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Association Between Exposure to Pyrethroid Insecticides and Risk of All-Cause and Cause-Specific Mortality in the General US Adult Population

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IMPORTANCE Widespread exposure to pyrethroid insecticides has been reported among the general population in the United States and worldwide. However, little is known about the association of pyrethroid exposure with long-term health outcomes in adults.

OBJECTIVE To examine the association of pyrethroid exposure with all-cause and cause-specific mortality among adults in the United States.

DESIGN, SETTING, AND PARTICIPANTS The nationally representative cohort included 2116 adults aged 20 years and older who participated in the US National Health and Nutrition Examination Survey conducted from 1999 to 2002 and provided urine samples for pyrethroid metabolite measurements. Participants were linked to mortality data from the survey date through December 31, 2015. Data were analyzed from May to August 2019.

EXPOSURES Urinary levels of 3-phenoxybenzoic acid, a general pyrethroid metabolite and commonly used biomarker for pyrethroid exposure, were determined by using high-performance liquid chromatography coupled with electrospray chemical ionization and tandem mass spectrometry.

MAIN OUTCOMES AND MEASURES Mortality from all causes, cardiovascular disease, and cancer.

RESULTS This cohort study of 2116 adults comprised 1145 women (weighted proportion, 51.6%) and 971 men (weighted, 48.4%), with a weighted mean (SE) age of 42.6 (0.5) years; 958 participants (weighted, 68.4%) were of non-Hispanic white ancestry, 646 (weighted, 14.7%) of Hispanic ancestry, 419 (weighted, 11.3%) of non-Hispanic black ancestry, and 93 (weighted, 5.6%) of other ancestry. During a median of 14.4 years (range, 0.1-16.8 years) of observation, 246 deaths occurred, including 41 associated with cardiovascular disease and 52 associated with cancer. Participants with higher urinary 3-phenoxybenzoic acid levels were at a higher risk of death during the follow-up period, with death occurring in 8.5% (unweighted, 75 of 709), 10.2% (unweighted, 81 of 701), and 11.9% (unweighted, 90 of 706) of participants across increasing tertiles of urinary 3-phenoxybenzoic acid levels. After adjustment for age, sex, race/ethnicity, socioeconomic status, dietary and lifestyle factors, body mass index, and urinary creatinine levels, the hazard ratios for all-cause mortality, cardiovascular disease mortality, and cancer mortality among participants with the highest tertile compared with those with the lowest tertile of urinary 3-phenoxybenzoic acid levels were 1.56 (95% CI, 1.08-2.26), 3.00 (95% CI, 1.02-8.80), and 0.91 (95% CI, 0.31-2.72), respectively.

CONCLUSIONS AND RELEVANCE In this nationally representative sample of US adults, environmental exposure to pyrethroid insecticides was associated with an increased risk of all-cause and cardiovascular disease mortality. Further studies are needed to replicate the findings and determine the underlying mechanisms.

Invited Commentary

Supplemental content

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Pyrethroids are a major class of insecticides that are synthetic analogues of pyrethrin, a naturally occurring insecticide found in the flowers of *Chrysanthemum cineraraefolum*.[1] Synthetic pyrethroids have insecticidal properties similar to pyrethrin, but they are more stable in the sunlight than pyrethrin.[2] In addition to agricultural use, pyrethroids are also widely used for residential pest control. Pyrethroids are found in a variety of consumer products, including household and garden insecticides, pet sprays and shampoos, lice treatments, and mosquito repellents. Pyrethroids are also used to prevent the consequences associated with the exposure of pregnant women to Zika virus.[3] Pyrethroids account for approximately 30% of the insecticide market worldwide. Although more than 1000 pyrethroids have been made, only about a dozen pyrethroid pesticides, such as permethrin, cypermethrin, deltamethrin, and cyfluthrin, are on the market in the United States.[4] Pyrethroid use has increased drastically in recent decades, owing to the phase-out of organophosphates from residential use.[4]

Widespread exposure to pyrethroid insecticides has been reported among the general population in the United States and worldwide.[5-7] Ingestion, inhalation, and, to a smaller degree, dermal absorption are the primary routes of exposure of the general population to pyrethroids.[1] After exposure, pyrethroids are quickly metabolized by cytochrome P450 enzymes and form different metabolites, including 3-phenoxybenzoic acid (3-PBA); 3-(2,2-dichlorovinyl)-2,2-dimethylcylopropane carboxylic acid (DCCA); 4-fluoro-3-phenoxybenzoic acid (4F-PBA); and (2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (DBCA), depending on the structure of the parent compound.[8] These metabolites are readily excreted in the urine. Therefore, urinary concentrations of these metabolites are considered ideal biomarkers of pyrethroid exposure. National biomonitoring data from the US National Health and Nutrition Examination Survey (NHANES) conducted from 1999 to 2002 reported that 3-PBA was the most frequently detected metabolite of pyrethroids in the US general population; an estimated two-thirds of individuals had measurable levels of 3-PBA in their urine samples.[5]

Pyrethroid insecticides gained popularity because of their effectiveness against insects and their low association with acute toxic effects in mammals. However, the consequences of chronic exposure to pyrethroids on long-term health outcomes in humans remain to be determined. Pyrethroid exposure can cause oxidative stress, inflammation, and DNA damage.[9,10] Epidemiological studies, although still limited, have suggested that environmental pyrethroid exposure may impair neurodevelopment,[11] interfere with reproductive health,[12-15] and increase the risk of major chronic diseases, such as diabetes,[16] cardiovascular disease (CVD),[17] and Parkinson disease.[18] However, those epidemiologic studies are mostly cross-sectional,[19] limiting their capacity to establish temporality for pyrethroid exposure and chronic disease outcomes. Moreover, despite the growing evidence suggesting that exposure to pyrethroids is linked to adverse health effects, the association between pyrethroid exposure and risk of mortality remains unknown.

Key Points

Question Is pyrethroid exposure associated with long-term mortality in the general US adult population?

Findings In this cohort study of a nationally representative sample of 2116 adults in the United States, higher exposure to pyrethroid insecticides, indicated by higher levels of general pyrethroid metabolite 3-phenoxybenzoic acid in urine samples, was associated with a higher risk of death from all causes or cardiovascular disease over 14 years of observation.

Meaning Environmental exposure to pyrethroid insecticides appears to be associated with an increased risk of long-term all-cause mortality and cardiovascular mortality in the US general adult population.

In the present study, we used data from a nationally representative cohort to examine the associations of pyrethroid exposure, measured by the general urinary biomarker 3-PBA, with all-cause and cause-specific mortality in US adults.

Methods

Study Population

The NHANES is a nationally representative health survey in the United States designed and administered by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC). The NHANES uses a complex, multistage probability sampling design to represent the US national, civilian, noninstitutionalized population.[20] The uniqueness of the NHANES is that it not only collects questionnaire data through in-person interviews, but it also performs health examinations and collects biospecimens for laboratory tests. The NCHS ethics review board has approved the NHANES protocol. Written informed consent was obtained from each participant. The institutional review board of the University of Iowa determined this study to be exempt because the data were deidentified.

For this analysis, we included adults 20 years and older participating in the NHANES from 1999 to 2002, with the exception of adults 60 years and older from the NHANES conducted between 1999 and 2000, during which pyrethroid metabolites were not measured in that subpopulation. We linked all participants to mortality outcome data through the end of 2015, allowing approximately 14 years of observation for mortality outcomes. Individuals with CVD or cancer at baseline were excluded.

Pyrethroid Exposure Assessment

Urine samples were stored under frozen (-20 °C) conditions until shipped to the CDC's National Center for Environmental Health for testing. Urinary concentrations of pyrethroid metabolites, including 3-PBA; cis-3-(2,2-dichlorovinyl)-2,2-dimethylcylopropane carboxylic acid (cis-DCCA); trans-3-(2,2-dichlorovinyl)-2,2-dimethylcylopropane carboxylic acid (trans-DCCA); 4F-PBA; and cis-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (cis-DBCA), cis-DCCA, trans-DCCA, 4F-BPA, and cis-DBCA were determined

by high-performance liquid chromatography coupled with electrospray chemical ionization and tandem mass spectrometry using validated laboratory methods.[5] The metabolite 3-PBA represents exposure to permethrin, cypermethrin, deltamethrin, allethrin, resmethrin, fenvalerate, cyhalothrin, fenpropathrin, and tralomethrin; cis-DCCA and trans-DCCA represent exposure to the cis and trans isomers, respectively, of permethrin, cypermethrin, and cyfluthrin; 4F-PBA is a specific metabolite of cyfluthrin; and cis-DBCA is a specific metabolite of deltamethrin. Approximately 70% of the NHANES population had a detectable level of 3-PBA, whereas only a small proportion of individuals had measurable levels of other metabolites of pyrethroids (eTable 1 in the Supplement). These findings suggest that the US general population is predominantly exposed to permethrin and cypermethrin.[5]

Human biomonitoring studies often use urinary concentrations of 3-PBA in spot urine samples to assess exposure to pyrethroid pesticides.[21] The 3-PBA level is a widely accepted biomarker of pyrethroid exposure because pyrethroids are rapidly metabolized to 3-PBA in humans, and a large percentage of the pyrethroids are excreted as urinary 3-PBA within 3 days after exposure.[22-24] Therefore, similar to a previous study,[11] we used 3-PBA as the biomarker for pyrethroid exposure in this analysis. The limit of detection for 3-PBA was 0.10 ng/mL. Following the methods described by the NCHS,[20] we excluded participants with outlier levels of 3-PBA, which may indicate unusual acute exposure to pyrethroids.

Ascertainment of Mortality Outcomes

We used data from the NHANES public-use linked mortality file from the survey date through December 31, 2015, which was linked by the NCHS to the National Death Index with a probabilistic matching algorithm to determine mortality status.[25] The National Death Index is an NCHS centralized database of all deaths in the United States. Data about the underlying causes of death were used for case definition according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*).[26] The NCHS classified CVD mortality as death caused by heart disease (*ICD-10* codes I00-I09, I11, I13, and I20-I51) or cerebrovascular disease (*ICD-10* codes I60-I69) and cancer mortality as death caused by malignant neoplasms (*ICD-10* codes C00-C97). This approach has been previously validated by the CDC and used in many CDC reports.[27-29]

Assessment of Covariates

Information about participant race/ethnicity, family income, educational level, smoking status, alcohol intake, physical activity, and dietary intake was collected using questionnaires. According to the 1997 standards from the US Office of Management and Budget, race/ethnicity was categorized as Hispanic (including Mexican and non-Mexican Hispanic), non-Hispanic white, non-Hispanic black, and other race/ethnicity. Family income was classified as the ratio of family income to the federal poverty level (<1.3, 1.3-3.5, and >3.5). A higher income-to-poverty ratio indicated a higher family income status. Self-reported education status was grouped as lower than high school, high school, and college or higher. In accordance with the NCHS classifications, individuals who smoked less than 100 cigarettes in their lifetime were defined as never smokers; those who had smoked more than 100 cigarettes but did not smoke at the time of the survey were defined as former smokers; and those who had smoked 100 cigarettes in their lifetime and smoked cigarettes at the time of the survey were defined as current smokers. Alcohol intake was categorized as none (0 g per day), moderate (0.1 to 27.9 g per day for men and 0.1-13.9 g per day for women), and heavy (≥28 g per day for men and ≥14 g per day for women). For physical activity, the questionnaire included an array of questions related to daily activities. Physical activity for each participant was categorized based on the recommended weekly amount of moderate-intensity to vigorous-intensity activity as follows: (1) below, indicating less than 150 minutes per week; (2) meets, indicating 150 to 300 minutes per week; and (3) exceeds, indicating more than 300 minutes per week. Dietary information was collected by 24-hour dietary recall interviews, from which total energy intake was calculated using the US Department of Agriculture's automated multiple-pass method. We used the Healthy Eating Index–2010 (HEI-2010) to indicate the overall quality of diet (scores ranged from 0-100, with 0 indicating the worst-quality diet and 100 indicating the best-quality diet).[30] Body weight and height were measured by trained health technicians in accordance with the NHANES anthropometry procedures, and body mass index (BMI) was calculated (weight in kilograms divided by height in meters squared). Urinary creatinine concentrations were determined using an automated colorimetric method based on a modified Jaffe reaction.

Statistical Analysis

Following the NHANES analytic guidelines,[31] we applied sampling weights, strata, and primary sampling units in the analyses to account for the unequal probability of selection, oversampling of certain subpopulations, and nonresponse adjustment.

Means and proportions of baseline characteristics were compared by using linear regression analyses for continuous variables and logistic regression analyses for categorical variables. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% CIs for the associations between pyrethroid exposure and risk of mortality. Follow-up time for each person was calculated as the difference between the NHANES examination date and the last known date alive or censored from the linked mortality file. In the fully adjusted model, we adjusted for age, sex, race/ethnicity, educational level, family income level, smoking status, alcohol intake, physical activity, total energy intake, overall diet quality indicated by HEI-2010 score, and BMI. To account for urine dilution, urinary creatinine levels were adjusted in all of the analysis models in this study, as previously recommended.[32] Furthermore, we performed stratified analyses and interaction analyses to examine whether the association differed by sex, race/ethnicity, diet quality, physical activity, and obesity status. Data were analyzed from May to August 2019. All statistical analyses were conducted using survey modules of SAS software, version 9.4 (SAS Institute). A 2-sided *P* value less than .05 was considered statistically significant.

Table 1. Characteristics of the Study Population According to Tertiles of Urinary 3-Phenoxybenzoic Acid Levels

Characteristic[a]	Total Participants (n = 2116)		Tertile 1 (n = 709)		Tertile 2 (n = 701)		Tertile 3 (n = 706)		*P* Value
	No. (%)	SE	No. (%)	SE	No. (%)	SE	No. (%)	SE	
Age, mean, y	42.6	0.5	42.9	0.8	42.3	0.7	42.5	0.8	.50
Sex									
Male	971 (48.4)	1.4	307 (47.4)	2.8	328 (49.6)	2.0	336 (48.3)	2.0	.77
Female	1145 (51.6)	1.4	402 (52.6)	2.8	373 (50.4)	2.0	370 (51.7)	2.0	
Race/ethnicity									
Hispanic	646 (14.7)	1.8	238 (15.2)	2.2	225 (15.8)	2.2	183 (12.9)	2.2	<.001
Non-Hispanic white	958 (68.4)	2.0	358 (72.6)	2.6	328 (70.1)	3.1	272 (62.0)	2.7	
Non-Hispanic black	419 (11.3)	1.5	73 (5.7)	0.8	125 (9.7)	2.0	221 (19.3)	2.3	
Other	93 (5.6)	0.7	40 (6.5)	1.4	23 (4.5)	1.0	30 (5.8)	1.1	
Educational level									
Less than high school	646 (19.9)	0.9	187 (14.6)	2.1	223 (21.9)	1.3	236 (24.1)	1.9	.01
High school	487 (24.8)	1.5	162 (25.3)	2.7	154 (23.5)	2.0	171 (25.5)	2.0	
College or higher	983 (55.3)	1.7	360 (60.1)	2.9	324 (54.6)	2.1	299 (50.4)	2.3	
Family income-to-poverty ratio									
<1.3	511 (18.4)	1.1	156 (17.5)	2.0	174 (18.5)	1.5	181 (19.3)	1.5	.01
1.3-3.5	756 (33.8)	1.3	239 (28.7)	2.2	255 (36.4)	1.6	262 (36.9)	2.6	
>3.5	642 (40.1)	2.0	254 (47.0)	3.2	200 (37.1)	2.1	188 (35.2)	2.4	
Missing data	207 (7.7)	0.9	60 (6.7)	1.3	72 (8.0)	1.1	75 (8.7)	1.4	
Smoking									
Never smoked	1142 (50.9)	1.3	395 (52.7)	2.1	376 (50.2)	2.8	371 (49.5)	1.8	.12
Formerly smoked	499 (25.5)	1.3	141 (21.8)	2.0	160 (26.0)	2.9	198 (29.4)	1.4	
Currently smokes	475 (23.6)	1.1	173 (25.5)	1.4	165 (23.8)	2.3	137 (21.1)	1.9	
Alcohol intake									
None	1520 (69.0)	1.3	523 (68.3)	2.2	512 (71.5)	2.7	485 (67.3)	2.1	.65
Moderate	204 (11.3)	0.9	68 (11.2)	1.9	62 (10.0)	1.5	74 (12.6)	1.5	
Heavy	314 (16.4)	0.9	97 (17.1)	1.6	104 (16.1)	1.8	113 (15.9)	1.6	
Missing data	78 (3.3)	0.5	21 (3.4)	0.9	23 (2.4)	0.6	34 (4.1)	1.0	
Physical activity[b]									
Below guidelines	1014 (41.9)	1.7	322 (39.5)	3.0	350 (42.7)	2.7	342 (43.7)	2.6	.51
Meets guidelines	294 (15.3)	1.2	115 (17.4)	1.8	94 (14.7)	2.2	85 (13.3)	1.3	
Exceeds guidelines	808 (42.9)	1.8	272 (43.1)	3.0	257 (42.5)	3.1	279 (43.0)	2.0	
Total energy intake, mean, kcal/d	2275.8	37.2	2320.5	56.3	2249.6	56.1	2251.3	67.9	.39
HEI-2010 score, mean	45.2	0.5	46.5	0.8	43.9	0.7	45.0	0.8	.01
BMI									
<25	724 (36.7)	249	264 (37.2)	2.6	231 (36.5)	1.9	244 (36.4)	2.3	.06
25-29	704 (32.4)	1.3	262 (36.8)	2.2	225 (29.6)	2.2	217 (30.1)	2.9	
≥30	617 (27.8)	1.3	177 (23.4)	2.0	219 (29.7)	2.0	221 (31.0)	2.1	
Missing data	71 (3.1)	0.4	21 (2.6)	0.8	26 (4.2)	0.6	24 (2.5)	0.6	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HEI-2010, Healthy Eating Index-2010.

[a] All means and SEs for continuous variables and percentages and SEs for categorical variables were weighted, with the exception of the number of participants. Because all numbers were rounded, percentages may not total 100%.

[b] Below guidelines indicates less than 150 minutes of moderate-intensity to vigorous-intensity activity per week; meets guidelines, 150 to 300 minutes per week; and exceeds guidelines, more than 300 minutes per week.

Results

This cohort study of 2116 adults aged 20 years and older comprised 1145 women (weighted proportion, 51.6%) and 971 men (weighted, 48.4%), with a weighted mean (SE) age of 42.6 (0.5) years; 958 participants (weighted, 68.4%) were of non-Hispanic white ancestry, 646 (weighted, 14.7%) of Hispanic ancestry, and 419 (weighted, 11.3%) of non-Hispanic black ancestry. During 29 416 person-years of observation (median follow-up, 14.4 years [range, 0.1-16.8] years), 246 deaths occurred, including 41 associated with CVD and 52 associated with cancer. Higher urinary 3-PBA levels were observed among non-Hispanic black participants and those with lower educational levels, lower family incomes, and poorer dietary quality (**Table 1**). Urinary 3-PBA levels before

Table 2. Association of Urinary 3-Phenoxybenzoic Acid Levels With All-Cause and Cause-Specific Mortality

Variable	Urinary 3-Phenoxybenzoic Acid Levels, HR (95% CI)		
	Tertile 1	Tertile 2	Tertile 3
Urinary 3-PBA level, median (range), ng/mL	0.07 (0.07-0.13)	0.26 (0.14-0.49)	1.00 (0.50-69.07)
All-cause mortality			
Deaths, No.	75	81	90
Model 1[a]	1 [Reference]	1.34 (0.88-2.03)	1.50 (1.08-2.10)
Model 2[b]	1 [Reference]	1.24 (0.85-1.81)	1.56 (1.08-2.26)
Cardiovascular disease mortality			
Deaths, No.	10	13	18
Model 1[a]	1 [Reference]	2.12 (0.63-7.10)	2.72 (1.13-6.56)
Model 2[b]	1 [Reference]	1.88 (0.59-6.01)	3.00 (1.02-8.80)
Cancer mortality			
Deaths, No.	18	18	16
Model 1[a]	1 [Reference]	0.80 (0.26-2.40)	1.12 (0.39-3.25)
Model 2[b]	1 [Reference]	0.61 (0.20-1.89)	0.91 (0.31-2.72)

Abbreviation: HR, hazard ratio.

[a] Model 1 was adjusted for age, sex, race/ethnicity, and urinary creatinine levels.

[b] Model 2 included model 1 variables plus educational level, family income status, smoking, alcohol intake, physical activity, total energy intake, Healthy Eating Index-2010 score, and body mass index (calculated as weight in kilograms divided by the square of height in meters).

Table 3. Stratified Analyses for Association of Urinary 3-Phenoxybenzoic Acid Levels With All-Cause Mortality[a]

Variable	Urinary 3-Phenoxybenzoic Acid Levels, HR (95% CI)			*P* Value for Interaction
	Tertile 1	Tertile 2	Tertile 3	
Sex				
Male	1 [Reference]	1.45 (0.87-2.44)	1.63 (0.94-2.84)	.25
Female	1 [Reference]	0.96 (0.59-1.55)	1.62 (0.99-2.65)	
Race/ethnicity				
White	1 [Reference]	1.17 (0.77-1.76)	1.39 (0.85-2.27)	.10
Nonwhite	1 [Reference]	1.56 (0.87-2.80)	2.28 (1.33-3.92)	
Diet quality[b]				
Lower	1 [Reference]	1.24 (0.69-2.22)	1.42 (0.75-2.70)	.51
Higher	1 [Reference]	1.21 (0.72-2.05)	1.75 (1.10-2.78)	
Physical activity level[c]				
Lower	1 [Reference]	1.09 (0.69-1.72)	1.85 (1.08-3.14)	.02
Higher	1 [Reference]	1.51 (0.72-3.15)	1.57 (0.85-2.90)	
Obesity				
BMI <30	1 [Reference]	1.44 (0.95-2.16)	1.21 (0.84-1.75)	.004
BMI ≥30	1 [Reference]	1.23 (0.59-2.56)	5.69 (2.73-11.86)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HR, hazard ratio.

[a] Analyses were adjusted for age, sex, race/ethnicity, urinary creatinine levels, educational level, family income status, smoking, alcohol intake, physical activity, total energy intake, Healthy Eating Index-2010 score, and BMI.

[b] Lower diet quality was defined as a healthy eating index score less than the median score and higher diet quality as a score equal to or greater than the median score.

[c] Lower physical activity level was defined as not meeting the physical activity guidelines and higher physical activity level as meeting or exceeding the guidelines.

and after creatine-adjustment, according to population characteristics, are available in eTable 2 and eTable 3 in the Supplement, respectively.

Participants with higher urinary 3-PBA levels were at a higher risk of death during the follow-up period, with death occurring in 8.5% (unweighted, 75 of 709), 10.2% (unweighted, 81 of 701), and 11.9% (unweighted, 90 of 706) of participants across increasing tertiles of urinary 3-PBA levels. After adjustment for age, sex, race/ethnicity, and urinary creatinine levels, participants with the highest tertile of urinary 3-PBA levels had a higher risk of all-cause mortality (HR, 1.50; 95% CI, 1.08-2.10) and CVD mortality (HR, 2.72; 95% CI, 1.13-6.56) compared with those with the lowest tertile of urinary 3-PBA levels (**Table 2**). The associations did not change appreciably after further adjustment for other covariates. In the fully adjusted model, which included demographic characteristics, socioeconomic status, dietary and lifestyle factors, BMI, and urinary creatinine levels, the HRs for all-cause mortality and CVD mortality among participants with the highest tertile compared with the lowest tertile of urinary 3-PBA levels were 1.56 (95% CI, 1.08-2.26) and 3.00 (95% CI, 1.02-8.80), respectively. Pyrethroid exposure was not associated with cancer mortality.

Stratified analyses indicated that the observed associations of pyrethroid exposure with all-cause mortality were stronger among individuals with obesity compared with individuals without obesity (HR, 5.69 [95% CI, 2.73-11.86] vs 1.21 [95% CI, 0.84-1.75]; *P* for interaction = .004) . The association did not significantly differ by sex, race/ethnicity, or diet quality (**Table 3**).

Discussion

In a prospective cohort of a nationally representative sample, we found that pyrethroid exposure was significantly associ-

ated with a higher risk of all-cause and CVD mortality in adults. The association persisted after adjustment for demographic characteristics, socioeconomic status, dietary and lifestyle factors, BMI, and urinary creatinine levels.

To our knowledge, this is the first study examining the association of pyrethroid exposure with the risk of mortality in humans. Our findings are in line with epidemiologic evidence, which, although limited, indicates a significant association between pyrethroid exposure and CVD.[17] In a case-control study of 72 patients with coronary heart disease and 136 healthy individuals in China, pyrethroid exposure was associated with a higher odds of coronary heart disease; the adjusted odds ratio of coronary heart disease, comparing the highest with the lowest tertile of urinary total pyrethroid metabolites, was 4.55 (95% CI, 1.80-11.54; P = .002).[17] In addition, pyrethroid-related cardiac toxic effects were observed in previous case reports.[33,34] Similar to our findings on cancer mortality, a previous analysis of the Agricultural Health Study found no association between pyrethroid exposure and cancer incidence among US adults.[35]

Although the potential mechanisms underlying the increased risk of all-cause and CVD mortality remain to be elucidated, pyrethroids are reported to be associated with adverse effects on the cardiovascular system in animal studies.[36] Rats exposed to permethrin during early life exhibited increased DNA damage, decreased heart cell membrane fluidity, increased cholesterol content, protein and lipid oxidation in heart cells, and higher levels of cholesterol and inflammatory cytokines in plasma in adulthood.[37] In addition, early life exposure to permethrin insecticide in rats has been associated with long-term cardiac consequences leading to cardiac hypotrophy, increased intracellular calcium influx, and increased nuclear factor erythroid 2–related factor 2 (Nrf2) messenger RNA levels in old age.[38] An in vitro study in fish (the crucian carp, *Carassius carassius*) suggests that deltamethrin is associated with arrhythmogenic effects on the fish heart, with irregularities in rate and rhythm of atrial beating and strong reductions in the force of atrial contraction, and that these effects may be owing to changes in sodium ion channel function.[39]

It is noteworthy that pyrethroids have also been associated with neurotoxic effects in humans. Pyrethroids exert neurotoxicity primarily through modification of the kinetics of voltage-gated sodium channels, resulting in prolongation of the deactivation of sodium channels.[40] However, in this study, we could not assess cause-specific mortality associated with neurological diseases because of the limited sample size. Further investigation regarding the association between pyrethroid exposure and the incidence of and mortality associated with neurological diseases is warranted.

Strengths and Limitations

This study has several strengths. We used nationally representative data from the NHANES, which allowed us to generalize our findings to a broader population. In addition, the NHANES collects comprehensive information about demographic characteristics, socioeconomic status, anthropometric measures, and diet and lifestyle factors, which allowed us to adjust for a variety of potential confounding factors.

The study also has limitations. First, spot urine samples were used to measure pyrethroid metabolites, which may not capture temporal variability and could lead to misclassification of habitual exposure to pyrethroid insecticides. However, previous biomonitoring studies[2] have reported that for short half-life chemicals, rapid clearance can be balanced by frequent exposure to yield a stable blood or urinary concentration. Moreover, given the prospective nature of this study, the random within-person error would be nondifferential, which could lead to an underestimation of the true association. Therefore, the true associations between pyrethroid exposure and mortality may be even stronger than the observed associations in this study.

Second, pyrethroids in the environment can be partially degraded into metabolites, including 3-PBA.[41,42] As a result, individuals may have some direct exposure to preexisting degraded metabolites of pyrethroids through diet or household dust, leading to misclassification (overestimation) of exposure to parent pyrethroid compounds in urinary biomonitoring studies.[43,44] However, this concern might be mitigated by recent studies indicating that such direct exposure to 3-PBA is actually low compared with parent pyrethroid compounds.[44,45] Moreover, such nondifferential misclassification in pyrethroid exposure is more likely to yield an underestimation of the association toward null and could not explain the increased risk of all-cause mortality and CVD mortality. Third, previous studies reported that the distribution of pyrethroid metabolites differs across countries, indicating that different subtypes of pyrethroid insecticides are in use in different countries.[7] Therefore, our findings may not be directly generalizable to other populations that are exposed to different types of pyrethroids. Further investigation in other populations is needed.

Fourth, it is possible that pyrethroid exposure occurs simultaneously with exposure to other common pesticides. In the NHANES conducted from 1999 to 2002, several pesticide metabolites were measured along with pyrethroid metabolites in the same participants. Among these metabolites, 3,5,6-trichloro-2-pyridinol, a metabolite of the organophosphate pesticide chlorpyrifos, was detected in urine samples from 78% of the participants, while other metabolites had a detection rate below 50%. In a sensitivity analysis with further adjustment for urine levels of 3,5,6-trichloro-2-pyridinol in the multivariable model, the association of urinary 3-PBA levels with all-cause mortality and CVD mortality became even stronger (data not shown). Finally, although we adjusted for many potential confounders, we could not rule out the possibility of residual confounding by unmeasured or unrecognized factors.

Conclusions

The findings from this prospective cohort indicated that environmental exposure to pyrethroid insecticides was sig-

nificantly associated with an increased risk of all-cause mortality in the US general adult population. The observed association is likely associated with pyrethroid-induced adverse effects on the cardiovascular system. Further studies are needed to replicate the findings and determine the underlying mechanisms.

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