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Associations between neonicotinoids and inflammation in US adults using hematological indices

NHANES 2015–2016

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Background: Toxicological studies suggest neonicotinoids increase oxidative stress and inflammation, but few epidemiological studies have explored these effects.

Methods: National Health and Nutrition Examination Survey (NHANES) 2015–2016 data were used to estimate associations between neonicotinoid exposure and inflammatory markers, including the C-reactive protein-to-lymphocyte count ratio (CLR), monocyte-to-high-density lipoprotein ratio (MHR), monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), derived NLR (dNLR), lymphocyte-to-monocyte ratio, platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) using linear and multinomial logistic regression models. Sex was evaluated as a potential modifier.

Results: Detection of any parent neonicotinoid (β = –0.62, 95% confidence interval [CI] = –0.98, –0.26) and imidacloprid (β = –0.48, 95% CI = –0.87, –0.10) was associated with decreased CLR. Clothianidin was linked to reduced MLR (β = –0.04, 95% CI = –0.07, –0.02), but increased lymphocyte-to-monocyte ratio (β = 0.52, 95% CI = 0.27, 0.77). Higher dNLR (β = 0.85; 95% CI = 0.26, 1.43) was noted with detection of any neonicotinoid metabolite. Moderately high PLR was observed with detection of any neonicotinoid metabolite (relative risk ratio [RRR] = 1.63, 95% CI = 1.27, 2.09) or 5-hydroxy-imidacloprid (RRR = 2.19, 95% CI = 1.40, 3.41). Sex-modified analyses showed positive associations in males and inverse associations in females for MHR (P_{int} = 0.099, clothianidin), PLR (P_{int} = 0.026, clothianidin), and SII (P_{int} = 0.056, any parent neonicotinoid; P_{int} = 0.002, clothianidin), while the opposite pattern was noted with CLR (P_{int} = 0.073, any parent neonicotinoid) and NLR (P_{int} = 0.084, clothianidin).

Conclusion: Neonicotinoids may be associated with inflammatory changes, with potential sexual dimorphism. Further studies are required to explore these findings.

Keywords: Neonicotinoids; Inflammation; Epidemiology; Hematological ratios

Introduction

Neonicotinoids, synthetic pesticides first developed in 1991, have gained popularity due to their broad-spectrum activity and insect-selective mechanism of action.[1] These pesticides target nicotinic acetylcholine receptors and have an affinity for insect-specific receptor subtypes, providing a greater margin of safety in mammals.[2] Common neonicotinoids include acetamiprid, clothianidin, imidacloprid, and thiacloprid. High levels of these chemicals have been detected globally in aquatic environments, pollinating insects such as honeybees, soil samples, nontarget flora and fauna, and household dust.[3–11] As neonicotinoids are commonly used in agriculture (especially imidacloprid and clothianidin), human exposure primarily occurs through food, water, diet, dust, and pollen.[12] Studies have reported high detection frequencies of acetamiprid, clothianidin, dinotefuran, flonicamid, imidacloprid, thiacloprid, and thiamethoxam in fruits and vegetables, while more than 90% of tap water sources in the United States (US) contain detectable levels of neonicotinoids, which implies that dietary intake is one of the main routes of neonicotinoid exposure.[13–16] Indoor dust samples from major cities in China show more than 95% detection frequencies of neonicotinoids, indicating that dust inhalation and ingestion are significant exposure routes for humans.[17,18]

What this study adds:
This research investigates the impact of neonicotinoids, a class of newer pesticides often used as substitutes for organophosphates and other legacy pesticides, on inflammatory changes in humans. Toxicological studies have shown that neonicotinoids contribute to increased oxidative stress by promoting the excessive release of reactive oxygen species. However, there is a notable gap in epidemiological studies exploring this connection. This study aims to examine the association between neonicotinoid exposure and novel hematological ratios used as markers of inflammatory changes in a representative sample of adults in the United States.

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This study uses publicly sourced data, available at https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2015.

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Several studies have shown detectable concentrations of neonicotinoids in humans.[12,18–22] Data from the 2015–2016 National Health and Nutritional Examination Survey (NHANES) revealed that nearly 50% of urine samples had detectable concentrations of at least one neonicotinoid biomarker.[23] Additionally, an international study covering countries such as China, Greece, Japan, Korea, Kuwait, Saudi Arabia, Vietnam, and the US reported that over 80% of urine samples had detectable levels of *N*-desmethyl-acetamiprid (a metabolite of acetamiprid) and 6-CN (a metabolite of imidacloprid), with significantly higher concentrations observed in samples from China and Vietnam.[24]

Neonicotinoids have been linked to several adverse health outcomes, including obesity, reproductive abnormalities, insulin and glucose dysregulation, and disruptions in hematological parameters.[25–29] Inflammatory changes resulting from oxidative stress induced by neonicotinoids are believed to be key mediators of systemic dysfunction and tissue damage. Oxidative stress generates reactive oxygen species (ROS) and reactive nitrogen species, which can damage DNA, proteins, and lipids within cells.[30] To repair this cell damage, the body activates mechanisms involving chemokines and growth factors, leading to the deployment of leukocytes, such as neutrophils and monocytes, to mitigate cell damage.[31] Hematological indices could serve as potential markers for chronic inflammation occurring at a systemic level. An epidemiological study from Mexico demonstrated that inflammation associated with pesticide exposure, particularly organophosphates, could be tracked through changes in hematological indices.[32] However, no epidemiological studies to date have specifically examined the association between neonicotinoid exposure and inflammation as characterized in biospecimens.

Chronic inflammation has been shown to alter blood cell levels in the body, particularly affecting neutrophils, lymphocytes, and platelets.[33] Neutrophils play a key role in regulating both innate and adaptive immunity by activating antigen-presenting cells. Similarly, platelets contribute to inflammatory processes by controlling the release of cytokines, such as interleukins, while lymphocytes help limit the spread of inflammation. Emerging hematological parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) have been increasingly used as markers of systemic inflammation across various fields, such as oncology, cardiology, nephrology, diabetes, and autoimmune disorders.[34–36] The systemic immune-inflammation index (SII), which combines neutrophils, lymphocytes, and platelet counts, has been recognized as a reliable indicator of systemic inflammation in a previous NHANES study assessing all-cause mortality.[37] SII has also been used to predict inflammatory changes in cardiovascular, neurological, metabolic, respiratory, and rheumatic diseases.[38] Additionally, the monocyte-to-high-density lipoprotein (HDL) ratio (MHR) has emerged as a useful tool for evaluating chronic inflammation and tumor prognosis.[39] These hematological markers offer valuable insights into the inflammatory processes underlying various diseases.

The primary aim of this study is to investigate the association between detectable urinary neonicotinoid levels and inflammation using hematological indices. To ensure generalizability to the US population, a representative sample of participants was analyzed from the NHANES 2015–2016 survey. A secondary aim is to assess the potential effect measure modification by sex, given existing evidence of differences in neonicotinoid metabolism between males and females.[40]

Methods

Data source and study participants

This study utilized data from the NHANES 2015–2016 survey, a national assessment of health and nutrition conducted on a representative sample of US adults and children through physical examinations and interviews. Funded by the National Center of Health Statistics, under the Centers for Disease Control and Prevention (CDC), the survey maintains confidentiality by deidentifying participant data. It accounts for clustering, stratification, and oversampling during data collection. The 2015–2016 cycle included 9971 participants from 15 counties across the US. Neonicotinoid levels were quantified in urine samples from one-third of participants, and hematological parameters were measured in blood samples from all participants aged 5 years and older. Of the total sample size, 2289 participants had data on at least one urinary neonicotinoid measure and at least one hematological ratio. Several exclusion criteria were applied to reduce confounding. Participants under the age of 20 (n = 881) were excluded to ensure that the study focused on adult participants. Confirmed pregnant participants (n = 17) were excluded so that changes during pregnancy would not skew the study outcome. Additionally, self-reported diagnoses of chronic liver disease (n = 36), arthritis (n = 377), and cancer (n = 138) were excluded, since these conditions are associated with inflammation and may influence the results. Finally, participants using steroids (n = 6) or antibiotics (n = 33) were excluded, as these medications can alter immune responses and hematological markers. After these exclusions, 914 participants were included in the final analysis.

Neonicotinoid assessment

Neonicotinoid measurement was conducted for four parent neonicotinoids – acetamiprid, clothianidin, imidacloprid, and thiacloprid – as well as two metabolites – 5-hydroxy-imidacloprid and *N*-desmethyl-acetamiprid. A 0.2 ml urine sample from each participant was analyzed. The process involved enzymatic hydrolysis of urinary conjugates, followed by online solid-phase extraction, reversed-phase high-performance liquid chromatography separation, and detection via isotope dilution-electrospray ionization tandem mass spectrometry.[41] Strict quality control, in line with CDC guidelines, ensured the accuracy and reliability of the results. The limits of detection (LOD) for the compounds (in µg/l) were as follows: 0.30 for acetamiprid, 0.20 for clothianidin, 0.40 for imidacloprid, 0.03 for thiacloprid, 0.40 for 5-hydroxy-imidacloprid, and 0.20 for *N*-desmethyl-acetamiprid. Neonicotinoid levels were categorized as "detect" (concentration greater than or equal to LOD) or "nondetect" (concentration less than LOD).

Hematological ratios

Whole blood samples were analyzed for all participants over the age of 5 years to obtain a complete blood count, which included a five-part differential count for erythrocytes (red blood cells), leukocytes (white blood cells), platelets, hemoglobin, red cell volume, and leukocyte subtypes. C-reactive protein (CRP) was measured in serum samples using the SYNCHRON system (Beckman Coulter, Brea, CA) high-sensitivity CRP reagent, based on the near-infrared particle immunoassay rate method. HDL was measured in serum samples through chemical reagents and photometric detection at 600 nm. For this study, several hematological ratios were derived from the data, including: (1) CRP-to-lymphocyte count ratio (CLR); (2) MHR; (3) monocyte-to-lymphocyte ratio (MLR); (4) NLR; 5) derived NLR (dNLR) calculated as neutrophils/(leukocytes-lymphocytes);[42] (6) LMR; (7) PLR; and (8) SII calculated as platelets × (neutrophils/lymphocytes).[43]

Statistical methods

Descriptive statistics were calculated for detectable concentrations of neonicotinoids among study participants. These

included percentiles and weighted percent detection levels. Overall, detection frequencies for all neonicotinoids were low, with weighted detection frequencies at 0.3%, 8.8%, 4.4%, 0.1%, 20.3%, and 35.5% for acetamiprid, clothianidin, imidacloprid, thiacloprid, 5-hydroxy-imidacloprid, and *N*-desmethyl-acetamiprid, respectively (see Table S1; http://links.lww.com/EE/A316). This study examined neonicotinoids as a dichotomous variable (detect versus nondetect, based on the LOD) due to low detection levels. Since acetamiprid and thiacloprid had very low detection frequencies of 0.3% and 0.1%, respectively, both compounds were excluded from the analysis. An analysis of variance (ANOVA) was conducted to determine significant differences in the distribution of neonicotinoids and hematological parameters associated with covariates such as sex, age, race/ethnicity, smoking status, alcohol use within the past year, body mass index (BMI), poverty income ratio (PIR), education level, and marital status.

Linear regression models were used to estimate the association between detectable levels of urinary neonicotinoids and specific hematological ratios (CLR, MHR, MLR, NLR, dNLR, and LMR). PLR and SII were categorized into quartiles, and multinomial logistic regression was used to estimate relative risk ratios (RRRs), with the lowest quartile serving as the reference group, to assess the relationship between detectable concentrations of neonicotinoids and hematological ratios. Since the distribution of PLR and SII values did not follow a normal distribution, we categorized PLR and SII into quartiles, which allowed for a more straightforward interpretation of results and made it easier to detect potential nonlinear associations. Additionally, quartiles were used to reduce the effects of outliers on the results, thus ensuring that our findings were more robust.

Strata, primary sampling units, and survey weights were incorporated into the analysis in accordance with NHANES guidelines. Covariates were selected based on a priori knowledge of potential associations with systemic inflammation and urinary neonicotinoid concentrations. These covariates included sex, age in years, race/ethnicity, smoking status based on quantified serum cotinine levels,[44] daily alcohol use in the past year, BMI in kg/m^2, income level assessed as the PIR, education level, and marital status. A bivariate analysis ($P < 0.20$) was conducted to inform the selection of covariates for the final model. The final covariates included age (categorized as 20–29, 30–39, 40–49, 50–59, 60–69, and >70 years), sex (male and female), race/ethnicity (non-Hispanic Asian/other race/multiracial, non-Hispanic White, non-Hispanic Black, and Mexican American/other Hispanic), smoking status (smoker and nonsmoker based on a 10 ng/ml serum cotinine cutoff), income level (low/middle income vs. high income, using a PIR cutoff of 5), and education level (less than high school, high school completed, and college level).

Effect measure modification by sex was assessed by including an interaction term between sex and detectable urinary neonicotinoid concentrations in the regression models, with $P_{int} < 0.10$ considered statistically significant. For sensitivity analyses, additional adjustments were included for type 2 diabetes and coronary heart disease diagnoses obtained from self-reported physician diagnoses, as these conditions are associated with chronic inflammation. This approach aimed to ensure a more comprehensive understanding of the relationships between neonicotinoid exposure, inflammation, and potential sex differences.

Results

Study participants

The mean age of participants in this study was 44.1 ± 16.2 years, with over 40% falling within the 30–49 years age range (see Table 1). There was a higher percentage of females (53.3%) compared with males (46.7%). Nearly 60% of the participants identified as non-Hispanic White. More than 85% of the participants were nonsmokers and had moderate to low alcohol consumption in the past year (defined as four or fewer drinks).[45] BMI values were generally high, with over one-third classified as obese. Approximately two-thirds of participants were categorized as low/middle income based on PIR cutoffs. Additionally, around 70% had some college education and were either married or living with a partner.

Mean values for CLR, MHR, MLR, NLR, dNLR, LMR, PLR, and SII were 1.9 ± 5.5, 0.01 ± 0.01, 0.3 ± 0.1, 2.0 ± 1.0, 3.3 ± 3.8, 4.2 ± 1.5, 116.5 ± 36.5, and 490.3 ± 229.5, respectively. Notably, females exhibited significantly higher values of LMR compared with males, while males had significantly elevated MHR and MLR levels. Participants aged 20–39 and 60–69 years showed higher values of dNLR, with MLR increasing with age. Non-Hispanic Blacks had higher CLR, dNLR, and LMR values. Non-Hispanic Whites had the highest levels of MLR, while SII and MHR were the highest among Mexican Americans and other Hispanic participants. Higher values of LMR and PLR were seen in smokers, while CLR and MHR levels were highest among participants classified as obese. Additionally, significantly higher SII and lower MHR values were seen in participants with higher educational attainment.

Among the participants in this study, approximately 13% had detectable levels of any parent neonicotinoid while around 45% had detectable levels of any neonicotinoid metabolite (see Table 2). Females had higher detectable levels of neonicotinoid metabolites (53.3%) compared with males (46.7%). Additionally, a higher prevalence of detectable neonicotinoid metabolites was observed in nonsmokers (86%) and participants with low or no alcohol consumption (88.7%). Notably, more than 50% of non-Hispanic Whites had detectable concentrations of any parent neonicotinoid.

Hematological parameters

An inverse association was observed between the presence of any parent neonicotinoid and imidacloprid with CLR, where detectable levels of any parent neonicotinoid were associated with a decrease of 0.62 (95% confidence interval [CI] = −0.98, −0.26) units for CLR and detectable levels of imidacloprid were associated with a 0.48 (95% CI = −0.87, −0.10) unit decrease in CLR (Table 3). Detectable levels of clothianidin were associated with a 0.04 unit decrease in MLR (95% CI = −0.07, −0.02), but a 0.52 unit increase in LMR (95% CI = 0.27, 0.77). Participants with detectable levels of any neonicotinoid metabolite were associated with higher values of dNLR ($\beta = 0.85$; 95% CI = 0.26, 1.43). No significant association was found between detectable levels of neonicotinoids with MHR or NLR.

Multinomial logistic regression indicated that participants with detectable neonicotinoid metabolites had 1.53 times the risk of moderately high PLR (95% CI = 1.27, 2.09) and 0.64 times the risk of high SII (95% CI = 0.42, 0.97) compared with participants with nondetectable levels of any neonicotinoid metabolite (see Table 4). Additionally, detectable levels of 5-hydroxy-imidacloprid were associated with 2.19 times (95% CI = 1.40, 3.41) the risk of moderately high PLR compared with nondetectable levels.

Effect measure modification by sex

There was evidence of effect measure modification by sex in the association between detectable levels of any neonicotinoid metabolite and CLR ($P_{int} = 0.073$). Specifically, there was a significant inverse association for males ($\beta = -0.63$; 95% CI = −1.23, −0.03), whereas there was a positive association that did not reach statistical significance observed among females (see Table 5). The association between clothianidin and MHR showed borderline evidence of effect measure modification by sex ($P_{int} = 0.099$), with a positive association seen in males and

Table 1.

Study population characteristics for adults based on hematological parameters (20+ years), NHANES 2015–2016[a]

	n (%)	CLR Mean (SD)	MHR Mean (SD)	MLR Mean (SD)	NLR Mean (SD)	dNLR Mean (SD)	LMR Mean (SD)
Total	914	1.9 (5.5)	0.01 (0.01)	0.3 (0.1)	2.0 (1.0)	3.3 (3.8)	4.2 (1.5)
Sex							
Male	474 (46.7)	1.4 (3.7)	0.014 (0.01)[b]	0.306 (0.13)[b]	2.1 (1.0)	3.3 (4.1)	3.8 (1.4)[b]
Female	440 (53.3)	1.7 (3.8)	0.010 (0.004)[b]	0.262 (0.09)[b]	2.1 (0.9)	3.0 (3.2)	4.3 (1.4)[b]
Age (years)							
20–29	211 (26.1)	1.2 (2.7)	0.01 (0.01)	0.261 (0.10)[b]	2.0 (1.0)	3.2 (3.3)[b]	4.3 (1.3)[b]
30–39	192 (22.1)	1.4 (2.3)	0.01 (0.01)	0.265 (0.11)[b]	2.1 (0.9)	3.9 (5.3)[b]	4.3 (1.6)[b]
40–49	182 (21.1)	1.2 (1.9)	0.01 (0.01)	0.279 (0.08)[b]	2.0 (0.7)	2.9 (2.6)[b]	3.9 (1.2)[b]
50–59	143 (15.9)	2.1 (6.0)	0.01 (0.01)	0.300 (0.13)[b]	2.2 (1.0)	2.6 (2.7)[b]	3.9 (1.4)[b]
60–69	116 (9.6)	1.8 (3.7)	0.01 (0.01)	0.347 (0.13)[b]	2.2 (1.0)	3.4 (4.3)[b]	3.3 (1.4)[b]
>70	70 (5.2)	2.7 (7.6)	0.01 (0.01)	0.357 (0.17)[b]	2.6 (1.5)	2.3 (1.5)[b]	3.3 (1.4)[b]
Race/ethnicity							
Non-Hispanic Asian/other race/multiracial	145 (12.7)	1.5 (3.7)[b]	0.011 (0.01)[b]	0.260 (0.10)[b]	2.0 (0.8)[b]	3.5 (3.9)[b]	4.4 (1.6)[b]
Non-Hispanic White	262 (58.0)	1.2 (1.7)[b]	0.012 (0.01)[b]	0.304 (0.12)[b]	2.2 (1.0)[b]	3.0 (3.5)[b]	3.8 (1.3)[b]
Non-Hispanic Black	197 (11.8)	2.4 (7.0)[b]	0.011 (0.01)[b]	0.256 (0.11)[b]	1.7 (0.9)[b]	4.2 (4.9)[b]	4.5 (1.6)[b]
Mexican American/other Hispanic	310 (17.5)	1.9 (5.1)[b]	0.013 (0.01)[b]	0.262 (0.09)[b]	2.1 (0.9)[b]	2.9 (3.1)[b]	4.2 (1.3)[b]
Serum cotinine (ng/ml)							
Smoker (≥10)	226 (14.1)	1.6 (4.1)	0.011 (0.01)[b]	0.3 (0.1)	2.1 (1.0)	3.3 (3.9)	4.1 (1.4)[b]
Nonsmoker (<10)	685 (86.0)	1.3 (2.2)	0.013 (0.01)[b]	0.3 (0.1)	2.1 (0.8)	2.9 (3.2)	3.8 (1.4)[b]
Alcohol use (drinks/day)							
High use (>4)	108 (11.3)	1.2 (1.5)	0.01 (0.01)	0.3 (0.1)	2.3 (1.0)	2.8 (3.3)	3.9 (1.5)
Low/no use (≤4)	483 (88.7)	1.5 (3.7)	0.01 (0.01)	0.3 (0.1)	2.1 (1.0)	3.2 (3.7)	3.9 (1.3)
BMI							
Underweight	14 (2.10)	1.1 (3.9)[b]	0.011 (0.01)[b]	0.3 (0.1)	2.1 (1.0)	4.0 (3.8)[b]	4.0 (1.4)
Normal	252 (30.8)	1.0 (4.3)[b]	0.010 (0.004)[b]	0.3 (0.1)	2.1 (0.9)	2.9 (2.7)[b]	3.9 (1.5)
Overweight	302 (31.2)	1.3 (2.3)[b]	0.012 (0.01)[b]	0.3 (0.1)	2.1 (1.0)	3.7 (4.6)[b]	4.1 (1.5)
Obese	342 (35.9)	2.2 (3.1)[b]	0.014 (0.01)[b]	0.3 (0.1)	2.1 (0.9)	2.9 (3.6)[b]	4.0 (1.3)
Poverty income ratio							
Low/middle income (<5)	673 (66.8)	1.5 (3.4)	0.01 (0.01)	0.3 (0.1)	2.0 (0.9)	3.1 (3.2)	4.1 (1.4)
High income (≥5)	232 (33.2)	1.6 (4.5)	0.01 (0.01)	0.3 (0.1)	2.2 (1.0)	3.3 (4.5)	3.8 (1.4)
Education							
Less than high school	197 (13.2)	1.7 (5.2)	0.013 (0.01)[b]	0.3 (0.1)	2.0 (0.8)	3.0 (2.8)	4.2 (1.3)
High school	205 (17.9)	1.6 (3.2)	0.012 (0.01)[b]	0.3 (0.1)	2.1 (0.9)	3.7 (5.0)	4.0 (1.3)
College	511 (69.0)	1.5 (3.5)	0.011 (0.01)[b]	0.3 (0.1)	2.1 (1.0)	3.1 (3.3)	4.0 (1.5)
Marital status							
Married/living with partner	571 (67.5)	1.5 (4.1)	0.01 (0.01)	0.3 (0.1)	2.1 (1.0)	3.2 (3.2)	4.0 (1.4)
Widowed/never married	234 (22.8)	1.4 (2.7)	0.01 (0.004)	0.3 (0.1)	2.1 (1.0)	3.5 (4.9)	4.1 (1.4)
Divorced/separated	109 (9.7)	1.8 (3.6)	0.01 (0.01)	0.3 (0.1)	2.3 (0.9)	2.6 (3.4)	3.9 (1.4)

[a]Percent, mean, and SD values presented are weighted to account for the NHANES complex survey design.
[b]Statistically different at $P < 0.05$.

an inverse association seen in females; however, the effect sizes were very small. Notable sex-based differences were found for clothianidin and several hematological parameters. A significant interaction by sex with clothianidin and NLR ($P_{int} = 0.084$) was observed, where males had an inverse association ($\beta = -0.51$; 95% CI = −0.92, −0.11) and females had an insignificant positive association. The reverse pattern was seen between clothianidin and PLR ($P_{int} = 0.026$), with a significant inverse association among females ($\beta = -1.45$; 95% CI = −2.72, −0.19) and an insignificant positive association in males (see Table 6). Additionally, males with detectable clothianidin had significantly higher SII values ($\beta = 2.93$; 95% CI = 0.84, 5.02) ($P_{int} = 0.002$), while an inverse but insignificant association was observed in females. Sex differences were found for the association between any parent neonicotinoid and SII ($P_{int} = 0.056$), with a significant positive association for males ($\beta = 1.72$; 95% CI = 0.08, 3.36) and an insignificant inverse association in females. No significant effect measure modification by sex was detected for the other neonicotinoid compounds and metabolites with the inflammation markers (Table S2; http://links.lww.com/EE/A316).

Sensitivity analyses

Rather than excluding participants with type 2 diabetes or coronary heart disease from our study, we adjusted for these conditions in our sensitivity analyses. This approach allowed us to assess whether these conditions confounded the association between detectable neonicotinoids with hematological parameters, without reducing the sample size. These conditions are prevalent and therefore may have limited our sample size, leading to limited statistical power of the study. It also helped generalize the findings of our study while controlling potential confounding effects.

Overall, the directionality of findings remained consistent after adjusting for type 2 diabetes and coronary heart disease separately (see Tables S3–S6; http://links.lww.com/EE/A316). The significant associations observed before these adjustments, as well as the magnitude of the effect sizes, were relatively stable and did not substantially change. This suggests that these conditions did not confound the relationships between detectable neonicotinoid levels and hematological parameters in this study.

Discussion

This is the first epidemiological study to investigate an association between neonicotinoids and inflammation using hematological indices in a representative sample of US adults. The findings indicate that detectable levels of any parent neonicotinoid, imidacloprid, and clothianidin were associated with lower CLR, while detectable levels of any parent neonicotinoid

Table 2.

Study population characteristics for adults based on detectable levels of neonicotinoids (20+ years), NHANES 2015–2016[a]

	n (%)	Detectable parent neonicotinoid n (%)	Detectable neonicotinoid metabolite n (%)
Total	914	114 (12.9)	390 (44.5)
Sex			
Male	474 (46.7)	65 (56.0)	179 (46.7)[b]
Female	440 (53.3)	49 (44.0)	211 (53.3)[b]
Age (years)			
20–29	211 (26.1)	22 (16.7)	94 (26.1)
30–39	192 (22.1)	24 (23.4)	86 (22.1)
40–49	182 (21.1)	29 (29.6)	85 (21.1)
50–59	143 (15.9)	20 (20.3)	50 (15.9)
60–69	116 (9.6)	14 (6.7)	46 (9.6)
>70	70 (5.2)	5 (3.4)	29 (5.2)
Race/ethnicity			
Non-Hispanic Asian/other race/multiracial	145 (12.7)	31 (18.5)[b]	77 (12.7)
Non-Hispanic White	262 (58.0)	28 (54.6)[b]	102 (58.0)
Non-Hispanic Black	197 (11.8)	20 (10.3)[b]	84 (11.8)
Mexican American/other Hispanic	310 (17.5)	35 (16.6)[b]	127 (17.5)
Serum cotinine (ng/ml)			
Smoker (≥10)	226 (14.1)	23 (20.9)	56 (14.1)[b]
Nonsmoker (<10)	685 (86.0)	90 (79.1)	332 (86.0)[b]
Alcohol use (drinks/day)			
High use (>4)	108 (11.3)	9 (10.5)	34 (11.3)[b]
Low/no use (≤4)	483 (88.7)	65 (89.5)	210 (88.7)[b]
BMI			
Underweight	14 (2.10)	1 (0.8)	3 (2.1)
Normal	252 (30.8)	47 (39.5)	106 (30.8)
Overweight	302 (31.2)	32 (32.7)	126 (31.2)
Obese	342 (35.9)	34 (27.0)	152 (35.9)
Poverty income ratio			
Low income (<5)	673 (66.8)	73 (61.6)	273 (62.4)
High income (≥5)	232 (33.2)	41 (38.4)	114 (37.6)
Education			
Less than high school	197 (13.2)	30 (17.3)	79 (13.2)
High school	205 (17.9)	16 (12.0)	69 (17.9)
College	511 (69.0)	68 (70.7)	242 (69.0)
Marital status			
Married/living with partner	571 (67.5)	77 (67.5)	252 (67.5)
Widowed/never married	234 (22.8)	26 (22.3)	96 (22.8)
Divorced/separated	109 (9.7)	11 (10.2)	42 (9.7)

[a]Percent, mean, and SD values presented are weighted to account for the NHANES complex survey design.
[b]Statistically different at $P < 0.05$.

Table 3.

Linear regression models of estimated differences (β) and 95% confidence intervals (CIs) for hematological parameters by detectable concentrations of urinary neonicotinoids in US adults, NHANES 2015–2016[a]

	CLR	MLR	dNLR	LMR	MHR	NLR
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Any parent neonicotinoid						
Detect	−0.62 (−0.98, −0.26)[b]	−0.02 (−0.05, 0.01)	0.59 (−0.17, 1.35)	0.26 (0.03, 0.50)[b]	−0.001 (−0.002, 0.001)	−0.15 (−0.47, 0.18)
Nondetect	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Clothianidin						
Detect	−0.65 (−1.13, −0.17)[b]	−0.04 (−0.07, −0.02)[b]	0.69 (−0.19, 1.58)	0.52 (0.27, 0.77)[b]	−0.001 (−0.003, 0.001)	−0.21 (−0.60, 0.19)
Nondetect	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Imidacloprid						
Detect	−0.48 (−0.87, −0.10)[b]	0.03 (−0.05, 0.10)	0.18 (−1.35, 1.72)	−0.26 (−0.78, 0.25)	<0.001 (−0.003, 0.004)	−0.01 (−0.38, 0.36)
Nondetect	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Any neonicotinoid metabolite						
Detect	−0.33 (−0.84, 0.19)	−0.001 (−0.02, 0.02)	0.85 (0.26, 1.43)[b]	0.11 (−0.12, 0.33)	<0.001 (−0.001, 0.001)	−0.05 (−0.24, 0.15)
Nondetect	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
5-Hydroxy-imidacloprid						
Detect	−0.31 (−0.81, 0.20)	0.02 (−0.03, 0.06)	−0.07 (−1.35, 1.20)	−0.05 (−0.51, 0.41)	<0.001 (−0.001, 0.002)	0.14 (−0.11, 0.38)
Nondetect	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
N-desmethyl-acetamiprid						
Detect	−0.33 (−0.85, 0.19)	<0.001 (−0.03, 0.03)	0.65 (−0.14, 1.44)	0.05 (−0.25, 0.35)	<0.001 (−0.001, 0.001)	−0.05 (−0.26, 0.16)
Nondetect	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)

[a]Adjusted by age, race/ethnicity, sex, education, income status, and smoking status.
[b]Statistically significant at $P < 0.05$.

Table 4.

Multinomial logistic regression models of relative risk ratios (RRR) and 95% confidence intervals (CIs) for blood ratio quartiles by detectable concentrations of urinary neonicotinoids in US adults, NHANES 2015–2016[a]

	PLR RRR (95% CI)			
	<87.47 (low)	87.47–109.44 (moderately high)	109.45–134.65 (high)	>134.65 (very high)
Any parent neonicotinoid				
Detect	-	0.79 (0.39, 1.59)	0.55 (0.29, 1.06)	0.78 (0.40, 1.52)
Nondetect		1.00 (ref)	1.00 (ref)	1.00 (ref)
Clothianidin				
Detect	-	0.56 (0.19, 1.62)	0.52 (0.26, 1.04)	0.86 (0.33, 2.23)
Nondetect		1.00 (ref)	1.00 (ref)	1.00 (ref)
Imidacloprid				
Detect	-	1.39 (0.39, 4.92)	0.59 (0.17, 2.12)	0.63 (0.15, 2.57)
Nondetect		1.00 (ref)	1.00 (ref)	1.00 (ref)
Any neonicotinoid metabolite				
Detect	-	1.63 (1.27, 2.09)[b]	0.74 (0.47, 1.17)	0.81 (0.43, 1.53)
Nondetect		1.00 (ref)	1.00 (ref)	1.00 (ref)
5-Hydroxy-imidacloprid				
Detect	-	2.19 (1.40, 3.41)[b]	0.93 (0.37, 2.29)	1.38 (0.57, 3.34)
Nondetect		1.00 (ref)	1.00 (ref)	1.00 (ref)
N-desmethyl-acetamiprid				
Detect	-	1.18 (0.83, 1.69)	0.81 (0.51, 1.29)	0.90 (0.53, 1.50)
Nondetect		1.00 (ref)	1.00 (ref)	1.00 (ref)
	SII RRR (95% CI)			
	<304.45 (low)	304.45–432.79 (moderately high)	432.80–584 (high)	>584 (very high)
Any parent neonicotinoid				
Detect	-	0.74 (0.32, 1.73)	0.80 (0.30, 2.14)	0.47 (0.20, 1.08)
Nondetect		1.00 (ref)	1.00 (ref)	1.00 (ref)
Clothianidin				
Detect	-	0.48 (0.17, 1.33)	0.65 (0.19, 2.24)	0.38 (0.13, 1.11)
Nondetect		1.00 (ref)	1.00 (ref)	1.00 (ref)
Imidacloprid				
Detect	-	1.80 (0.57, 5.69)	1.16 (0.38, 3.55)	0.88 (0.33, 2.36)
Nondetect		1.00 (ref)	1.00 (ref)	1.00 (ref)
Any neonicotinoid metabolite				
Detect	-	0.88 (0.51, 1.51)	0.64 (0.42, 0.97)[b]	0.84 (0.48, 1.45)
Nondetect		1.00 (ref)	1.00 (ref)	1.00 (ref)
5-Hydroxy-imidacloprid				
Detect	-	1.32 (0.59, 2.92)	0.75 (0.44, 1.28)	1.40 (0.64, 3.09)
Nondetect		1.00 (ref)	1.00 (ref)	1.00 (ref)
N-desmethyl-acetamiprid				
Detect	-	0.77 (0.44, 1.34)	0.73 (0.39, 1.37)	0.81 (0.50, 1.32)
Nondetect		1.00 (ref)	1.00 (ref)	1.00 (ref)

[a]Adjusted by age, race/ethnicity, sex, education, income status, and smoking status.
[b]Statistically significant at $P < 0.05$.

were associated with higher LMR. Additionally, dNLR and PLR showed a positive association with detectable levels of any neonicotinoid metabolite, while detectable levels of 5-hydroxy-imidacloprid showed a positive association with PLR. Results varied by sex, with a positive association seen in males and an inverse association seen in females for MHR, PLR, and SII, while the reverse was observed for the association with CLR and NLR. These sex-specific differences highlight the potential for differential effects of neonicotinoid exposure on inflammatory responses in males and females.

Hematological ratios have recently been used as indicators of inflammation-based health outcomes in humans, such as cardiovascular disease, COVID-19, type II diabetes, malignancies, metabolic syndrome, and rheumatic diseases.[46–51] Most studies report an increase in hematological parameters in conditions involving inflammation, except for LMR, which tends to decrease. However, in the current study, we observed a decrease in CLR and an increase in LMR, which contrasts with these previous findings. The discrepancy in CLR could be explained by its role as a biomarker of acute inflammation, as CRP levels are usually elevated during acute inflammatory responses.[52,53] Acute inflammation often leads to increased lymphocyte consumption to combat oxidative damage, resulting in higher CLR levels. In contrast, chronically elevated CRP is more commonly associated with long-term infections or arthritic conditions.[54] Since this study focused on chronic inflammation in otherwise healthy participants, the findings may not align with the current literature, which predominantly examines acute inflammation or disease states. Studies reporting elevated levels of LMR have done so primarily for cancers such as cervical, colorectal, hepatocellular, and thyroid cancers.[47,55,56] There is a lack of studies examining the association of LMR in the context of systemic inflammation in generally healthy individuals. Chronic inflammation leads to an influx of lymphocytes and macrophages, which may potentially explain the increase in LMR observed in this study. Furthermore, while the effectiveness of biomarkers can vary depending on the context, multiple studies have demonstrated that hematological parameters, such as NLR, PLR, and SII, are reliable indicators of chronic inflammation across a range of conditions, including cardiovascular, metabolic, and autoimmune diseases.[40–46] Given their widespread use and validation in previous research, these parameters provide a robust framework for assessing inflammation in our study.

The elevated levels of dNLR and PLR associated with any neonicotinoid metabolite and 5-hydroxy-imidacloprid in our study are in line with the current literature.[48,50,57,58] Additionally,

Table 5.

Estimated differences and 95% confidence intervals in CLR, MHR, and NLR by detectable parent and metabolite urinary neonicotinoid compounds in US adults, stratified by sex, NHANES 2015–2016[a]

		Males	Females
	P_{int}	β (95% CI)	β (95% CI)
CLR			
Any parent neonicotinoid			
Detect	0.393	−0.80 (−1.27, −0.33)[c]	−0.39 (−1.15, 0.37)
Nondetect	-	1.00 (ref)	1.00 (ref)
Any neonicotinoid metabolite			
Detect	0.073[b]	−0.63 (−1.23, −0.03)[c]	−0.02 (−0.66, 0.61)
Nondetect	-	1.00 (ref)	1.00 (ref)
Clothianidin			
Detect	0.255	−0.90 (−1.45, −0.36)[c]	−0.38 (−1.17, 0.41)
Nondetect	-	1.00 (ref)	1.00 (ref)
5-Hydroxy-imidacloprid			
Detect	0.715	−0.39 (−1.20, 0.43)	−0.22 (−0.72, 0.27)
Nondetect	-	1.00 (ref)	1.00 (ref)
MHR			
Any parent neonicotinoid			
Detect	0.173	<0.001 (−0.002, 0.003)	−0.002 (−0.003, −0.0003)[c]
Nondetect	-	1.00 (ref)	1.00 (ref)
Any neonicotinoid metabolite			
Detect	0.936	<0.001 (−0.002, 0.002)	<0.001 (−0.001, 0.001)
Nondetect	-	1.00 (ref)	1.00 (ref)
Clothianidin			
Detect	0.099[b]	0.001 (−0.003, 0.004)	−0.002 (−0.004, −0.001)[c]
Nondetect	-	1.00 (ref)	1.00 (ref)
5-Hydroxy-imidacloprid			
Detect	0.370	0.001 (−0.001, 0.002)	<0.001 (−0.002, 0.002)
Nondetect	-	1.00 (ref)	1.00 (ref)
NLR			
Any parent neonicotinoid			
Detect	0.357	−0.27 (−0.68, 0.14)	0.004 (−0.48, 0.49)
Nondetect	-	1.00 (ref)	1.00 (ref)
Any neonicotinoid metabolite			
Detect	0.666	−0.07 (−0.26, 0.11)	−0.02 (−0.30, 0.26)
Nondetect	-	1.00 (ref)	1.00 (ref)
Clothianidin			
Detect	0.084[b]	−0.51 (−0.92, −0.11)[c]	0.11 (−0.50, 0.73)
Nondetect	-	1.00 (ref)	1.00 (ref)
5-Hydroxy-imidacloprid			
Detect	0.756	0.11 (−0.21, 0.42)	0.17 (−0.17, 0.51)
Nondetect	-	1.00 (ref)	1.00 (ref)

[a]Adjusted by age, race/ethnicity, sex, education, income status, and smoking status.
[b]Statistically significant at $P_{int} < 0.10$.
[c]Statistically significant at $P < 0.05$.

a study using NHANES data showed significant inverse associations between 5-hydroxy-imidacloprid and neutrophils, which can explain the observed increase in dNLR in the current study.[29] dNLR is one of the primary indicators of systemic inflammation, along with NLR and SII, and has been linked to increased efficacy of programmed cell death ligand 1, which is an immune checkpoint inhibitor responsible for regulating cell damage due to inflammation.[59,60] An elevation in platelet levels, as seen in PLR, is associated with inflammatory changes due to a potential link to increased angiogenesis.[61] Platelets play an important role in the production of inflammatory mediators such as cytokines and chemokines, contributing to the body's inflammatory response, while high cortisol levels may lead to a decrease in lymphocytes. This may explain why there is an increase in PLR associated with detectable levels of neonicotinoid metabolites in this study. Additionally, these findings align with the idea that neonicotinoid exposure may contribute to inflammatory responses, reflected through hematological markers.

Neonicotinoids are associated with mitochondrial damage through the inhibition of adenosine triphosphate production, which can increase levels of intracellular free radicals and stimulate ROS pathways, subsequently inducing oxidative stress and cell destruction through altered signaling pathways.[62] Additionally, neonicotinoids stimulate nicotinic acetylcholine receptors, which can lead to a calcium (Ca^{2+}) imbalance in the mitochondria, ultimately contributing to oxidative stress, DNA damage, cell death, lipid peroxidation, and oxidation of cell proteins. A study conducted among male farmers in Thailand showed that clothianidin was associated with reduced mean corpuscular hemoglobin concentration, which may indicate chronic inflammation; however, it is unclear whether these findings can be extrapolated to other blood cells.[63] The same study also found an insignificant inverse association between neonicotinoid concentrations and leucocyte counts, which may be due to a small sample size (n = 143). Few studies have examined this association, and future prospective studies may be warranted in order to understand the exact mechanisms through which neonicotinoids can influence hematological cell ratios. Discordant findings in the current study may be attributed to varying exposure concentrations, differences in the timing of exposure, and the presence of confounding factors such as latent infections or exposure to other environmental chemicals.

The findings for effect measure modification by sex seem to indicate that males may be more susceptible to the effects of

Table 6.

Estimated differences and 95% confidence intervals in PLR and SII by detectable parent and metabolite urinary neonicotinoid compounds in US adults, stratified by sex, NHANES 2015–2016[a]

		Males	Females
	P_{int}	β (95% CI)	β (95% CI)
PLR			
Any parent neonicotinoid			
Detect	0.199	0.66 (–0.53, 1.84)	–0.53 (–1.48, 0.42)
Nondetect	-	1.00 (ref)	1.00 (ref)
Any neonicotinoid metabolite			
Detect	0.712	0.24 (–0.56, 1.03)	0.08 (–0.65, 0.82)
Nondetect	-	1.00 (ref)	1.00 (ref)
Clothianidin			
Detect	0.026[b]	1.16 (–0.47, 2.80)	–1.45 (–2.72, –0.19)[c]
Nondetect	-	1.00 (ref)	1.00 (ref)
5-Hydroxy-imidacloprid			
Detect	0.185	–0.86 (–2.20, 0.48)	0.20 (–0.80, 1.20)
Nondetect	-	1.00 (ref)	1.00 (ref)
SII			
Any parent neonicotinoid			
Detect	0.056[b]	1.72 (0.08, 3.36)[c]	–0.26 (–1.64, 1.12)
Nondetect	-	1.00 (ref)	1.00 (ref)
Any neonicotinoid metabolite			
Detect	0.793	0.14 (–0.35, 0.62)	0.26 (–0.68, 1.20)
Nondetect	-	1.00 (ref)	1.00 (ref)
Clothianidin			
Detect	0.002[b]	2.93 (0.84, 5.02)[c]	–0.24 (–1.69, 1.20)
Nondetect	-	1.00 (ref)	1.00 (ref)
5-Hydroxy-imidacloprid			
Detect	0.023[b]	–0.86 (–1.72, 0.003)	0.21 (–0.60, 1.01)
Nondetect	-	1.00 (ref)	1.00 (ref)

[a]Adjusted by age, race/ethnicity, sex, education, income status, and smoking status.
[b]Statistically significant at $P_{int} < 0.10$.
[c]Statistically significant at $P < 0.05$.

neonicotinoid-mediated inflammation compared with females. A few epidemiological studies have shown significant differences with respect to sex.[25–27] This could be attributed to differences in neonicotinoid metabolism and inflammatory response associated with sex. For example, a study in China showed that concentrations of neonicotinoids were higher in males compared with females due to potential differences in metabolism and dietary intake between sexes.[33] Another explanation could be related to sex differences associated with oxidative stress. A review showed that males had higher levels of oxidative stress markers (such as ROS) compared with females.[64] This could be related to estrogen in females acting as a protective factor. Estrogen's phenolic hydroxyl group acts as a powerful antioxidant, neutralizing free radicals. Additionally, estradiol (a form of estrogen) has been linked to an increase in *Mn-SOD* gene expression, which scavenges free radicals and decreases nicotinamide adenosine dinucleotide phosphate oxidase activity, further reducing the production of free radicals.[65–67] However, differences in inflammation due to sex may be linked to several interrelated mechanisms, including hormonal and metabolic variations which need further investigation.

The current study has several strengths. First, the use of NHANES data provided a large, nationally representative sample of the US population, which enhances the generalizability of the findings. Additionally, the availability of extensive covariate data allowed for the control of multiple potential confounders in this study. Second, this is the first epidemiological study to evaluate the association between neonicotinoids and inflammation using hematological ratios, while also examining effect measure modification by sex, contributing novel insights into sex-specific differences in these associations.

However, there are some limitations that should be considered while interpreting these findings. First, the cross-sectional study design limits the ability to establish causality and temporality within the study. Second, since detection levels of neonicotinoids were low, they were analyzed as a dichotomous variable (detect vs. nondetect), preventing the examination of a dose–response relationship between individual neonicotinoid compounds and hematological ratios. Third, since neonicotinoids were analyzed in a single urine sample, there could be exposure misclassification. This is because neonicotinoids have a short half-life in mammals and a single measurement may not fully reflect the cumulative exposure or body burden.[54] Finally, neonicotinoids are only one of several environmental chemicals that may be associated with oxidative stress, alongside air pollutants, persistent organic pollutants, polycyclic aromatic hydrocarbons, pesticides, and heavy metals.[68] The potential for synergistic or antagonistic effects between these chemicals was not accounted for, which may influence the observed associations.

This study is the first to examine the association between detectable concentrations of neonicotinoids and inflammation using hematological indices in a nationally representative population. Findings suggest that neonicotinoids may be linked to inflammatory changes as a result of oxidative stress. Specifically, a decrease in CLR and an increase in LMR, dNLR, 5-hydroxy-imidacloprid, and PLR were associated with detectable levels of neonicotinoids. Sex-specific results showed some evidence of effect measure modification by sex; however, the directionality of association for males and females was mixed. The results can be interpreted as more representative of general chronic inflammatory changes associated with exposure to detectable concentrations of neonicotinoids, which may indicate that the use of neonicotinoids as pesticides may be a potential health hazard. However, the cross-sectional nature of the study limits the ability to infer causality. Further studies are required in order to establish the association over time, through the use of a prospective study design and repeated measures of neonicotinoid concentrations.

Additionally, toxicological studies should analyze specific neonicotinoid mechanisms responsible for oxidative stress and inflammation.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

References

1. Hladik ML, Main AR, Goulson D. Environmental risks and challenges associated with neonicotinoid insecticides. *Environ Sci Technol*. 2018;52:3329–3335.
2. Selvam V, Srinivasan S. Neonicotinoid Poisoning and Management. *Indian J Crit Care Med*. 2019;23(Suppl 4):S260-S262.
3. Casillas A, De La Torre A, Navarro I, Sanz P, Martínez MLA. Environmental risk assessment of neonicotinoids in surface water. *Sci Total Environ*. 2022;809:151161.
4. Han M, Wang Y, Yang Z, et al. Neonicotinoids residues in the honey circulating in the Chinese market and health risk on honeybees and humans. *Environ Pollut*. 2022;313:120146.
5. Huang Y, Zhang B, Xue J, et al. A pilot nationwide survey on the concentrations of neonicotinoids and their metabolites in indoor dust from China: application for human exposure. *Bull Environ Contam Toxicol*. 2022;109:900–909.
6. Langdon KW, Schumann R, Stelinski LL, Rogers ME. Spatial and temporal distribution of soil-applied neonicotinoids in citrus tree foliage. *J Econ Entomol*. 2018;111:1788–1798.
7. Mitchell EAD, Mulhauser B, Mulot M, Mutabazi A, Glauser G, Aebi A. A worldwide survey of neonicotinoids in honey. *Science*. 2017;358:109–111.
8. Niu YH, Wang L, Wang Z, Yu SX, Zheng JY, Shi ZH. High-frequency monitoring of neonicotinoids dynamics in soil-water systems during hydrological processes. *Environ Pollut*. 2022;292:118219.
9. Renaud M, Akeju T, Natal-da-Luz T, et al. Effects of the neonicotinoids acetamiprid and thiacloprid in their commercial formulations on soil fauna. *Chemosphere*. 2018;194:85–93.
10. Roy CL, Chen D. High population prevalence of neonicotinoids in sharp-tailed grouse and greater prairie-chickens across an agricultural gradient during spring and fall. *Sci Total Environ*. 2023;856:159120.
11. Zhang P, Ren C, Sun H, Min L. Sorption, desorption and degradation of neonicotinoids in four agricultural soils and their effects on soil microorganisms. *Sci Total Environ*. 2018;615:59–69.
12. Klingelhöfer D, Braun M, Brüggmann D, Groneberg DA. Neonicotinoids: a critical assessment of the global research landscape of the most extensively used insecticide. *Environ Res*. 2022;213:113727.
13. Craddock HA, Huang D, Turner PC, Quirós-Alcalá L, Payne-Sturges DC. Trends in neonicotinoid pesticide residues in food and water in the United States, 1999–2015. *Environ Health*. 2019;18:7.
14. Kim J, Wang W, Lee S, Park JH, Oh JE. Concentrations and distributions of neonicotinoids in drinking water treatment plants in South Korea. *Environ Pollut*. 2021;288:117767.
15. Shi YH, Xiao JJ, Liu YY, et al. Interactions of food matrix and dietary components on neonicotinoid bio accessibility in raw fruit and vegetables. *Food Funct*. 2019;10:289–295.
16. Wan Y, Wang Y, Xia W, He Z, Xu S. Neonicotinoids in raw, finished, and tap water from Wuhan, Central China: assessment of human exposure potential. *Sci Total Environ*. 2019;675:513–519.
17. Wang A, Mahai G, Wan Y, et al. Neonicotinoids and carbendazim in indoor dust from three cities in China: spatial and temporal variations. *Sci Total Environ*. 2019;695:133790.
18. Zhang H, Shen K, Wu R, et al. Occurrence and distribution of neonicotinoids and characteristic metabolites in paired urine and indoor dust from young adults: implications for human exposure. *Environ Res*. 2021;199:111175.
19. Harada KH, Tanaka K, Sakamoto H, et al. Biological monitoring of human exposure to neonicotinoids using urine samples, and neonicotinoid excretion kinetics. *PLoS One*. 2016;11:e0146335.
20. Laubscher B, Diezi M, Renella R, et al. Multiple neonicotinoids in children's cerebro-spinal fluid, plasma, and urine. *Environ Health*. 2022;21:10.
21. Osaka A, Ueyama J, Kondo T, et al. Exposure characterization of three major insecticide lines in urine of young children in Japan—neonicotinoids, organophosphates, and pyrethroids. *Environ Res*. 2016;147:89–96.
22. Wrobel SA, Bury D, Belov VN, et al. Rapid quantification of seven major neonicotinoids and neonicotinoid-like compounds and their key metabolites in human urine. *Anal Chim Acta*. 2023;1239:340680.
23. Ospina M, Wong LY, Baker SE, Serafim AB, Morales-Agudelo P, Calafat AM. Exposure to neonicotinoid insecticides in the U.S. general population: data from the 2015–2016 National Health and Nutrition Examination Survey. *Environ Res*. 2019;176:108555.
24. Li AJ, Kannan K. Profiles of urinary neonicotinoids and dialkylphosphates in populations in nine countries. *Environ Int*. 2020;145:106120.
25. Godbole AM, Moonie S, Coughenour C, Zhang C, Chen A, Vuong AM. Exploratory analysis of the associations between neonicotinoids and measures of adiposity among US adults: NHANES 2015–2016. *Chemosphere*. 2022;300:134450.
26. Mendy A, Pinney SM. Exposure to neonicotinoids and serum testosterone in men, women, and children. *Environ Toxicol*. 2022;37:1521–1528.
27. Vuong AM, Zhang C, Chen A. Associations of neonicotinoids with insulin and glucose homeostasis parameters in US adults: NHANES 2015–2016. *Chemosphere*. 2022;286:131642.
28. Wang L, Ma C, Wei D, et al. Health risks of neonicotinoids chronic exposure and its association with glucose metabolism: a case-control study in rural China. *Environ Pollut*. 2023;334:122213.
29. Yang C, Liang J. Associations between neonicotinoid metabolites and hematologic parameters among US adults in NHANES 2015–2016. *Environ Sci Pollut Res*. 2022;30:26327–26337.
30. Wang X, Anadón A, Wu Q, et al. Mechanism of neonicotinoid toxicity: impact on oxidative stress and metabolism. *Annu Rev Pharmacol Toxicol*. 2018;58:471–507.
31. Chen L, Deng H, Cui H, et al. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget*. 2018;9:7204–7218.
32. Ruíz-Arias MA, Medina-Díaz IM, Bernal-Hernández YY, et al. Hematological indices as indicators of inflammation induced by exposure to pesticides. *Environ Sci Pollut Res*. 2022;30:19466–19476.
33. Choe JY, Lee CU, Kim SK. Association between novel hematological indices and measures of disease activity in patients with rheumatoid arthritis. *Medicina (Kaunas)*. 2023;59:117.
34. Targońska-Stępniak B, Zwolak R, Piotrowski M, Grzechnik K, Majdan M. The relationship between hematological markers of systemic inflammation (neutrophil-to-lymphocyte, platelet-to-lymphocyte, lymphocyte-to-monocyte ratios) and ultrasound disease activity parameters in patients with rheumatoid arthritis. *J Clin Med*. 2020;9:2760.
35. López-Verdugo F, Furuzawa-Carballeda J, Romero-Hernández F, et al. Hematological indices as indicators of silent inflammation in achalasia patients: a cross-sectional study. *Medicine (Baltim)*. 2020;99:e19326.
36. Hao X, Li D, Wu D, Zhang N. The relationship between hematological indices and autoimmune rheumatic diseases (ARDs), a meta-analysis. *Sci Rep*. 2017;7:10833.
37. Xia Y, Xia C, Wu L, Li Z, Li H, Zhang J. Systemic immune inflammation index (SII), system inflammation response index (SIRI) and risk of all-cause mortality and cardiovascular mortality: a 20-year follow-up cohort study of 42,875 US adults. *J Clin Med*. 2023;12:1128.
38. Li L, Chen K, Wen C, Ma X, Huang L. Association between systemic immune-inflammation index and chronic kidney disease: a population-based study. *PLoS One*. 2024;19:e0292646.
39. Wang P, Guo X, Zhou Y, et al. Monocyte-to-high-density lipoprotein ratio and systemic inflammation response index are associated with the risk of metabolic disorders and cardiovascular diseases in the general rural population. *Front Endocrinol (Lausanne)*. 2022;13:944991.
40. Zhang T, Song S, Bai X, et al. A nationwide survey of urinary concentrations of neonicotinoid insecticides in China. *Environ Int*. 2019;132:105114.
41. Baker SE, Serafim AB, Morales-Agudelo P, Vidal M, Calafat AM, Ospina M. 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*. 2019;411:669–678.
42. Capone M, Giannarelli D, Mallardo D, et al. Baseline neutrophil-to-lymphocyte ratio (NLR) and derived NLR could predict overall survival in patients with advanced melanoma treated with nivolumab. *J ImmunoTher Cancer*. 2018;6:74.
43. Hu B, Yang XR, Xu Y, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. *Clin Cancer Res*. 2014;20:6212–6222.
44. Vartiainen E, Seppälä T, Lillsunde P, Puska P. Validation of self-reported smoking by serum cotinine measurement in a community-based study. *J Epidemiol Community Health*. 2002;56:167–170.

45. Pearson MR, Kirouac M, Witkiewitz K. Questioning the validity of the 4+/5+ binge or heavy drinking criterion in college and clinical populations. *Addiction*. 2016;111:1720–1726.
46. Gambardella C, Mongardini FM, Paolicelli M, et al. Role of inflammatory biomarkers (NLR, LMR, PLR) in the prognostication of malignancy in indeterminate thyroid nodules. *Int J Mol Sci*. 2023;24:6466.
47. Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M, Kitas GD. The platelet-to-lymphocyte ratio as an inflammatory marker in rheumatic diseases. *Ann Lab Med*. 2019;39:345–357.
48. Liu CC, Ko HJ, Liu WS, et al. Neutrophil-to-lymphocyte ratio as a predictive marker of metabolic syndrome. *Medicine (Baltimore)*. 2019;98:e17537.
49. Ning X, Wu C, Song B, Wang HM, Jin HZ. Evaluation of hematological inflammatory parameters in patients with palmoplantar pustulosis. *Int J Dermatol*. 2024;63:1713.
50. Tonduangu N, Le Borgne P, Lefebvre F, et al; Crems Network Clinical Research In Emergency Medicine And Sepsis Clr. Prognostic value of C-reactive protein to lymphocyte ratio (CLR) in emergency department patients with SARS-CoV-2 infection. *J Pers Med*. 2021;11:1274.
51. Ye Z, Hu T, Wang J, et al. Systemic immune-inflammation index as a potential biomarker of cardiovascular diseases: a systematic review and meta-analysis. *Front Cardiovasc Med*. 2022;9:933913.
52. He G, Ji R, Huo X, et al; China PEACE Collaborative Group. Long-term trajectories of high-sensitivity C-reactive protein level among patients with acute heart failure. *J Inflamm Res*. 2023;16:359–371.
53. Nehring SM, Goyal A, Patel BC. C reactive protein. In: *StatPearls*. StatPearls Publishing; 2023.
54. Chan JCY, Chan DL, Diakos CI, et al. The lymphocyte-to-monocyte ratio is a superior predictor of overall survival in comparison to established biomarkers of resectable colorectal cancer. *Ann Surg*. 2017;265:539–546.
55. Liu J, Liu S, Gao L, et al. Predicting postoperative blood inflammatory biomarkers using pre-operative heart rate variability in patients with cervical cancer. *Front Physiol*. 2021;12:696208.
56. Yang YT, Jiang JH, Yang HJ, Wu ZJ, Xiao ZM, Xiang BD. The lymphocyte-to-monocyte ratio is a superior predictor of overall survival compared to established biomarkers in HCC patients undergoing liver resection. *Sci Rep*. 2018;8:2535.
57. Li S, Zou J, Liu C, et al. Baseline derived neutrophil-to-lymphocyte ratio as a prognostic biomarker for non-colorectal gastrointestinal cancer patients treated with immune checkpoint blockade. *Clin Immunol*. 2020;212:108345.
58. Qiu W, Shi Q, Chen F, Wu Q, Yu X, Xiong L. The derived neutrophil to lymphocyte ratio can be the predictor of prognosis for COVID-19 Omicron BA.2 infected patients. *Front Immunol*. 2022;13:1065345.
59. Alessi A, Trevisan C, Citron A, et al. Dietary inflammatory index is associated with lung function in healthy older adults. *Nutrition*. 2022;99-100:111653.
60. Mathur K, Kurbanova N, Qayyum R. Platelet-lymphocyte ratio (PLR) and all-cause mortality in general population: insights from national health and nutrition education survey. *Platelets*. 2019;30:1036–1041.
61. Costas-Ferreira C, Faro LRF. Neurotoxic effects of neonicotinoids on mammals: what is there beyond the activation of nicotinic acetylcholine receptors? A systematic review. IJMS. *Int J Mol Sci*. 2021;22:8413.
62. Duzguner V, Erdogan S. Chronic exposure to imidacloprid induces inflammation and oxidative stress in the liver & central nervous system of rats. *Pestic Biochem Physiol*. 2012;104:58–64.
63. Xu X, Wang X, Yang Y, et al. Neonicotinoids: mechanisms of systemic toxicity based on oxidative stress-mitochondrial damage. *Arch Toxicol*. 2022;96:1493–1520.
64. Suwannarin N, Prapamontol T, Isobe T, et al. Association between Haematological Parameters and Exposure to a Mixture of Organophosphate and Neonicotinoid Insecticides among Male Farmworkers in Northern Thailand. *Int J Environ Res Public Health*. 2021;18:10849.
65. Kander MC, Cui Y, Liu Z. Gender difference in oxidative stress: a new look at the mechanisms for cardiovascular diseases. *J Cell Mol Med*. 2017;21:1024–1032.
66. Miller AA, Drummond GR, Mast AE, Schmidt HW, Sobey CG. Effect of gender on NADPH-oxidase activity, expression, and function in the cerebral circulation: role of estrogen. *Stroke*. 2007;38:2142–2149.
67. Vina J, Gambini J, Lopez-Grueso R, Abdelaziz KM, Jove M, Borras C. Females live longer than males: role of oxidative stress. *Curr Pharm Des*. 2011;17:3959–3965.
68. Zheng F, Gonçalves FM, Abiko Y, Li H, Kumagai Y, Aschner M. Redox toxicology of environmental chemicals causing oxidative stress. *Redox Biol*. 2020;34:101475.