



# Dietary zinc intake and body mass index as modifiers of the association between household pesticide exposure and infertility among US women: a population-level study

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## Abstract

Clinical studies on the relationship between pesticide exposure at home and infertility in the general population are scarce. Whether the antioxidant nutrients or other health-related factors affect the pesticide–infertility relationship remains unknown. This nationwide study screened 29,400 participants of the National Health and Nutrition Examination Surveys conducted between 2013 and 2018. The participants were subdivided according to dietary zinc intake based on the recommended dietary allowances as the low-zinc and high-zinc groups (< 8 and ≥ 8 mg/day, respectively), and according to body mass index (BMI; cut-off 28 kg/m<sup>2</sup>) as the low-BMI and high-BMI groups. Participants who were exposed to pesticides at home had an increased risk of infertility (odds ratio [OR] = 1.56, 95% confidence intervals [CI]: 1.06–2.29). The incidence of infertility differed in low-zinc and high-zinc groups (OR, 95% CI: 2.38, 1.40–4.06 vs. 0.98, 0.53–1.79, respectively), indicating an interaction between pesticide exposure and zinc intake in households ( $P=0.047$ ), which suggests that a zinc-rich diet may reduce the risk of pesticide-induced infertility. Similarly, the relationship between pesticide exposure and infertility risk differed in the low-BMI and high-BMI groups (OR, 95% CI: 0.90, 0.42–1.93 vs. 2.23, 1.39–3.58, respectively;  $P=0.045$ ), suggesting that high BMI may intensify the infertility risk caused by pesticide exposure. These new findings reveal the antagonistic and synergistic effect of zinc and obesity, respectively, in pesticide-induced infertility risk and suggest that individuals who are obese and on a low-zinc diet may be more susceptible to infertility induced by household pesticide exposure.

**Keywords** Infertility · Household pesticide exposure · Dietary zinc intake · Obesity · General population

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## Introduction

Worldwide, an estimated 2.3 billion kg pesticides are used in agriculture annually, and pesticides enter our daily lives in a variety of ways (Juntarawijit and Juntarawijit 2018; Nougadère et al. 2020; de Gavelle et al. 2016; Sieke et al. 2018; Ferré et al. 2018; Benbrook and Davis 2020). Research has increased the extant concerns that the permissible pesticide levels in food may be too high for humans, especially vulnerable groups, such as pregnant women (Vandenberg et al. 2012; Hayes et al. 2002). Fucic et al. showed that many pesticides are endocrine disruptors, and that exposure to even very low doses of pesticides may produce observable biological effects, such as diabetes, neurodegenerative diseases, cancer, and birth defects (Fucic et al. 2021). Recently, Chiu et al. reported that eating fruits or vegetables with pesticide that were within the normal human exposure range was associated with adverse reproductive outcomes in humans (Chiu et al. 2018).

Given the ubiquity of pesticide exposure, eating fewer fruits and vegetables seems like a ‘better’ option. However, evidence of a relationship between diet and female fertility and of a lower fruit intake with infertility has increasingly accumulated (Skoracka et al. 2021). To improve their chances of conception, many women request treatment with dietary supplements with variable ingredients (Vitagliano et al. 2021). A systematic review by Salas-Huetos et al. indicated that daily diets rich in some antioxidant nutrients, such as vitamin C, vitamin E, selenium, and zinc, were inversely associated with low semen quality parameters (Salas-Huetos et al. 2017). Owing to these conflicting results, the relationship between pesticide exposure and infertility needs to be further investigated. The risks of using pesticides in home have also been overlooked. Clinical studies of the relationship between household pesticide exposure and infertility are limited, and Morris emphasised the need to replicate the association between pesticide exposure and infertility (Morris 2018). In addition, obesity is strongly associated with infertility and is a major contributor to various causes of infertility (Sharma et al. 2013; Talmor and Dunphy 2015). Dietary factors and physical fitness might affect the relationship between pesticide exposure and infertility in infertile individuals who are exposed to pesticides.

Therefore, we aimed to explore whether effect modifiers, such as dietary zinc intake and body mass index (BMI), could modulate the relationship between pesticide exposure and infertility and to analyse how the dietary zinc intake and BMI affect this association.

## Materials and methods

### Study population and data sources

The nationally representative population and data included in this study were sourced from the National Health and Nutrition Examination Survey (NHANES), conducted by the National Center for Health Statistics (NCHS) and Centers for Disease Control and Prevention (CDC), that used a complex, multi-stage, stratified sample survey to obtain data representative of the entire non-institutionalised US population. Continuous public data from the NHANES database (three cycles: 2013–2014, 2015–2016, and 2017–2018) were included in the analysis because only three cycles containing the infertility questionnaire were completed before the coronavirus disease pandemic. We collected demographic, examination, dietary, and questionnaire data. During the data processing, we excluded individuals for whom data on pesticide exposure, infertility, dietary intakes, BMI, and other covariates were missing. The final analysis dataset included 2680 American women.

### Ethical approval

The study was approved by the NCHS Ethics Review Board, and the original protocol is available online (<https://www.cdc.gov/nchs/nhanes/irba98.htm>). All participants aged 18 to 46 years were included and provided written informed consent.

### Infertility

Infertility was defined based on the response to the following item in the questionnaire: ‘Have you ever tried and failed to get pregnant for at least a year?’ The response ‘yes’ was defined as ‘ever infertile’, the response ‘no’ was defined as ‘fertile’, and participants with missing responses were excluded from the study (Gleason et al. 2019).

### Household pesticide exposure

Household pesticide exposure was defined based on the response to the following item in the questionnaire: ‘In the past 7 days, were there any chemical products used in your/his/her home to control fleas, roaches, ants, termites, or other insects?’ The response ‘yes’ was defined as ‘household pesticide exposure’, the response ‘no’ was defined as ‘no household pesticide exposure’, and participants with missing responses were excluded from the study (Chen et al. 2020a, b). Moreover, to further understand the effects of pesticide exposure, we explored the relationship between pesticide metabolites in urine and infertility risk. With other covariates complete, a total of 616 participants with chlorophenol metabolites in urine (NHANES 2013–2014, and 2015–2016), and 738 participants with organophosphate metabolites in urine (NHANES 2015–2016, and 2017–2018) were available for the analysis.

### Dietary antioxidant nutrient intake

The 24-h dietary antioxidant nutrient intake data were obtained by dietary recall interview, and all interview data were collected by trained professionals in mobile examination centres. The 24-h recall interview collection method is the most commonly used method to determine dietary intake in large surveys and has been used by the NHANES for many years based on consensus among expert panels (Ahluwalia et al. 2016). The recommended dietary allowances (RDA) for zinc, selenium, vitamin E, and vitamin C for women are 8 mg/day, 55 µg/day, 15 mg/day, and 75 mg/day, respectively. Based on the RDA values, the zinc, selenium, vitamin E, and vitamin C intake data were categorised into two groups (low and high groups).

## Potential covariates

Our study considered the following variables as covariates: age, race/ethnicity, family income, smoking status, educational level, marital status, work activity, cotinine, waist circumference, BMI, alcohol consumption, and dietary intakes, such as zinc, selenium, vitamin E, vitamin C, caffeine, folate, sodium, potassium, phosphorus, calcium, magnesium, copper, iron, lycopene, beta-cryptoxanthin, beta-carotene, vitamin A, vitamin D, vitamin K, lutein-zeaxanthin, niacin, use of multivitamins, energy, protein, and fibre. In this study, we categorised race/ethnicity as non-Hispanic white, non-Hispanic black, other Hispanic, Mexican–American, and other races. Family income was defined using the poverty income ratio. Education level (as defined by the NHANES) was classified as ‘did not graduate from high school’, ‘high school graduate’, and ‘college graduate or above’. Marital status was classified as ‘married or lives with partner’ and ‘lives alone’. BMI was obtained from examination data, and the participants were categorised into two groups based on the value of 28 kg/m<sup>2</sup>. Participants were asked if they had smoked more than 100 cigarettes previously, and those who answered that they had been smoking over several days or daily were classified as ‘current smokers’; those who were not smoking currently were classified as ‘former smokers’; and those who had not smoked at least 100 cigarettes previously were regarded as ‘never smokers’. Work activity was categorised as vigorous, moderate, and light work activities.

## Statistical analysis

The statistical software packages of R (<http://www.R-project.org>, The R Foundation) and Free Statistics software version 1.3 were used for all analyses (Yang et al. 2021). Categorical and continuous variables are represented by the number (*n*) and percentage (%), and mean and standard deviations, respectively. The statistical methods used in the analyses include the chi-square test, two-tailed Student’s *t* test, and logistic regression. Model 1 did not consider any variables in the univariate analysis. In model 2, age and race/ethnicity were considered in the multivariate analysis. In combination with previous evidence, and in order to obtain more robust results, the following covariates were further adjusted in model 3 based on model 2: family income, smoking status, educational level, marital status, work activity, cotinine, waist circumference, BMI, alcohol consumption, and dietary intakes, such as zinc, selenium, vitamin E, vitamin C, caffeine, folate, sodium, potassium, phosphorus, calcium, magnesium, copper, iron, lycopene, beta-cryptoxanthin, beta-carotene, vitamin A, vitamin D, vitamin K, lutein-zeaxanthin, niacin, use of multivitamins,

energy, protein, and fibre. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated. The subgroup analyses according to the dietary antioxidant nutrient intake and BMI were performed using the stratified multivariate logistic regression model. We tested for potential interaction among the subgroups by using a likelihood ratio test comparing the model with only common non-interaction term against adding a term to the model in which the two predictor variables [pesticide exposure at home × subgroup variable (dietary antioxidant nutrient intake or BMI)] are multiplied. A two-sided *P* < 0.05 was considered statistically significant.

## Results

### Baseline characteristics of the study population

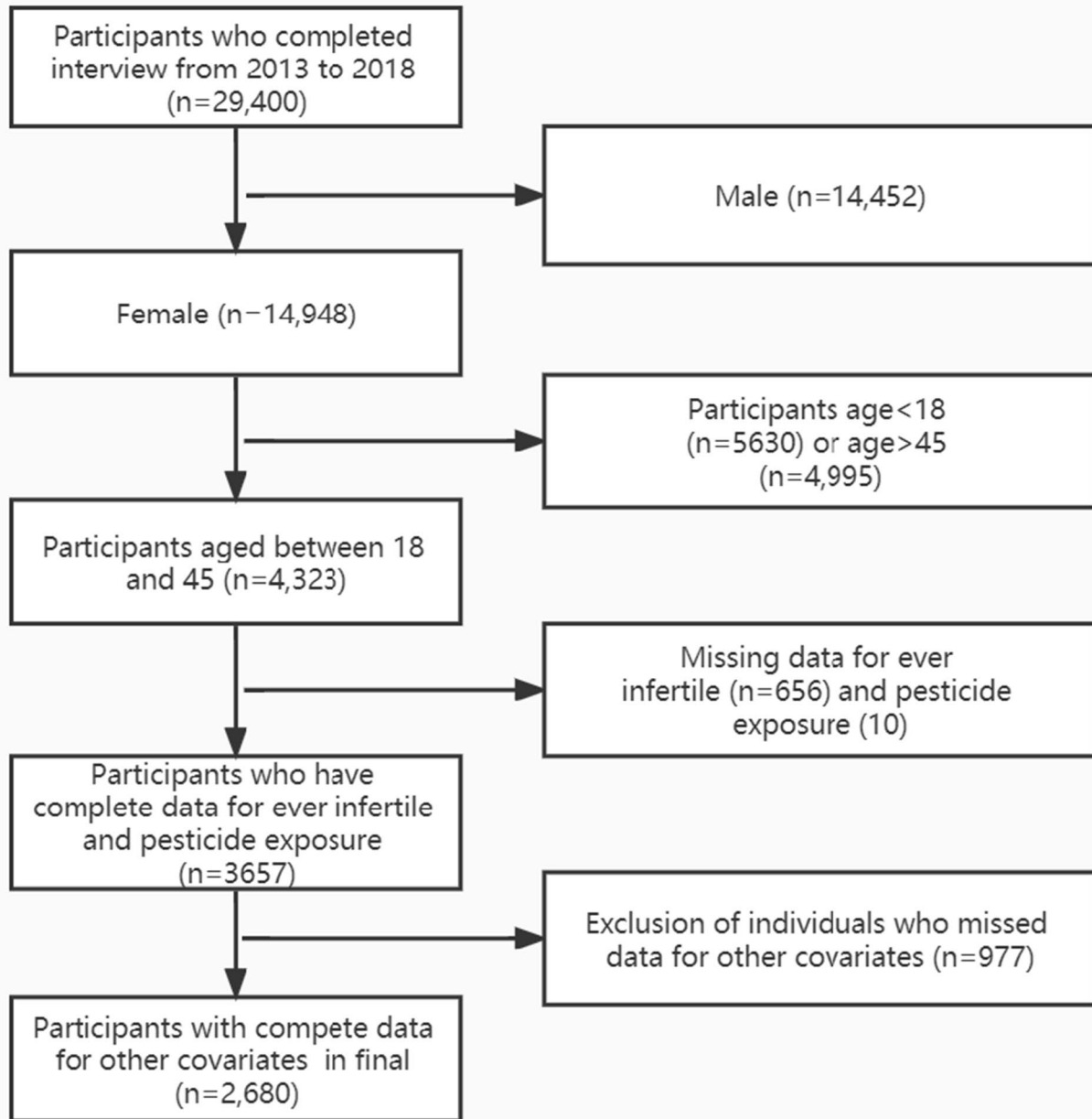
A flowchart of the exclusion and inclusion criteria is shown in Fig. 1. As shown in Table 1, among the 2860 participants who met the criteria for inclusion in the final analysis, 242 (9.0%) reported exposure to pesticides in their households. The mean age of participants in our study population was 32.7 ± 7.5 years, and 11.9% of the participants self-reported ever infertility. There were no significant differences between the pesticide exposure and non-exposure groups except for race/ethnicity, poverty income ratio, marital status, smoking status, cotinine, and infertility. The mean value of zinc, selenium, vitamin E, and vitamin C daily intake in the study population were 8.7 mg, 94.8 ug, 6.9 mg, and 45.1 mg, respectively, and the daily intake of vitamin E, and vitamin C was below the RDA value. Pesticide use in the study population was more likely to occur in lower-income households. Infertility rates in the pesticide non-exposure and exposure groups were 11.5% and 16.1%, respectively.

### Association between covariates and infertility risk

The univariate analyses revealed that age, family income, BMI, waist circumference, marital status, and smoking status were associated with infertility. Dietary antioxidant intake, including zinc, selenium, vitamin E, and vitamin C, was un-associated with infertility (Supplementary Table 1).

### Association between pesticide exposure at home and infertility risk

As shown in Table 2, in model 1, individuals exposed to pesticides in their households had a higher risk of infertility than those unexposed (OR 1.48, 95% CI: 1.03–2.13, *P* = 0.035). Similar results were obtained using



**Fig. 1** Flowchart of the study

model 2, which was adjusted for sociodemographic data (OR 1.5, 95% CI: 1.03–2.17,  $P=0.033$ ), and a higher risk was observed in model 3, which was adjusted for all the covariates that are listed in Table 1 (OR 1.56, 95% CI 1.06–2.29,  $P=0.024$ ). Among associations between urinary concentrations of pesticide metabolites and infertility risk, Dimethylphosphate was associated with infertility risk (OR = 1.05, 95% CI: 1.00–1.09,  $P=0.043$ ) (Supplementary Table 2).

### High dietary zinc intake weakens the association between pesticide exposure and infertility risk

A significant interaction was observed between zinc intake and household pesticide exposure for infertility (interaction likelihood ratio test:  $P=0.047$ ; Table 3). Stratified analysis based on zinc intake showed that, in the high dietary zinc group, infertility rates in the pesticide-exposed and -unexposed groups were 11.5% and 11.6%, respectively.

**Table 1** Baseline characteristics of the study sample

Variables	Total (n = 2680)	Pesticide unexposed (n = 2438)	Pesticide exposed (n = 242)	P value
<b>Demographic</b>				
Age, mean (SD), (years)	32.7 ± 7.5	32.7 ± 7.5	32.8 ± 8.1	0.885
<b>Race, n (%)</b>				
Mexican American	442 (16.5)	396 (16.2)	46 (19)	0.009
Non-Hispanic White	938 (35.0)	866 (35.5)	72 (29.8)	
Non-Hispanic Black	568 (21.2)	498 (20.4)	70 (28.9)	
Other Hispanic	266 (9.9)	244 (10)	22 (9.1)	
Other race	466 (17.4)	434 (17.8)	32 (13.2)	
Poverty income ratio, median (IQR)	1.9 (1.0, 3.7)	2.0 (1.0, 3.8)	1.6 (0.8, 2.8)	
<b>Education_level, n (%)</b>				
College education or above	1768 (66.0)	1621 (66.5)	147 (60.7)	0.197
Graduated from high school	514 (19.2)	461 (18.9)	53 (21.9)	
Did not graduate from high school	398 (14.9)	356 (14.6)	42 (17.4)	
<b>Marital_status, n (%)</b>				
Married or live with partner	1573 (58.7)	1448 (59.4)	125 (51.7)	0.024
Live alone	1107 (41.3)	990 (40.6)	117 (48.3)	
BMI, (kg/m <sup>2</sup> ) median (IQR)	28.2 (23.3, 34.2)	28.2 (23.4, 34.4)	28.1 (23.2, 33.8)	
Waist_circumference, (cm) Median (IQR)	93.6 (82.1, 107.2)	93.7 (82.1, 107.6)	92.7 (81.8, 104.8)	0.432
<b>Smoke, n (%)</b>				
Never	1878 (70.1)	1719 (70.5)	159 (65.7)	0.019
Former	302 (11.3)	280 (11.5)	22 (9.1)	
Current	500 (18.7)	439 (18)	61 (25.2)	
<b>Work activity, n (%)</b>				
Light	1482 (55.3)	1356 (55.6)	126 (52.1)	0.291
Moderate	709 (26.5)	646 (26.5)	63 (26)	
Vigorous	489 (18.2)	436 (17.9)	53 (21.9)	
Cotinine, (ng/ml) median (IQR)	0.0 (0.0, 2.3)	0.0 (0.0, 1.6)	0.1 (0.0, 36.3)	<0.001
<b>Dietary</b>				
Alcohol, (gm) median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.807
Caffeine, (mg) median (IQR)	72.0 (5.0, 150.0)	72.0 (5.0, 150.0)	61.5 (8.0, 159.8)	0.68
Energy, (kcal) median (IQR)	1850.0 (1381.0, 2366.0)	1843.0 (1380.0, 2359.0)	1998.0 (1412.0, 2492.0)	0.137
Protein, (gm) median (IQR)	67.5 (49.1, 91.6)	67.6 (49.4, 91.5)	65.7 (45.8, 91.7)	0.575
Fibre, (gm) median (IQR)	13.4 (8.7, 19.7)	13.5 (8.8, 19.9)	12.7 (8.0, 18.5)	0.106
Folat, (mcg) median (IQR)	306.0 (205.0, 445.0)	304.0 (207.0, 445.0)	311.5 (186.2, 440.8)	0.672
Sodium, (mg) median (IQR)	3008.0 (2145.0, 3971.0)	2994.0 (2146.0, 3963.0)	3158.0 (2144.0, 4103.0)	0.277
Potassium, (mg) median (IQR)	2136.0 (1525.0, 2841.0)	2131.0 (1527.0, 2848.0)	2174.0 (1471.0, 2824.0)	0.612
Phosphorus, (mg) median (IQR)	1158.0 (832.8, 1530.0)	1158.0 (834.8, 1528.0)	1157.0 (821.2, 1541.0)	0.656
Calcium, (mg) median (IQR)	783.0 (506.0, 1110.0)	783.0 (505.0, 1109.0)	781.0 (509.5, 1114.0)	0.846
Copper, (mg) median (IQR)	1.0 (0.7, 1.4)	1.0 (0.7, 1.4)	1.0 (0.7, 1.3)	0.96
Iron, (mg) median (IQR)	11.1 (7.8, 15.3)	11.1 (7.8, 15.3)	11.0 (7.4, 15.8)	0.908
Magnesium, (mg) median (IQR)	247.0 (178.0, 331.2)	247.5 (178.2, 332.0)	238.5 (173.2, 315.0)	0.186
Lycopene, (mcg) median (IQR)	1731.0 (13.8, 5177.0)	1720.0 (12.0, 5177.0)	1910.0 (111.0, 5004.0)	0.566
Beta-cryptoxanthin, (mcg) median (IQR)	25.0 (7.0, 80.0)	26.0 (7.0, 81.0)	23.0 (6.0, 63.5)	0.188
Beta-carotene, (mcg) median (IQR)	706.0 (262.0, 2240.0)	718.5 (264.0, 2254.0)	570.5 (248.5, 1923.0)	0.153
Vitamin A, (mcg) median (IQR)	434.0 (231.8, 720.0)	437.0 (234.2, 720.8)	395.0 (209.2, 702.8)	0.174
Vitamin D, (mcg) median (IQR)	2.6 (0.9, 5.2)	2.6 (0.9, 5.2)	2.7 (0.6, 4.9)	0.331
Vitamin K, (mcg) median (IQR)	67.9 (37.1, 135.2)	68.8 (37.4, 136.6)	62.9 (36.2, 129.0)	0.398
Lutein-zeaxanthin, (mcg) median (IQR)	689.5 (316.0, 1442.0)	699.5 (317.2, 1452.0)	555.0 (298.0, 1285.0)	0.176
Niacin, (mg) median (IQR)	20.4 (14.1, 27.8)	20.4 (14.2, 27.7)	20.4 (13.5, 28.6)	0.932
Use of multivitamin, n (%)				0.507

**Table 1** (continued)

Variables	Total (n=2680)	Pesticide unexposed (n=2438)	Pesticide exposed (n=242)	P value
No	2653 (99.0)	2412 (98.9)	241 (99.6)	
Yes	27 (1.0)	26 (1.1)	1 (0.4)	
<b>Antioxidants</b>				
Vitamin C, (mg) median (IQR)	45.1 (18.8, 104.7)	45.2 (18.8, 105.2)	43.0 (19.4, 97.1)	0.95
Vitamin E, (mg) median (IQR)	6.9 (4.5, 10.5)	6.9 (4.5, 10.4)	6.9 (4.3, 11.3)	0.726
Selenium, (mcg) median (IQR)	94.8 (67.5, 129.4)	94.8 (67.9, 129.1)	95.5 (63.4, 131.5)	0.998
Zinc, (mg) median (IQR)	8.7 (6.0, 12.0)	8.7 (6.0, 11.9)	8.6 (5.8, 12.2)	0.564
<b>Infertile, n (%)</b>				
Fertile	2361 (88.1)	2158 (88.5)	203 (83.9)	
Ever infertile	319 (11.9)	280 (11.5)	39 (16.1)	0.044

**Table 2** Association between pesticide exposure at home and infertility risk

	N (%)	OR	95% CI	P value
<b>Model 1<sup>a</sup></b>				
No pesticide exposure	2483 (11.5)	Reference		
Pesticide exposure	242 (16.1)	1.48	1.03–2.13	0.035
<b>Model 2<sup>b</sup></b>				
No pesticide exposure	2483 (11.5)	Reference		
Pesticide exposure	242 (16.1)	1.50	1.03–2.17	0.033
<b>Model 3<sup>c</sup></b>				
No pesticide exposure	2483 (11.5)	Reference		
Pesticide exposure	242 (16.1)	1.56	1.06–2.29	0.024

OR, odds ratio; CI, confidence intervals

<sup>a</sup>Model 1: unadjusted

<sup>b</sup>Model 2: adjusted for sociodemographic covariates

<sup>c</sup>Model 3: adjusted for all covariates listed in Table 1

The association between pesticide exposure and infertility risk was not statistically significant in the multivariate logistic analysis (OR 0.98, 95% CI: 0.53–1.79,  $P=0.937$ ). However, in the low dietary zinc group, infertility rates in the exposed and unexposed groups were 21.4% and 11.3%,

respectively. Among participants with low zinc intake, exposure to pesticides was associated with a 138% higher risk of infertility (OR 2.38, 95% CI: 1.40–4.06,  $P=0.001$ ). Significant interactions were not observed between the intake of other antioxidant nutrients (selenium, vitamin E, and vitamin C) and pesticide exposure with regard to infertility (interaction likelihood ratio tests:  $P=0.334$ ,  $P=0.356$ , and  $P=0.560$ , respectively; Supplementary Tables 3–5).

### High BMI strengthens the association between pesticide exposure and infertility risk

Table 4 shows an interaction between BMI and household pesticide exposure for infertility (interaction likelihood ratio test:  $P=0.045$ ). In the low BMI ( $<28$  kg/m<sup>2</sup>) group, infertility rates in the pesticide-exposed and -unexposed groups were 7.4% and 8.6%, respectively. The association between pesticide exposure and infertility risk was not statistically significant in the multivariate logistic analysis (OR 0.90, 95% CI: 0.42–1.93,  $P=0.790$ ). However, in the high-BMI ( $\geq 28$  kg/m<sup>2</sup>) group, infertility rates in the exposed and unexposed groups were 24.8% and 14.2%, respectively. Among participants with a higher BMI, exposure to pesticides was associated with a 123% increased risk of infertility (OR 2.23, 95% CI: 1.39–3.58,  $P=0.001$ ).

**Table 3** Association between pesticide exposure at home and infertility risk by dietary zinc intake

Subgroup	N (%)	OR	95% CI	P value	P value for interaction
<b>Zinc intake (<math>&lt;8</math> mg/day)</b>					
No pesticide exposure	1069 (11.3)	Reference			
Pesticide exposure	112 (21.4)	2.38	1.40–4.06	0.001	
<b>Zinc intake (<math>\geq 8</math> mg/day)</b>					
No pesticide exposure	1369 (11.6)	Reference			
Pesticide exposure	130 (11.5)	0.98	0.53–1.79	0.937	0.047

OR, odds ratio; CI, confidence intervals

Adjusted for all covariates listed in Table 1

**Table 4** Associations between pesticide exposure at home and infertility risk by BMI

Subgroup	N (%)	OR	95% CI	P value	P value for interaction
BMI (< 28 kg/m <sup>2</sup> )					0.045
No pesticide exposure	1193 (8.6)	Reference			
Pesticide exposure	121 (7.4)	0.90	0.42–1.93	0.79	
BMI (≥ 28 kg/m <sup>2</sup> )					
No pesticide exposure	1245 (14.2)	Reference			
Pesticide exposure	121 (24.8)	2.23	1.39–3.58	0.001	

OR, odds ratio; CI, confidence intervals

Adjusted for all covariates listed in Table 1

## Discussion

In a nationally representative sample of adult women in the US general population, we explored the association between pesticide exposure at home and infertility risk, and then examined the modifiers of this relationship. In the low dietary zinc intake group, pesticide exposure was associated with a 1.38-fold increased risk of infertility compared with the pesticide-unexposed group. No association was found between pesticide use at home and infertility in the high dietary zinc intake group, which indicates that zinc intake may play a protective role against pesticide-exposure-induced infertility. Conversely, in the high-BMI group, pesticide exposure induced a 1.23-fold increase in the risk of infertility, whilst no association between pesticide exposure and infertility was found in the low-BMI group, thereby suggesting a synergistic effect of BMI on the infertility risk that is triggered by household pesticide exposure. Therefore, our results indicate that dietary zinc intake and BMI act as modifiers of the association between household pesticide exposure and infertility.

Numerous studies have shown that occupational exposure or residence near agricultural environments where pesticides are frequently used confers a higher risk of adverse reproductive health outcomes (Shirangi et al. 2008; Naidoo et al. 2011; Razi et al. 2016; Settini et al. 2008; Rahimi et al. 2020). In the few studies that found no such association (Bell et al. 2001; Willis et al. 1993), dietary zinc intake might not have been considered. Approximately 20% of the world's population and 10% of the US population have zinc deficiency (Chen et al. 2020a, b). Moreover, studies exploring the influence of pesticides on infertility in the general population are limited. Our results further explored that pesticide exposure at home is associated with infertility risk in the general population. Our results are in line with the results of a recent study by Chiu et al., which showed that dietary pesticide exposure, even through fruits and vegetables, is associated with infertility (Chiu et al. 2018), which raises widespread concerns about dietary pesticide exposure. Pesticides demonstrate their toxic influence on humans and animals via oxidative stress-mediated pathways (Weis et al.

2021; Sharma et al. 2020; Pašková et al. 2011). However, fruits and vegetables, as part of our healthy diet, contain many antioxidant nutrients, such as zinc, selenium, vitamin C, and vitamin E (Millen et al. 2016). However, it remains unknown whether these antioxidant nutrients or other health-related factors affect the pesticide–infertility relationship.

Our results showed a significant association between pesticide exposure and infertility in the low-zinc diet group but not in the high-zinc diet group, suggesting a beneficial effect of daily zinc intake as recommended based on the RDA. We found that other antioxidant nutrients did not have the same effect as zinc. Different nutrient elements may not have the same effect intensity, and further experimental studies are needed to elucidate their effects. Dietary supplements containing zinc are important for fertility (Garolla et al. 2020; Mumford et al. 2020; Vickram et al. 2021). Kerns et al. proposed that zinc is an essential ion for the ability of mammalian sperm to fertilise an ovum (Kerns et al. 2018). Similarly, Ebisch et al. concluded that zinc is important in the pathogenesis and prevention of infertility, considering its antioxidant properties (Ebisch et al. 2007). However, a new rigorous randomised controlled trial conducted by Schisterman et al. revealed that zinc supplementation did not significantly improve live birth rates among couples seeking infertility treatment (Schisterman et al. 2020), which disregarded the effect of some important potential factors, such as pesticide exposure. Despite these inconsistent results, given that zinc supplementation can alleviate infertility caused by pesticide exposure in daily life, we believe that zinc supplementation is necessary for the infertile population. In addition, zinc, as a cofactor, is essential for the functioning of more than 300 enzymes (Vallee and Falchuk 1993). Zinc is the only metallic element that is required in all six classes of enzymes, i.e., lyases, ligases, transferases, isomerases, oxidoreductases, and hydrolases (Kerns et al. 2018). Upon entering the body, pesticides are metabolised by a number of biological metabolic enzymes, including paraoxonase and glutathione S-transferase (Volk et al. 2011), and zinc supplementation may be beneficial in accelerating the metabolic elimination of pesticides. Furthermore, zinc interacts with cell membranes to counter the effects of various harmful

substances that cause oxidative damage (Malhotra and Dhawan 2014). Goel et al. found that zinc supplementation played a potentially protective role in alleviating toxicity induced by chlorpyrifos in rats (Goel et al. 2005).

A significant association between pesticide exposure and infertility was found in the high BMI-group but not in the low-BMI group, suggesting the potential impact of obesity on this association. Obesity is associated with various adverse reproductive outcomes, including anovulation, infertility, and an increased risk of miscarriage (Talmor and Dunphy 2015). The mechanism of obesity-related decline in female fertility occurs through influences on endometrial receptivity, oocyte quality, and the hypothalamic-pituitary-ovarian axis (Ramlau-Hansen et al. 2007; Van Der Steeg et al. 2008). A clinical study conducted by Zhang et al. found a positive association between pesticide exposure and obesity (Zhang et al. 2019). However, the exact mechanism whereby obesity interacts with pesticides to cause infertility is still unclear. Notably, Gutgesell et al. concluded that, given their lipophilic nature, many pesticides can accumulate in fatty tissue (Gutgesell et al. 2020). Therefore, it is reasonable to believe that the synergistic effect of obesity and pesticide exposure on infertility risk occurs because the excess fat in the body delays the excretion of pesticides, thereby exacerbating their toxic effects. Further experimental studies are necessary to verify our hypothesis.

Our study had some limitations. First, the inherent nature of cross-sectional studies precludes the inference of a temporal cause-effect relationship. Second, detailed information, such as the type, intensity, frequency, and duration of household pesticide exposure, which may have various effects on infertility, was unavailable in the NHANES database. Third, self-reported data may have introduced recall bias in mobile examination centre interviews. However, the incidence of infertility and pesticide exposure was generally consistent with that reported in the existing literature (Chen et al. 2020a, b; Glazer et al. 2019). Fourth, though the multi-stage stratified probability design method was used, the participants in the NHANES database are American citizens and are not fully representative of people living in other regions of the world. Given these limitations, well-designed multi-centre, controlled trials may be needed to confirm our findings.

## Conclusion

In summary, we found an association between household pesticide exposure and infertility risk in the general adult female population. For the first time, we have reported the antagonistic effects of zinc and the synergistic

effects of obesity in the mediation of pesticide-induced infertility. Though these new findings raise the concern that obese individuals who are on a low-zinc diet may be more susceptible to infertility triggered by the chronic toxicity of inevitable pesticide exposure in daily life, more evidence from randomised controlled studies is needed. Furthermore, experimental studies are essential to elucidate the exact interplay among zinc, obesity, pesticides, and infertility.

**Abbreviations** NHANES: National Health and Nutrition Examination Survey; NCHS: National Center for Health Statistics; CDC: Centers for Disease Control and Prevention

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**Author contribution** JGH drafted the manuscript, LQH collected the clinical data, and JY reviewed data analyses. All authors read and approved the final manuscript.

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**Data availability** The data underlying this article will be shared on reasonable request to the corresponding author.

## Declarations

**Ethics approval and consent to participate** The study was approved by the NCHS Ethics Review Board, and the original protocol is available online (<https://www.cdc.gov/nchs/nhanes/irba98.htm>). All participants aged 18 to 46 years were included and provided written informed consent.

**Consent for publication** Not applicable.

**Conflict of interest** The authors declare no competing interests.

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