Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

The Relationship Between Urinary Neonicotinoid Concentrations and Obesity Among Individuals Aged 35 to 74 in Guangxi, China

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Background: The increasing worldwide incidence of overweight and obesity poses a significant health concern. The global application of neonicotinoids (NEOs) continues to rise. However, the relationship between NEOs and obesity remains unclear in middle-aged and elderly Chinese individuals.

Objective: The purpose of this cross-sectional study was to assess the association between urinary concentrations of NEOs and obesity among individuals aged 35–74 years in Guangxi, China.

Methods: In this cross-sectional study, urinary concentrations of 10 NEOs were analyzed in 862 participants. Overweight and obesity (OWO) was defined as body mass index (BMI) ≥24 kg/m^2, and abdominal obesity (ABO) was assessed by waist circumference (WC; male ≥90 cm, female ≥85 cm). The association between NEOs and obesity was evaluated through multinomial logistic regression, generalised linear models (GLM), quantile g-estimation (Qgcomp), and Bayesian kernel machine regression (BKMR). Machine learning models with Shapley Additive Explanations (SHAP) were used to explore the predictive contribution of NEOs and traditional risk factors to obesity.

Results: Multivariate logistic regression showed that clothianidin (CLO), N-desmethyl-acetamiprid (NACE), and imidacloprid (IMI) were positively associated with Group 4 (with both OWO and ABO). The GLM model revealed a significant positive association between NACE and ABO (OR = 1.177, 95% CI: 1.046, 1.328, $p < 0.05$). In females, CLO was associated with OWO, while IMI was associated with both OWO and ABO. In males, NACE was associated with OWO and ABO. Both the Qgcomp and BKMR models indicated that mixed NEOs exposure was significantly correlated with obesity, showing a positive relationship for OWO in females and ABO in males. Machine learning identified CLO and NACE as factors significantly associated with obesity.

Conclusion: Research findings indicated that CLO, NACE, IMI, and NEOs mixture were positively associated with obesity, with CLO and NACE serving as significant factors.

Keywords: neonicotinoids, overweight and obesity, abdominal obesity, machine learning

Introduction

Obesity and related health issues are now significant global health challenges, ranking fifth among leading mortality causes.[1] The World Health Organization reported that 2.5 billion adults globally were overweight and 890 million were obese in 2022.[2] Furthermore, China has the highest global incidence rates of overweight and obesity.[3] The interaction of genetic predisposition, lifestyles, and environmental conditions contributes to obesity.[4] However, these factors do not

https://doi.org/10.2147/DMSO.S581758
Received: 17 November 2025
Accepted: 21 February 2026
Published: 10 March 2026

fully account for the aetiology of obesity at the population level. The endocrine-disrupting chemicals, including pesticides/herbicides, household products, plasticizers, surfactants, and cosmetics, are associated with obesity and may significantly contribute to its progression.[5,6] Research indicates that subclinical fluctuations in thyroid hormone levels are associated with body fat percentage,[7] implying that subtle endocrine disruption may contribute to obesity. Therefore, neonicotinoid compounds have garnered significant attention due to their widespread exposure and potential to disrupt endocrine functions.[8]

Neonicotinoids (NEOs) represent a novel class of synthetic insecticides that have been deployed as replacements for legacy organophosphate and carbamate compounds.[9] NEOs selectively activate insect nicotinic acetylcholine receptors (nAChRs) to exert pesticidal action.[10] NEOs are increasingly used globally due to their broad insecticidal properties, distinct neurotoxic mechanisms, and presumed low mammalian toxicity.[11] Research reports indicate that global NEOs production reached 20,000 metric tons annually in 2010;[12] by 2014, NEOs represented more than 25% the insecticide market worldwide.[13] However, research indicates a low NEOs uptake efficiency of approximately 5% in crops, while most disperse into the surrounding environment.[14,15] NEOs are widely distributed throughout environmental matrices, including soils,[16] aquatic systems,[17] and atmospheric samples.[18,19] In recent years, NEOs have been measured in multiple human biospecimens, including serum, urine, and hair.[20] This indicates comprehensive human exposure to NEOs, which could lead to adverse health outcomes, including neurotoxicity,[21] reproductive toxicity,[22] and developmental toxicity.[23] As a major agricultural nation, China is a significant producer and consumer of NEOs, leading to substantial health risks from population exposure to these compounds.[24,25]

NEOs exposure may be associated with obesity. Animal research has revealed that exposure to imidacloprid in mice promotes the development of fat cells and increases fat storage in adipose tissue.[26] Simultaneously, the cellular experiment showed that fipronil stimulated adipogenesis through the AMP-activated protein kinase α pathway.[27] Additionally, numerous studies have shown the relationship between NEOs and obesity among diverse populations, including pregnant women,[28] children,[29] and adolescents.[30] Despite increasing evidence from various populations, the relationship between NEOs and obesity among individuals aged 35 to 74 years in China has not been explored in any studies. Research indicates that approximately 90% of middle-aged and elderly individuals are affected by cardiovascular-renal-metabolic syndrome.[31] Furthermore, the agricultural workforce is undergoing pronounced aging, evidenced by the proportion of workers aged 55.[32] Therefore, investigating the relationship between NEOs exposure and obesity in the 35–74 age group has significant public health implications.

Furthermore, the multifactorial nature of obesity limits the explanatory power of models based solely on conventional determinants, which fail to fully capture non-linear associations and interaction effects among demographic, socioeconomic, and behavioral predictors.[33] Recently, machine learning has demonstrated significant advantages in disease prediction, offering superior accuracy and robustness.[34] Although numerous studies have demonstrated associations between environmental pollutants and obesity, no research has systematically included these exposures as novel variables within frameworks for obesity using machine learning methods. By constructing machine learning models to identify key variables associated with obesity, this approach offers a novel research perspective for exploring the complex relationships underlying obesity.

Therefore, this cross-sectional study aims to investigate the association between NEOs and obesity in individuals aged 35–74 years, hypothesizing that: (1) this association is positive, and (2) it is sex-specific. To test these hypotheses, we used data from the Prospective Cohort of Chronic Diseases in Guangxi Ethnic Minority Natural Population, and employed machine learning to identify key obesity-associated variables.

Methods

Study Participants

The study subjects were drawn from the Prospective Cohort of Chronic Diseases in Guangxi Ethnic Minority Natural Population, as detailed in prior research.[35,36] This cohort primarily consists of residents from rural areas with generally lower levels of education.

 https://doi.org/10.2147/DMSO.S581758

Research participants met the following inclusion criteria: (1) aged between 35 and 74 years; (2) native to Guangxi and having resided there for over 5 years; and (3) having provided voluntary written informed consent. Research exclusion criteria included: (1) participants with missing urine samples or insufficient sample volume; (2) participants with any cancer diagnosis; (3) participants with missing variable data. Ultimately, this study included 862 participants. All participants provided informed consent. As illustrated in Figure 1.

Covariates

This study collected data on participants' sex, age, education, residence, smoking status (categorised as never, former/current), and drinking status (categorised as never, former/current) through questionnaire administration.

Concurrently, this study collected data on the frequency of consumption of eight different food groups: staple foods, vegetables, fruits, eggs, aquatic products, meat and poultry, legumes and nuts, and milk and dairy products.[37] A score of 1 was assigned if the response for a food group was "almost daily" or "at least once weekly," otherwise, no points were awarded. The dietary diversity score (DDS) was calculated by summing the scores across all eight food categories.

Additionally, alanine aminotransferase (ALT), aspartate aminotransferase (AST), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TG), and uric acid (UA) were obtained through serum biochemical analysis or routine urinalysis.

Definition of OWO and ABO

Trained staff measured all participants' height, weight, and waist circumference (WC). Calculation of body mass index (BMI) was based on weight in kilograms divided by height in meters squared. The diagnosis of overweight and obesity (OWO) and abdominal obesity (ABO) was based on criteria stipulated in the Chinese Guidelines for Diagnosis and Treatment of Obesity (2024 Edition).[38] This guideline is derived from large-scale epidemiological data on the Chinese population and more accurately reflects the body fat distribution characteristics of Chinese adults than international standards. Specifically, OWO was defined as BMI ≥24.0 kg/m^2, while ABO was defined by WC thresholds of ≥90.0 cm for males and ≥85.0 cm for females.[38]

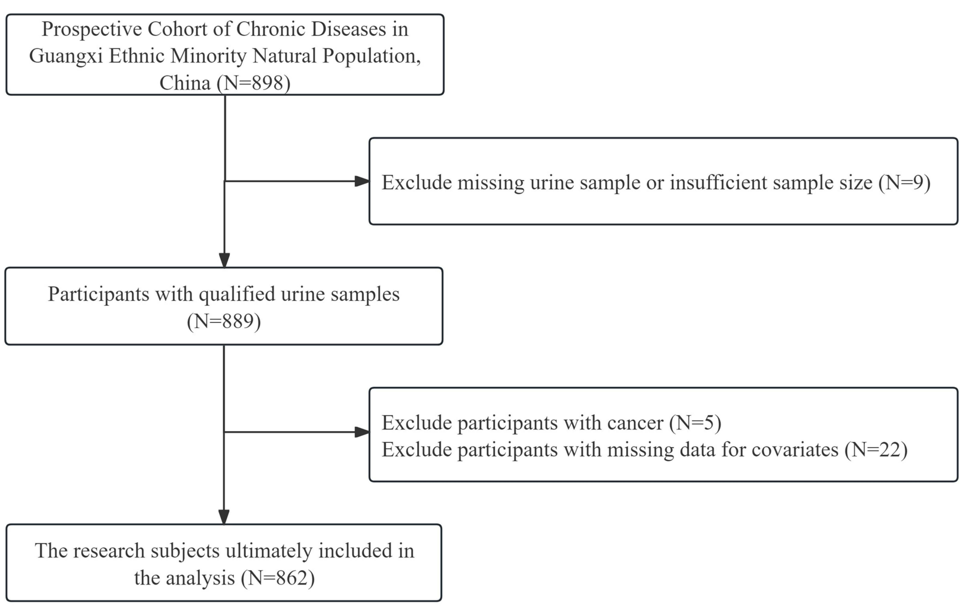

Figure 1 Process flowchart for selecting eligible participants for the Prospective Cohort of Chronic Diseases in Guangxi Ethnic Minority Natural Population, China.

 https://doi.org/10.2147/DMSO.S581758

Determination of NEOs in Urine Sample

Urine is the most commonly used and recognized biological matrix in human biomonitoring of NEOs.[11] This cross-sectional study analyzed single first-morning void urine samples from fasted participants to measure the concentrations of 10 NEOs, including acetamiprid (ACE), imidacloprid (IMI), nitenpyram (NIT), thiamethoxam (THIA), fipronil (FLU), thiacloprid (TMX), clothianidin (CLO), dinotefuran (DIN), sulfoxaflor (SUL), and N-desmethyl-acetamiprid (NACE). Specific detection methods and quality control measures are described in Text S1 and Table S1. The urinary concentrations of the analytes were corrected by urinary creatinine, which was determined using Cayman's Creatinine.[39] The creatinine adjustment formula is:

$$C(\mu\ g/g\ creatinine)=[C_n\ (ng/mL)/C_c(mg/dL)] \times 100 \tag{1}$$

In equation (1), C_n denotes the NEOs urinary concentration, C_c represents the urinary creatinine concentration, and C signifies the NEOs adjusted for creatinine. The corrected concentrations below the limit of detection (LOD) were assigned a value equal to the LOD value divided by the square root of 2.[40]

Statistical Analysis

This study employed Q-Q plots to assess the normality of continuous variables. Data that followed a normal distribution were expressed as mean ± standard deviation, and intergroup comparisons conducted using independent samples *t*-tests. Conversely, non-normally distributed variables were presented as median (interquartile range), and intergroup comparisons were performed using the Mann–Whitney *U*-test. Categorical variables were reported as frequencies (percentages), with intergroup differences evaluated using Chi-square tests. To ensure sufficient confidence, this study only analyzed NEOs with detection frequencies of 50% or higher.[41,42] Given that NEOs exposure concentrations displayed a skewed distribution, a natural logarithm (Ln) transformation was applied to NEOs concentrations for use as continuous variables.

The multivariable logistic regression model was used to examine the relationships between NEOs and various obesity phenotypes, categorized by BMI and waist circumference. Additionally, a generalized linear model with a binomial distribution and a logit link function was employed to analyze the association between urinary concentrations of NEOs, OWO, and ABO.

The Quantile g-computation (Qgcomp) and Bayesian Kernel Machine Regression (BKMR) models were utilized to assess the joint impact of NEOs exposure levels on OWO and ABO. The Qgcomp model is highly effective at analyzing nonlinear relationships between mixed exposures and outcomes, and can quantify the relative contribution of each exposure.[43] We utilized this model to assess the combined effects of four NEOs (CLO, NACE, IMI, TMX) on obesity (OWO and ABO). A binomial distribution served as the link function, with the quantile parameter q set to 3. BKMR is a flexible and robust method for assessing the combined effects of multiple exposures on outcomes by modeling complex nonlinear relationships through its kernel function.[44] This study further employed the BKMR model to create a probabilistic link function and utilized a Markov Chain Monte Carlo (MCMC) algorithm for hierarchical variable selection. After processing the mixed exposure data for 10,000 iterations, the posterior inclusion probability (PIP) for each exposure variable was computed, with PIP > 0.50 serving as the significance threshold. All models were adjusted for potential confounding factors, including age, sex, education, residence, smoking status, drinking status, and DDS, AST, ALT, FBG, HDL-C, LDL-C, TC, TG, UA, SBP, and DBP.

Furthermore, this study utilized six machine learning algorithms to identify critical feature variables, including Decision Tree (DT), K-Nearest Neighbours (KNN), Light Gradient Boosting Machine (LightGBM), Multilayer Perceptron (MLP), Random Forest (RF), and eXtreme Gradient Boosting (XGBoost). Given the sensitivity of KNN and MLP to feature scaling, we standardized continuous features using Z-scores for these two algorithms. The dataset was randomly split into a training set (70%) and a test set (30%). Five-fold cross-validation was performed on the training set,[45] and grid search was used for hyperparameter optimization. The best model was selected by plotting receiver operating characteristic (ROC) curves and evaluating performance metrics,[46] including the area under the curve (AUC), accuracy, sensitivity, and specificity. The interpretability of the model was analyzed using the Shapley Additive Explanations (SHAP) methodology. Final model evaluation was conducted on the independent test set. Finally, a sensitivity analyze was conducted using BMI and WC as continuous variables to further explore the relationship between NEOs exposure and both measures.

All statistical analyzes were performed in R (version 4.2.2) with significance at $p < 0.05$.

Result

Study Participants

This study included 862 participants, of whom 310 (35.96%) had OWO and 204 (23.67%) had ABO. The OWO group was younger than the non-OWO group (51.18 ± 9.07 vs 52.84 ± 10.07, $p = 0.014$). Conversely, the ABO group was significantly older than the non-ABO group (53.51 ± 9.42 vs 51.85 ± 9.83, $p = 0.030$). Both the OWO group (90.65% vs 9.35%) and the ABO group (91.67% vs 8.33%) demonstrated lower education levels. Additionally, the OWO and ABO groups had significantly higher levels of BMI, WC, DBP, SBP, UA, TC, TG, and LDL-C (all $p < 0.05$). HDL-C levels were significantly lower ($p < 0.001$). As shown in Table 1.

Table 1 Baseline Characteristics of Study Participants

Characteristics	OWO			ABO		
	No (n=552)	Yes (n=310)	*p* Value	No (n=658)	Yes (n=204)	*p* Value
Age (years)	52.84 ± 10.07	51.18 ± 9.07	0.014	51.85 ± 9.83	53.51 ± 9.42	0.030
Sex (%)			0.861			0.610
Female	331 (59.96)	184 (59.35)		390 (59.27)	125 (61.27)	
Male	221 (40.04)	126 (40.65)		268 (40.73)	79 (38.73)	
Education (%)			0.049			0.048
Less than high school	475 (86.05)	281 (90.65)		569 (86.47)	187 (91.67)	
High school or above	77 (13.95)	29 (9.35)		89 (13.53)	17 (8.33)	
Residence (%)			0.538			0.934
Urban	38 (6.88)	18 (5.81)		43 (6.53)	13 (6.37)	
Rural	514 (93.12)	292 (94.19)		615 (93.47)	191 (93.63)	
Smoking status (%)			0.964			0.525
Never	407 (73.73)	229 (73.87)		482 (73.25)	154 (75.49)	
Former/Current	145 (26.27)	81 (26.13)		176 (26.75)	50 (24.51)	
Drinking status (%)			0.973			0.296
Never	384 (69.57)	216 (69.68)		464 (70.52)	136 (66.67)	
Former/Current	168 (30.43)	94 (30.32)		194 (29.48)	68 (33.33)	
ALT (μ/L)	16 (13, 21)	18.1 (14, 26)	<0.001	16.75 (13, 22)	18 (14, 25.75)	0.004
AST (μ/L)	20 (17, 24)	19 (16, 23)	0.371	20 (17, 24)	19 (16, 23)	0.135
BMI (kg/m^2)	21.17 ± 1.92	26.56 ± 2.60	<0.001	22.06 ± 2.70	26.50 ± 3.13	<0.001
DDS	5.38 ± 1.24	5.42 ± 1.24	0.689	5.41 ± 1.26	5.36 ± 1.19	0.702
FBG (mmol/L)	4.52 (4.30, 4.71)	4.49 (4.31, 4.74)	0.831	4.48 (4.29, 4.69)	4.57 (4.35, 4.77)	0.007
HDL-C (mmol/L)	1.48 ± 0.35	1.28 ± 0.30	<0.001	1.46 ± 0.34	1.26 ± 0.30	<0.001
LDL-C (mmol/L)	2.80 ± 0.75	2.99 ± 0.83	<0.001	2.82 ± 0.75	3.01 ± 0.87	0.002
TC (mmol/L)	4.89 ± 0.88	5.11 ± 0.99	0.001	4.91 ± 0.89	5.15 ± 1.04	0.001
TG (mmol/L)	0.88 (0.68, 1.24)	1.36 (0.89, 2.01)	<0.001	0.92 (0.70, 1.30)	1.46 (0.89, 2.21)	<0.001
WC (cm)	76 (71, 81)	88 (83, 92)	<0.001	77 (72, 82)	91 (88,95)	<0.001
DBP (mmHg)	75.85 ± 8.46	78.96 ± 8.91	<0.001	76.37 ± 8.51	78.91 ± 9.23	<0.001
SBP (mmHg)	118.33 ± 14.90	123.10 ± 15.27	<0.001	118.86 ± 14.93	123.88 ± 15.44	<0.001
UA (μmol/L)	311.97 ± 83.15	357.90 ± 96.01	<0.001	317.25 ± 85.51	364.11 ± 97.62	<0.001

Notes: [a]The *p* value was obtained from the *t*-test, Mann–Whitney *U*-test, or Chi-square test.

Abbreviations: OWO, overweight and obesity; ABO, abdominal obesity; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; UA, uric acid; BMI, body mass index; WC, waist circumference.

Measurement of Urinary NEOs

The urinary concentrations of the ten NEOs are summarized in Table S2. NACE exhibited the highest detection rate (95.82%), followed by TMX (82.02%), CLO (54.99%), and IMI (50.00%). To ensure sufficient confidence, this study analyzed only NEOs with detection frequencies ≥50%,[41,42] including CLO, IMI, NACE, and TMX. The correlations among the four NEOs are illustrated in Figure S1. The result indicated correlations among the four NEOs from 0.27 to 0.51, with CLO and TMX exhibiting the highest correlation (r = 0.51, $p < 0.001$).

Multinomial Logistic Regression

We classified participants into four groups based on BMI and WC: Group 1 (Low BMI + Low WC), Group 2 (High BMI + Low WC; OWO only), Group 3 (Low BMI + High WC; ABO only), and Group 4 (High BMI + High WC; both OWO and ABO). The results indicated that after adjusting for potential confounders, NACE (OR = 1.325, 95% CI: 1.034, 1.698, $p = 0.026$) demonstrated a positive association with Group 3. In Group 4, CLO (OR = 1.124, 95% CI: 1.015, 1.245, $p = 0.025$), NACE (OR = 1.180, 95% CI: 1.030, 1.351, $p = 0.017$), and IMI (OR = 1.188, 95% CI: 1.004, 1.406, $p = 0.045$) exhibited significant positive associations. As shown in Table 2.

Generalized Linear Model

This study employed GLM to assess the relationships of urinary NEOs exposure with OWO and ABO (Table 3). The results demonstrated that CLO had significant positive associations with OWO (Model 2: OR = 1.090, 95% CI: 1.017, 1.169, $p < 0.05$) and ABO (Model 2: OR = 1.095, 95% CI: 1.013, 1.184, $p < 0.05$). A positive and statistically significant association between NACE and ABO was maintained (Model 3: OR=1.177; 95% CI: 1.046, 1.328, $p < 0.05$) even after

Table 2 Relationships Between Urinary NEOs Concentrations and Different Types of Obesity by Multinomial Logistic Regression Analysis

Exposure[a]	OR (95% CI)	*p* Value
Group 2 (High BMI + Low WC)[b]		
CLO	1.017 (0.919, 1.126)	0.738
NACE	1.079 (0.950, 1.225)	0.244
IMI	1.093 (0.923, 1.294)	0.301
TMX	0.941 (0.828, 1.070)	0.353
Group 3 (Low BMI+ High WC)[b]		
CLO	0.948 (0.782, 1.148)	0.583
NACE	**1.325 (1.034, 1.698)**	**0.026**
IMI	1.184 (0.878, 1.598)	0.268
TMX	1.104 (0.871, 1.399)	0.413
Group 4 (High BMI + High WC)[b]		
CLO	**1.124 (1.015, 1.245)**	**0.025**
NACE	**1.180 (1.030, 1.351)**	**0.017**
IMI	**1.188 (1.004, 1.406)**	**0.045**
TMX	1.037 (0.911, 1.181)	0.581

Notes: [a] The exposure concentration of NEOs has been subjected to Ln conversion treatment. [b]The Group 1 (Low BMI + Low WC) was used as the reference. The model was adjusted for age, sex, education, residence, smoking status, drinking status, ALT, AST, DDS, FBG, HDL-C, LDL-C, TC, TG, UA, SBP, DBP. Bold indicates statistically significant differences ($p < 0.05$).

Abbreviations: NEOs, neonicotinoids; OR, odds ratio; CI, confidence interval; CLO, clothianidin; NACE, N-desmethyl-acetamiprid; IMI, imidacloprid;TMX, thiacloprid.

Table 3 Associations of Urinary NEOs Exposure with OWO and ABO in Generalized Linear Models

NEOs[a]	Outcomes	Model 1 [OR (95% CI)]	Model 2 [OR (95% CI)]	Model 3 [OR (95% CI)]
CLO	OWO ABO	**1.097 (1.025, 1.175)*** **1.081 (1.001, 1.167)***	**1.090 (1.017, 1.169)*** **1.095 (1.013, 1.184)***	1.072 (0.989, 1.163) 1.085 (0.992, 1.187)
NACE	OWO ABO	**1.145 (1.052, 1.249)*** **1.166 (1.059, 1.287)***	**1.142 (1.046, 1.248)*** **1.199 (1.085, 1.327)***	1.107 (0.997, 1.229) **1.177 (1.046, 1.328)***
IMI	OWO ABO	1.118 (0.995, 1.255) 1.102 (0.967, 1.251)	1.108 (0.984, 1.246) 1.125 (0.985, 1.281)	1.125 (0.982, 1.290) 1.147 (0.990, 1.328)
TMX	OWO ABO	1.031 (0.946, 1.124) 1.074 (0.975, 1.184)	1.023 (0.937, 1.116) 1.078 (0.977, 1.190)	0.977 (0.882, 1.082) 1.068 (0.953, 1.197)

Notes: Model 1: unadjusted; Model 2: adjusted for age, sex, education, residence, smoking status, drinking status, DDS; Model 3: adjusted for age, sex, education, residence, smoking status, drinking status, AST, ALT, DDS, FBG, HDL-C, LDL-C, TC, TG, UA, SBP, DBP. [a] The exposure concentration of NEOs has been subjected to Ln conversion treatment. * and bold significant at $p < 0.05$.

adjusting for potential confounders. Analysis showed no significant associations between IMI or TMX and either obesity phenotype.

The sex-stratified results from the fully adjusted model (Model 3) are as follows. In females, CLO exposure showed a significant positive association with OWO (Model 3: OR = 1.134, 95% CI: 1.023, 1.258, $p < 0.05$); IMI exposure exhibited a positive association with both OWO (Model 3: OR = 1.193, 95% CI: 1.001, 1.424, $p < 0.05$) and ABO (Model 3: OR = 1.244, 95% CI: 1.031, 1.501, $p < 0.05$). In males, NACE showed significant positive associations with OWO (Model 3: OR = 1.237, 95% CI: 1.035, 1.486, $p < 0.05$) and ABO (Model 3: OR = 1.381, 95% CI: 1.119, 1.724, $p < 0.05$). The results of sex stratification are presented in Table S3.

Qgcomp Model

In the overall population, the Qgcomp model indicated a positive association between mixed NEOs exposure and ABO (OR = 1.964, 95% CI: 1.181, 3.266, $p = 0.009$), with IMI showing the strongest positive effect (0.766) after adjusting for all covariates. Additionally, mixed exposure to NEOs demonstrated a marginally significant positive association with OWO (OR = 1.568, 95% CI: 0.989, 2.484, $p = 0.055$), with IMI contributing the most significant positive effect (0.533). As illustrated in Figure 2 and Table S4.

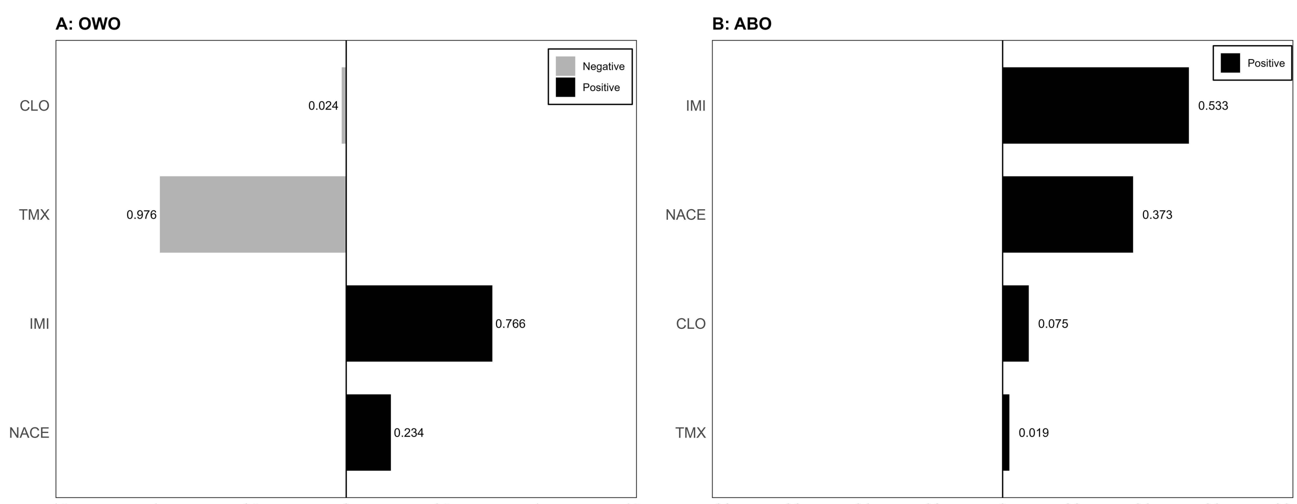

Figure 2 The weights of the positive and negative partial effects of NEOs on overweight and obesity (OWO) and abdominal obesity (ABO) were estimated based on the quantile g-estimation (Qgcomp) model. The model was adjusted for age, sex, education, residence, smoking status, drinking status, ALT, AST, DDS, FBG, HDL-C, LDL-C, TC, TG, UA, SBP, DBP. (**A**) OWO; (**B**) ABO.

Sex-stratified analysis found that the relationships between NEOs mixture and obesity were modified by sex. In females, mixed NEOs exposure was positively associated with both OWO (OR = 2.053, 95% CI: 1.141, 3.695, p = 0.016) and ABO (OR = 2.089, 95% CI: 1.103, 3.954, p = 0.024); IMI and CLO had the most significant positive contributions. However, no statistically significant associations were observed in males. As shown in Figure S2 and Table S4.

BKMR Model

The BKMR model revealed that exposure to mixed NEOs was positively correlated with ABO in the overall population after adjusting for all covariates. A positive dose-response relationship was observed between the concentration of the NEOs mixture and ABO, with a marked increase in the strength of association at or above the 70th percentile. Furthermore, CLO had the highest PIP (0.611) for OWO, and NACE had the highest PIP (0.737) for ABO. As illustrated in Figure 3 and Table S5.

Sex-stratified analyzes indicated that among females, the risk of OWO significantly increased with higher exposure concentrations to NEOs, particularly when NEOs levels were at or above the 55th percentile. In males, exposure to a mixture of NEOs was positively correlated with ABO, and this association was significantly stronger at or above the 65th percentile of exposure concentration. In females, CLO exhibited the highest PIP (0.635) for OWO, while IMI showed the highest PIP (0.630) for ABO. In males, NACE demonstrated the highest PIP for both OWO (0.680) and ABO (0.949). As shown in Figures S3 and Table S5.

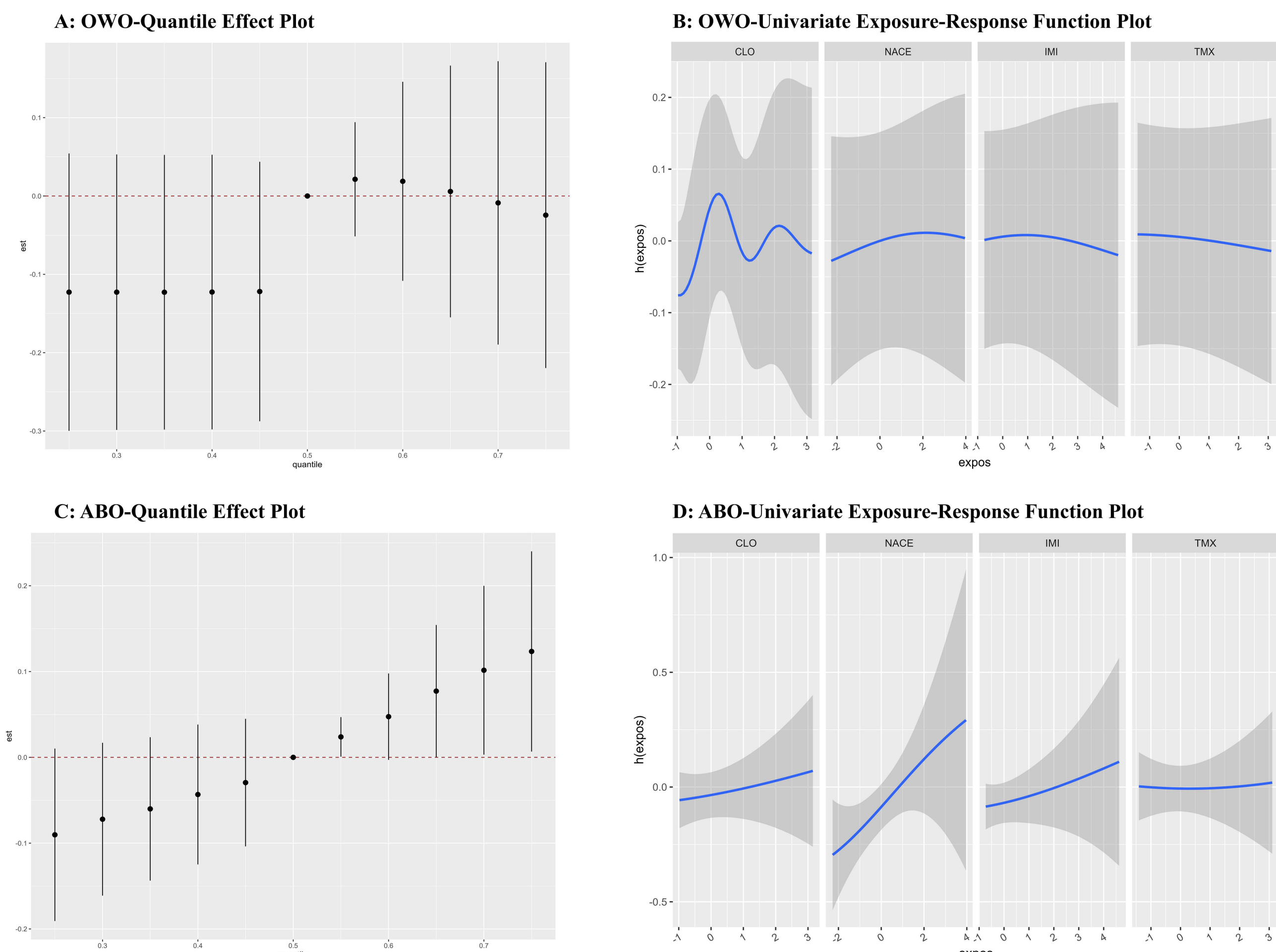

Figure 3 The association between urinary NEOs and both OWO and ABO was analyzed using the BKMR model. The model was adjusted for age, sex, education, residence, smoking status, drinking status, ALT, AST, DDS, FBG, HDL-C, LDL-C, TC, TG, UA, SBP, DBP. (**A**) Quantile effect plots for OWO. (**B**) Univariate exposure-response function plots for OWO. (**C**) Quantile effect plots for ABO. (**D**) Univariate exposure-response function plots for ABO.

Machine Learning

This study employed six machine learning algorithms (DT, KNN, LightGBM, MLP, RF, and XGBoost) to explore the relative importance of NEOs (CLO, NACE, IMI, TMX) versus traditional risk factors (age, sex, education, residence, smoking status, drinking status, ALT, AST, DDS, FBG, HDL-C, LDL-C, TC, TG, UA, SBP, DBP) in OWO and ABO. The ROC curves for each algorithm in the OWO and ABO prediction models are shown in Figures S4 and S5, respectively. A summary of various performance evaluation metrics across different algorithms is provided in Tables S6 and S7. Results from six machine learning algorithms showed that MLP and RF achieved the highest AUC values on the OWO and ABO test sets, respectively (MLP: training set 0.863, test set 0.739; RF: training set 0.901, test set 0.739). Therefore, we selected these two models for subsequent SHAP analysis to evaluate the contribution of each variable to OWO and ABO.

To clarify the model outputs, we conducted visualization analyzes of the MLP and RF models using Shapley Additive Explanations. The SHAP analysis of the MLP model shows that CLO is the fourth most important feature among the 21 variables for OWO and is positively associated with OWO. SHAP analysis of the RF model indicates that NACE is the fifth most important feature for ABO and is positively correlated with ABO. Additionally, IMI was also recognized as a key feature associated with ABO, ranking eighth among mean absolute SHAP values. SHAP analysis showed that traditional risk factors, including ALT, AST, UA, TG, and HDL-C, were significant determinants of obesity. As shown in Figure 4.

Sensitivity Analysis

This study further conducted sensitivity analyzes using continuous BMI and WC, with results presented in Table S8. For each unit increase in urinary NACE concentration, BMI increased by 0.139 kg/m^2 (95% CI: 0.017, 0.260; p = 0.025), and WC increased by 0.470 cm (95% CI: 0.136, 0.804; p = 0.006).

Discussion

This cross-sectional study provides the first evidence on the relationship between urinary NEOs concentrations and obesity among Chinese individuals aged 35 to 74 years. The results indicate that CLO, NACE, IMI, and mixed NEOs exposure are significantly associated with obesity, and these associations differ by sex. Furthermore, machine learning models identify CLO and NACE as key factors associated with obesity. These findings provide new epidemiological evidence for understanding the association between NEOs and obesity.

This study measured urinary concentrations of ten NEOs. Among these, NACE, TMX, CLO, and IMI exhibited higher detection rates, whereas DIN, ACE, SUL, and NIT demonstrated lower detection rates. The detection rates and concentrations of NEOs in urine samples from Guangxi residents differed from those in other regions. A study of 160 university students in Guangzhou, China, reported a CLO detection rate of 92% and a median concentration of 0.19 ng/mL.[47] Both values are lower than those measured in the Guangxi population. A Japanese study of 30 pregnant women reported NEO detection rates in urine, with NACE (95.3%) and THX (84.7%) comparable to those in our study, while CLO (89.3%) was significantly higher.[48] Urinalysis of 15,327 American adults for NEOs revealed lower detection rates for NACE (32.1%), CLO (7.4%), and IMI (4.2%) than in our study, while rates for ACE (0.3%) and THIA (0.05%) were similar.[49] Due to diverse human exposure pathways and the influence of regional diets and lifestyles, the detection rates and concentrations of NEOs can vary significantly across different geographical regions.[50,51] Future efforts should focus on strengthening monitoring in regions with elevated NEOs exposure levels and conducting prospective studies to clarify their association with health outcomes, thereby providing scientific evidence for future regulatory decisions.

Urinary levels of CLO, NACE, and IMI were significantly associated with obesity in this study. This positive relationship is consistent with prior epidemiological and toxicological research. Wu et al[30] reported that CLO was associated with obesity rates, and NACE showed a positive correlation with the waist-to-height ratio and was associated with obesity severity. A study involving 204 Chinese urban women aged 25–45 found that IMI concentrations in hair samples were positively correlated with BMI.[52] A toxicological study indicated that maternal exposure to CLO was dose-dependently associated with increased average birth weight of offspring.[26,53,54] Another animal study observed that IMI

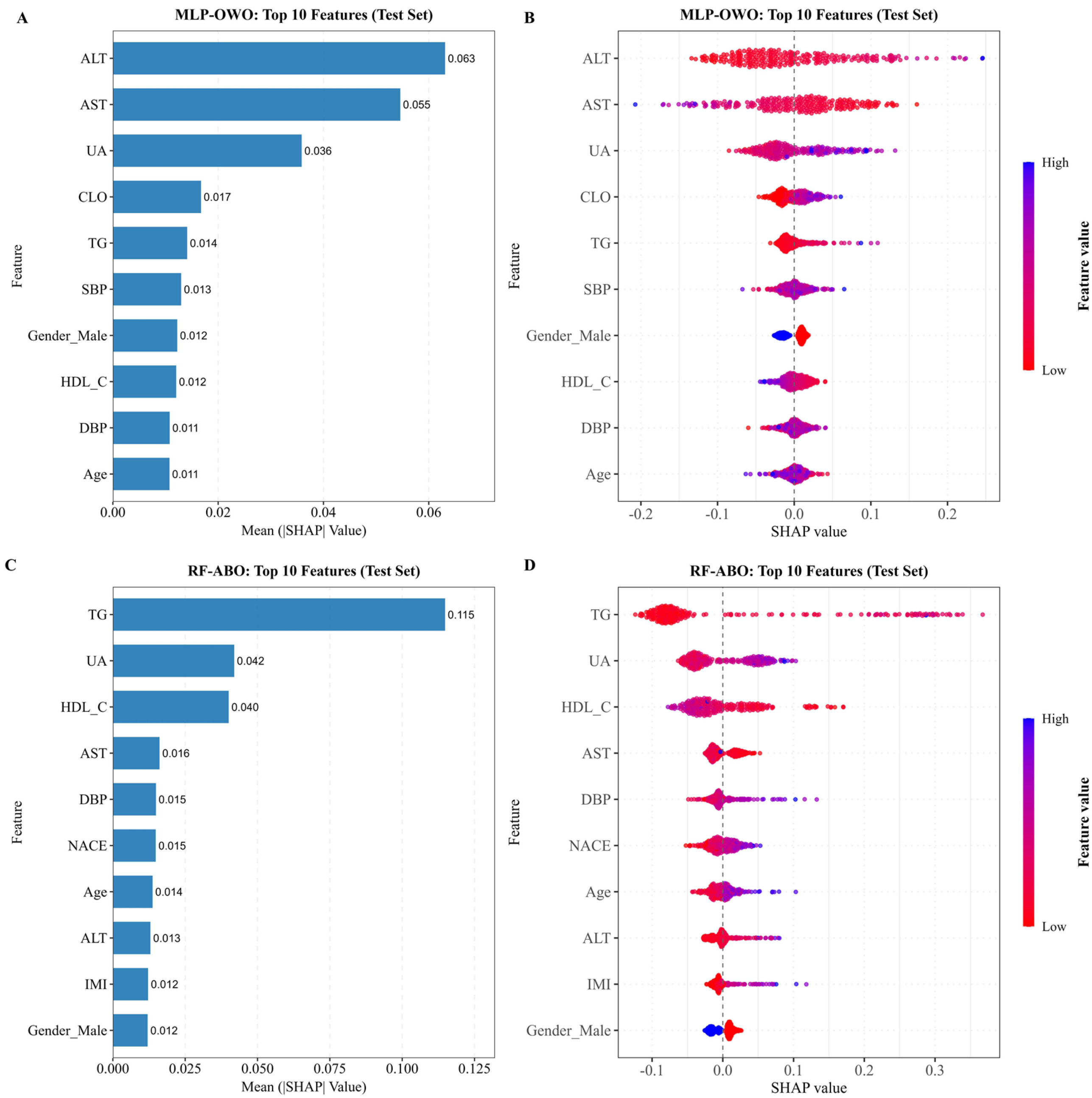

Figure 4 Feature importance and Shapley Additive Explanations (SHAP) value distribution of the Multilayer Perceptron (MLP) and Random Forest (RF) models (Test Set). (**A, C**) Feature importance bar chart; (**B, D**) SHAP beeswarm plot.

combined with a high-fat diet elevated body weight and adipose mass in both male[54] and female mice.[26] Moreover, Yang et al[55] reported a positive association between TMX and BMI z-score in 7–11-year-olds from China. Although previous research has shown an association between TMX and obesity, our epidemiological analysis did not identify such a correlation. The differences between this study and previous research findings may arise from variations in the geographical locations of the study subjects, their age distributions, exposure concentrations to NEOs, and detection rates.

The mixture models (Qgcomp and BKMR) revealed a significant association between urinary concentrations of NEOs and obesity, which we hypothesize may be related to oxidative stress induced by NEOs.[56,57] A study reported that concentrations of NACE and IMI in urine were positively correlated with oxidative stress markers.[58–60] Lu et al[59] found that the positive correlation between NEOs and obesity indicators was mediated by 8-iso-PGF2α. Moreover, previous animal and cellular research has shown that oxidative stress may contribute to obesity by promoting preadipocyte proliferation, differentiation, and hypertrophy, as well as by altering food intake.[61–63] This study also identified sex-specific associations: NEOs exposure was significantly associated with OWO in females and with ABO in males, potentially attributable to differences in sex hormones. Research has shown that IMI concentration was positively associated with cortisol, cortisone, and testosterone levels.[64] Additionally, Li et al[65] found that CLO, ACE, and FLU were most effective in activating and upregulating the G protein-coupled estrogen receptor. Therefore, we hypothesize that the association between NEOs and obesity may be mediated through oxidative stress and hormones based on existing cellular and animal experimental evidence. However, the role of these mechanisms in human populations remains a scientific hypothesis that requires further validation.

Machine learning algorithms are a branch of artificial intelligence that can address the impact of complex, nonlinear relationships in high-dimensional data, enabling more accurate capture of big data. They are widely used in the medical field for predicting various diseases.[66,67] This study is the first to apply machine learning to identify key variables associated with obesity within a dataset integrating four NEOs and 17 traditional risk factors. The results showed that CLO and NACE were particularly significant among all the factors. The SHAP results are consistent with those from the GLM model and the mixture models (BKMR and Qgcomp). Moreover, conventional risk factors such as ALT and TG significantly contribute to obesity, consistent with findings observed in previous research.[68,69] It is worth to note that this study involves multiple statistical tests across various exposures, outcomes, and models, which may increase the probability of chance discoveries. Nevertheless, given the internal consistency of the observed associations, the findings of this study may provide valuable clues for early identification of obesity and subsequent research.

This study is the first to investigate the association between NEOs exposure and obesity in individuals aged 35–74 by employing a large sample, mixture models, and machine learning methods. The findings not only address a gap in the current evidence base but also provide novel insights for a comprehensive evaluation of the impact of NEOs on public health. Nevertheless, several limitations of this study should be considered. Firstly, this study employed a cross-sectional design and relied solely on a single urine sample, limiting causal inference and potentially failing to reflect long-term exposure levels accurately. Secondly, the study lacked data on covariates, including dietary pesticide exposure, occupational pesticide use, and physical activity. Thirdly, the study did not examine the combined effects of NEOs with other environmental endocrine disruptors. Finally, the machine learning model was trained on a cohort from a single region in Guangxi, and its generalizability requires external validation.

Conclusion

The findings of this cross-sectional study indicated that exposure to the CLO, NACE, IMI, and NEOs mixture was positively associated with obesity among individuals aged 35 to 74 in Guangxi, China, with sex differences observed. Furthermore, machine learning analysis identified CLO and NACE as important features associated with obesity. Future studies should conduct prospective cohort research with larger sample sizes and incorporate additional potential covariates to validate and expand upon our findings.

Data Sharing Statement

Data set are available from the corresponding author on reasonable request.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Guangxi Medical University (Approval No. 20170206-1). All participants provided written informed consent.

Acknowledgments

All the study participants are greatly acknowledged.

Author Contributions

Liujuan Ou: Investigation, Methodology, Writing - Original Draft, Writing-Review and Editing. Junshang Wen: Formal analysis, Writing – review & editing, Methodology, Validation. Wanhui Li: Methodology, Data Curation, Investigation, Writing -Editing. Xin Qin: Investigation, Data Curation, Writing -Editing. Xiaolin Wu: Investigation, Data Curation, Writing-Review & Editing. Qihua Zhu: Resources, Validation, Investigation, Writing -Editing. Junwang Gu: Investigation, Data Curation, Writing -Editing. Huishen Huang: Investigation, Data Curation, Writing -Editing. Xiaohong Liu: Investigation, Data Curation, Writing -Editing. Xiaoqiang Qiu: Conceptualization, Methodology, Resources, Supervision, Writing-Review & Editing. Dongping Huang: Investigation, Methodology, Writing - Original Draft, Writing - Review & Editing, Project administration, Resources, Supervision, Funding acquisition. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the National Natural Science Foundation of China (Grant number 22366007) and the Guangxi Natural Science Foundation of China (Grant number 2024GXNSFAA010391).

Disclosure

The authors report no conflicts of interest in this work.

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