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RESEARCH ARTICLE

Associations of pyrethroid exposure with skeletal muscle strength and mass

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Abstract

This study aimed to examine the associations of pyrethroid exposure with handgrip strength and skeletal muscle mass and potential modification effects in US adults. The data from the National Health and Nutrition Examination Survey was used. Handgrip strength was determined with a handgrip dynamometer, and we quantified muscle mass by using the appendicular skeletal muscle index (ASMI). Urinary 3-Phenoxybenzoic Acid (3-PBA), a validated biomarker for pyrethroid exposure, was used in the primary analysis. After adjusting for other covariates, participants exposed to the highest tertile of 3-PBA exposure had significantly lower handgrip strength ($\beta = -1.88$, 95% CI: –3.29, –0.23, $P = 0.026$) than those exposed to the lowest tertile of 3-PBA. Similarly, the 3-PBA exposure was marginally significantly associated with ASMI (Tertile 3 vs. Tertile 1: $\beta = -0.07$, 95% CI: –0.14, –0.01, $P = 0.056$). Significant interactions were found between 3-PBA and body mass index (BMI) on handgrip strength and ASMI ($P_{\text{interaction}} < 0.05$), which indicated a potential moderation effect of BMI on the associations. In conclusion, pyrethroid exposure was adversely associated with handgrip strength and skeletal muscle mass, especially in overweight and obese populations. Further studies are warranted to confirm our results and to explore the potential mechanisms.

Keywords Pyrethroid · 3–Phenoxybenzoic acid · Handgrip strength · Skeletal muscle mass

Introduction

Handgrip strength and skeletal muscle mass are reliable measurements to evaluate muscle quality and quantity (Roberts et al. 2011). In 2018, the European Working Group of Sarcopenia in Older People 2 (EWGSOP2) recommend to evaluate handgrip strength and appendicular skeletal muscle mass in the diagnosis of sarcopenia (Cruz-Jentoft et al. 2019). Recently, multiple studies have found that weaker handgrip strength is associated with physical health, including cardiovascular disease, type 2 diabetes, respiratory, and cancer outcomes, and mental health (Alfaro-Acha et al. 2006; Celis-Morales et al. 2018; Kim 2019; Fraser et al. 2021). On the other hand, skeletal muscle mass plays an important role in protein metabolism and body glucose metabolism (Wolfe 2006, Merz & Thurmond 2020). It is reported that muscle mass was also inversely related to the risk of cardiovascular disease, metabolic syndrome, diabetes

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Highlights
- We firstly explored the association of pyrethroid exposure with muscle quality.
- Pyrethroid exposure is adversely associated with muscle quality.
- Stronger association of pyrethroid exposure with muscle quality in obese people.

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and mortality (Kim et al. 2014, 2015; Burrows et al. 2017, Kelley & Kelley 2017).

As synthetic pesticides extracted from naturally occurring pyrethrins, pyrethroids were widely used to control pests in domestic indoor and agricultural settings (Singh et al. 2022). Nowadays, the use of pyrethroid pesticides has increased dramatically due to the restrictions of acutely toxic insecticides (e.g., organophosphate pesticides) (Williams et al. 2008; Horton et al. 2011). Pyrethroid exposure can be through different ways (e.g., dietary intake and residential application) (Fortes et al. 2013; Lu et al. 2013). Prior studies, including ours, have shown that environmental pyrethroid exposure would increase the risk of cardiovascular disease, diabetes and other health problems (Park et al. 2019; Xue et al. 2021; Zuo et al. 2022). Pyrethroid exposure was known to be related to inflammation and oxidative stress (Mostafalou & Abdollahi 2013, Chrustek et al. 2018). Higher pro-inflammatory cytokines may result in lower muscle mass and lower handgrip strength (Visser et al. 2002). Similarly, oxidative stress may contribute to fiber atrophy and breakage (McKenzie et al. 2002). However, to our knowledge, the effects of pyrethroid exposure on handgrip strength and skeletal muscle mass are not reported. Additionally, a positive association between endocrine-disrupting chemical mixture (e.g., phthalate metabolites, phenols, parabens, and pyrethroid pesticides metabolite) and dyslipidemia and weight gain have been reported (Gore et al. 2015; Pinos et al. 2021; Kim et al. 2022). This indicated that pyrethroids were more deeply deposited in adipose tissue, persons with overweight and obese might be more susceptible and persistently affected by pyrethroids.

We hypothesized that exposure to pyrethroids is associated with handgrip strength and skeletal muscle mass. Here, using the data from National Health and Nutrition Examination Survey (NHANES), we examined the cross-sectional associations of pyrethroid metabolites [e.g. 3–phenoxybenzoic acid(3-PBA)] with handgrip strength and skeletal muscle mass and explored the potential effect modification.

Material and methods

Study population

Data comes from the NHANES, a cross-sectional study with national representativeness conducted to evaluate the health and nutritional status of the US population. The protocol has been approved by the National Center for Health Statistics Ethics Review Board and all participants provided written informed consent (https://www.cdc.gov/nchs/nhanes/about_nhanes.htm). Two survey cycles (NHANES2011-2014) were available to examine the association between pyrethroid exposure and handgrip strength. After excluding participants who reported having cancer, and those with missing data on 3–phenoxybenzoic acid (3-PBA), handgrip strength, or on other covariance, 2,317 participants remained (Supplemental Figure 1). Four survey cycles (NHANES1999-2002 and 2011–2014) were available to examine the association between pyrethroid exposure and skeletal muscle mass. Consistently, participants who were ≤ 20 years and had cancer were restricted from our analysis. Those with missing information on skeletal muscle mass, 3-PBA, or missing any information on covariates were further excluded. Finally, a total of 3069 participants remained (Supplemental Figure 2).

Pyrethroid exposure assessment

Pyrethroid metabolites were collected from spot urine specimens, stored under –20 ℃ and transported to CDC's National Center for Environmental Health laboratory for measurement through confirmed methods of high–performance liquid chromatography coupled with electrospray chemical ionization and tandem mass spectrometry (Barr et al. 2010). We used urinary metabolite measurements of 3-PBA, trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid (trans-DCCA), cis-3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid (cis-DCCA), 4-fluoro-3-phenoxybenzoic acid (4-F-3PBA) and cis-3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid (cis-DBCA). Detailed descriptions of the laboratory procedures were provided elsewhere (https://www.cdc.gov/nchs/nhanes/about_nhanes.htm). 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; 4 F-PBA is a specific metabolite of cyfluthrin, and cis-DBCA is a specific metabolite of deltamethrin(Barr et al. 2010). Therefore, we used 3-PBA in the main analysis, as a represent biomarker for a wide range of pyrethroid exposure.

Definition of outcome

Handgrip strength was measured by a dynamometer (Takei Digital Grip Strength Dynamometer, Model T.K.K.5401). The examination excluded participants who were unable to hold the dynamometer with both hands (e.g., missing both arms, both hands, thumbs on both hands, or paralyzed in both hands) and had surgery on either hand or wrist within the last 3 months. After adjusting the grip size properly, the participants were asked to squeeze the dynamometer as hard as they could three times using left and/or right hands, with each interval of 60 s in a standing position unless the participant was physically limited. The combined handgrip strength is in kilograms and was calculated as the total of the maximum readings for each hand.

All body composition measurements were scanned using whole–body dual–energy X–ray absorptiometry (DXA) (Hologic, Inc., Bedford, Massachusetts). Appendicular skeletal mass was calculated based on the sum of the lean soft tissue from the arms and legs. Appendicular skeletal muscle index (ASMI) was used to quantify the muscle mass, which was calculated as ASMI = ASM (kg) / height (m^2) (Baumgartner et al. 1998).

Covariates

NHANES collected information on age, sex, race/ethnicity, education, poverty income ratio (PIR), smoking status, alcohol intake, physical activity and body mass index (BMI) by using standardized questionnaires. Age and BMI were treated as continuous variables. Ethnic groups contained non–Hispanic white, non–Hispanic black, Mexican American and others. Education was categorized as less than 9th grade, 9–11th grade and high school education or higher. Marital status was classified as married/cohabiting, widowed/divorced/separated, and never married. PIR was classified as < 1.3, 1.3–3.5 and > 3.5 (Bao et al. 2020). Participants were grouped as never smokers (smoked less than 100 cigarettes in their lifetime), current smokers (had smoked more than 100 cigarettes and smoked during the research) and former smokers (had smoked more than 100 cigarettes and quitted smoking during the research) (Xue et al. 2021). Drinkers were defined as consuming ≥ 12 alcoholic drinks in a lifetime. The exercise was considered as participants who have at least once a month ≥ 10 min of moderate or severe activities (Hong et al. 2021). Continuous simulation of total energy intake based on data collected from 24–hour dietary recall interviews. Hypertension was defined as diastolic blood pressure ≥ 90 mmHg and (or) systolic blood pressure ≥ 140 mmHg, reporting the use of anti-diabetic medication (Kim et al. 2021). The participants whose answer of "Has a doctor or other health professional ever told you that you had congestive heart failure/coronary heart disease/angina pectoris/stroke?" was "yes" were defined as cardiovascular disease (Liao et al. 2020). Diabetes was defined as self–reported use of hypoglycemic medicines, the level of fasting glucose ≥ 126 mg/dL or HbA1c ≥ 6.5% (Zuo et al. 2022). Participants who answered "yes" to the question "Have you ever been told by a doctor or health professional that you have arthritis" was defined as having arthritis (Brooks et al. 2018).

Statistical analysis

The geometric mean and its 95% confidence interval (CI) were reported for urinary 3-PBA concentrations and creatinine-corrected 3-PBA. The normal distribution of urinary 3-PBA was obtained by log transformation. Multivariable linear regression was used to estimate the associations of 3-PBA exposure (categorized by tertiles) with handgrip strength and ASMI. Model 1 was adjusted for age, sex and urinary creatinine, model 2 was further adjusted for race/ethnicity, education, poverty income ratio, marital status, smoking, drinking, BMI, exercise and total energy intake, model 3 was additionally adjusted for hypertension, diabetes, cardiovascular disease and arthritis. Meanwhile, linear regression based on three-knots restricted cubic splines was performed to examine the nonlinear regression. Further, we conducted subgroup analyses by age (≤ 44, 45–59, ≥ 60 years), sex, and BMI (< 25 and ≥ 25 kg/m^2), and additionally detected the potential effect modifications. All statistical analyses were conducted with STATA, version 17.1 using the survey command. $P < 0.05$ was considered to be statistically significant.

Results

Characteristics of participants

Among 2317 eligible participants included in the analyses of the association between 3-PBA and handgrip strength, 1148 (49.55%) were females, the mean age was 46.57 years, and the mean handgrip strength was 72.62 kg. There were statistical differences in smoking, drinking, marital status, cardiovascular disease, total energy intake and handgrip strength between males and females. In the analysis of the relationship between 3-PBA and skeletal muscle mass, 3069 participants were included, 1478 (48.16%) of them were female, the average age was 41.47 years, and the mean ASMI was 7.89 kg/m^2. There were similar trends for the differences between males and females (Table 1).

Association of pyrethroid metabolites with handgrip strength

After adjusting for age, sex and urine creatinine, participants exposed to the highest tertile of 3-PBA exposure had significantly lower handgrip strength (β = –2.11, 95% CI: –3.88, –0.34, $P = 0.021$) than those exposed to the lowest tertile of 3-PBA. Further adjusting for race/ethnicity, education, poverty income ratio, marital status, smoking, drinking, BMI, exercise and total energy intake, the negative association was observed (β = –1.73, 95% CI: –3.34, –0.13, $P = 0.035$). When further adjusting for hypertension, diabetes, cardiovascular disease and arthritis, the association remained unchanged (β = –1.88, 95% CI: –3.29, –0.23, $P = 0.026$) (Table 2). Consistently, we did not observe a nonlinear association between 3-PBA and handgrip strength (Fig. 1A).

Association of pyrethroid metabolites with ASMI

After adjusting for age, sex and urine creatinine, race/ethnicity, education, poverty income ratio, marital status, smoking, drinking, BMI, hypertension, diabetes, cardiovascular disease and arthritis, the 3-PBA exposure was marginally

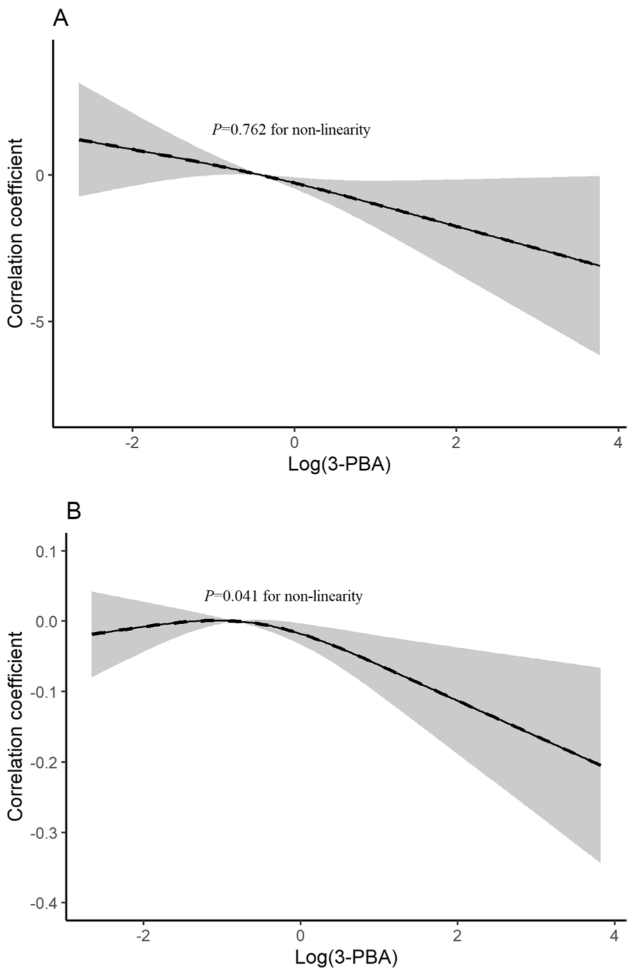

Fig. 1 Non-linear relationship of 3-Phenoxybenzoic Acid (3-PBA) with handgrip strength (**A**) and appendicular skeletal muscle index (ASMI) (**B**). *Adjusted for age, gender, race/ethnicity, marital status, education, the ratio of family income to poverty, smoking, drinking, urinary creatinine, exercise and total energy intake

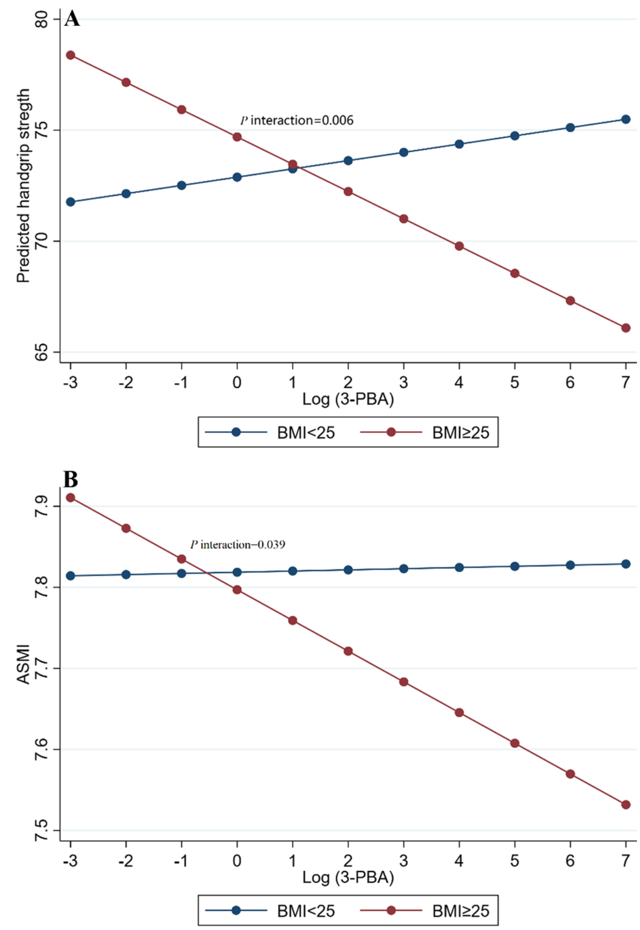

Fig. 2 The interaction between body mass index (BMI) and 3-Phenoxybenzoic Acid (3-PBA) on handgrip strength (**A**) and appendicular skeletal muscle index (ASMI) (**B**). Age, gender, race/ethnicity, marital status, education, the ratio of family income to poverty, smoking, drinking, urinary creatinine, exercise, total energy intake and BMI were adjusted in the model

significantly associated with ASMI (Tertile(T)3 vs. T1: β = -0.07, 95% CI: –0.14, –0.01, $P = 0.056$) (Table 2). Further, we found a non-linear association between 3-PBA and ASMI, and ASMI started to decrease when the 3-PBA level reached 0.146 µg/L (P for non-linearity = 0.041) (Fig. 1B).

Subgroup analysis

Significant interactions were found between 3-PBA and BMI on handgrip strength and ASMI (P interaction < 0.001), which indicated a potential moderation effect of BMI on the associations (Fig. 2). When stratified by BMI, the result showed significant differences between 3-PBA and handgrip strength in overweight and obese participants (T2, β = –0.93, 95% CI: –3.19, 1.35, $P = 0.415$; T3, β = –3.29, 95% CI: –5.27, –1.30, $P = 0.002$), but not observed among lean ones (T2, β = 1.27, 95% CI: –0.99, 3.53, $P = 0.262$; T3, β = 2.44, 95% CI: –0.72, 5.60, $P = 0.126$). Consistently, there was a significant association between 3-PBA and ASMI among the population with overweight and obesity (T2, β = –0.06, 95% CI: –0.13, 0.02, $P = 0.143$; T3, β = –0.12, 95% CI: –0.21, –0.04, $P = 0.005$), but not in lean ones (Table 3). We did not find significant interactions for age and sex (Supplemental Tables 1 and 2).

Sensitivity analysis

We found a significantly negative association between urinary trans-DCCA and ASMI but did not find any significant associations for cis-DBCA, cis-DCCA or 4-F-3PBA (Table 4). The associations of trans-DCCA and 4-F-3PBA with handgrip strength also did not reach significance. Associations of urinary cis-DBCA with handgrip strength were not examined because urinary cis-DBCA and cis-DCCA were not measured

Table 1 Characteristics of the study participants

	Handgrip strength			Skeletal muscle mass		
	Males ($n = 1{,}169$)	Females ($n = 1{,}148$)	*P* value	Males ($n = 1{,}591$)	Females ($n = 1{,}478$)	*P* value
Age, mean (SD), y	46.19 (17.32)	46.96 (16.75)	0.280	40.92 (14.40)	42.06 (14.24)	0.028
Race/ethnicity (%)			0.542			0.664
Mexican American	137 (11.72)	115 (10.02)		281 (17.66)	258 (17.46)	
Other Hispanic	108 (9.24)	115 (10.02)		105 (6.60)	117 (7.92)	
Non-Hispanic White	491 (42.00)	467 (40.68)		727 (45.69)	651 (44.05)	
Non-Hispanic Black	259 (22.16)	276 (24.04)		318 (19.99)	301 (20.37)	
Other Race	174 (14.88)	175 (15.24)		160 (10.06)	151 (10.22)	
Educational (%)			0.281			0.176
Less than 9th grade	75 (6.42)	59 (5.14)		136 (8.55)	104 (7.04)	
9-11th grade	154 (13.17)	139 (12.11)		244 (15.34)	211 (14.28)	
High school education or higher	940 (80.41)	950 (82.75)		1211 (76.12)	1163 (78.69)	
The ratio of family income to poverty (%)			0.320			0.356
< 1.3	390 (33.36)	401 (34.93)		464 (29.16)	444 (30.04)	
1.3–3.5	401 (34.30)	409 (35.63)		578 (36.33)	560 (37.89)	
> 3.5	378 (32.34)	338 (29.44)		549 (34.51)	474 (32.07)	
Smoking (%)			< 0.001			< 0.001
Never smoked	555 (47.48)	753 (65.59)		745 (46.83)	925 (62.58)	
Formerly smoked	313 (26.78)	202 (17.60)		392 (24.64)	254 (17.19)	
Currently smokes	301 (25.75)	193 (16.81)		454 (28.54)	299 (20.23)	
Drinking (%)			< 0.001			< 0.001
Yes	992 (84.86)	731 (63.68)		1339 (84.16)	945 (63.94)	
No	177 (15.14)	417 (36.32)		252 (15.84)	533 (36.06)	
Exercise (%)			0.020			< 0.001
Yes	654 (55.95)	587 (51.13)		987 (62.04)	825 (55.82)	
No	515 (44.05)	561 (48.87)		604 (37.96)	653 (44.18)	
Marital status (%)			< 0.001			< 0.001
Married/cohabiting	711 (60.82)	616 (53.66)		991 (62.29)	853 (57.71)	
Widowed/divorced/separated	180 (15.40)	276 (24.13)		192 (12.07)	293 (19.82)	
Never married	278 (23.78)	255 (22.21)		408 (25.64)	332 (22.46)	
Hypertension (%)			0.398			0.127
Yes	407 (34.82)	419 (36.50)		410 (25.77)	417 (28.21)	
No	762 (65.18)	729 (63.50)		1181 (74.23)	1061 (71.79)	
Diabetes mellitus (%)			0.369			0.474
Yes	172 (14.71)	154 (13.41)		144 (9.05)	123 (8.32)	
No	999 (85.29)	993 (86.59)		1447 (90.95)	1355 (91.68)	
Cardiovascular disease (%)			0.004			0.021
Yes	129 (11.04)	87 (7.58)		100 (6.29)	65 (4.40)	
No	1040 (88.96)	1061 (92.42)		1491 (93.71)	1413 (95.60)	
Arthritis (%)			< 0.001			< 0.001
Yes	232 (19.85)	320 (27.87)		202 (12.70)	277 (18.74)	
No	937 (80.15)	828 (72.13)		1389 (87.30)	1201 (81.26)	
Body mass index (kg/m^2)	28.62 (6.11)	29.79 (8.08)	< 0.001	27.96 (5.72)	28.82 (7.15)	< 0.001
Total energy intake (kcal)	2417.54 (923.14)	1806.59 (693.71)	< 0.001	1591 (1042.309)	1578 (714.869)	< 0.001
Urinary 3-PBA uncorrected (μg/L)[a]	0.71 (0.66, 0.77)	0.68 (0.63, 0.74)	0.361	0.46 (0.43, 0.49)	0.46 (0.43, 0.49)	0.932
Urinary 3-PBA creatinine corrected (μg/g)[a]	0.61 (0.57, 0.65)	0.83 (0.77, 0.89)	< 0.001	0.37 (0.81, 1.98)	0.54 (0.50, 0.57)	< 0.001
Handgrip strength (kg)	88.53 (19.33)	56.42 (11.98)	< 0.001	–	–	–
ASMI (kg/m^2)	–	–	–	8.75 (1.42)	6.96 (1.42)	< 0.001

3-PBA 3-phenoxybenzoic acid, *ASMI* Appendicular skeletal muscle index

[a]Geometric means (95% CI) were presented

Table 2 Association of urinary 3-phenoxybenzoic acid levels with handgrip strength and skeletal muscle mass among US adults

Volume-based 3-PBA levels	Model 1		Model 2		Model 3	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Handgrip strength						
Tertile 1 (< 0.385)	Reference	–	Reference	–	Reference	–
Tertile 2 (0.385–1.09)	-0.25 (-1.83, 1.33)	0.752	-0.12 (-1.63, 1.39)	0.876	-0.25 (-1.72, 1.22)	0.729
Tertile 3 (> 1.09)	-2.11 (-3.88, -0.34)	0.021*	-1.73 (-3.34, -0.13)	0.035*	-1.88 (-3.29, -0.23)	0.026*
Appendicular skeletal muscle index						
Tertile 1 (< 0.251)	Reference	–	Reference	–	Reference	–
Tertile 2 (0.251–0.787)	0.03 (-0.12, 0.18)	0.680	-0.02 (-0.09, 0.05)	0.535	-0.02 (-0.09, 0.04)	0.494
Tertile 3 (> 0.787)	-0.01 (-0.15, 0.13)	0.927	-0.06 (-0.13, -0.01)	0.077	-0.07 (-0.14, -0.01)	0.056

3-PBA 3-phenoxybenzoic acid, *CI* Confident interval

Model 1: adjusted for age, sex and urine creatinine

Model 2: adjusted for Model 1 covariates plus race/ethnicity, education, marital status, the ratio of family income to poverty, smoking, drinking, body mass index, intakes of energy and exercises

Model 3: adjusted for Model 2 covariates plus hypertension, diabetes mellitus, cardiovascular disease and arthritis

Table 3 Association of urinary 3-phenoxybenzoic acid levels with handgrip strength and skeletal muscle mass by body mass index among US adults

Urinary 3-Phenoxybenzoic Acid Levels	Model 1		Model 2		Model 3	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Handgrip strength						
BMI < 25						
Tertile 1 (< 0.385)	Reference	–	Reference	–	Reference	–
Tertile 2 (0.385–1.09)	1.85 (-0.62, 4.32)	0.136	1.27 (-0.99, 3.53)	0.262	1.22 (-1.08, 3.52)	0.289
Tertile 3 (> 1.09)	2.83 (-0.40, 6.07)	0.084	2.44 (-0.72, 5.60)	0.126	1.97 (-1.24, 5.18)	0.221
BMI ≥ 25						
Tertile 1 (< 0.385)	Reference	–	Reference	–	Reference	–
Tertile 2 (0.385–1.09)	-1.00 (-3.35, 1.35)	0.391	-0.93 (-3.19, 1.35)	0.415	-1.08 (-3.34, 1.19)	0.341
Tertile 3 (> 1.09)	-3.68 (-5.80, -1.57)	0.001	-3.29 (-5.27, -1.30)	0.002	-3.22 (-5.12, -1.32)	0.002
Appendicular skeletal muscle index						
BMI < 25						
Tertile 1 (< 0.251)	Reference	–	Reference	–	Reference	–
Tertile 2 (0.251–0.787)	0.03 (-0.09, 0.15)	0.629	0.04 (-0.06, 0.14)	0.408	0.04 (-0.06, 0.13)	0.440
Tertile 3 (> 0.787)	0.05 (-0.09, 0.19)	0.485	0.08 (-0.02, 0.17)	0.102	0.07 (-0.02, 0.17)	0.116
BMI ≥ 25						
Tertile 1 (< 0.251)	Reference	–	Reference	–	Reference	–
Tertile 2 (0.251–0.787)	-0.01 (-0.19, 0.18)	0.948	-0.06 (-0.13, 0.02)	0.143	-0.06 (-0.14, 0.02)	0.126
Tertile 3 (> 0.787)	-0.01 (-0.16, -0.15)	0.923	-0.12 (-0.21, -0.04)	0.005	-0.13 (-0.21, -0.05)	0.003

3-PBA 3-phenoxybenzoic acid, *BMI* Body mass index (kg/m^2), *CI* Confident interval

Model 1: adjusted for age, sex and urine creatinine

Model 2: adjusted for Model 1 covariates plus race/ethnicity, education, marital status, the ratio of family income to poverty, smoking, drinking, body mass index, intakes of energy and exercises

Model 3: adjusted for Model 2 covariates plus hypertension, diabetes mellitus, cardiovascular disease and arthritis

in NHANES 2011–2014. We also performed sensitivity analyses for the association of 3-PBA with handgrip strength and skeletal muscle mass by excluding participants with diabetes, cardiovascular disease or arthritis. All results remained similar trend of 3-PBA with handgrip strength and skeletal muscle mass (Supplemental Table 3). In addition, we excluded smokers and drinkers (523 participants for handgrip strength and 551 participants for ASMI were available) from the population

Table 4 Associations of urinary cis-DCCA (*n* = 1533), cis-DBCA (*n* = 1471), trans-DCCA (*n* = 2243/1495) and 4-F-3PBA (*n* = 2337/1543) with handgrip strength and skeletal muscle mass

	Handgrip strength		Appendicular skeletal muscle index	
	β (95% CI)	*P* value	β (95% CI)	*P* value
Cis-DCCA				
Model 1	–	–	0.16 (-0.05, 0.38)	0.137
Model 2	–	–	0.01 (-0.08, 0.09)	0.939
Model 3	–	–	0.01 (-0.08, 0.08)	0.951
Cis-DBCA				
Model 1	–	–	0.05 (-0.45, 0.54)	0.849
Model 2	–	–	0.18 (-0.04, 0.39)	0.106
Model 3	–	–	0.18 (-0.04, 0.39)	0.104
Trans-DCCA				
Model 1	-1.04 (-2.86, 0.78)	0.253	0.27 (-0.47, -0.07)	0.009
Model 2	-1.06 (-2.60, 0.47)	0.169	-0.08 (-0.15, 0.01)	0.044
Model 3	-1.28 (-2.82, 0.26)	0.100	-0.09 (-0.16, -0.01)	0.024
4-F-3PBA				
Model 1	0.92 (-1.71, 3.55)	0.483	0.26 (-0.01, 0.42)	0.062
Model 2	0.96 (-1.40, 3.31)	0.416	0.07 (-0.04, 0.18)	0.226
Model 3	1.38 (-1.12, 3.87)	0.270	0.07 (-0.04, 0.18)	0.180

cis-DCCA cis-3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid, *cis-DBCA* cis-3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid; trans-DCCA = trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid, *4-F-3PBA* 4-fluoro-3-phenoxybenzoic acid, *CI* Confident interval

Metabolites were dichotomized as detected vs. undetected, and the undetected group was treated as a reference

Model 1: adjusted for age, sex and urine creatinine

Model 2: adjusted for Model 1 covariates plus race/ethnicity, education, marital status, the ratio of family income to poverty, smoking, drinking, body mass index, intakes of energy and exercises

Model 3: adjusted for Model 2 covariates plus hypertension, diabetes mellitus, cardiovascular disease and arthritis

and also found negative associations of 3-PBA with handgrip strength (T2, β = 0.31, 95% CI: –3.39, 4.01, *P* = 0.865; T3, β = –1.05, 95% CI: –5.24, 3.13, *P* = 0.612) and ASMI (T2, β = –0.26, 95% CI: –3.84, 3.33, *P* = 0.885; T3, β = –0.91, 95% CI: –5.07, 3.25, *P* = 0.658), although did not reach a statistical significance.

Discussion

In this cross-sectional study among a representative population of adults from NHANES, we demonstrated that higher concentrations of urinary 3-PBA were associated with weaker handgrip strength and lower ASMI. Meanwhile, interactions between BMI and 3-PBA exposure on handgrip strength and ASMI were identified. In the subgroup analysis, we found a significant association between urinary pyrethroid exposure and handgrip strength and ASMI in overweight and obese populations, but not in lean ones.

To the best of our knowledge, this was the first study to explore the associations of pyrethroid exposure with handgrip strength and skeletal muscle mass. Prior studies found a significant association between 3-PBA exposure and type 2 diabetes (Park et al. 2019; Liang et al. 2022). Another study among the US adult population from NHANES showed that exposure to 3-PBA was longitudinally associated with an increased risk of all-cause and cardiovascular disease mortality (Bao et al. 2020). In addition, the associations between 3-PBA and BMI have been reported in the adult population (Yoshinaga et al. 2014). Our findings suggested that skeletal muscle may play a role in the associations between pyrethroid exposure and cardiometabolic diseases.

In this study, significant differences between higher concentrations of 3-PBA with weaker handgrip strength and ASMI were found especially in people with overweight and obesity. Similarly, Xue Q et al. found the relationships of 3-PBA with coronary heart disease and diabetes were more significant among individuals with higher BMI, (Xue et al. 2021). In a cohort study, the results indicated that the risk of all-cause mortality was stronger among participants exposed to pyrethroids who were obese (Bao et al. 2020).

There are several potential pathways for the effect of pyrethroids on handgrip strength and skeletal muscle mass. First, many studies have confirmed the associations between oxidative stress and muscle cells atrophy and necrosis (Powers & Jackson 2008, Musarò et al. 2010; Powers et al. 2011; Murakami et al. 2012), and pyrethroid exposure potentially increase oxidative stress (Chrustek et al. 2018, Ravula & Yenugu 2021). Second, a cohort study among adults and children in the Czech found that pyrethroid metabolites were associated with DNA methylation (DNAm) biomarkers (Janoš et al. 2023), while DNAm age acceleration had a negative relationship with handgrip strength (Peterson et al. 2023). Third, studies have indicated exposure to pyrethroids may cause inflammation (Meng & Yu 2010). Intracellular redox imbalance might active signalling pathways such as NF–κB, which induced the release of proinflammatory factors such as IL–6 and TNF–a, thus leading to the loss of muscle mass and muscle atrophy (Li et al. 1998; Langen et al. 2001; Chung et al. 2009). Consistently, we also found that C-reactive protein (CRP) could explain 5.6%(95%CI: 3.3–16.9%) of the association between 3-PBA and ASMI (data not shown). Last, estrogens and androgens play a role to maintain mass and strength in bones and muscles (Almeida et al. 2017), while the function of hormone receptors might be disrupted by pyrethroid metabolites (Du et al. 2010, Castiello & Freire 2021). Therefore, estrogens and/or androgens receptors might have a mediating influence when skeletal muscle is exposed to pyrethroids.

One of the major strengths was that we for the first time explored the associations of pyrethroid exposure with handgrip strength and skeletal muscle mass. There were serval limitations in our study. First, as a cross-sectional study, the reverse causality between the pyrethroid exposures and handgrip strength was hard to exclude. Second, due to the short half-life of pyrethroid metabolites and the lack of long-term urine pyrethroid measurements, the spot urine samples may not well reflect realistic exposure to pyrethroids. Third, besides the covariates adjusted in our regression analyses model, some potential confounded factors still existed and influenced our result. Finally, the effects of specific types of pyrethroids on cardiometabolic risk should be further studied.

Conclusion

There are negative associations of pyrethroid exposure with handgrip strength and ASMI, particularly in overweight and obese populations. Further studies are required to confirm the results and to examine the underlying mechanisms.

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Author contributions GH was responsible for the conceptualization and supervision. The first draft of the manuscript was written by ZF. XC, MLL, LZ, BYZ, GJZ and HYC critically reviewed the manuscript.

Data Availability The data are available from NHANES.

Declarations

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent to publish We affirm that all authors have agreed for submission of the paper to ESPR and are fullyaware of ethical responsibilities.

Competing interests The authors declare no competing interests.

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