Exploratory analysis of the associations between neonicotinoids and measures of adiposity among US adults: NHANES 2015–2016

Amruta M. Godbole [a], Sheniz Moonie [a], Courtney Coughenour [b], Cai Zhang [c], Aimin Chen [d], Ann M. Vuong [a],*

[a] *Department of Epidemiology and Biostatistics, University of Nevada Las Vegas, School of Public Health, Las Vegas, NV, United States*
[b] *Department of Environmental and Occupational Health, University of Nevada Las Vegas, School of Public Health, Las Vegas, NV, United States*
[c] *Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China*
[d] *Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States*

HIGHLIGHTS

- Neonicotinoid compounds may be associated with the pathogenesis of adiposity.
- Acetamiprid was inversely associated with all the adiposity measures examined.
- 5-hydroxy-imidacloprid was positively associated with being overweight/obese.
- Sex differences were seen with *N*-desmethyl-acetamiprid and some adiposity measures.

ARTICLE INFO

ABSTRACT

Background: Toxicology studies suggest that neonicotinoids may be associated with adiposity development via thyroid hormone disruption and increased oxidative stress. Prior epidemiological studies report mixed results for the association between neonicotinoids and adiposity measures.

Objective: To examine the association between detectable concentrations of parent neonicotinoids (imidacloprid, acetamiprid, clothianidin) and neonicotinoid metabolites (5-hydroxy-imidacloprid, *N*-desmethyl-acetamiprid) with adiposity measures among US adults, and whether sex modifies the associations for neonicotinoid metabolites with adiposity.

Methods: National Health and Nutrition Examination Survey (NHANES) 2015–2016 data was utilized to estimate covariate-adjusted associations between detectable neonicotinoids and fat mass index (FMI), lean mass index (LMI), waist circumference, body fat percentage, and body mass index (BMI) using multiple linear regression. We estimated incidence rate ratios (IRRs) for overweight or obese status with detectable neonicotinoid concentrations using Poisson's modified regression. Sampling strategies were accounted for in the regression models.

Results: Detectable levels of acetamiprid were associated with a decrease in FMI ($\beta = -3.17$ kg/m^2, 95% CI [-4.79, -1.54]), LMI ($\beta = -3.17$ kg/m^2, 95% CI [-5.17, -1.17]), body fat percentage ($\beta = -4.41$, 95% CI [-8.20, -0.62]), waist circumference ($\beta = -9.80$ cm, 95% CI [-19.08, -0.51]), and BMI ($\beta = -3.88$ kg/m^2, 95% CI [-7.25, -0.51]) among adults. In contrast, detectable levels of 5-hydroxy-imidacloprid were associated with greater rates of being overweight/obese (IRR = 1.11, 95% CI [1.04, 1.18]) and increased LMI ($\beta = 0.67$ kg/m^2, 95% CI [0.04, 1.29]). Sex modified the association between *N*-desmethyl-acetamiprid and LMI ($p_{int} = 0.075$) with a positive association among males ($\beta = 1.14$ kg/m^2, 95% CI [0.38, 1.90]), and an insignificant inverse association in females. Sex also modified the association for *N*-desmethyl-acetamiprid with FMI ($p_{int} = 0.095$) and body fat percentage ($p_{int} = 0.072$), with suggestive evidence showing positive associations for males and inverse associations for females.

* Corresponding author. Department of Epidemiology and Biostatistics, University of Nevada, Las Vegas School of Public Health, 4700 S. Maryland Parkway, MS 3063, Las Vegas, NV, 89119-3063, United States.
E-mail address: ann.vuong@unlv.edu (A.M. Vuong).

Conclusion: Detectable concentrations of acetamiprid were inversely associated with adiposity, while there were mixed findings for 5-hydroxy-imidacloprid. Findings suggest sex differences, though results are not clear with regard to the directionality of the association by sex.

1. Introduction

Neonicotinoids are nicotine-based insecticides frequently used to protect agricultural crops from pest-related damage, and to kill other pests (Bass and Field, 2018). Neonicotinoids became widely popular after their introduction in 1991 since they were effective on pests that were resistant to other insecticides (Nauen et al., 2008). Bayer CropScience discovered the first neonicotinoid compound, imidacloprid, in 1991. It remains the most widely used neonicotinoid to date (Nauen et al., 2008). Subsequently, other neonicotinoid compounds such as clothianidin, acetamiprid, thiamethoxam, dinotefuran, and thiacloprid, were made commercially available (Ihara and Matsuda, 2018). Neonicotinoids have a long half-life in soil (6 months–3 years), which leads to concerns regarding their exposure in humans (Goulson, 2013).

An environmental study showed that 72% of the fruits and 45% of the vegetables tested had detectable levels of multiple neonicotinoids, while freshwater sources in California showed the presence of imidacloprid in 89% of the samples, with 19% exceeding Environmental Protection Agency (EPA) toxicity limits (1.05 μg/L) (Chen et al., 2014; Starner and Goh, 2012). A study conducted using the National Health and Nutritional Examination Survey (NHANES) data showed that almost 50% of the participants had detectable concentrations of urinary metabolites of at least one type of neonicotinoid, with acetamiprid (35%) and imidacloprid metabolites (19.7%) being detected most frequently (Ospina et al., 2019). Hair samples collected from Chinese women in two cities indicated the presence of five different neonicotinoids (imidacloprid, acetamiprid, thiamethoxam, clothianidin, and thiacloprid), with imidacloprid detected in 99% of the samples (Peng et al., 2020), while a 250-fold increase in concentrations of neonicotinoids (imidacloprid, acetamiprid, dinotefuran, nitenpyram, nithiazine, clothianidin, thiacloprid, and thiamethoxam) was seen in urine samples of Japanese women from 1994 to 2011 (Ueyama et al., 2015). Among studies examining participants with occupational use of neonicotinoids, the presence of seven types of neonicotinoids was detected in urine samples of farmers in Japan, with thiamethoxam, dinotefuran, imidacloprid, and clothianidin present in 96–100% of the samples (Han et al., 2018).

Evidence suggests neonicotinoids may be associated with adverse health outcomes among adults (Hernández et al., 2008; Marfo et al., 2015). Neonicotinoid concentrations among farmers have been associated with reduced total lung capacity and residual volume; neonicotinoids were also associated with 7 times higher likelihood of developing respiratory symptoms (Hernández et al., 2008). Acetamiprid and thiamethoxam metabolites were positively associated with several neo-nicotinic symptoms, including memory loss, tremors, headaches, fatigue, chest pain, muscle spasms, and coughing, as compared to individuals displaying other or no symptoms (Marfo et al., 2015). Animal studies show that neonicotinoids have endocrine disruptive properties. Imidacloprid exposure in rats is positively related to reductions in testosterone, subsequently leading to infertility (Mikolic and Karaconji, 2018). Imidacloprid also reduces thyroid hormone levels in other species, which can disturb the hypothalamus-pituitary-thyroid axis (Leemans et al., 2019). Furthermore, neonicotinoids have been shown to suppress natural hormone function as well as disrupt regular hormone synthesis and metabolism (Mikolic and Karaconji, 2018). These mechanisms have been linked to the potential obesogenic actions of neonicotinoids. Toxicological studies have shown that imidacloprid disrupts steroid hormone as well as insulin regulation, which can potentiate metabolic changes leading to obesity (Mikolic and Karaconji, 2018). Disruption of steroid hormone regulation by endocrine disrupting chemicals (EDCs), coupled with EDC induced dysfunction of growth

hormone and estrogen can lead to an increase in the size and number of adipocytes during the developmental years (Grun and Blumberg, 2009). Epidemiological studies have shown a positive association between neonicotinoid compounds imidacloprid and *N*-desmethyl-acetamiprid and body mass index (BMI) in adults and children, respectively (Peng et al., 2020; Wang et al., 2020).

This study examined the association between detectable concentrations of neonicotinoids and measures of adiposity in adults using a representative sample from the 2015–2016 cycle of NHANES. This study also assessed whether sex modified the relationship between neonicotinoid metabolites and adiposity.

2. Methods

2.1. Data source and study population

This exploratory cross-sectional study utilized data from the 2015–2016 cycle of NHANES since neonicotinoids were only quantified in a subset of the population within this cycle. The 2015–2016 cycle sampled 15,327 people across 30 survey locations. Of these, 9,971 completed the interview and 9,544 were examined. Inclusion criteria for the study population in the present analysis were adults over the age of 19 years who had at least one reported urinary neonicotinoid measured (among imidacloprid, acetamiprid, clothianidin, 5-hydroxy-imidacloprid, and *N*-desmethyl-acetamiprid) along with at least one reported measure of adiposity (among fat mass, lean mass, body fat percentage, waist circumference, and BMI) (N = 1699). One hundred and sixty-three pregnant women were excluded resulting in 1675 participants included in the study analyses.

2.2. Neonicotinoids

Neonicotinoids measured included imidacloprid, acetamiprid, clothianidin, and thiacloprid. Additionally, 5-hydroxy-imidacloprid (a metabolite of imidacloprid) and *N*-desmethyl-acetamiprid (a metabolite of acetamiprid) were measured. For each subject, 0.2 mL (ml) urine was used as a sample for analysis. Enzymatic hydrolysis of urinary conjugates of the target neonicotinoids was performed, followed by online solid phase extraction, reversed phase high-performance liquid chromatography separation, and isotope dilution-electrospray ionization tandem mass spectrometry detection (Baker et al., 2019). This method has a precision range between 3.7 and 10.2%, while its accuracy is between 91.2 and 116% (Baker et al., 2019). *N*-desmethyl-acetamiprid had the highest detection frequency (32.4%), followed by 5-hydroxy-imidacloprid (20%), clothianidin (7.7%), imidacloprid (4.1%), and acetamiprid (0.3%) (Supplemental Table S1). Given relatively low detection frequencies, we analyzed neonicotinoids as "detect" versus "non-detect." Thiacloprid was not examined given its low detection frequency (0.02%). Additionally, variables were created for: 1) any detectable parent neonicotinoid (imidacloprid, acetamiprid, or clothianidin); and 2) any detectable neonicotinoid metabolite (5-hydroxy-imidacloprid or *N*-desmethyl-acetamiprid). Participants who had concentrations above the limit of detection for either imidacloprid, acetamiprid, or clothianidin were considered to have detectable concentrations of a parent neonicotinoid. Those who had concentrations of imidcloprid, acetamiprid, and clothianidin that were all less than the limit of detection were considered as having non-detectable parent neonicotinoids. The same methodology was applied to define any detectable neonicotinoid metabolites with 5-hydroxy-imidacloprid and *N*-desmethyl-acetamiprid. About 11.6% of individuals in the study sample had detectable

levels of any parent neonicotinoid, and 43% had detectable levels of neonicotinoid metabolites.

2.3. Adiposity measures

Height was measured at the Mobile Examination Center (MEC) by trained technicians using a stadiometer. A digital weighing scale was used to measure weight. Each participant was allowed to only wear underwear and a standard MEC examination gown while their weight was being measured. BMI was calculated by dividing weight in kilograms by height squared in meters, and then rounded off to one decimal point. BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (30 kg/m^2 or more) (Centers for Disease Control [CDC], 2020).

A steel retractable measuring tape was used to record waist circumference. Before recording waist measurements, subjects were asked to clip their shirt gowns above the waist, while the measuring tape was aligned along the line of both iliac crests and wrapped around the waist to record a measurement (NHANES Anthropometry Procedures Manual, 2016). Dual energy X-ray absorptiometry (DXA) was used to calculate fat mass, lean mass, and total body fat. Based on these values, fat mass index (FMI) and lean mass index (LMI) were derived by dividing fat mass by height squared, and lean mass by height squared, respectively (Zhu et al., 2017). FMI and LMI are reported to be better measures of adiposity as compared to BMI since they specifically assess fat and lean mass, respectively, while also serving as a better representation of central fat mass (Han et al., 2010; Kyle et al., 2003).

2.4. Statistical methods

All analyses were weighted to account for clustering of samples, measurement errors, oversampling, and missing measurements. Linear regression models were used to estimate βs and corresponding 95% confidence intervals (CIs) for the associations between detectable levels of neonicotinoids and continuous measures of adiposity, which included LMI, FMI, waist circumference, BMI, and body fat percentage. Poisson's modified regression was used to estimate incidence rate ratios (IRRs) and corresponding 95% CIs for the associations between detectable levels of neonicotinoids and being overweight or obese, as well as separately for overweight and obese participants. In order to examine effect measure modification by sex, a product term between the detectable neonicotinoid metabolites and sex was included in the previously described models. Prior research has indicated that the statistical power to assess for interactions is lower than for the main effects (Aguinis, 1995). As such, we considered a $P < 0.10$ as statistically significant for the interaction term in the effect measure modification analyses (Aguinis, 1995; Thiese et al., 2016). Covariates included in the final model were based on bivariate analysis with neonicotinoid compounds and measures of adiposity ($P < 0.20$). These included age, sex, race/ethnicity, marital status, self-reported current health status, and thyroid issues. We completed a secondary analysis examining the association between neonicotinoids and adiposity measures by smoking status to determine whether associations differed.

The sensitivity analyses were adjusted for daily caloric intake, bisphenol A (BPA) concentrations, and physical activity. Additionally, associations were examined after removing participants whose FMI, LMI, BMI or waist circumference were beyond 3 standard deviations from the mean. Lastly, we checked all models for their robustness by examining how the main estimates for neonicotinioids behaved when regression specifications were modified. All statistical data analyses were completed using the Stata 16.1 software.

3. Results

3.1. Study participants

The participants were relatively evenly distributed by sex, with over one-third between the ages of 40–60 years (36.6%) (Table 1). A majority of the participants were Non-Hispanic white, married or living with a partner, and had a high monthly family income. Approximately 52% were physically active, and 42% self-reported either excellent or good health. Most of the participants did not have thyroid conditions (89%) and were non-smokers (76%). Among the study participants, 70% were overweight or obese, with a mean BMI of 29.3 kg/m^2. Average waist circumference was 100.2 cm, with an average FMI of 9.7 kg/m^2 and LMI of 18.3 kg/m^2. Average body fat percentage was 32.6%. Males were significantly more likely than females to have greater waist circumference, lower FMI, higher LMI, and lower body fat percentage. Mexican-American/Other Hispanic participants were more likely to have a higher body fat percentage, while Non-Hispanic blacks were more likely to have a higher BMI and a greater waist circumference. Participants with a higher BMI were more likely to self-report a poor or fair current health status and have a higher prevalence of thyroid related issues. Those who were divorced or separated were more likely to have a higher body fat percentage compared to single or unmarried participants. A greater waist circumference was associated with being older, having a fair or poor current health status, and having thyroid related problems. Individuals reporting good health status were less likely to be overweight or obese, and had lower BMI, waist circumference, and FMI. Participants with detectable levels of any parent neonicotinoid were more likely to be Non-Hispanic white, while participants with detectable levels of neonicotinoid metabolites were more likely to be non-smokers.

3.2. Neonicotinoids and measures of adiposity

Detectable levels of any parent neonicotinoid were not significantly associated with measures of adiposity ($P > 0.05$) (Table 2). However, detectable levels of any neonicotinoid metabolite were associated with a 0.62 kg/m^2 increase in LMI (95% CI [0.03, 1.21]). Significant inverse associations were seen between acetamiprid and FMI, LMI, body fat percentage, waist circumference, and BMI. Specifically, detectable levels of acetamiprid in urine were associated with approximately a 3 kg/m^2 decrease in FMI (95% CI [−4.79, −1.54]) and LMI (95% CI [−5.17, −1.17]) compared to levels below the detection limit. Similarly, detectable levels of acetamiprid were associated with a decrease of approximately 4% in body fat percentage (95% CI [−8.20, −0.62]) and almost 4 kg/m^2 in BMI (95% CI [−7.25, −0.51]). Additionally, detectable levels of acetamiprid were associated with a decrease of nearly 10 cm in waist circumference (95% CI [−19.08, −0.51]). Of the neonicotinoid metabolites, 5-hydroxy-imidacloprid had a positive association with LMI (β = 0.67 kg/m^2, 95% CI [0.04, 1.29]). There was no association between imidacloprid, clothianidin, or *N*-desmethyl-acetamiprid with any measures of adiposity observed. Detectable concentration of 5-hydroxy-imidacloprid was associated with a 11% increase in incidence of being overweight/obese (95% CI [1.04, 1.18]) (Table 3). Although the individual results for the associations with being overweight or being obese separately were not statistically significant, a positive trend in the association was observed for imidacloprid and clothianidin among overweight participants, while obese participants showed an inverse trend in the association with parent neonicotinoids. Subgroup analysis based on smoking status found that imidacloprid had a significant positive association with body fat percentage among smokers (β=5.03, 95% CI [1.43, 8.62]), while there was no association among non-smokers (Supplemental Table S2).

Table 1
Study population characteristics for neonicotinoids and adiposity measures among adults (20+ years), NHANES 2015–2016[a].

Characteristics	n (%)	Overweight/ obese n (%)	BMI (kg/m^2) Mean (SD)	Waist circumference (cm) Mean (SD)	FMI (kg/m^2) Mean (SD)	LMI (kg/m^2) Mean (SD)	Fat percentage Mean (SD)	Detectable parent neonicotinoid n (%)	Detectable neonicotinoid metabolite n (%)
Total	1675	1226 (69.9)	29.3 (6.9)	100.2 (17.1)	9.7 (4.3)	18.3 (3.4)	32.6 (8.4)	193 (11.6)	711 (42.9)
Sex									
P-value		0.071	0.756	<0.001	<0.001	<0.001	<0.001	0.531	0.090
Male	798 (48.8)	588 (50.7)	29.4 (6.6)	102.8 (17.0)	7.9 (3.5)	19.8 (3.1)	26.8 (6.3)	95 (51.5)	304 (45.0)
Female	877 (51.2)	638 (49.3)	29.3 (7.2)	97.7 (16.8)	11.5 (4.4)	16.9 (3.0)	38.3 (6.0)	98 (48.5)	407 (55.0)
Age (years)									
P-value		<0.001	0.067	0.006	0.006	0.065	0.005	0.139	0.923
20–29	283 (18.1)	167 (13.6)	27.6 (7.9)	92.6 (19.3)	8.7 (4.7)	17.7 (3.3)	30.2 (9.6)	35 (16.4)	126 (18.6)
30–39	277 (17.4)	195 (17.1)	29.8 (7.4)	99.9 (16.7)	9.9 (4.6)	19.0 (3.6)	32.0 (8.1)	31 (18.2)	128 (18.2)
40–49	300 (17.8)	233 (18.8)	29.4 (6.1)	100.6 (14.3)	10.0 (3.7)	18.3 (3.2)	33.7 (7.2)	44 (25.5)	134 (18.1)
50–59	270 (18.8)	202 (19.4)	29.7 (6.6)	101.7 (15.6)	10.4 (4.1)	18.3 (3.3)	34.5 (8.0)	35 (20.9)	101 (18.2)
60–69	291 (15.7)	231 (17.6)	30.6 (7.2)	105.5 (18.2)	–	–	–	20 (7.9)	116 (14.6)
>70	254 (12.3)	198 (13.5)	28.8 (5.4)	103.0 (14.5)	–	–	–	28 (11.1)	106 (12.4)
Race/ethnicity									
P-value		<0.001	0.005	0.031	0.005	0.039	0.010	0.017	0.206
Non-Hispanic Asian/Other Race/Multiracial	259 (10.1)	136 (8.5)	27.9 (6.5)	96.1 (16.0)	9.2 (3.4)	17.7 (3.1)	32.7 (6.7)	47 (16.2)	134 (12.0)
Non-Hispanic White	523 (63.5)	360 (61.2)	28.9 (6.8)	100.4 (17.4)	9.4 (4.2)	18.0 (3.3)	32.2 (8.4)	51 (58.3)	197 (61.7)
Non-Hispanic Black	390 (11.3)	311 (12.7)	31.2 (7.6)	101.8 (18.1)	10.5 (5.1)	19.3 (3.4)	32.5 (9.9)	43 (10.9)	168 (11.5)
Mexican-American/Other Hispanic	503 (15.1)	419 (17.6)	30.7 (6.8)	101.0 (15.2)	10.7 (4.6)	19.1 (3.4)	33.9 (8.3)	52 (14.6)	212 (14.9)
Marital status									
P-value		0.064	0.344	0.119	0.084	0.441	0.001	0.500	0.051
Married/Living with partner	980 (63.6)	733 (65.6)	29.5 (6.9)	101.1 (17.1)	9.9 (4.2)	18.5 (3.5)	32.9 (8.0)	115 (61.5)	428 (67.3)
Widowed/Never married	444 (23.1)	300 (20.6)	28.5 (7.2)	97.8 (17.8)	9.1 (4.7)	18.0 (3.1)	31.0 (9.4)	56 (27.4)	180 (20.5)
Divorced/Separated	251 (13.3)	193 (13.8)	29.7 (6.6)	100.5 (15.6)	10.4 (4.1)	18.3 (3.3)	34.4 (7.9)	22 (11.2)	103 (12.2)
Monthly family income									
P-value		0.358	0.340	0.634	0.172	0.557	0.479	0.970	0.194
High	749 (63.0)	534 (62.3)	29.1 (6.8)	100.2 (16.9)	9.5 (4.1)	18.2 (3.4)	32.4 (7.9)	95 (63.1)	343 (66.4)
Medium	235 (12.9)	167 (12.5)	29.0 (6.7)	99.2 (17.3)	10.0 (4.9)	18.3 (3.2)	32.8 (9.7)	23 (12.5)	93 (11.8)
Low	568 (24.1)	437 (25.2)	30.2 (7.7)	101.4 (18.1)	10.3 (4.7)	18.7 (3.4)	33.3 (8.6)	56 (24.5)	218 (21.7)
Current health status									
P-value		<0.001	<0.001	<0.001	<0.001	0.001	<0.001	0.669	0.283
Excellent/Very good	504 (41.7)	304 (34.6)	27.2 (5.7)	94.9 (15.0)	8.6 (3.7)	17.5 (3.0)	30.8 (8.4)	63 (45.1)	228 (45.0)
Good	644 (41.4)	490 (44.6)	30.3 (7.1)	103.2 (17.5)	10.2 (4.5)	18.7 (3.5)	33.1 (8.2)	69 (39.8)	262 (40.3)
Fair/Poor	390 (16.9)	333 (20.8)	32.3 (7.5)	107.3 (17.5)	11.7 (4.6)	19.4 (3.5)	35.6 (7.9)	40 (15.1)	157 (14.7)
Physical activity									
P-value		0.607	0.431	0.667	0.680	0.837	0.580	0.533	0.489
Active	438 (52.4)	296 (51.1)	28.2 (6.6)	97.2 (17.4)	9.1 (4.0)	18.2 (3.3)	31.3 (8.1)	71 (55.3)	216 (54.0)
Inactive	382 (47.6)	269 (48.9)	28.7 (6.8)	98.0 (16.0)	9.3 (4.1)	18.1 (3.2)	31.9 (8.7)	49 (44.7)	185 (46.0)
Thyroid issues									
P-value		0.007	0.006	0.019	0.016	0.394	<0.001	0.796	0.948
Present	178 (11.1)	141 (13.0)	31.1 (7.4)	104.3 (17.2)	12.1 (4.7)	17.8 (3.4)	38.3 (5.9)	18 (11.6)	73 (11.2)
Absent	1496 (88.9)	1084 (87.0)	29.1 (6.8)	99.7 (17.0)	9.5 (4.2)	18.4 (3.4)	32.1 (8.4)	175 (88.4)	638 (88.8)
Calorie intake (kcal)									
P-value		0.939	0.982	0.307	0.002	0.004	<0.001	0.910	0.105
<1447	390 (21.2)	288 (21.2)	29.3 (6.9)	99.0 (17.0)	11.2 (4.6)	18.0 (3.5)	36.4 (7.2)	47 (19.7)	165 (20.9)
1447–1975	386 (24.2)	280 (23.7)	29.2 (7.4)	99.8 (18.1)	10.1 (4.6)	17.5 (3.3)	34.4 (8.3)	37 (24.0)	153 (21.2)

Table 1 (*continued*)

Characteristics	n (%)	Overweight/obese n (%)	BMI (kg/m²) Mean (SD)	Waist circumference (cm) Mean (SD)	FMI (kg/m²) Mean (SD)	LMI (kg/m²) Mean (SD)	Fat percentage Mean (SD)	Detectable parent neonicotinoid n (%)	Detectable neonicotinoid metabolite n (%)
1976–2531	388 (27.7)	294 (28.2)	29.4 (6.4)	100.9 (15.6)	9.9 (4.1)	18.3 (3.1)	33.1 (8.1)	41 (26.8)	161 (26.4)
>2531	388 (26.9)	278 (27.0)	29.5 (6.9)	101.7 (17.7)	8.6 (3.8)	19.3 (3.4)	28.7 (7.9)	49 (29.5)	177 (31.5)
Smoking status									
P-value		0.891	0.532	0.246	0.495	0.278	0.219	0.091	<0.001
Smoker	390 (24.2)	274 (24.1)	29.6 (7.3)	101.4 (17.9)	9.4 (4.3)	18.7 (3.5)	31.5 (8.4)	36 (19.4)	103 (15.4)
Non-smoker	1222 (75.8)	911 (75.9)	29.2 (6.7)	99.8 (16.7)	9.7 (4.2)	18.2 (3.3)	32.8 (8.3)	150 (80.6)	580 (84.6)
BPA (µg/g cr)									
P-value		0.098	0.140	0.036	0.373	0.287	0.258	0.836	0.920
<0.6	414 (24.4)	309 (25.8)	29.5 (6.5)	101.7 (16.8)	9.6 (4.0)	18.7 (3.3)	31.9 (7.8)	55 (26.1)	191 (25.1)
0.6–0.99	417 (24.1)	304 (23.1)	29.2 (7.1)	99.2 (17.7)	9.7 (4.6)	18.4 (3.3)	32.2 (8.6)	51 (23.5)	181 (23.8)
1–1.8	411 (25.6)	290 (23.8)	28.7 (6.7)	98.3 (16.0)	9.5 (4.4)	18.0 (3.2)	32.4 (8.8)	46 (27.4)	172 (24.7)
>1.8	413 (26.0)	312 (27.4)	30.0 (7.2)	102.2 (17.5)	10.3 (4.3)	18.4 (3.6)	33.9 (8.4)	36 (23.0)	160 (26.4)

[a] Percent, mean, and SD values presented are weighted to account for the NHANES complex survey design.

Table 2

Estimated differences (β) and 95% confidence intervals (CI) in adiposity measures by detectable concentrations of urinary neonicotinoids in US adults, NHANES, 2015–2016[a].

	Fat mass index (N = 822) β (95% CI)	Lean mass index (N = 844) β (95% CI)	Body fat % (N = 824) β (95% CI)	Waist circumference (cm) (N = 1462) β (95% CI)	BMI (kg/m²) (N = 1517) β (95% CI)
Any parent neonicotinoid					
Detect	−0.14 (−1.11, 0.82)	−0.45 (−1.35, 0.44)	0.24 (−0.96, 1.44)	−1.67 (−4.74, 1.41)	−0.77 (−2.27, 0.73)
Non-detect	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Acetamiprid					
Detect	−3.17 (−4.79, −1.54)	−3.17 (−5.17, −1.17)	−4.41 (−8.20, −0.62)	−9.80 (−19.08, −0.51)	−3.88 (−7.25, −0.51)
Non-detect	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Clothianidin					
Detect	−0.10 (−1.21, 1.01)	−0.49 (−1.66, 0.68)	0.40 (−1.27, 2.07)	−0.94 (−4.63, 2.74)	−0.71 (−2.37, 0.95)
Non-detect	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Imidacloprid					
Detect	0.05 (−1.40, 1.49)	−0.06 (−1.15, 1.02)	0.28 (−1.64, 2.20)	−2.04 (−5.77, 1.69)	−0.53 (−2.61, 1.55)
Non-detect	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Any neonicotinoid metabolite					
Detect	0.24 (−0.37, 0.86)	0.62 (0.03, 1.21)	−0.15 (−1.01, 0.70)	−0.47 (−2.36, 1.42)	0.15 (−0.65, 0.95)
Non-detect	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
5-hydroxy-imidacloprid					
Detect	0.17 (−0.58, 0.93)	0.67 (0.04, 1.29)	−0.15 (−1.43, 1.13)	−0.61 (−2.94, 1.72)	−0.03 (−0.91, 0.84)
Non-detect	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
N-desmethyl-acetamiprid					
Detect	0.30 (−0.36, 0.96)	0.60 (−0.06, 1.26)	−0.05 (−0.90, 1.00)	−0.01 (−2.35, 2.33)	0.28 (−0.60, 1.17)
Non-detect	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)

[a] Adjusted by age, race/ethnicity, sex, marital status, current health status, and thyroid status.

Table 3
Incidence rate ratios (IRRs) and 95% confidence intervals (CI) in overweight/obese measures by detectable concentrations of urinary neonicotinoids in US adults, NHANES, 2015–2016[a].

	Overweight/Obese	Overweight	Obese
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
Any parent neonicotinoid			
Detect	0.91 (0.69, 1.19)	1.17 (0.79, 1.74)	0.72 (0.50, 1.05)
Non-detect	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Acetamiprid			
Detect	0.60 (0.33, 1.08)	0.55 (0.20, 1.51)	0.64 (0.20, 2.00)
Non-detect	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Clothianidin			
Detect	0.85 (0.64, 1.12)	1.13 (0.70, 1.83)	0.67 (0.43, 1.04)
Non-detect	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Imidacloprid			
Detect	1.04 (0.79, 1.37)	1.24 (0.70, 2.17)	0.87 (0.51, 1.46)
Non-detect	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Any neonicotinoid metabolite			
Detect	1.04 (0.97, 1.11)	1.03 (0.76, 1.40)	1.04 (0.83, 1.31)
Non-detect	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
5-hydroxy-imidacloprid			
Detect	1.11 (1.04, 1.18)	1.08 (0.81, 1.46)	1.13 (0.90, 1.42)
Non-detect	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
N-desmethyl-acetamiprid			
Detect	1.02 (0.93, 1.13)	1.05 (0.77, 1.44)	1.00 (0.78, 1.28)
Non-detect	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)

[a] Adjusted by age, race/ethnicity, sex, marital status, health status, and thyroid status.

3.3. Effect measure modification by sex

There was evidence of effect measure modification by sex for the association between *N*-desmethyl-acetamiprid and LMI (*P* for interaction = 0.075) (Fig. 1). A significant positive association was observed between detectable urinary *N*-desmethyl-acetamiprid and LMI among males (β = 1.14 kg/m^2, 95% CI [0.38, 1.90]), while a null association was observed in females (β = 0.14 kg/m^2, 95% CI [−0.79, 1.07]). There was evidence of significant sex differences between *N*-desmethyl-acetamiprid and FMI (*P* for interaction = 0.095) and body fat percentage (*P* for interaction = 0.072). Males had a positive association while females had an inverse association, however the sex-specific regression estimates were not statistically significant (*P* > 0.05). Effect measure modification by sex was not significant for the associations between neonicotinoid metabolites with waist circumference and BMI (Supplemental Table S3). Similar results were observed for the association with being overweight or obese (Supplemental Table S4).

3.4. Sensitivity analyses

Additional adjustment for BPA concentrations as well as removal of outliers for FMI, LMI, waist circumference, and BMI did not change the overall conclusions of the study (results not shown). However, after additionally adjusting for daily caloric intake, 5-hydroxy-imidacloprid was no longer associated with LMI (Supplemental Tables S5 and S6). Lastly, adjusting for physical activity resulted in some findings that were no longer significant, including the inverse associations between acetamiprid with body fat percentage, waist circumference, and BMI as well as the positive association between 5-hydroxy-imidacloprid and LMI (Supplemental Tables S7 and S8). However, an inverse association was still observed between acetamiprid with FMI and LMI. Additionally, it was found that clothianidin had a significant inverse association with LMI and BMI. With regard to the effect measure modification analyses by sex, adjustment for daily kilocalorie intake showed that sex differences for the association between *N*-desmethyl-acetamiprid and FMI were no longer present (Supplementary Tables S9 and S10). Similarly, adjustment for physical activity no longer showed evidence of sex differences between imidacloprid and *N*-desmethyl-acetamiprid with LMI (Supplementary Tables S11 and S12). Lastly, our conclusions did not differ following the examination of the structural validity of the statistical models using robustness checks when regression specifications were modified.

4. Discussion

The findings of this study were mixed. While it was observed that detectable levels of acetamiprid in urine were inversely associated with several adiposity measures in adults, detectable levels of 5-hydroxy-imidacloprid were significantly associated with greater odds of being overweight/obese. Further, any detectable neonicotinoid metabolite and 5-hydroxy-imidacloprid were associated with increased LMI. Evidence of effect measure modification by sex was present, however, the findings were inconsistent.

Previous toxicological studies in other mammalian species have shown mixed results with respect to the association between neonicotinoids and adiposity. Some studies have reported an inverse association between acetamiprid and obesity (Mosbah et al., 2018; Sheets et al., 2016; Terayama et al., 2016, 2018). Terayama et al. (2016, 2018) conducted a study in 8-week old mice by having four groups, including a control group, a group given dimethyl sulfoxide, a group given 10 times greater than the No Observed Adverse Effect Level (NOAEL) of acetamiprid, and a group given 100 times greater than the NOAEL acetamiprid. They observed that mice administered acetamiprid at a level 100 times greater than the NOAEL showed a significant decrease in body weight as compared to the control group or the group given a dose of acetamiprid 10 times greater than NOAEL. Similarly, Mosbah et al. (2018) reported that male Wistar rats aged 8–12 weeks old given 27 mg/kg/day acetamiprid in their diet over a 45 day period exhibited a greater decrease in weight as compared to the control group. Sheets et al. (2016) divided 25–30 pregnant rats into four groups, where each group was administered a different dosage of acetamiprid. Outcome assessment was done on the 20th gestational day, where it was observed that there was a 4–5% decrease in body weight among the pregnant rats dosed with acetamiprid as compared to the control group. Additionally, they also observed that the offspring of these rats had a 5–10% lower body weight compared to offspring of the control group, when measured on the first postnatal day (PND). Imidacloprid had an inverse association with body weight in adult mice (Arfat et al., 2014; Burke et al., 2018) and female rats (Bhardwaj et al., 2010). However, Sun et al. (2016, 2017) observed that imidacloprid was associated with an increase in
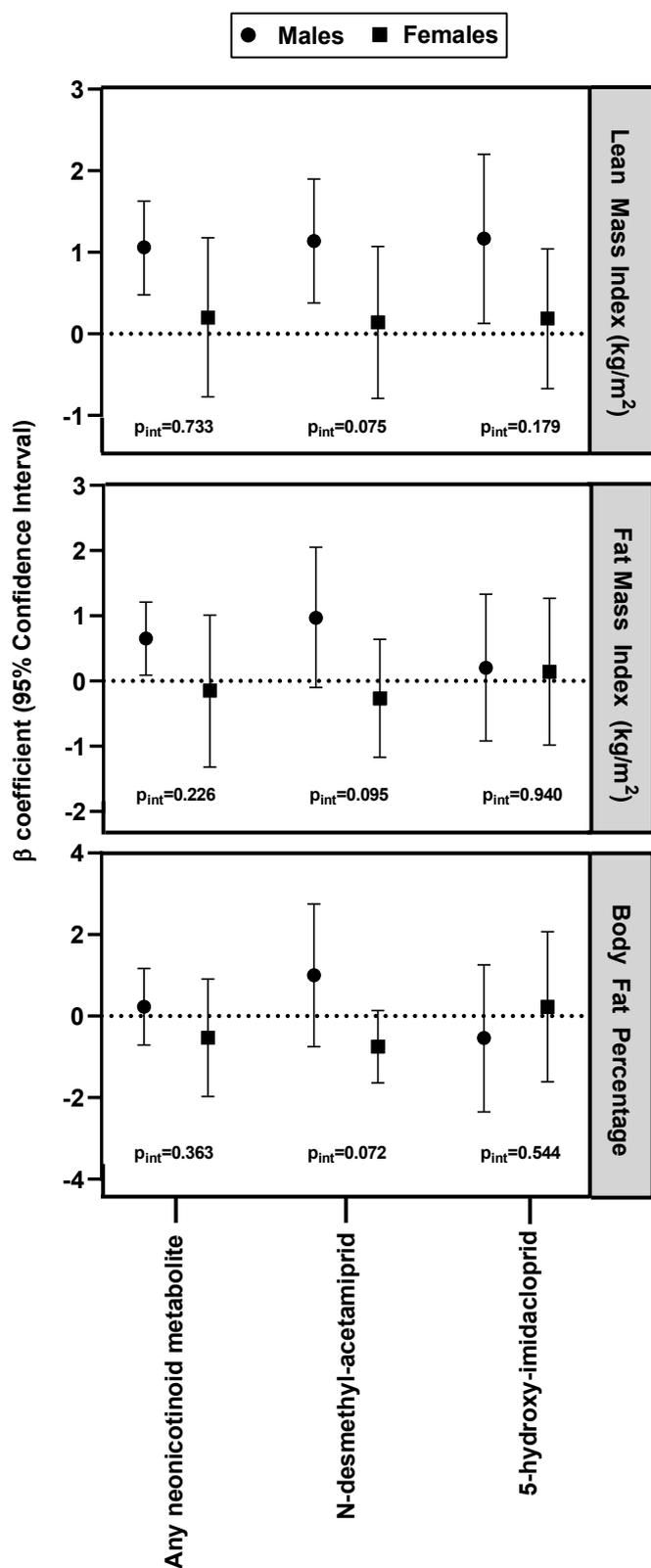
Fig. 1. Association between detectable levels of neonicotinoid metabolites with adiposity measures in adults by sex. Adjusted by age, race/ethnicity, sex, marital status, current health status, and thyroid status.

body weight, with similar positive associations seen with clothianidin and body weight (Tanaka, 2012).

Neonicotinoids may be associated with decreased adiposity for a few reasons. Imidacloprid toxicity has been associated with a reduction in

appetite among mice. A study by Burke et al. (2018) showed that mice fed an imidacloprid rich diet subsequently reduced their food intake, which led to a decrease in body weight. This was attributed to an increase in cholinergic activity secondary to chronic neonicotinoid exposure. An increase in cholinergic activity leads to changes in acetylcholine receptor (AchR) signaling frequency, which is partially responsible for appetite suppression (Herman et al., 2016). Imidacloprid has also been linked to a potential "anorexic" effect among exposed white-tailed songbirds as compared to the controls (Eng et al., 2019). Additionally, there is evidence to support alteration of gut microflora as a result of imidacloprid toxicity, specifically in Acetobacter and Lactobacillus genera (Yuan et al., 2019). Imidacloprid is chemically similar to acetamiprid, hence these mechanisms of action may explain the findings of our study as well.

Imidacloprid has been associated with the exacerbation of metabolic stress which may lead to weight gain (Sun et al., 2017). Disruptions in metabolic homeostasis are associated with an increased production of glucocorticoids, which are catalysts for an increased rate of adipocyte development and differentiation (Karalis et al., 2009). This mechanism is consistent with the development of obesity, which could explain the positive associations between 5-hydroxy-imidacloprid and LMI seen in this study.

Mixed findings in the present study for 5-hydroxy-imidacloprid may be partially attributed to the usage of BMI to categorize individuals as overweight and obese. Although BMI is a common measure used to assess obesity, it is not a good indicator of the type of body mass assessed and is unable to make a distinction between fat mass and lean mass (Weber et al., 2014). Our findings show that 5-hydroxy-imidacloprid increases fat mass along with an increase in lean mass, which may explain its positive association with LMI and being overweight or obese.

While 5-hydroxy-imidacloprid showed a significant positive association with being overweight/obese, the parent neonicotinoid (imidacloprid) was not associated with any measures of adiposity. A potential reason could be related to a higher detection frequency observed for 5-hydroxy-imidacloprid (20.0%) as compared to imidacloprid (4.1%) among the study participants. Metabolism of imidacloprid in rats showed that it is not distributed to adipose tissue (Sheets, 2010). This might explain why imidacloprid demonstrated non-significant findings in this study.

Effect modification by sex was observed for the associations between *N*-desmethyl-acetamiprid with FMI, LMI and body fat percentage, though it is unclear whether males or females are more sensitive to neonicotinoids. A significant positive association was observed between detectable urinary *N*-desmethyl-acetamiprid and LMI among males, while a null association was observed in females. Sex differences seen in the association between neonicotinoid metabolites and adiposity may be due to different biological mechanisms. Findings by Lukowicz et al. (2018) indicate that increased oxidative stress in male mice may be responsible for the adipogenic effect of neonicotinoids. This generates higher levels of triglycerides in the liver, which may be responsible for weight changes. However, another study on male rats observed an increase in cholinergic activity induced by clothianidin, which subsequently increased intestinal motility, leading to a reduction in body weight (Onaru et al., 2020). In female mice, findings indicated that neonicotinoids may be responsible for the activation of peroxisome proliferator-activated receptor (PPAR)-alpha (a prominent receptor involved in fatty acid metabolism) as well as the release of free radicals, which may be responsible for an increase in fat metabolism, subsequently leading to reduced body weight (Lukowicz et al., 2018). A protective effect generated by estrogen could also be a reason for reduced adiposity associated with neonicotinoid exposure (Sun et al., 2017). This could explain the mixed directionality of the association seen among males and females in this study. However, Sun et al. conducted two separate studies on male and female mice, both of which showed an increase in weight associated with imidacloprid, which led them to conclude that neonicotinoid associated weight gain is

independent of sex (2016; 2017).

Epidemiological studies conducted have reported positive and null associations between neonicotinoids and adiposity (Makris et al., 2019; Peng et al., 2020; Wang et al., 2020). Peng et al. (2020) observed that increased concentrations of imidacloprid in hair samples were positively associated with BMI among Chinese women aged 25–45 years. In contrast, a null association was observed between concentrations of a neonicotinoid metabolite (6-chloronicotinic acid) and BMI z-scores in a randomized controlled trial among 11–12-year-old children from 6 schools in Cyprus, where the control group was given an organic diet while the other group had a regular diet (Makris et al., 2019). However, detectable levels of *N*-desmethyl-acetamiprid in urine were associated with greater odds of being obese among a cohort of 7–11-year-old children in Shanghai, China, although results were only borderline significant (Wang et al., 2020). The present study did not find a positive association between *N*-desmethyl-acetamiprid and obesity. A possible reason could be due to the differences in the detection frequencies of *N*-desmethyl-acetamiprid. This study had a detection frequency of 32.4% in urine for *N*-desmethyl-acetamiprid, while the study by Wang et al. (2020) had a detection frequency of 62.4%. The higher detection frequency, along with differences related to geographic location may explain the differences in the results.

This study had several strengths, including the usage of data from NHANES, a nationally representative population, which increases the generalizability of the findings. Second, the use of NHANES data made it possible to adjust for a wide range of potential confounders. Third, a number of sensitivity analyses were performed to ensure the final conclusions did not change, including additionally adjusting for BPA concentrations, daily kilocalorie intake, and weekly physical activity levels. Fourth, a comprehensive list of adiposity measures was used. Previous epidemiological studies only used BMI (Makris et al., 2019; Peng et al., 2020; Wang et al., 2020). Fifth, effect measure modification by sex was analyzed. This had not been examined in previous epidemiological studies to our knowledge, although some toxicological studies have reported on potential sex differences in the association with neonicotinoids and adiposity (Bhasker and Mohanty, 2014; Burke et al., 2018; Lukowicz et al., 2018; Tanaka, 2012).

This study had a number of limitations. First, since this was a cross-sectional exploratory study, a temporal association between neonicotinoids and adiposity cannot be made. Second, neonicotinoids have a short half-life. Quantified concentrations of neonicotinoids may not reflect true exposure of neonicotinoids over time, which may have led to misclassification bias. Third, since a number of questions were self-reported, there could be a reporting bias. Fourth, a two-year cycle data may not be sufficient to study sex-specific associations. Fifth, detection frequencies of neonicotinoids were lower than in previous epidemiological studies, which may affect the results. Further, some findings should be interpreted with caution given the low detection frequencies of several neonicotinoid compounds. In particular, the inverse associations between detectable concentrations of acetamiprid with FMI, LMI, body fat percentage, waist circumference, and BMI as acetamiprid had a detection frequency of 0.3%. Finally, this study did not examine a dose related response since neonicotinoid measures were examined as "detect" versus "non-detect."

5. Conclusion

The current study was the first to our knowledge to examine whether exposure to neonicotinoids is associated with adiposity in US adults. Findings were inconsistent since acetamiprid had an inverse association with adiposity measures, while 5-hydroxy-imidacloprid had a positive association with being overweight/obese, and a positive association with LMI. There was evidence of effect modification by sex in the association, however, results were inconsistent with regard to the directionality by sex. Future research should focus on examining the association between neonicotinoids and adiposity using a prospective study design. Additionally, further studies should examine this association in geographic locations with higher neonicotinoid use.

Credit author statement

All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept (**AMG, AMV**), design (**AMG, AMV**), analysis (AMG), interpretation of data (**AMG, SM, CC, CZ, AC, AMV**), writing (**AMG**), or revision of the manuscript (**AMG, SM, CC, CZ, AC, AMV**).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2022.134450.

References

Aguinis, H., 1995. Statistical power problems with moderated multiple regression in management research. J. Manag. 21 (6), 1141–1158. https://doi.org/10.1016/0149-2063(95)90026-8.

Arfat, Y., Mahmood, N., Tahir, M.U., Rashid, M., Anjum, S., Zhao, F., Li, D.J., Sun, Y.L., Hu, L., Zhihao, C., Yin, C., Shang, P., Qian, A.R., 2014. Effect of imidacloprid on hepatotoxicity and nephrotoxicity in male albino mice. Toxicology Reports 1, 554–561. https://doi.org/10.1016/j.toxrep.2014.08.004.

Baker, S.E., Serafim, A.B., Morales-Agudelo, P., Vidal, M., Calafat, A.M., Ospina, M., 2019. Quantification of DEET and neonicotinoid pesticide biomarkers in human urine by online solid-phase extraction high-performance liquid chromatography-tandem mass spectrometry. Anal. Bioanal. Chem. 411 (3), 669–678. https://doi.org/10.1007/s00216-018-1481-0.

Bass, C., Field, L.M., 2018. Neonicotinoids. Curr. Biol.: CB 28 (14), R772–R773. https://doi.org/10.1016/j.cub.2018.05.061.

Bhardwaj, S., Srivastava, M.K., Kapoor, U., Srivastava, L.P., 2010. A 90 days oral toxicity of imidacloprid in female rats: morphological, biochemical and histopathological evaluations. Food Chem. Toxicol. : An International Journal Published for the British Industrial Biological Research Association 48 (5), 1185–1190. https://doi.org/10.1016/j.fct.2010.02.009.

Bhaskar, R., Mohanty, B., 2014. Pesticides in mixture disrupt metabolic regulation: in silico and in vivo analysis of cumulative toxicity of mancozeb and imidacloprid on body weight of mice. Gen. Comp. Endocrinol. 205, 226–234. https://doi.org/10.1016/j.ygcen.2014.02.007.

Burke, A.P., Niibori, Y., Terayama, H., Ito, M., Pidgeon, C., Arsenault, J., Camarero, P.R., Cummins, C.L., Mateo, R., Sakabe, K., Hampson, D.R., 2018. Mammalian susceptibility to a neonicotinoid insecticide after fetal and early postnatal exposure. Sci. Rep. 8 (1), 16639. https://doi.org/10.1038/s41598-018-35129-5.

CDC, 2020. *About Adult BMI*. Healthy Weight, Nutrition, and Physical Activity. https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html.

Chen, M., Tao, L., McLean, J., Lu, C., 2014. Quantitative analysis of neonicotinoid insecticide residues in foods: implication for dietary exposures. J. Agric. Food Chem. 62 (26), 6082–6090. https://doi.org/10.1021/jf501397m.

Eng, M.L., Stutchbury, B., Morrissey, C.A., 2019. A neonicotinoid insecticide reduces fueling and delays migration in songbirds. Science (New York, N.Y.) 365 (6458), 1177–1180. https://doi.org/10.1126/science.aaw9419.

June 18 National Health and Nutrition Examination Survey, 2018. https://www.cdc.gov/visionhealth/vehss/data/national-surveys/national-health-and-nutrition-examination-survey.html.

Goulson, D., 2013. Review: an overview of the environmental risks posed by neonicotinoid insecticides. J. Appl. Ecol. 50, 977–987 doi:10.1111/1365-2664.12111.

Grün, F., Blumberg, B., 2009. Endocrine disrupters as obesogens. Mol. Cell. Endocrinol. 304 (1–2), 19–29. https://doi.org/10.1016/j.mce.2009.02.018.

Han, S.S., Kim, K.W., Kim, K.I., Na, K.Y., Chae, D.W., Kim, S., Chin, H.J., 2010. Lean mass index: a better predictor of mortality than body mass index in elderly Asians. J. Am. Geriatr. Soc. 58 (2), 312–317. https://doi.org/10.1111/j.1532-5415.2009.02672.x.

Han, W., Tian, Y., Shen, X., 2018. Human exposure to neonicotinoid insecticides and the evaluation of their potential toxicity: an overview. Chemosphere 192, 59–65. https://doi.org/10.1016/j.chemosphere.2017.10.149.

Herman, A.M., Ortiz-Guzman, J., Kochukov, M., Herman, I., Quast, K.B., Patel, J.M., Tepe, B., Carlson, J.C., Ung, K., Selever, J., Tong, Q., Arenkiel, B.R., 2016. A cholinergic basal forebrain feeding circuit modulates appetite suppression. Nature 538 (7624), 253–256. https://doi.org/10.1038/nature19789.

Hernández, A.F., Casado, I., Pena, G., Gil, F., Villanueva, E., Pla, A., 2008. Low level of exposure to pesticides leads to lung dysfunction in occupationally exposed subjects. Inhal. Toxicol. 20 (9), 839–849. https://doi.org/10.1080/08958370801905524.

Ihara, M., Matsuda, K., 2018. Neonicotinoids: molecular mechanisms of action, insights into resistance and impact on pollinators. Current Opinion in Insect Science 30, 86–92. https://doi.org/10.1016/j.cois.2018.09.009.

Karalis, K.P., Giannogonas, P., Kodela, E., Koutmani, Y., Zoumakis, M., Teli, T., 2009. Mechanisms of obesity and related pathology: linking immune responses to metabolic stress. FEBS J. 276 (20), 5747–5754. https://doi.org/10.1111/j.1742-4658.2009.07304.x.

Kyle, U.G., Schutz, Y., Dupertuis, Y.M., Pichard, C., 2003. Body composition interpretation. Contributions of the fat-free mass index and the body fat mass index. Nutrition 19 (7–8), 597–604. https://doi.org/10.1016/s0899-9007(03)00061-3.

Leemans, M., Couderq, S., Demeneix, B., Fini, J.B., 2019. Pesticides with potential thyroid hormone-disrupting effects: a review of recent data. Front. Endocrinol. 10, 743. https://doi.org/10.3389/fendo.2019.00743.

Lukowicz, C., Ellero-Simatos, S., Régnier, M., Polizzi, A., Lasserre, F., Montagner, A., Lippi, Y., Jamin, E.L., Martin, J.F., Naylies, C., Canlet, C., Debrauwer, L., Bertrand-Michel, J., Al Saati, T., Théodorou, V., Loiseau, N., Mselli-Lakhal, L., Guillou, H., Gamet-Payrastre, L., 2018. Metabolic effects of a chronic dietary exposure to a low-dose pesticide cocktail in mice: sexual dimorphism and role of the constitutive androstane receptor. Environ. Health Perspect. 126 (6), 067007 https://doi.org/10.1289/EHP2877.

Makris, K.C., Konstantinou, C., Andrianou, X.D., Charisiadis, P., Kyriacou, A., Gribble, M.O., Christophi, C.A., 2019. A cluster-randomized crossover trial of organic diet impact on biomarkers of exposure to pesticides and biomarkers of oxidative stress/inflammation in primary school children. PLoS One 14 (9), e0219420. https://doi.org/10.1371/journal.pone.0219420.

Marfo, J.T., Fujioka, K., Ikenaka, Y., Nakayama, S.M., Mizukawa, H., Aoyama, Y., Ishizuka, M., Taira, K., 2015. Relationship between urinary N-desmethyl-acetamiprid and typical symptoms including neurological findings: a prevalence case-control study. PLoS One 10 (11), e0142172. https://doi.org/10.1371/journal.pone.0142172.

Mikolić, A., Karačonji, I.B., 2018. Imidacloprid as reproductive toxicant and endocrine disruptor: investigations in laboratory animals. Arh. Hig. Rad. Toksikol. 69 (2), 103–108. https://doi.org/10.2478/aiht-2018-69-3144.

Mosbah, R., Djerrou, Z., Mantovani, A., 2018. Protective effect of Nigella sativa oil against acetamiprid induced reproductive toxicity in male rats. Drug Chem. Toxicol. 41 (2), 206–212. https://doi.org/10.1080/01480545.2017.1337127.

Nauen, R., Jeschke, P., Copping, L., 2008. In focus: neonicotinoid insecticides. Pest Manag. Sci. 64 (11), 1081. https://doi.org/10.1002/ps.1659.

Onaru, K., Ohno, S., Kubo, S., Nakanishi, S., Hirano, T., Mantani, Y., Yokoyama, T., Hoshi, N., 2020. Immunotoxicity evaluation by subchronic oral administration of clothianidin in Sprague-Dawley rats. J. Vet. Med. Sci. 82 (3), 360–372. https://doi.org/10.1292/jvms.19-0689.

Ospina, M., Wong, L.Y., Baker, S.E., Serafim, A.B., Morales-Agudelo, P., Calafat, A.M., 2019. Exposure to neonicotinoid insecticides in the U.S. General population: data from the 2015-2016 national health and nutrition examination survey. Environ. Res. 176, 108555. https://doi.org/10.1016/j.envres.2019.108555.

Peng, F.J., Hardy, E.M., Mezzache, S., Bourokba, N., Palazzi, P., Stojiljkovic, N., Bastien, P., Li, J., Soeur, J., Appenzeller, B., 2020. Exposure to multiclass pesticides among female adult population in two Chinese cities revealed by hair analysis. Environ. Int. 138, 105633. https://doi.org/10.1016/j.envint.2020.105633.

Sheets, L.P., 2010. Chapter 95 - Imidacloprid: A Neonicotinoid Insecticide. Hayes' Handbook of Pesticide Toxicology, third ed. Academic Press https://doi-org.ezproxy.library.unlv.edu/10.1016/B978-0-12-374367-1.00095-1.

Sheets, L.P., Li, A.A., Minnema, D.J., Collier, R.H., Creek, M.R., Peffer, R.C., 2016. A critical review of neonicotinoid insecticides for developmental neurotoxicity. Crit. Rev. Toxicol. 46 (2), 153–190. https://doi.org/10.3109/10408444.2015.1090948.

Starner, K., Goh, K.S., 2012. Detections of the neonicotinoid insecticide imidacloprid in surface waters of three agricultural regions of California, USA, 2010-2011. Bull. Environ. Contam. Toxicol. 88 (3), 316–321. https://doi.org/10.1007/s00128-011-0515-5.

Sun, Q., Xiao, X., Kim, Y., Kim, D., Yoon, K.S., Clark, J.M., Park, Y., 2016. Imidacloprid promotes high fat diet-induced adiposity and insulin resistance in male C57BL/6J mice. J. Agric. Food Chem. 64 (49), 9293–9306. https://doi.org/10.1021/acs.jafc.6b04322.

Sun, Q., Qi, W., Xiao, X., Yang, S.H., Kim, D., Yoon, K.S., Clark, J.M., Park, Y., 2017. Imidacloprid promotes high fat diet-induced adiposity in female C57BL/6J mice and enhances adipogenesis in 3T3-L1 adipocytes via the AMPkα-mediated pathway. J. Agric. Food Chem. 65 (31), 6572–6581. https://doi.org/10.1021/acs.jafc.7b02584.

Tanaka, T., 2012. Reproductive and neurobehavioral effects of clothianidin administered to mice in the diet. Birth Defects Res. Part B Dev. Reproductive Toxicol. 95 (2), 151–159. https://doi.org/10.1002/bdrb.20349.

Terayama, H., Endo, H., Tsukamoto, H., Matsumoto, K., Umezu, M., Kanazawa, T., Ito, M., Sato, T., Naito, M., Kawakami, S., Fujino, Y., Tatemichi, M., Sakabe, K., 2016. Acetamiprid accumulates in different amounts in murine brain regions. Int. J. Environ. Res. Publ. Health 13 (10), 937. https://doi.org/10.3390/ijerph13100937.

Terayama, H., Qu, N., Endo, H., Ito, M., Tsukamoto, H., Umemoto, K., Kawakami, S., Fujino, Y., Tatemichi, M., Sakabe, K., 2018. Effect of acetamiprid on the immature murine testes. Int. J. Environ. Health Res. 683–696. https://doi.org/10.1080/09603123.2018.1504897, 28(6).

Thiese, M.S., Ronna, B., Ott, U., 2016. P value interpretations and considerations. J. Thorac. Dis. E928–E931. https://doi.org/10.21037/jtd.2016.08.16, 8(9).

Ueyama, J., Harada, K.H., Koizumi, A., Sugiura, Y., Kondo, T., Saito, I., Kamijima, M., 2015. Temporal levels of urinary neonicotinoid and dialkylphosphate concentrations in Japanese women between 1994 and 2011. Environ. Sci. Technol. 49 (24), 14522–14528. https://doi.org/10.1021/acs.est.5b03062.

Wang, H., Yang, D., Fang, H., Han, M., Tang, C., Wu, J., Chen, Y., Jiang, Q., 2020. Predictors, Sources, and Health Risk of Exposure to Neonicotinoids in Chinese School Children: A Biomonitoring-Based Study, vol. 143. Environment International, p. 105918. https://doi.org/10.1016/j.envint.2020.105918. Advance online publication.

Weber, D.R., Leonard, M.B., Shults, J., Zemel, B.S., 2014. A comparison of fat and lean body mass index to BMI for the identification of metabolic syndrome in children and adolescents. J. Clin. Endocrinol. Metabol. 99 (9), 3208–3216. https://doi.org/10.1210/jc.2014-1684.

Yuan, X., Pan, Z., Jin, C., Ni, Y., Fu, Z., Jin, Y., 2019. Gut microbiota: an underestimated and unintended recipient for pesticide-induced toxicity. Chemosphere 227, 425–434. https://doi.org/10.1016/j.chemosphere.2019.04.088.

Zhu, K., Hunter, M., James, A., Lim, E.M., Cooke, B.R., Walsh, J.P., 2017. Discordance between fat mass index and body mass index is associated with reduced bone mineral density in women but not in men: the Busselton Healthy Ageing Study. Osteoporos. Int. : A journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 28 (1), 259–268. https://doi.org/10.1007/s00198-016-3710-8.