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Full Length Article

Exposure to pesticides and the prevalence of diabetes in a rural population in Korea

Sungjin Park[a,b], Sung-Kyung Kim[c,d], Jae-Yeop Kim[c,d], Kyungsuk Lee[e], Jung Ran Choi[f], Sei-Jin Chang[d], Choon Hee Chung[g], Kyu-Sang Park[h,i], Sung-Soo Oh[c,d,*], Sang-Baek Koh[c,d,f,j,*]

[a] *Department of Medicine, Yonsei University Graduate School, Seoul, Republic of Korea*
[b] *Department of Occupational and Environmental Medicine, Hongseong Medical Center, Hongseong, Republic of Korea*
[c] *Department of Occupational and Environmental Medicine, Wonju Severance Christian Hospital, Wonju College of Medicine, Yonsei University, Wonju, Republic of Korea*
[d] *Department of Preventive Medicine and Institute of Occupational and Environmental Medicine, Wonju College of Medicine, Yonsei University, Wonju, Republic of Korea*
[e] *National Academy of Agricultural Science, Rural Development Administration, Jeonju, Republic of Korea*
[f] *Institute of Genomic Cohort, Wonju College of Medicine, Yonsei University, Wonju, Republic of Korea*
[g] *Department of Internal Medicine, Wonju College of Medicine, Yonsei University, Wonju, Republic of Korea*
[h] *Mitohormesis Research Center, Wonju College of Medicine, Yonsei University, Wonju, Republic of Korea*
[i] *Department of Physiology, Wonju College of Medicine, Yonsei University, Wonju, Republic of Korea*
[j] *Center for Global Health and Social Medicine, Institute of Poverty Alleviation and International Development, Yonsei University, Wonju, Republic of Korea*

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ABSTRACT

Background: Among the adverse health effects of exposure to pesticides, an association with diabetes has been reported. However, there is a lack of epidemiologic studies on the health effects of exposure to pesticides, particularly investigating the association between occupational pesticide exposure and diabetes prevalence.
Purpose: The present study examined the association between pesticide exposure and prevalence of diabetes in a rural population in Korea.
Methods: This cross-sectional study used data from the Korea Farmers Cohort study, and included 2559 participants in the baseline survey between November 2005 and January 2008. We performed a clinical examination including blood sampling and assessed data on diabetes diagnosis, demographics, and pesticide exposure. Logistic regression was performed to evaluate the association between pesticide exposure and diabetes prevalence, adjusting for age, sex, monthly income, and marital status. In addition, a stratified analysis by body mass index (BMI) was conducted, with two categories: normal weight ($< 25\,kg/m^2$) and overweight or obese ($\geq 25\,kg/m^2$).
Results: At baseline, the prevalence of diabetes was 9.30%. Pesticide exposure was associated with the risk of diabetes after adjustment for covariates. In the analysis stratified by BMI, all the variables related to pesticide exposure were associated with prevalence of diabetes in the overweight or obese group, whereas no significant association was found in the normal weight group.
Conclusion: Exposure to pesticides was associated with diabetes, and this association was stronger in overweight or obese individuals than in normal weight individuals. Further longitudinal studies that consider information on BMI are necessary.

1. Introduction

Diabetes mellitus is a chronic disorder with the lack of insulin or the unresponsiveness of cells to insulin leading to hyperglycemia. There are three major types of diabetes, type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM) (International Diabetes Federation, 2017).

Diabetes is a public health concern worldwide. According to recent estimates from the International Diabetes Federation (IDF), 8.8% (425 million) people aged 20–79 years had diabetes worldwide in 2017, and

* Corresponding authors at: Department of Preventive Medicine and Institute of Occupational and Environmental Medicine, Wonju College of Medicine, Yonsei University, 20 Ilsan-ro, Wonju, Gangwon-do, 220-701, Republic of Korea.
E-mail addresses: psjin9318@gmail.com (S. Park), stacte@yonsei.ac.kr (S.-K. Kim), kimjy87330@gmail.com (J.-Y. Kim), leeks81@korea.kr (K. Lee), christinae@yonsei.ac.kr (J.R. Choi), chang0343@yonsei.ac.kr (S.-J. Chang), cchung@yonsei.ac.kr (C.H. Chung), qsang@yonsei.ac.kr (K.-S. Park), oss0609@yonsei.ac.kr (S.-S. Oh), kohhj@yonsei.ac.kr (S.-B. Koh).

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this number is expected to increase to 9.9% (629 million) by 2045. Around 4 million adults worldwide were estimated to die from diabetes in 2017, which correlates to one death every eight seconds. Moreover, the economic burden of diabetes continues to grow. Globally, the annual healthcare of diabetes alone cost 232 billion US dollars in 2007, which significantly increased to 727 billion US dollars by 2017 (International Diabetes Federation, 2017).

The complications of diabetes include foot ulcer, visual impairment, renal failure, infection, and cognitive dysfunction (International Diabetes Federation, 2017; Wang et al., 2013). Most of these, including cognitive impairment, are secondary to chronic hyperglycemia which has been unrecognized for a prolonged period (Bal et al., 2011). Long-term exposure to prolonged hyperglycemia induces significant alterations in both the peripheral and central nervous systems (Wang et al., 2013). Diabetes is associated with cognitive dysfunction, and memory deficit and people with diabetes encounter a high risk of depression, dementia, and Alzheimer's disease (Biessels et al., 2006; Gaudieri et al., 2008; Riederer et al., 2011). All these changes occur secondary to chronic hyperglycemia and reduce the quality of life of diabetic patients (Malone et al., 2008).

Besides traditional risk factors of T2DM such as population aging, sedentary lifestyles and unhealthy diets leading to obesity (Basu et al., 2013), environmental factors have recently received focus as possibly contributing to diabetes. Among these factors, persistent organic pollutants (POPs) such as dioxin, polychlorinated biphenyl (PCB), and organochlorine (OC) pesticides, are lipophilic, stored in adipose tissues, and generally have very long half-lives (months to several years) (Lind and Lind, 2018). A positive relationship between diabetes and other agents with relatively shorter half-lives including organophosphate (OP) pesticides, pyrethroids, and phenoxy herbicides, has also been revealed mainly from experimental studies (Starling et al., 2014).

The global usage of pesticides, estimated to be around 6 billion pounds in 2012 (US Environmental Protection Agency, 2017), has been steadily growing in developing countries in Asia and Latin America (Cha et al., 2014). The consumption of pesticide per hectare (ha) peaked in 2008, and declined to 10.1 kg/ha by 2012 (Food and Agriculture Organization of the United Nations (FAO), 2017). However, it was still far higher than the rates of other industrialized countries such as the US (2.6 kg/ha), and Germany (3.8 kg/ha) (Food and Agriculture Organization of the United Nations (FAO), 2017). Agriculture in Korea has tended to be dependent on pesticides to raise productivity in small-sized farms, where the labor force is insufficient due to the dramatic reduction and aging of the rural population (Organisation for Economic Co-operation and Development, 2008). A great number of pesticides containing numerous chemical ingredients have been used in Korea (Cha et al., 2014), and the extensive use of diverse pesticides increases concern about the potential influence of exposure to pesticides on diabetes.

Several studies have investigated the effects of pesticide use on diabetes, although more frequently with animal studies than epidemiologic studies (Juntarawijit and Juntarawijit, 2018). Moreover, relatively few studies researched the association between diabetes and occupational pesticide exposure instead of background pesticide exposure (Evangelou et al., 2016). Among these, only two studies using the Agricultural Health Study (AHS) data were large-scale prospective studies (Montgomery et al., 2008; Starling et al., 2014), whereas the remaining investigations were generally small-sized studies (Evangelou et al., 2016).

Because evidence of the linkage between diabetes and pesticide use is relatively novel, research is still needed to uncover further details regarding this association. The present study aimed to analyze the association between the prevalence of diabetes and pesticide exposure using data on a community-based rural population in Korea, and shed light on the confounding effect of body mass index (BMI) on the above association using stratified analysis.

2. Materials and methods

2.1. Study population

This study was undertaken using data from participants of the Korea Farmers Cohort study, which aimed to elucidate associations between pesticide exposure and various diseases. The goal of the above population-based prospective cohort study was to determine the prevalence, incidence, and risk factors of common and preventable chronic disorders such as diabetes, hypertension, metabolic syndrome, and cardiovascular disease. The participants enrolled in the study were mostly farmers and farm managers living in the rural areas of Wonju and Pyeongchang, Gangwon-do, Korea. Each participant provided a written informed consent before the study was initiated, and was asked to answer questionnaires in a face-to-face interview. The study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Wonju Christian Hospital.

The baseline survey was conducted with 5178 adults between November 2005 and January 2008. Among them, 2568 participants who had information on pesticide exposure were included. However, we excluded nine subjects with incomplete information on age or sex. Thus, 2559 subjects were included in the final analysis (Fig. 1).

2.2. Data collection

We collected data using a standardized modified questionnaire developed in the AHS to gather information on pesticide exposure and clinical features in both baseline and follow-up surveys (Dosemeci et al., 2002; Koh et al., 2017). Information on demographic characteristics including age, sex, BMI, alcohol consumption, smoking status, educational level, monthly income, and marital status were obtained via self-reported questionnaires. Participants also provided information about their medical history and pesticide exposure.

2.3. Covariates

Age was treated as a continuous variable and was categorized into

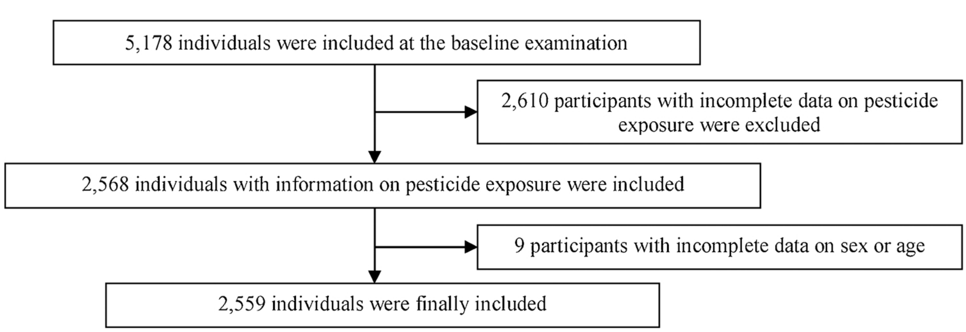

Fig. 1. The study population of the Korean Farmers Cohort Study.

Table 1
Demographic characteristics of the study participants (n = 2559).

Demographic characteristics	Participants, n (%)
Sex, n (%)	
Male	1048 (40.95)
Female	1511 (59.05)
Age (years), n (%)	
< 50	752 (29.39)
50-59	958 (37.44)
≥60	849 (33.18)
Smoking status, n (%)	
Nonsmoker	1817 (71.28)
Ex-smoker	335 (13.14)
Current smoker	397 (15.57)
Alcohol use, n (%)	
No	1347 (52.82)
Yes	1203 (47.18)
BMI (kg/m^2), n (%)	
< 25	1501 (58.84)
≥25	1050 (41.16)
Monthly income (Korean won), n (%)	
< 1,500,000	1331 (58.15)
≥1,500,000	958 (41.85)
Educational level, n (%)	
Primary school or below	1230 (48.29)
Middle school or above	1317 (51.71)
Marital status	
Married	2257 (88.68)
Others	288 (11.32)
Diabetes	
No	2321 (90.70)
Yes	238 (9.30)

three groups (< 50, 50–59, ≥60 years). Smoking status was categorized into three groups (non-smoker, ex-smoker, current smoker). Alcohol use was categorized into two groups according to current alcohol drinking (no, yes). Educational level was grouped into two categories (completion of primary school or lower, completion of middle school or higher). Monthly income was divided into two groups according to family income per month (< 1,500,000, ≥1,500,000 KR Won). Marital status was divided into two groups (married or other status). BMI was treated as a continuous variable and was categorized into two groups (< 25, ≥25 kg/m^2).

2.4. Exposure assessment

Participants were asked to complete the questionnaires with reasonable reliability and validity and to provide detailed information on their use of pesticides (Coble et al., 2005; Thomas et al., 2010). They were asked to report if they had ever been a farmer, if they had ever mixed or applied any pesticides, the number of years of pesticide use, and the average number of days per year of pesticide use.

Exposure to pesticides may occur during transportation, mixing, applying of pesticides, as well as cleaning and repairing equipment. Factors that can influence the intensity of exposure include type of activity (e.g. application, mixing), method of application (e.g. hand spray, backpack), use of personal protective equipment (PPE) (e.g. rubber gloves, respirators), and personal work practices and hygiene (e.g. changing into clean clothes or taking a bath after pesticide use). In this study, information about these factors was included in the analysis.

Based on these items, the intensity level of pesticide exposure and cumulative exposure index (CEI) were calculated as follows:

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

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

Mixing status was divided into two groups (never mixed, and mixed, assigned 0, and 9, respectively), and the application method was divided into eight groups (does not apply, aerial-aircraft, in furrow/banded, boom on tractor, backpack, hand spray, mist blower/fogger, and airblast, which had six scales assigned 0, 1, 2, 3, 8, 9, 9, and 9, respectively). Repair status was divided into two groups according to the status of repairing equipment, and PPE was scored according to the use of protective equipment in combination with their types. The detailed algorithm was described elsewhere (Dosemeci et al., 2002).

Both the duration (0, < 20, and ≥20 years) and frequency (0, < 10, and ≥10 days average per year) of pesticide use were categorized into three groups, and both the intensity level, and CEI of pesticide exposure were categorized into three groups based on their medians (0, lower than the median, higher than the median).

2.5. Outcome variable

The outcome was the prevalence of diabetes. Participants were considered to have diabetes if (a) their fasting plasma glucose (FPG) was ≥126 mg/dL, or (b) their 2-hour plasma glucose was ≥200 mg/dL during oral glucose tolerance test (OGTT) with 75 g oral glucose load, or (c) their HbA1c was ≥6.5%, or (d) they reported a current use of insulin or antidiabetic medication.

2.6. Statistical analysis

All analyses were performed with the SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina). Chi-square tests were performed to estimate differences in the prevalence of diabetes according to covariates and to calculate p-values. Multiple logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs). Logistic regressions were adjusted for age, sex, monthly income, and marital status. In addition, a stratified analysis by BMI was conducted with two categories (< 25 and ≥25 kg/m^2). All p-values < 0.05 were considered statistically significant.

3. Results

The descriptive figures of the study population are listed in Table 1. Of the 2559 adults who participated in this study, 9.30% (238 people) reported having diabetes at the baseline examination. At enrollment, age ranged from 39 to 79 years (mean ± SD 55.08 ± 8.03 years). The average BMI was 24.5 kg/m^2.

The number and proportions of cases were as follows: 114 (4.45%) had FPG level ≥126 mg/dL, 94 (3.67%) had 2-h plasma glucose level ≥200 mg/dL, 130 (5.08%) had HbA1c level ≥6.5%, and 167 (6.53%) reported currently taking antidiabetic medications at the baseline survey. As a result, the prevalence of diabetes was 9.30% (238 people) at the baseline examination.

Age, sex, smoking status, BMI, monthly income, and educational level were significantly associated with prevalence of diabetes (Table 2). The participants with diabetes were more likely to be male, older, and have a higher BMI, a lower monthly income, and a lower educational level. Smoking status was significantly associated with prevalence of diabetes. However, because all female participants who had diabetes were non-smokers, the relationships between smoking status and diabetes prevalence were not significant in both sexes.

All the variables linked with exposure to pesticides had a significant association with diabetes prevalence (Table 3). Prevalence of diabetes was much higher in study participants who had ever been a farmer, or had ever used any pesticides, than in those who had not. All cumulative indices with pesticide exposure were shown to have a positive relationship with prevalence of diabetes. Among these indices, duration (years), frequency (average days per year), and CEI of pesticide use associated with an increased prevalence of diabetes. However, the same relationship was not found with intensity level, where the highest prevalence of diabetes was found in the lower intensity level group.

The ORs of diabetes were significantly elevated with ever use of pesticides, duration, frequency, intensity level, and CEI of pesticide use,

Table 2
Prevalence of diabetes according to general characteristics (n = 2559).

Demographic characteristics	Prevalence of diabetes, n, (%)	p-value*
Sex		< .0001
Male	127 (12.12)	
Female	111 (7.35)	
Age (years), n (%)		< .0001
< 50	29 (3.86)	
50-59	102 (10.65)	
≥60	107 (12.60)	
Smoking status, n (%)		0.0222
Nonsmoker	152 (8.37)	
Ex-smoker	43 (12.84)	
Current smoker	42 (10.58)	
Alcohol use, n (%)		0.1260
No	114 (8.46)	
Yes	124 (10.31)	
BMI (kg/m^2), n (%)		< .0001
< 25	109 (7.26)	
≥25	129 (12.29)	
Monthly income (Korean won), n (%)		< .0001
< 1,500,000	158 (11.87)	
≥1,500,000	52 (5.43)	
Educational level, n (%)		< .0001
Primary school or below	150 (12.20)	
Middle school or above	88 (6.68)	
Marital status		0.7363
Married	209 (9.26)	
Others	29 (10.07)	

* p-value from chi-square test.

Table 3
Prevalence of diabetes according to pesticide exposure (n = 2559).

Pesticide-related variables	Prevalence of diabetes, n, (%)	p-value*
Farmer		< .0001
No	73 (6.15)	
Yes	165 (12.06)	
Pesticide use		< .0001
No	84 (6.17)	
Yes	129 (13.14)	
Years of pesticide use		< .0001
0	116 (7.11)	
< 20	31 (11.40)	
≥20	91 (13.87)	
Frequency of pesticide use (per year)		< .0001
0	122 (7.31)	
< 10	28 (10.69)	
≥10	88 (13.99)	
Intensity level of pesticide exposure		< .0001
0	109 (6.93)	
Lower group	65 (13.37)	
Higher group	64 (12.80)	
CEI of pesticide use		< .0001
0	109 (6.95)	
Lower group	51 (12.32)	
Higher group	59 (14.71)	

Intensity level = (mixing status + application method + equipment repair status) × personal protective equipment.
CEI, Cumulative Exposure Index = (intensity level × spraying year × spraying day per year).
* p-value from chi-square test.

in the logistic regression model adjusted for age, sex, monthly income, and educational level (Table 4). Pesticide use (OR 1.58 95% CI 1.13–2.21), ≥20 years of pesticide use (OR 1.51 95% CI 1.07–2.14), ≥10 days of pesticide use per year (OR 1.53 95% CI 1.09–2.15), pesticide exposure at a lower intensity level (OR 1.55 95% CI 1.07–2.24), pesticide exposure at a higher intensity level (OR 1.53 95% CI 1.06–2.22), and a higher CEI (OR 1.54 95% CI 1.03–2.30), all increased the ORs of diabetes significantly. Ever farming (OR 1.35 95% CI 0.97–1.88), < 20 years of pesticide use (OR 1.42 95% CI 0.89-2.26), < 10 days of pesticide use per year (OR 1.07 95% CI 0.66–1.73), and a lower level of CEI (OR 1.42 95% CI 0.96–2.11), were not significantly associated with diabetes.

Table 4
Odds ratios of diabetes associated with pesticide exposure.

Variables	Crude OR (95% CI)	Adjusted OR (95% CI)*
Farmer	**2.09 (1.57-2.79)**	1.35 (0.97-1.88)
Pesticide use	**2.30 (1.72-3.07)**	**1.58 (1.13-2.21)**
Years of pesticide use		
< 20	**1.68 (1.11-2.55)**	1.42 (0.89-2.26)
≥20	**2.10 (1.57-2.81)**	**1.51 (1.07-2.14)**
Frequency of pesticide use (per year)		
< 10	1.52 (0.98-2.34)	1.07 (0.66-1.73)
≥10	**2.06 (1.54-2.76)**	**1.53 (1.09-2.15)**
Intensity level of pesticide exposure		
Lower group	**2.07 (1.50-2.87)**	**1.55 (1.07-2.24)**
Higher group	**1.97 (1.42-2.73)**	**1.53 (1.06-2.22)**
CEI of pesticide use		
Lower group	**1.88 (1.32-2.68)**	1.42 (0.96-2.11)
Higher group	**2.31 (1.65-3.24)**	**1.54 (1.03-2.30)**

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), OR, Odds Ratio, CI, Confidence Interval.
Bold shows the statistical significance of the odds ratios.
* Adjusted for age, sex, monthly income, and educational level.

Stratified analysis for BMI was conducted (Table 5). None of the variables related to pesticide exposure were significantly associated with the ORs of diabetes in the normal weight group after adjusting for age, sex, monthly income, and educational level, whereas all the variables linked with pesticide exposure significantly increased the ORs of diabetes in the overweight or obese group.

4. Discussion

In this cross-sectional study, the prevalence rate of diabetes was estimated to be 9.30%. The prevalence of diabetes had a positive correlation with most of the pesticide exposure indices. All variables such as ever farming, ever use, duration, frequency, intensity level, and CEI of pesticide use, were found to have a significant association with prevalence of diabetes in the overweight or obese group, even after adjusting for possible risk factors. Also, in the lower and higher groups, both the intensity level and CEI were significantly associated with the increased risk of developing diabetes.

Researchers have investigated the relationship between diabetes and POPs including pesticides (Lind and Lind, 2018) since the landmark study conducted by Lee et al. (2006) that induced a great interest on this topic. A recently published meta-analysis showed a significant relationship between levels of OC pesticides, PCBs, dioxins and diabetes (Song et al., 2016). Some studies have suggested that chronic occupational exposure to OP pesticides might also increase diabetes risk (Leso et al., 2017; Malekirad et al., 2013; Raafat et al., 2012).

Neurologic impairments are the complications of diabetes as mentioned earlier. Pesticide exposure has been well-known as a risk factor for neurologic diseases such as cognitive dysfunction or Parkinson's disease (Cha et al., 2014), and it has also been reported to have the association with diabetes which was found in this study as well. Therefore, pesticide exposure may have an indirect effect on neurological diseases which are mediated by diabetes as complications, in addition to its direct neurotoxicity. Although we have investigated only the association between pesticide exposure and diabetes in this study, further research to reveal the diabetes-mediated neurotoxicity of pesticide will be necessary.

Table 5
Odds ratios of diabetes associated with pesticide exposure after stratification by BMI.

Variables	BMI			
	< 25 (n = 1501)		≥25 (n = 1050)	
	Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
Farmer	**1.60 (1.07-2.39)**	0.87 (0.54-1.39)	**2.55 (1.67-3.90)**	**1.93 (1.19-3.13)**
Pesticide use	**1.61 (1.07-2.43)**	0.90 (0.56-1.46)	**3.03 (1.98-4.64)**	**2.50 (1.54-4.06)**
Years of pesticide use				
< 20	1.16 (0.58-2.32)	0.91 (0.43-1.92)	**2.00 (1.16-3.45)**	**1.89 (1.03-3.48)**
≥20	**1.71 (1.11-2.61)**	0.99 (0.60-1.64)	**2.40 (1.60-3.61)**	**2.12 (1.31-3.42)**
Frequency of pesticide use (per year)				
< 10	1.06 (0.53-2.12)	0.63 (0.29-1.33)	**1.94 (1.10-3.44)**	1.61 (0.85-3.05)
≥10	**1.67 (1.09-2.57)**	1.01 (0.61-1.66)	**2.34 (1.57-3.50)**	**2.13 (1.33-3.49)**
Intensity level of pesticide exposure				
Lower group	1.34 (0.81-2.23)	0.85 (0.48-1.49)	**2.81 (1.80-4.37)**	**2.48 (1.49-4.13)**
Higher group	**1.69 (1.05-2.72)**	1.05 (0.61-1.81)	**2.14 (1.36-3.38)**	**2.07 (1.23-3.49)**
CEI of pesticide use				
Lower group	1.20 (0.68-2.13)	0.80 (0.43-1.49)	**2.43 (1.52-3.87)**	**2.11 (1.24-3.57)**
Higher group	**2.18 (1.35-3.54)**	1.07 (0.60-1.91)	**2.31 (1.43-3.72)**	**2.05 (1.16-3.62)**

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), OR, Odds Ratio, CI, Confidence Interval.
Bold shows the statistical significance of the odds ratios.
* Adjusted for age, sex, monthly income, and educational level.

The biological mechanism of the pathogenesis underlying the relationship of T2DM with pesticide exposure remains generally unknown. However, several epidemiological and experimental studies imply a strong linkage between T2DM and background exposure to OC pesticides (Lee et al., 2014). OC pesticides have various molecular and cellular targets, thus they are not considered to have a single mode of action (Evangelou et al., 2016). The primary mechanisms underlying the pathogenesis of T2DM include inflammatory reaction in adipose tissues, ectopic fat accumulation in the liver, and muscle, pancreas, and mitochondrial dysfunction. All of these mechanisms are linked with the OC pesticides (Lee et al., 2014). Moreover, both human and animal studies have indicated that OC pesticides inhibit insulin secretion and sensitivity, acting as endocrine-disrupting agents (Lind and Lind, 2018). Although most countries have banned the use and production of OC pesticides (Cha et al., 2014), those who have ever used these pesticides are accompanied by the potential risk of diabetes due to their residual effects.

Despite the relatively limited number of studies on OP pesticides, evidence from animal studies have indicated that exposure to OP pesticides is related to hyperglycemia (Seifert, 2001). Unlike POPs, OP pesticides are degraded more easily, and they have a shorter half-life. Thus, animal experimental studies exploring a short-term outcome after exposure to such chemicals have been conducted more often (Montgomery et al., 2008). In the pathogenesis of T2DM, the pancreas is unable to achieve sufficient insulin production, leading to hyperglycemia and T2DM. Pancreatic B cells have acetylcholine receptors involved in insulin production dependent on the blood glucose level (Duttaroy et al., 2004). In animal studies the OP pesticide acted as an inhibitor of acetylcholinesterase, which caused an accumulation of acetylcholine and a decrease in insulin production (Rahimi and Abdolahi, 2007; van Koppen and Kaiser, 2003). In this study, the exposure to pesticides was assessed using detailed questionnaires. Several previous studies have used similar methods of exposure assessment (Leso et al., 2017; Malekirad et al., 2013; Montgomery et al., 2008; Raafat et al., 2012; Starling et al., 2014). Among studies using data from the AHS, the investigation by Montgomery et al. found that both ever use and cumulative days of use of the seven pesticides were associated with increased risk of incident diabetes in licensed pesticide applicators (Montgomery et al., 2008). Furthermore, Starling et al. identified a positive relationship between ever use of the five pesticides and incident diabetes among female spouses of farmers (Starling et al., 2014). A more recent study conducted in Thailand used the same method to find significant associations between four pesticides and prevalence of diabetes (Juntarawijit and Juntarawijit, 2018). However, these studies had calculated the lifetime cumulative days of use by multiplying only duration and frequency of pesticide use. On the other hand, our study calculated the intensity level considering working habits and calculated CEI multiplying the intensity level by lifetime cumulative days of pesticide use in order to assess cumulative pesticide exposure more carefully.

This study analyzed the association between diabetes prevalence and pesticide exposure with stratification by BMI. The stratified analysis showed a positive relationship after adjustment only in participants who were overweight or obese. This result was in line with those of previous studies which revealed that the association between POPs, including pesticides, and diabetes risk was stronger in participants who were overweight and/or obese than in participants with a normal weight (Airaksinen et al., 2011; Gasull et al., 2012; Lee et al., 2006; Montgomery et al., 2008), whereas one study did not find the effect modification by BMI in the causal relationship between diabetes and pesticide exposure (Turyk et al., 2009).

In a study using the National Health and Nutrition Examination Survey data by Lee et al. (2006), the association between blood concentrations of six individual POPs and prevalence of T2DM were much stronger in participants who were overweight and obese than in those with a normal weight. Meanwhile, a significant relationship between T2DM and the sum of the six POPs was also observed in participants with a normal weight. A study by Airaksinen et al. (2011) on the association between prevalence diabetes and POPs showed a similar result. However, the risk of T2DM in the normal weight participants was not increased even by a higher level of exposure to POPs in the above study. Gasull et al. (2012) also indicated that the association between prevalence of diabetes and blood levels of PCB was stronger in participants who were overweight and obese than in those with a normal weight. Taken together, these cross-sectional studies have suggested a synergistic effect of overweight and exposure to POPs on the risk of T2DM.

A study using the AHS data (Montgomery et al., 2008) found no significant association between incident diabetes and the use of pesticides in the participants with normal weight, while stronger associations were present in participants with overweight and obesity. Adult subjects from the islands of Spain were reported to have a higher serum level of POPs in those with BMI ≥ 25 kg/m^2 than in those with normal weight (Henriquez-Hernandez et al., 2017). Meanwhile, in a cohort study in the US, BMI did not modify the effect of dichlorodiphenyldichloroethylene on the development of diabetes (Turyk et al., 2009).

Lipophilic POPs such as OC pesticides, dioxins, and PCBs, accumulate largely in adipose tissues, and the amount of fat mass affects serum levels of the pollutants (Lind and Lind, 2018). Given positive relationships between diabetes and POPs observed even in populations with normal weight (Arrebola et al., 2013; Gasull et al., 2012; Lee et al., 2006), POPs stored in adipose tissues may promote the development of diabetes independent of BMI (Lee et al., 2006; Porta, 2006).

Some researchers have proposed that the epidemic of obesity worldwide may be partly attributable to the flooding of endocrine-disrupting chemicals (EDCs), and that exposure to these "obesogenic" chemicals including PCBs and other pesticides may accelerate weight gain in exposed populations (Lind and Lind, 2018). However, among the EDCs known for inducing obesity, only dichlorodiphenyltrichloroethylene (DDT) pesticide has the best evidence for a possible obesogenic effect (Lind and Lind, 2018).

In our study, the associations between diabetes and pesticide exposure did not exhibit a linear trend, especially in the higher BMI group, with slightly higher ORs in the lower exposure group than in the higher exposure group. This inverse relationship accounted for the effect of a very high level of BMI in a previous study (Arrebola et al., 2013). In our study, this may be considered as the misclassification during exposure assessment by using the cumulative exposure indices. More evidence is still needed to shed light on this relationship.

The role of BMI still remains unclear in the causal link between pesticide exposure and the development of diabetes. As also suggested by Airaksinen et al. (2011), however, a strong association observed in our study implies that overweight and exposure to pesticides may have a synergistic effect on the development of diabetes.

Our study calculated the intensity level and CEI to assess lifetime cumulative pesticide exposure in more detail. We included more than 2500 participants in the analyses, which is one of the strengths of this study, since most studies investigating pesticide exposure by measurement of serum biomarkers were small-sized studies (Evangelou et al., 2016). Although a number of investigations examining associations between diabetes and pesticide exposure defined the outcome variable based on a self-reported history of physician-diagnosed diabetes (Gasull et al., 2012; Henriquez-Hernandez et al., 2017; Jaacks and Staimez, 2015; Montgomery et al., 2008; Starling et al., 2014), we defined the diabetes status using FPG, 2-h plasma glucose level, HbA1c, and current use of antidiabetic medication, following the recommendations of the National Toxicology Program Workshop (Thayer et al., 2012).

Any causal relationship must be cautiously assessed owing to the cross-sectional design of the study. However, in the rural area in Korea where the study took place, migration of the population was expected to be relatively rare (Lee et al., 2013) and thus the distribution of the characteristics related to pesticide exposure was also considered to be relatively consistent. Taken together, our results from the baseline survey may contain information on potential long-term effects of pesticide exposure. Another limitation is some misclassification when we evaluated the pesticide exposure via questionnaires rather than biomarkers of pesticides. However, the exposure assessment using metabolites of each pesticide has been used very restrictively, because the metabolites are not specific to each pesticide and there have been technological constraints (Maroni et al., 2000). Therefore, the exposure assessment using questionnaires, which was also used in our study, has been widely used when measuring pesticide exposure (Lee et al., 2010). We collected data via a standardized modified questionnaire developed by AHS to minimize recall bias, and the questionnaire has been reported to have substantial reliability for epidemiological studies (Lee et al., 2010). Finally, we could not use data regarding the types of pesticides used and discuss their half-lives or biological mechanisms of action. Although the participants were asked to answer the items which had detailed information about the types of pesticides, including the names of chemicals or products, partial product names, manufacturer names, targets, or formulation of products via a standardized questionnaire, they were unable to answer accurately or specifically possibly due to the great number of types of pesticides in South Korea (Cha et al., 2014) and their old ages. That is why most of the participants were unable to recall the types of pesticides used and answered inaccurately or failed to answer the items.

5. Conclusions

Despite these limitations, the current study found the association between pesticide exposure and prevalence of diabetes in a rural population in Korea. Long-term exposure to pesticides may contribute to the increased prevalence of diabetes, and a higher BMI may have a synergistic effect with pesticide exposure on the risk of developing diabetes. Further prospective research must be conducted to confirm this causal pathway, and to shed light on the role of BMI in that pathway.

Conflict of interest

The authors declare no conflict of interest.

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