure.

Table 5. RRs of MetS related with pesticide exposure

Pesticide-related variables	Crude RR (95% CI)	Adjusted RR (95% CI)*	Adjusted RR (95% CI)**
Pesticide use			
No	1 (reference)	1 (reference)	1 (reference)
Yes	**1.71 (1.31-2.23)**	**1.81 (1.37-2.40)**	**1.96 (1.43-2.70)**
Mixing status of pesticide			
No	1 (reference)	1 (reference)	1 (reference)
<50% of time mixed	**1.97 (1.42-2.74)**	**2.09 (1.48-2.94)**	**2.18 (1.52-3.12)**
50%+ of time mixed	1.29 (0.93-1.78)	**1.44 (1.02-2.02)**	1.44 (0.99-2.09)
Application method			
No	1 (reference)	1 (reference)	1 (reference)
Seed treatment or distribute tablet	1.53 (0.90-2.62)	1.73 (0.99-3.05)	1.75 (0.96-3.18)
Backpack	**1.40 (1.00-1.96)**	**1.54 (1.07-2.22)**	**1.60 (1.09-2.35)**
Mist blower/fogger or air-blast	**1.54 (1.09-2.19)**	**1.63 (1.14-2.34)**	**1.67 (1.13-2.46)**
Years of pesticide use			
0	1 (reference)	1 (reference)	1 (reference)
≤12	**1.86 (1.35-2.55)**	**2.03 (1.45-2.83)**	**2.21 (1.55-3.17)**
>12	**1.58 (1.15-2.18)**	**1.65 (1.19-2.29)**	**1.76 (1.22-2.54)**
Frequency of pesticide use (per year)			
0	1 (reference)	1 (reference)	1 (reference)
1-25	**1.85 (1.37-2.50)**	**2.00 (1.47-2.71)**	**2.22 (1.59-3.08)**
>25	**1.54 (1.10-2.16)**	**1.58 (1.10-2.27)**	**1.60 (1.06-2.42)**
Scores for PPE			
0	1 (reference)	1 (reference)	1 (reference)
0.1-0.8	**1.74 (1.27-2.38)**	**1.80 (1.29-2.50)**	**1.74 (1.27-2.38)**
1	**1.68 (1.22-2.32)**	**1.83 (1.32-2.54)**	**1.68 (1.22-2.32)**
Intensity level of pesticide exposure			
0	1 (reference)	1 (reference)	1 (reference)
Lower group	**1.68 (1.23-2.29)**	**1.77 (1.29-2.43)**	**1.80 (1.29-2.50)**
Higher group	**1.49 (1.07-2.08)**	**1.66 (1.16-2.37)**	**1.83 (1.32-2.54)**
CEI of pesticide use			
0	1 (reference)	1 (reference)	1 (reference)
Lower group	**1.63 (1.18-2.25)**	**1.72 (1.23-2.40)**	**1.84 (1.29-2.62)**
Higher group	**1.56 (1.14-2.13)**	**1.72 (1.23-2.41)**	**1.75 (1.20-2.55)**

Intensity level = (mixing status + application method + equipment repair status) × personal protective equipment

Abbreviations: CEI, Cumulative Exposure Index = (intensity level × spraying year × spraying day per year), RR, Relative Risk, CI, Confidence Interval

*Adjusted for age, sex

**Adjusted for age, sex, smoking status, alcohol use, regular exercise, education, and marital status

Bold shows the statistical significance of the odds ratios

5. RRs of MetS incidence by variables related to pesticide exposure in male subjects

In Table 6, the RRs of MetS incidence were significantly elevated in the "ever used pesticides" group than in the reference group after adjustment for age, gender, smoking status, alcohol use, regular exercise, education, and marital status (RR 2.06, 95% CI 1.21–3.53). The group of "<50% of time mixed" (RR 2.27, 95% CI 1.27–4.07), mist blower/fogger or air–blast application (RR 2.16, 95% CI 1.12–4.16), "≤12 years of pesticide use" (RR 2.54, 95% CI 1.44–4.49), 1–25 days of pesticide use per year (RR 2.39, 95% CI 1.34–4.25), lower score group of PPE (RR 2.39, 95% CI 1.34–4.25), pesticide exposure at a lower intensity (RR 2.01, 95% CI 1.10–3.68), and pesticide exposure at a higher CEI (RR 2.15, 95% CI 1.18–3.91) increased the RRs of MetS incidence most significantly in each category of variables related to pesticide exposure.

Table 6. RRs of MetS related to pesticide exposure for men

Pesticide-related variables	Crude RR (95% CI)	Adjusted RR (95% CI)*	Adjusted RR (95% CI)**
Pesticide use			
No	1 (reference)	1 (reference)	1 (reference)
Yes	1.35 (0.84–2.18)	1.35 (0.83–2.21)	**2.06 (1.21–3.53)**
Mixing status of pesticide			
No	1 (reference)	1 (reference)	1 (reference)
<50% of time mixed	1.70 (0.98–2.97)	1.70 (0.97–3.00)	**2.27 (1.27–4.07)**
50%+ of time mixed	1.16 (0.68–1.96)	1.16 (0.67–1.99)	1.57 (0.86–2.89)
Application method			
No	1 (reference)	1 (reference)	1 (reference)
Seed treatment or tablet distribution	1.10 (0.48–2.52)	1.10 (0.47–2.55)	1.62 (0.65–3.99)
Backpack	1.15 (0.66–2.00)	1.15 (0.66–2.02)	**1.80 (1.00–3.23)**
Mist blower/fogger or air-blaster	1.36 (0.75–2.45)	1.36 (0.75–2.46)	**2.16 (1.12–4.16)**
Years of pesticide use			
0	1 (reference)	1 (reference)	1 (reference)
≤12	1.65 (0.99–2.76)	1.65 (0.98–2.79)	**2.54 (1.44–4.49)**
>12	1.01 (0.55–1.87)	1.01 (0.54–1.89)	1.52 (0.78–2.98)
Frequency of pesticide use (per year)			
0	1 (reference)	1 (reference)	1 (reference)
1–25	1.47 (0.86–2.52)	1.47 (0.86–2.52)	**2.39 (1.34–4.25)**
>25	1.24 (0.71–2.18)	1.24 (0.69–2.22)	1.74 (0.92–3.31)
Scores for PPE			
0	1 (reference)	1 (reference)	1 (reference)
0.1–0.8	1.16 (0.65–2.07)	1.16 (0.64–2.09)	1.79 (0.95–3.34)
1	1.54 (0.91–2.61)	1.54 (0.90–2.63)	**2.39 (1.32–4.32)**
Intensity level of pesticide exposure			
0	1 (reference)	1 (reference)	1 (reference)
Lower group	1.40 (0.81–2.41)	1.40 (0.80–2.43)	**2.01 (1.10–3.68)**
Higher group	1.18 (0.68–2.04)	1.18 (0.67–2.06)	1.80 (0.98–3.32)
CEI of pesticide use			
0	1 (reference)	1 (reference)	1 (reference)
Lower group	1.18 (0.65–2.13)	1.18 (0.65–2.15)	1.68 (0.89–3.15)
Higher group	1.35 (0.80–2.26)	1.35 (0.79–2.28)	**2.15 (1.18–3.91)**

Intensity level = (mixing status + application method + equipment repair status) × personal protective equipment

Abbreviations: CEI, Cumulative Exposure Index = (intensity level × spraying year × spraying day per year), RR, Relative Risk, CI, Confidence Interval

*Adjusted for age and sex

**Adjusted for age, sex, smoking status, alcohol use, regular exercise, education, and marital status

Bold shows the statistical significance of the RRs

6. RRs of MetS incidence by variables related to pesticide exposure in female subjects

In Table 7, the RR of MetS incidence was significantly elevated in the "ever used pesticides" group than in the reference group after adjustment for age, gender, smoking status, alcohol use, regular exercise, education, and marital status (RR 1.86, 95% CI 1.28–2.69). The group of "<50% of time mixed" (RR 2.09, 95% CI 1.34–3.25), seed treatment or tablet distribution (RR 2.14, 95% CI 1.02–4.52), "≤12 years of pesticide use" (RR 1.98, 95% CI 1.27–3.09), 1–25 days of pesticide use per year (RR 2.01, 95% CI 1.33–3.03), lower score group of PPE (RR 1.78, 95% CI 1.19–2.66), pesticide exposure at a lower intensity (RR 1.78, 95% CI 1.19–2.66), and pesticide exposure at a lower CEI (RR 1.24, 95% CI 1.24–2.81) increased the RRs of MetS incidence most significantly in each category of variables related to pesticide exposure.

Table 7. RRs of MetS related to pesticide exposure for women

Pesticide-related variables	Crude RR (95% CI)	Adjusted RR (95% CI)*	Adjusted RR (95% CI)**
Pesticide use			
No	1 (reference)	1 (reference)	1 (reference)
Yes	**2.14 (1.55–2.96)**	**2.07 (1.50–2.87)**	**1.86 (1.28–2.69)**
Mixing status of pesticide			
No	1 (reference)	1 (reference)	1 (reference)
<50% of time mixed	**2.48 (1.65–3.71)**	**2.29 (1.51–3.48)**	**2.09 (1.34–3.25)**
50%+ of time mixed	**1.63 (1.07–2.49)**	**1.69 (1.11–2.56)**	1.44 (0.91–2.28)
Application method			
No	1 (reference)	1 (reference)	1 (reference)
Seed treatment or tablet distribution	**2.90 (1.51–5.57)**	**2.85 (1.49–5.45)**	**2.14 (1.02–4.52)**
Backpack	**1.94 (1.25–3.00)**	**1.84 (1.18–2.86)**	1.57 (0.97–2.53)
Mist blower/fogger or air-blaster	**1.81 (1.16–2.82)**	**1.68 (1.08–2.62)**	1.43 (0.90–2.28)
Years of pesticide use			
0	1 (reference)	1 (reference)	1 (reference)
≤12	**2.25 (1.48–3.41)**	**2.14 (1.41–3.27)**	**1.98 (1.27–3.09)**
>12	**2.08 (1.44–3.01)**	**2.03 (1.41–2.93)**	**1.78 (1.16–2.71)**
Frequency of pesticide use (per year)			
0	1 (reference)	1 (reference)	1 (reference)
1–25	**2.23 (1.55–3.20)**	**2.27 (1.58–3.25)**	**2.14 (1.46–3.15)**
>25	**2.02 (1.31–3.10)**	**1.81 (1.18–2.80)**	1.43 (0.87–2.37)
Scores for PPE			
0	1 (reference)	1 (reference)	1 (reference)
0.1–0.8	**2.38 (1.65–3.44)**	**2.20 (1.51–3.21)**	**2.01 (1.33–3.03)**
1	**1.89 (1.25–2.86)**	**1.93 (1.28–2.90)**	**1.67 (1.06–2.65)**
Intensity level of pesticide exposure			
0	1 (reference)	1 (reference)	1 (reference)
Lower group	**2.00 (1.37–2.92)**	**1.93 (1.33–2.82)**	**1.78 (1.19–2.66)**
Higher group	**2.14 (1.41–3.26)**	**2.07 (1.36–3.16)**	**1.67 (1.03–2.70)**
CEI of pesticide use			
0	1 (reference)	1 (reference)	1 (reference)
Lower group	**2.12 (1.45–3.11)**	**2.01 (1.36–2.96)**	**1.87 (1.24–2.81)**
Higher group	**1.98 (1.31–2.99)**	**1.96 (1.31–2.94)**	1.57 (0.99–2.51)

Intensity level = (mixing status + application method + equipment repair status) × personal protective equipment

Abbreviations: CEI, Cumulative Exposure Index = (intensity level × spraying year × spraying day per year), RR, Relative Risk, CI, Confidence Interval

*Adjusted for age and sex

**Adjusted for age, sex, smoking status, alcohol use, regular exercise, education, and marital status

Bold shows the statistical significance of the RRs

V. Discussion

At enrolment, MetS prevalence was 30.3%. After removal of a subject with MetS at baseline, when we compared the incidence of MetS after about 2.6 years depending on whether pesticide was used or not, the incidence of MetS was 20.7% in the pesticide using group. In the group not exposed to pesticides, the incidence of MetS was 12.1%, which was a statistically significant difference (p–value <0.0001). In the analysis stratified by gender, the RR for the incidence of MetS in men (adjusted for age, smoking status, alcohol use, regular exercise, education, and marital status) was 2.06 (95% CI 1.21–3.53) vs. 1.86 (95% CI 1.28–2.69) in women, for the pesticide–using group compared with the group that did not use pesticides. To the best of our knowledge, this study is the first to compare the relationship between the incidence of MetS and pesticides.

Depending on the ethnicity, age, gender, and race of the study population, the worldwide prevalence of MetS was reported to be between 10% and 84%[26,27]. In this study, the prevalence of MetS in the pesticide–using group at the start of this study was 30.3%. In the western world, about 20% of adults have MetS[28], while, in most countries of the Asia–Pacific region, approximately 25% or more of the adult population are affected by MetS[29]. As it is known that lifestyle, such as westernised meals and lack of exercise, is related to the occurrence of MetS, it is said that lifestyle modification is necessary for the treatment of MetS[30,31]. However, these unhealthy factors are relatively not common in rural areas[32,33], and further research is needed to find factors related to the occurrence of MetS and suitable treatment tools for use in rural areas.

A recent study showed that the duration of pesticide use in summer was 1.6 times greater in rural areas than in urban areas (95% CI 1.0–2.7)[34]. In addition, children living in agricultural communities have greater urine levels of metabolites associated with organophosphorous (OP) pesticide exposure compared to urban counterparts[35]. In our study, the pesticide–using group showed a much higher incidence of MetS and the RR of MetS incidence was higher than that of the pesticide not–using group. These results may explain that pesticides play a role in the development of MetS in rural areas compared with urban areas, as pesticides were mainly used more in rural areas.

According to a previous study, OP pesticide–related workers are exposed to greater oxidative stress[11,13]. Furukawa et al. reported that the pathogenic mechanism of MetS was related to increased oxidative stress[37]. In addition, MetS–related manifestations, comprising atherosclerosis, hypertension, and T2D, are related to increased oxidative stress[38]. The correlation that exposure to pesticides increases oxidative stress and that oxidative stress plays an important role during the pathophysiological episode of MetS indicates that there may be a link between pesticide exposure and the occurrence of MetS. Some researchers have demonstrated that exposure to persistent organic pollutants (POPs), especially organochlorine pesticides, causes MetS[8]. The results of our study are consistent with previous studies.

In Table 5, the variables related to pesticide exposure did not have a significant positive dose–response relationship with MetS incidence. Instead, MetS incidence was increased more in the groups which reflect a low concentrations of pesticide exposure. We also found that the RRs for MetS development was higher in the group with high cumulative exposure than in the group with cumulative exposure, even in the pesticide–using group, only in men (RR 2.15, 95% CI 1.18–3.91). This suggested that a dose–response relationship between pesticide exposure and the occurrence of MetS cannot be generalised.

We found that there were gender differences in RR for MetS incidence related to pesticide exposure. This may be explained by a difference in workplace exposures. According to previous studies in South Korea, pesticide spraying is directly performed by male farmers and female farmers assist in the main pesticide application[39,40]. In this study, we examined gender–related differences in variables related to exposure to pesticides and found that the percentage of male subjects using pesticides was higher than that of female subjects. In addition, the proportion of men with high exposure to pesticide exposure was significantly higher than that of women. This may be one of the reasons why the RR of MetS was different for each gender in our study. Previous studies[39,40] have also shown that the time of pesticide application and pesticide metabolites were higher in male farmers. The metabolism of the chemicals may have different results in men and women exposed to chemicals[41]. In some biomonitoring studies, there are gender differences in exposure to OP pesticides[42] and herbicides[43]. These previous studies supported our findings of why the RR for MetS incidence was different in each gender.

In this study, women were exposed to lower concentrations of pesticides than men. As shown in Table 7, the RRs for the development of MetS was higher in the groups that were exposed to lower concentrations of pesticide. This pattern was not observed in men. These inconsistencies are considered to occur because MetS owing to pesticide exposure in female subjects may be greater at lower level exposures rather than higher exposures. In previous studies, researchers proposed that endocrine disruptors (EDCs) could exert strong biological responses at low doses, but weak effects at higher doses, leading to an inverted U–shaped graph[44,45]. Many EDCs, including pesticides, exert low–dose effects that are defined as those that occur in the range of human exposures or effects observed at doses below those used conventionally[46,47]. For example, Lee et al. found that the association of the 31 POPs with the incidence of T2D had an inverted U–shaped curve[7]. When we examined the relationship between pesticide exposure and MetS, in especially in women, the adjusted RRs of all variable categories that reflected low pesticide exposure were highest and the risk decreased as the exposure level increased, leading to an inverted U–shaped association.

Although previous studies have shown cross–sectional relationships between pesticide use and MetS[7,48], in this longitudinal study, we investigated the relationship between pesticide exposure and the incidence of MetS by using detailed questionnaires. A number of prior studies using data from the AHS have used similar approaches to exposure assessment. However, this research considered the lifetime cumulative days of use by multiplication of only the frequency and duration of pesticide exposure. In contrast, we calculated the intensity level considering the habit of spraying pesticides and also calculated the CEI through the multiplication of the intensity level and the lifetime cumulative days of pesticide use to allow the measurement of cumulative pesticide exposure more carefully.

We included more than 1,100 participants in the analyses, which is one of the strengths of this study; in contrast, most studies evaluating pesticide exposure through the measurement of serum biomarkers were small[49].

Some limitations and uncertainties of this study should be considered. First, since demographic shifts were expected to be infrequent in rural areas of Wonju and Pyeongchang, where our study was initiated[50], the distribution of the characteristics related to pesticide exposure was regarded to be comparatively stable. Thus, we assumed that our results from the baseline survey may contain information on the potential chronic effects of pesticide exposure, without measurement of the change in pesticide exposure by the alternation of any pesticide application behavior during the follow–up period. Additionally, the change of pesticide application behavior (such as protective gear wear, pesticide spraying time, etc.) during the follow-up period, compliance with the usage information provided in the product manual for pesticide application, intake foods or water contaminated with pesticide, and non-occupational exposure from applications to public place[5] were not considered in this study. In subsequent studies, these various variables that may influence pesticide exposure levels should be included in an analysis for more accurate occupational pesticide exposure assessment. Second, the type of pesticide was not included in the questionnaire, so it was not known which pesticide was more closely related to the occurrence of MetS. These Insufficient assessments about occupational and non-occupational pesticide exposure are the major source of the uncertainties in this study. Third, our estimates could be different in other races and countries, and it may be difficult to generalize our results. Fourth, the assessment of pesticide exposure was dependent on the memory of each subject, which may lead to some misclassification, and recall bias may be another limitation of this study. Lastly, the follow-up term was relatively short (2.64 year), and we could not assess whether the relationship between pesticide exposure and incidence of MetS would last for a longer follow-up. To reduce the degree of uncertainty in this study, subjects without data related to occupational pesticide exposure or data related to MetS were excluded, and we analyzed the study subjects that is stratified by gender.

On the other hand, excluding subjects with MetS at baseline to estimate the incidence of MetS can lead to the possibility of weakening the explanatory power about the new onset of a MetS by removing subjects who developed MetS as a result of persistent pesticide exposure from the past at baseline. Therefore, we have presented the association of pesticide exposure and the prevalence of MetS at baseline in supplementary data. The number of criteria for MetS was higher in the pesticide exposure group (Appendix 1), and the difference in pesticide application behavior was observed between the groups with and without the MetS (Appendix 2). In the group with MetS, the proportion of the pesticide users and the higher CEI of pesticide exposure was greater than the group without MetS. The appendix 3 shows that pesticide exposure moderately increased the risk of MetS (OR = 1.26, 95% CI 0.99-1.61), and the risk of MetS was also greater in the group with the higher CEI of pesticide exposure (OR = 1.57, 95% CI, 1.14–2.00). These provided some supports for our findings that pesticides have contributions to MetS.

VI. Conclusions

In spite of these limitations, the present study provides the first description of the relationship between pesticide exposure and the incidence of MetS in a rural population. We found that chronic and high–level exposure to pesticides may have contributed to the increased incidence of MetS, especially in men. In addition, we found that there was an inverse U–shaped non–monotonic dose–response relationship between pesticide exposure and MetS incidence. Further larger prospective studies involving detailed information on pesticides must be conducted to confirm this causal relationship.

This study suggests additional risk factors for MetS, such as pesticide exposure, and may lead to adequate treatment paradigms for MetS in rural areas. This study shows that the incidence of MetS increases with pesticide exposure, and more related studies may help to further elucidate the recent epidemic of MetS.

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ABSTRACT (IN KOREAN)

대사증후군 발생 원인으로서의 농약 노출에 관한 연구

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배경

대사증후군은 농약 노출과 관련 될 수 있는 유해한 건강 영향이다. 그러나 농약 사용과 대사증후군 발생 사이의 관계에 대한 역학적 연구는 거의 없다. 본 연구는 한국의 농촌 인구집단에서 농약 노출과 대사증후군 발병률 사이의 관련성을 조사하였다.

대상 및 방법

본 연구에서는 농촌 인구에서 농약 사용과 대사증후군 발병 사이의 인과 관계를 조사했다. 1,162 명의 연구대상자에 대한 원주 평창 농업인 코호트 연구의 반복 측정 데이터를 분석하였다. 농약 노출과 대사증후군 사이의 관계를 추정하고, 상대 위험도(Relative risk)와 95 % 신뢰 구간(CI)을 계산하기 위해 로버스트 포아송 회귀분석(Poisson regression with a robust error variance)을 시행 하였다.

결과

농약 노출 집단에서 대사증후군의 발생률은 20.7 % 이었다. 농약 사용은 대사증후군 발생의 상대 위험도를 증가시켰다. 여성에서는 대사증후군 및 농약 노출과 관련된 저용량 건강 영향 효과(low-dose effects)를 관찰하였다.

결론

농약 노출은 대사증후군의 발생과 관련이 있다. 농약 노출로 인한 대사증후군 발생의 상대위험도는 남녀간에 차이가 있다.

주제어 (Keywords) : 대사증후군, 농약 노출, 코호트, 포아송 회귀분석, 상대위험도.

Appendix - Supplementary data

Appendix 1. Baseline demographic characteristics of subjects according to the use of pesticides before excluding subjects with MetS (n=1,748)

	Pesticide use		
	No (n=883)	Yes (n=865)	
Demographic characteristics	Mean (±SD)* or Frequency (%)**		p-value
Sex			
Male	292 (38.3%)	471 (61.7%)	<.0001
Female	591 (60%)	394 (40%)	
Age (years)	54 (±8.1)	55.5 (±7.8)	<.0001
SBP (mmHg)	128.1 (±17.5)	128.2 (±17.9)	0.95
DBP (mmHg)	82.1 (±11.4)	83 (±11.8)	0.13
Fasting glucose (mg/dL)	92.3 (±14.8)	96.1 (±20.3)	<.0001
HDL–C (mg/dL)	46.4 (±10.5)	11 (±0.4)	0.57
TG (mg/dL)	135.7 (±88.6)	158.3 (±104.2)	<.0001
Waist circumference (cm)	81.8 (±8.8)	85.2 (±8.5)	<.0001
MetS criterion (n)	1.7 (±1.2)	2.1 (±1.2)	<.0001
Subjects with MetS	223 (25.3%)	294 (34.0%)	
Smoking status			
Non–smoker	679 (55.2%)	552 (44.8%)	<.0001
Ex–smoker	84 (38.0%)	137 (62.0%)	
Current smoker	117 (40.9%)	169 (59.1%)	
Alcohol use			
No	535 (57.1%)	402 (42.9%)	<.0001
Yes	344 (42.9%)	458 (57.1%)	
Regular exercise			
No	545 (42.8%)	730 (57.3%)	<.0001
Yes	331 (72.1%)	128 (27.9%)	
Education			
Primary school or below	351 (38.2%)	569 (61.9%)	<.0001
Middle school or above	528 (64.2%)	294 (35.8%)	
Marital status			
Married	764 (49.1%)	793 (50.9%)	<.01
Others	116 (65.5%)	61 (34.5%)	
BMI (kg/m^2)			
<25	551 (53.6%)	477 (46.4%)	<.001
≥25	332 (46.2%)	387 (53.8%)	

*p–value from t-test

**p–value from chi-square test

Appendix 2. Baseline differences in the use of pesticides according to the Mets (n=1,748)

Pesticide--related variables	No MetS, n (%)	MetS, n (%)	p-–value*
Pesticide use			<.0001
No	660 (56.8%)	223 (46.1%)	
Yes	502 (43.2%)	261 (53.9%)	
Mixing status of pesticide			<.001
No	103 (20.4%)	49 (18.7%)	
<50% of time mixed	145 (28.8%)	66 (25.2%)	
50%+ of time mixed	256 (50.8%)	147 (56.1%)	
Application method			<.0001
No	80 (15.8%)	26 (9.9%)	
Seed treatment or tablet distribution	58 (11.5%)	33 (12.6%)	
Backpack	202 (40.0%)	127 (48.3%)	
Mist blower/fogger or air--blaster	165 (32.7%)	77 (29.3%)	
Years of pesticide use			<.0001
0	660 (56.8%)	223 (46.0%)	
≤12	272 (23.4%)	127 (26.2%)	
>12	230 (19.8%)	135 (27.8%)	
Frequency of pesticide use (per year)			<.0001
0	660 (56.8%)	223 (46.0%)	
1-–25	319 (27.5%)	147 (30.3%)	
>25	183 (15.8%)	115 (23.7%)	
Scores for PPE			<.0001
0	660 (56.8%)	223 (46.0%)	
0.1-–0.8	231 (19.9%)	132 (27.2%)	
1	271 (23.3%)	130 (26.8%)	
Intensity level of pesticide exposure			<.001
0	695 (59.8%)	233 (48.0%)	
Lower group	205 (17.6%)	105 (21.7%)	
Higher group	262 (22.6%)	147 (30.3%)	
CEI of pesticide use			<.0001
0	695 (59.8%)	233 (48.0%)	
Lower group	216 (18.6%)	92 (19.0%)	
Higher group	251 (21.6%)	160 (33.0%)	

*p-–value from chi-–square test

Appendix 3. OR of MetS related to pesticide exposure in baseline

Pesticide-related variables	Crude OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI)**
Pesticide use			
No	1 (reference)	1 (reference)	1 (reference)
Yes	**1.54 (1.24-1.90)**	**1.25 (1.00-1.57)**	1.26 (0.99-1.61)
Mixing status of pesticide			
No	1 (reference)	1 (reference)	1 (reference)
<50% of time mixed	1.29 (0.93-1.78)	1 (0.72-1.40)	1 (0.71-1.42)
50%+ of time mixed	**1.62 (1.27-2.07)**	1.28 (0.99-1.66)	1.28 (0.97-1.68)
Application method			
No	1 (reference)	1 (reference)	1 (reference)
Seed treatment or tablet distribution	**1.69 (1.08-2.65)**	1.18 (0.74-1.89)	1.18 (0.73-1.91)
Backpack	**1.87 (1.43-2.43)**	**1.40 (1.06-1.86)**	**1.37 (1.02-1.84)**
Mist blower/fogger or air-blaster	**1.39 (1.02-1.88)**	1.14 (0.83-1.56)	1.15 (0.82-1.61)
Years of pesticide use			
0	1 (reference)	1 (reference)	1 (reference)
≤12	**1.36 (1.07-1.75)**	1.11 (0.86-1.44)	1.12 (0.85-1.47)
>12	**1.86 (1.41-2.46)**	**1.52 (1.14-2.03)**	**1.54 (1.13-2.10)**
Frequency of pesticide use (per year)			
0	1 (reference)	1 (reference)	1 (reference)
1–25	**1.36 (1.07-1.75)**	1.11 (0.86-1.44)	1.12 (0.85-1.47)
>25	**1.86 (1.41-2.46)**	**1.52 (1.14-2.03)**	**1.54 (1.13-2.10)**
Scores for PPE			
0	1 (reference)	1 (reference)	1 (reference)
0.1–0.8	**1.69 (1.30-2.20)**	1.29 (0.98-1.7)	1.30 (0.97-1.74)
1	**1.42 (1.10-1.84)**	1.23 (0.94-1.6)	1.24 (0.93-1.65)
Intensity level of pesticide exposure			
0	1 (reference)	1 (reference)	1 (reference)
Lower group	**1.53 (1.16-2.02)**	1.18 (0.88-1.58)	1.18 (0.87-1.61)
Higher group	**1.67 (1.30-2.15)**	**1.35 (1.04-1.76)**	**1.37 (1.03-1.81)**
CEI of pesticide use			
0	1 (reference)	1 (reference)	1 (reference)
Lower group	1.27 (0.96-1.69)	1.03 (0.77-1.38)	1.05 (0.77-1.43)
Higher group	**1.90 (1.48-2.44)**	**1.49 (1.15-1.93)**	**1.51 (1.14-2.00)**

Intensity level = (mixing status + application method + equipment repair status) × personal protective equipment

Abbreviations: CEI, Cumulative Exposure Index = (intensity level × spraying year × spraying day per year), RR, Relative Risk, CI, Confidence Interval

*Adjusted for age and sex

**Adjusted for age, sex, smoking status, alcohol use, regular exercise, education, and marital status

Bold shows the statistical significance of the ORs