Received: 19 May 2023 | Revised: 14 September 2023 | Accepted: 17 September 2023

DOI: 10.1002/JPER.23-0322

JOURNAL OF Periodontology

ORIGINAL ARTICLE

The associations of coffee consumption, coffee types, and caffeine metabolites with periodontitis: Results from NHANES 2009–2014

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Funding information
High-Level Talents Research Start-up Project of Fujian Medical University, Fujian, China, Grant/Award Number: XRCZX2018001; Joint Funds for Innovation of Science and Technology of Fujian Province, Fujian, China, Grant/Award Number: 2021Y9015

Abstract

Background: Coffee is one of the world's most popular beverages and is the main dietary source of caffeine for most people. The various molecular effects of caffeine suggest that it may enhance bone loss. The purpose of the present study was to investigate the relationship of coffee, coffee types, and caffeine metabolites with periodontitis.

Methods: Data were obtained from the National Health and Nutrition Examination Survey (NHANES) 2009–2014. Total coffee and different types of coffee consumption were acquired through a 24-h dietary recall. Urinary caffeine metabolites were quantified using high-performance liquid chromatography–electrospray ionization–tandem quadrupole mass spectrometry (HPLC–ESI–MS/MS). The association of coffee, coffee types, and caffeine metabolites with periodontitis and its severity were assessed using multivariable logistic regression.

Results: A total of 3309 eligible participants were included. After adjusting for potential confounding variables, a positive association was observed between coffee consumption (particularly certain types of coffee) and periodontitis. Notably, a positive correlation was also found between total coffee intake and the severity of periodontitis. Additionally, for urinary caffeine metabolites, there was a significant positive association between 1-methyluric acid (1-MU), 1,3-dimethyluric acid (1,3-DMU), 3,7-dimethyluric acid (3,7-DMU), 1,7-dimethylxanthine (1,7-DMX), or 5-actlyamino-6-amino-3-methyluracil (AAMU) and periodontitis, with adjusted odds ratios and 95% confidence intervals of 1.10

Qiansi Chen and Ruiyang Ge contributed equally to this work.

(1.02, 1.19), 1.86 (1.05, 3.29), 0.94 (0.90, 0.98), 1.29 (1.03, 1.62), and 1.15 (1.05, 1.26), respectively.

Conclusions: The present study suggests a positive association of coffee intake (especially certain coffee types) and caffeine metabolites (1-MU, 1,3-DMU, 3,7-DMU, 1,7-DMX, and AAMU) with periodontitis and its severity.

KEYWORDS
caffeine, coffee, metabolite, oral health, periodontitis

1 | INTRODUCTION

Periodontitis is a widespread chronic inflammatory disease that leads to the loss of connective tissue and bone support, and it is the leading cause of tooth loss in adults.[1,2] The prevalence of periodontitis is approaching 1.1 billion worldwide.[3] Periodontitis affects 42.2% of adults over the age of 30 in the United States, and 7.8% of adults suffer from severe periodontitis.[4] Previous epidemiological evidence has shown a positive association between periodontitis and a wide range of chronic diseases, such as diabetes, hypertension, atherosclerotic disease, and cancer.[5–8] Therefore, it is of great importance to investigate the factors influencing periodontitis.

Coffee is one of the most favored drinks in the world, contains high levels of caffeine, and is the primary dietary source of caffeine for most populations.[9,10] Coffee contains ingredients with antioxidant and anti-inflammatory properties, such as caffeine, chlorogenic acid, and caffeic acid, and it is considered one of the richest antioxidant drinks.[11] Nevertheless, the various molecular effects of caffeine indicate that it may enhance bone loss,[12] and alveolar bone resorption is a marker of periodontitis, suggesting that the relationship between coffee and periodontitis is of great concern. However, the results remain controversial across studies. Some studies have shown a positive association between coffee and periodontitis,[13] while others have found a negative association or lack of association between coffee and periodontitis.[14,15] In addition, most previous studies were limited to the relationship between total coffee intake and periodontitis, and they rarely involved coffee types and caffeine metabolites.[13,16,17] Therefore, using data from a representative national sample of the National Health and Nutrition Examination Survey (NHANES), the present study aimed to systematically explore the relationship of coffee, coffee types, and caffeine metabolites with periodontitis.

2 | MATERIALS AND METHODS

2.1 | Data collection and study population

The present study was based on data from NHANES 2009–2014,[18–20] which was a research project designed to evaluate the state of health and nutrition of American adults and children by combining the following information: interviews regarding demographic, socioeconomic, diet, and health-related issues; examinations that include medical, dental, and physiological measurements; and laboratory tests conducted by professionally trained medical workers. A total of 10,714 adults received periodontal examinations. We excluded those who had not completed 24-h dietary recall data ($n = 618$) and had incomplete laboratory test data ($n = 6787$). We ultimately included 3309 participants for subsequent analysis. The study flow is described in detail in Figure S1 in the online *Journal of Periodontology*. The present study included three 2-year cycles, and these 6 years were the only years in the NHANES protocol that included a full-mouth periodontal examination, excluding third molars. Information on technical aspects of the project, such as design of the samples, periodontal data collection techniques, and data usability, is available on NHANES.[21] The Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS) Ethics Review Board approved the oral health data collection protocol for the present study, and all survey participants signed an informed consent form. The present study was undertaken in accordance with the Declaration of Helsinki (1975; revised 2013) and did not require approval from the Institutional Review Board of Fujian Medical University because we used nonidentifying information from the NHANES database.

2.2 | Periodontal examination

Whole-mouth periodontal examination was conducted by dental examiners for participants who were ≥30 years old and had at least one natural tooth. All dental examiners were both trained and calibrated by the survey reference inspector. Probing depth (PD) and gingival recession were measured at six sites on each tooth using a colored-coded periodontal probe that was scaled at 2-mm intervals. The professional censor checked all four quadrants and the measurement results by rounding to the nearest millimeter. An algorithm was used in the data input procedure to auto-calculate the clinical attachment loss (AL), which is the distance between the pulp-enamel junction and the bottom of the probe pocket.[22,23] Based on the above measurements, participants were classified into no, mild, moderate, or severe periodontitis groups according to the CDC/American Academy of Periodontology (AAP) definition. The specific definitions are as follows: (1) mild periodontitis—more than two interdental sites with AL ≥3 mm but <4 mm, more than two interdental sites with PD ≥4 mm but <5 mm (not on the same tooth), or one site with PD ≥5 mm; (2) moderate periodontitis—more than two interdental sites with AL ≥4 mm but <6 mm or more than two interdental sites with PD ≥5 mm (not on the same tooth); (3) severe periodontitis—more than two interdental sites with AL ≥6 mm (not on the same tooth) and more than one interdental sites with PD ≥5 mm; and (4) participants were classified as having no periodontitis if they did not fall into any of the above categories of periodontitis.[24]

2.3 | Dietary assessment of coffee consumption

Consumption data for coffee intake were obtained from NHANES 2009–2014 dietary data. Coffee consumption was summarized based on the results of a 24-h dietary recall interview. We used food codes and food descriptions from the Food and Nutrient Database for Dietary Studies (FNDDS) database[25] to identify coffee beverages, classifying coffee as sweetened coffee, unsweetened coffee, caffeinated coffee, decaffeinated coffee, coffee with fat, fat-free coffee, and coffee with milk. The specific coffee classifications can be found in Table S1 in the online *Journal of Periodontology*. The specific collection process is available in the Mobile Examination Center (MEC) In-Person Dietary Interviewers Procedures Manual on NHANES.[26–28]

2.4 | Measurement of urinary caffeine metabolites

The urinary metabolites of caffeine were quantified by high-performance liquid chromatography–electrospray ionization–tandem quadrupole mass spectrometry (HPLC–ESI–MS/MS) with stable isotope-labeled internal standards. The 15 metabolites included 1-methyluric acid (1-MU), 3-methyluric acid (3-MU), 7-methyluric acid (7-MU), 1,3-dimethyluric acid (1,3-DMU), 1,7-dimethyluric acid (1,7-DMU), 3,7-dimethyluric acid (3,7-DMU), 1,3,7-trimethyluric acid (1,3,7-TMU), 1-methylxanthine (1-MX), 3-methylxanthine (3-MX), 7-methylxanthine (7-MX), 1,3-dimethylxanthine (1,3-DMX), 1,7-dimethylxanthine (1,7-DMX), 3,7-dimethylxanthine (3,7-DMX), 1,3,7-trimethylxanthine (1,3,7-TMX), and 5-actlyamino-6-amino-3-methyluracil (AAMU). The detailed specimen-processing instructions are available in the NHANES Laboratory Methods: Caffeine & Caffeine Metabolites—Urine.[29]

2.5 | Covariates

The following potential confounders were included as covariates: age, sex, race (Mexican American, non-Hispanic White, non-Hispanic Black, or other races), marital status (married, unmarried but have or had a partner, or never married), education level (less than high school, high school, or college and above), poverty to income ratio (PIR), body mass index (BMI; normal: <25 kg/m2; overweight: 25–30 kg/m2; and obese: ≥30 kg/m^2), diabetes (yes or no), hypertension (yes or no), alcohol use (never, former [a history of day-drinking], mild [1 ≤ cups < 2 per day for women, 2 ≤ cups < 3 per day for men], moderate [2 ≤ cups < 3 per day for women, 3 ≤ cups < 4 per day for men], or heavy [≥3 cups per day for women and ≥4 cups for men]),[30] smoking status (never [less than 100 tobacco cigarettes smoked in a lifetime], former [smoked over 100 tobacco cigarettes in life but now completely nonsmoking], current [smoked over 100 tobacco cigarettes in life and still smoke occasionally or daily]),[31] and dietary inflammatory index (DII)[32] divided into three groups according to tertile. The PIR was used to define income levels and was defined as the proportion of family income to the poverty line. Participants with a doctor-diagnosed history of diabetes or antihyperglycemic drug use were considered to have diabetes. Participants who had a history of being diagnosed as hypertensive or on antihypertensive medication with a systolic blood pressure

≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg were defined as hypertensive. The calculation of DII refers to the previously developed revised version.[32]

2.6 | Statistical analysis

Categorical and continuous variables were expressed as medians (25%, 75% quantile) or numbers (percentages) and compared by the Mann–Whitney *U* test or chi-square test, respectively. Laboratory exam weight (WTSC2YR) provided by NHANES was used for all estimations in the analyses. We first divided the participants into two groups according to periodontal status (periodontitis group [those with mild, moderate, or severe periodontitis] and nonperiodontitis group). A weighted binary logistic regression model was applied to evaluate the relationship of total coffee, sweetened coffee, unsweetened coffee, caffeinated coffee, decaffeinated coffee, coffee with milk, coffee with fat, or fat-free coffee with periodontitis. Restricted cubic splines (RCSs) were applied to explore the nonlinear correlation between periodontitis and coffee ingestion. Participants were further divided into four groups (no periodontitis, mild periodontitis, moderate periodontitis, and severe periodontitis), and an unordered multinomial logistic regression model (because the parallelism test was not satisfied) was used to explore whether coffee intake was related to the severity of periodontitis. Furthermore, a weighted linear regression model was used to analyze the relationship of coffee consumption with mean AL, mean PD, or number of teeth.

Given the correlations between metabolites, least absolute shrinkage and selection operator (LASSO) regression was performed to select metabolites associated with periodontitis using 10-fold cross-validation and minimum criteria. LASSO regression is a shrinkage method that can actively select from a large and potentially multicollinear set of variables in the regression, resulting in a more relevant and interpretable set of predictors.[33] The association between urinary caffeine metabolites (after creatinine adjustment) and periodontitis was assessed by weighted multivariable logistic regression. Additionally, given that caffeine intake during pregnancy was reported to be associated with an increased risk of restricted fetal growth[9,34] and pregnant women may reduce their coffee consumption, a sensitivity analysis by excluding pregnant and breastfeeding women was also performed to assess the robustness of the present results. The E-value analysis was conducted to quantify the potential implications of residual confounding.[35] All statistical analyses were performed by R version 4.1.3, and a two-tailed $p < 0.05$ indicated statistical significance.

3 | RESULTS

The differences in sociodemographic characteristics between participants with and without periodontitis are shown in Table 1. Individuals with periodontitis were more likely to be male, smokers, heavy drinkers, and less educated than individuals without periodontitis. Participants with periodontitis had a significantly higher prevalence of obesity, hypertension, and diabetes than participants without periodontitis.

Table 2 shows the relationship among coffee consumption, types of coffee, and periodontitis. The estimated odds ratio (OR) and 95% confidence interval (CI) for periodontitis per interquartile range (IQR) increase in total coffee intake (g/day) was 1.23 (1.09, 1.38) in Model 1. After additional adjustment for hypertension and diabetes, the OR for periodontitis per IQR increase in total coffee intake (g/day) was 1.22 (95% CI: 1.09, 1.37). This significant relationship was maintained in the sensitivity analysis (see Table S2 in the online *Journal of Periodontology*). Regarding different types of coffee, the positive association was significant for unsweetened coffee, caffeinated coffee, fat-free coffee, or coffee with milk in Models 1 and 2. The results of the RCS analysis showed that the OR increased with total coffee, caffeinated coffee, unsweetened coffee, and fat-free coffee intake (Figure 1).

Participants were then categorized into four groups as follows: no, mild, moderate, and severe periodontitis. Unordered multinomial logistic regression indicated that coffee consumption was significantly related to the severity of periodontitis, and the ORs and 95% CIs for moderate and severe periodontitis per IQR increase were 1.14 (1.00, 1.30) and 1.31 (1.11, 1.55), respectively (Table 3). Additionally, there was a positive correlation between total coffee consumption and mean AL, and there was a negative correlation between total coffee ingestion and the number of teeth, which persisted after additional adjustment for diabetes and hypertension (see Table S3 in the online *Journal of Periodontology*).

Of the 15 urinary caffeine metabolites, 3-MU, 7-MU, 1,7-DMU, 3,7-DMU, 1,3,7-TMU, 1-MX, 3-MX, 7-MX, 1,3-DMX, 1,7-DMX, and 3,7-DMX had statistically significant differences between participants with and without periodontitis (Figure 2). Because the caffeine metabolites had significant correlations (Figure 3A), LASSO regression was used to select 11 caffeine metabolites (1-MU, 7-MU, 1,3-DMU, 1,7-DMU, 3,7-DMU, 1,3,7-TMU, 1-MX, 3-MX, 7-MX, 1,7-DMX, and AAMU) associated with periodontitis when $\log(\lambda) = -5.74$ (Figure 3B). LASSO coefficient profiles of 15 caffeine metabolites are displayed in Figure 3C. These association patterns remained significant even after adjusting for covariates (Figure 3D). Additionally, in the

TABLE 1 Characteristics of study population, National Health and Nutrition Examination Survey (NHANES) 2009–2014 ($N = 3309$).

Characters	Total $N = 3309$	Nonperiodontitis $n = 1653$	Periodontitis $n = 1656$	p value
Age (years), median (25%, 75% quantile)	50.0 (40.0, 60.0)	47.0 (38.0, 57.0)	55.0 (44.0, 65.0)	<0.001
PIR, median (25%, 75% quantile)	3.4 (1.7, 5.0)	4.0 (2.3, 5.0)	2.5 (1.3, 4.5)	<0.001
Age, *n* (%)				<0.001
<65 years	2611 (78.9)	1416 (88.4)	1195 (73.9)	
≥65 years	698 (21.1)	237 (11.6)	461 (26.1)	
Sex, *n* (%)				<0.001
Female	1689 (51.0)	982 (57.7)	707 (41.8)	
Male	1620 (49.0)	671 (42.3)	949 (58.2)	
Race, *n* (%)				<0.001
Mexican American	459 (13.9)	168 (5.1)	291 (10.8)	
Non-Hispanic Black	683 (20.6)	269 (7.8)	414 (15.1)	
Non-Hispanic White	1462 (44.2)	866 (76.3)	596 (59.1)	
Other	705 (21.3)	350 (10.8)	355 (15.0)	
Marital status, *n* (%)				<0.001
Married	1976 (59.7)	1055 (69.1)	921 (57.1)	
Never married	384 (11.6)	203 (10.0)	181 (11.0)	
Unmarried but have/had partner	948 (28.7)	395 (20.9)	553 (31.9)	
Educational level, *n* (%)				<0.001
Less than high school	737 (22.3)	234 (9.1)	503 (22.2)	
High school	715 (21.6)	295 (16.4)	420 (25.9)	
Some college or above	1852 (56.1)	1123 (74.5)	729 (51.9)	
Smoking status, *n* (%)				<0.001
Never	1892 (57.2)	1079 (65.5)	813 (47.5)	
Former/current	1416 (42.8)	574 (34.5)	842 (52.5)	
Alcohol consumption, *n* (%)				<0.001
Never	430 (13.7)	205 (10.4)	225 (11.3)	
Former	573 (18.2)	208 (11.1)	365 (20.9)	
Mild	1109 (35.3)	613 (41.9)	496 (36.0)	
Moderate	494 (15.7)	305 (20.6)	189 (12.8)	
Heavy	539 (17.1)	244 (16.0)	295 (19.0)	
BMI (kg/m2), *n* (%)				0.011
<25	842 (25.5)	452 (27.6)	390 (23.3)	
25–30	1156 (35.1)	581 (36.9)	575 (34.5)	
≥30	1299 (39.4)	616 (35.5)	683 (42.2)	
Hypertension, *n* (%)				<0.001
No	1870 (56.5)	1052 (66.0)	818 (52.1)	
Yes	1439 (43.5)	601 (34.0)	838 (47.9)	
Diabetes, *n* (%)				<0.001
No	2875 (87.3)	1515 (94.6)	1360 (85.4)	
Yes	418 (12.7)	124 (5.4)	294 (14.6)	
DII, *n* (%)				0.167
Q1 (−4.557 to 0.581)	1103 (33.3)	588 (36.8)	515 (32.6)	
Q2 (0.581–2.403)	1103 (33.3)	534 (33.8)	569 (35.6)	
Q3 (2.403–5.380)	1103 (33.3)	531 (29.4)	572 (31.8)	

Abbreviations: BMI, body mass index; DII, dietary inflammatory index; PIR, poverty to income ratio.

TABLE 2 Association of total coffee and different types of coffee consumption with periodontitis in National Health and Nutrition Examination Survey (NHANES) 2009–2014.

Variables	Model 1		Model 2	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Total coffee intake (g/day)[a]	1.23 (1.09, 1.38)	0.002	1.22 (1.09,1.37)	0.001
Sweetened coffee[b]				
No	Ref		Ref	
Yes	0.81 (0.20,3.31)	0.760	0.78 (0.20,3.08)	0.710
Unsweetened coffee[b]				
No	Ref		Ref	
Yes	1.36 (1.08,1.71)	0.010	1.34 (1.06,1.68)	0.010
Caffeinated coffee[b]				
No	Ref		Ref	
Yes	1.34 (1.07,1.68)	0.010	1.32 (1.06,1.65)	0.020
Decaffeinated coffee[b]				
No	Ref		Ref	
Yes	1.34 (0.82,2.20)	0.240	1.31 (0.78,2.18)	0.290
Coffee with fat[b]				
No	Ref		Ref	
Yes	0.50 (0.10,2.47)	0.380	0.50 (0.10,2.45)	0.370
Fat-free coffee[b]				
No	Ref		Ref	
Yes	1.35 (1.08,1.69)	0.010	1.33 (1.06,1.66)	0.010
Coffee with milk[b]				
No	Ref		Ref	
Yes	1.35 (1.07,1.69)	0.010	1.33 (1.06,1.66)	0.010

Note: Model 1—adjusted for age, sex, race, educational level, marital status, poverty to income ratio, body mass index, alcohol drinking, smoking status, and dietary inflammatory index. Model 2—additionally adjusted for hypertension and diabetes.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Total coffee intake (g/day) was standardized according to interquartile range (IQR) to estimate the ORs per IQR increase in levels of coffee.

[b]Those who never drank any type of coffee were set as the reference. "No" indicates not drinking any type of coffee, while "Yes" indicates drinking the corresponding type of coffee.

sensitivity analyses that excluded pregnant and breastfeeding women, the results did not change significantly (see Table S4 in the online *Journal of Periodontology*). We also used E-value analysis to assess the effect of residual confounding factors, and the results indicated that the observed associations in this study were moderately robust to unmeasured confounding (see Tables S5–S6 in the online *Journal of Periodontology*).

4 | DISCUSSION

In the present large cross-sectional study of US adults, there was a positive association between total coffee consumption and periodontitis. Similar positive associations were observed for unsweetened coffee, caffeinated coffee, coffee with milk, or fat-free coffee with periodontitis. Of note, urinary caffeine metabolites (1-MU, 1,3-DMU, 3,7-DMU, 1,7-DMX, and AAMU) were positively associated with periodontitis. Given that coffee consumption is a potentially modifiable lifestyle, these results indicated that reducing coffee consumption may have considerable public health significance for the prevention of periodontitis. In agreement with several previously conducted studies, the present study demonstrated that coffee consumption was positively related to periodontitis.[13,16,36] However, the results from recent meta-analyses do not support a significant relationship between coffee intake and periodontitis.[11,17] Drinking coffee is an integral part of daily life for people worldwide, but coffee types and personal preferences in different regions and populations vary widely, which may have contributed to the heterogeneity of the results. In the present study, we observed a significant positive correlation between the intake of caffeinated coffee and periodontitis. Previous studies have shown that caffeine decreases 1,25(OH)D-induced vitamin D receptor (VDR) expression and alkaline phosphatase activity in human osteoblasts, which are markers of osteoblast

JOURNAL OF Periodontology

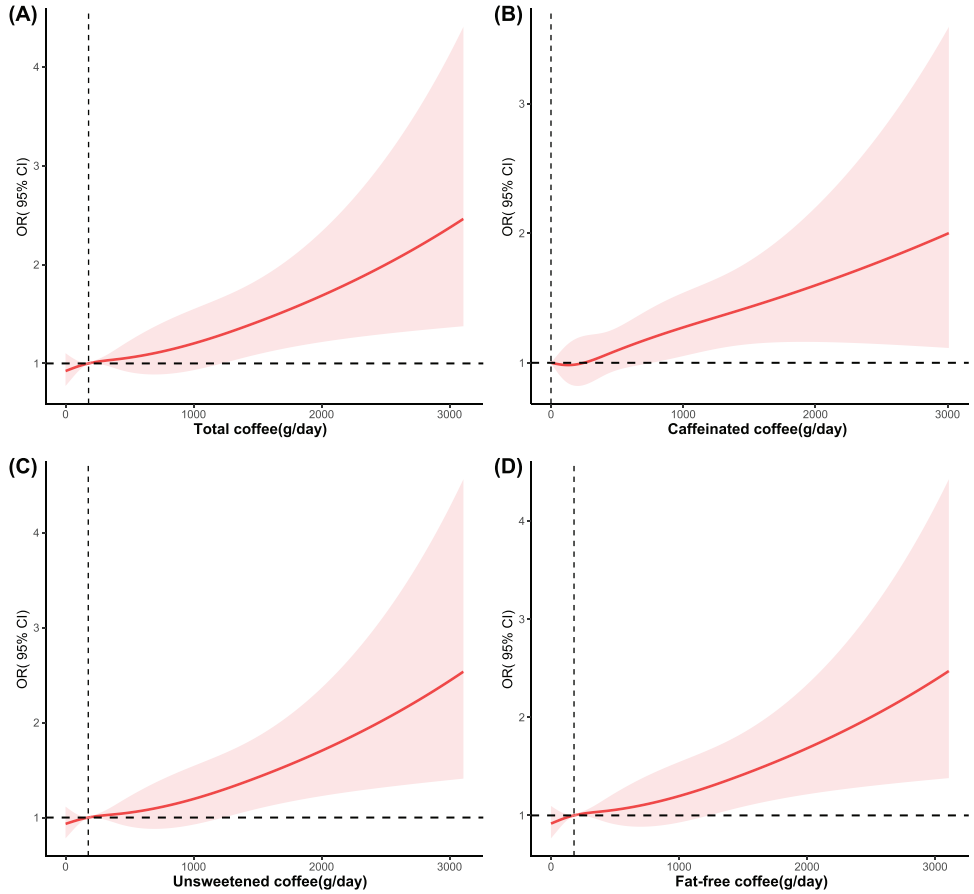

FIGURE 1 Restricted cubic splines of the association between coffees and periodontitis. (A) Total coffee. (B) Caffeinated coffee. (C) Unsweetened coffee. (D) Fat-free coffee. OR, odds ratio; CI, confidence interval.

TABLE 3 Multinomial logistic regression analysis of association between total coffee consumption and severity of periodontitis.

	Model 1		Model 2	
Variables	OR (95% CI) per IQR increase	*p* value	OR (95% CI) per IQR increase	*p* value
No periodontitis	Ref	Ref	Ref	Ref
Mild periodontitis	0.86 (0.61, 1.22)	0.409	0.86 (0.61, 1.22)	0.406
Moderate periodontitis	1.14 (1.00, 1.30)	0.046	1.14 (1.00, 1.30)	0.046
Severe periodontitis	1.30 (1.10, 1.53)	0.003	1.31 (1.11, 1.55)	0.002

Note: Participants were classified into nonperiodontitis, mild, moderate, and severe periodontitis groups, according to the Centers for Disease Control and Prevention/American Academy of Periodontology (CDC/AAP) case definition for periodontitis. Coffee consumption was standardized according to IQR to estimate ORs per IQR increase in levels of coffee. Model 1—adjusted for age, sex, race, educational level, marital status, poverty to income ratio, body mass index, alcohol drinking, smoking status, and dietary inflammatory index. Model 2—additionally adjusted for hypertension and diabetes.
Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio.

activity.[37] A previous study has reported that drinking sweetened coffee could increase the risk of periodontitis, but no significant association between sweetened coffee and periodontitis was found in this study.[38] The possible explanation for this inconsistent result may be that fewer people in the study population drank sweetened coffee, and these findings remain to be verified in future studies with larger sample sizes.

Of note, the present study found a positive association between total coffee intake and the severity of periodontitis. There were some previous studies reporting certain correlations between alveolar crestal height loss and AL or PD.[39,40] Caffeine has been shown to increase urinary calcium excretion capacity[12] and inhibit the proliferation of osteoblast-like cells.[41] In addition, caffeine competitively inhibits adenosine receptors (A1, A2A, A2B, and

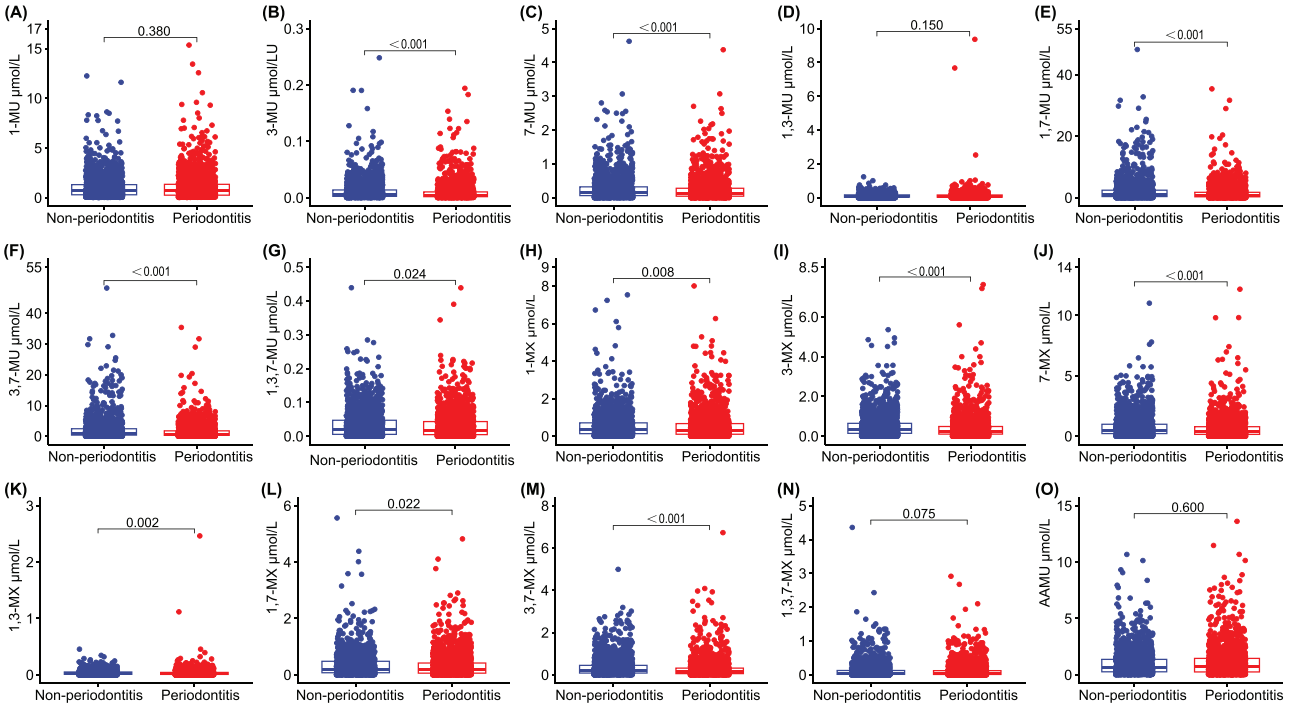

FIGURE 2 Box plots of urinary caffeine metabolites in periodontitis and nonperiodontitis groups. (A) 1-methyluric acid (1-MU). (B) 3-MU. (C) 7-MU. (D) 1,3-dimethyluric acid (1,3-DMU). (E) 1,7-DMU. (F) 3,7-DMU. (G) 1,3,7-trimethyluric acid (1,3,7-TMU). (H) 1-methylxanthine (1-MX). (I) 3-MX. (J) 7-MX. (K) 1,3-dimethylxanthine (1,3-DMX). (L) 1,7-DMX. (M) 3,7-DMX. (N) 1,3,7-trimethylxanthine (1,3,7-TMX). (O) 5-actlyamino-6-amino-3-methyluracil (AAMU).

A3), which have direct and indirect effects on bone transformation, and all four receptors are expressed by both undifferentiated osteoblast precursors and differentiated osteoblasts.[42–44] Due to potential recall bias associated with utilizing the 24-h dietary recall approach to acquire data on participants' consumption of coffee, the present study additionally examined the correlation between urinary caffeine metabolites and periodontitis. Most of the caffeine ingested by humans is absorbed within 45 min,[9] and the half-life of caffeine in adults is typically 2.2–3.5 h.[45] Therefore, urinary caffeine metabolites can reflect the level of recent coffee intake to a certain extent. Interestingly, certain caffeine metabolites, such as 1-MU, 1,3-DMU, 3,7-DMU, 1,7-DMX, and AAMU, were found to be significantly associated with periodontitis in the present study. AAMU is a metabolite of methylxanthine and has biological activity. Methylxanthines are the main adenosine receptor antagonists, and they also inhibit phosphodiesterase, regulate GABA receptors, and regulate intracellular calcium levels. Methylxanthines affect many tissues and are involved in the regulation of cyclic adenosine monophosphate (cAMP), which affects the activity of nonsteroidal hormones, estrogens, and androgens, ultimately affecting bone homeostasis.[46] Although the mechanisms involved have not yet been elucidated, a previous study has indicated that the association between theophylline in urine and total bone mineral density is negative,[47] and theophylline is a metabolic precursor of 1,3-DMU, which may provide a possible explanation for the association observed in the present study.

To the best of our knowledge, this is the first study to systematically investigate the association of coffee consumption, different types of coffee, and caffeine metabolites with periodontitis using a large nationally comprehensive population. However, the present study had several limitations. First, because the study design was a cross-sectional, we were unable to determine a causal relationship between coffee consumption and periodontitis. Second, regarding coffee with sugar and milk, the present study only evaluated the total consumption of coffee with sugar and coffee with milk, and the specific types and amount of sugar and milk content were unavailable in NHANES, which prevented the assessment of the relationship between the specific types and amount of sugar or milk added and periodontitis. Third, although we cannot completely exclude the possibility of residual confounding, E-values indicated that the observed associations in this study cannot be completely explained away by unmeasured confounders. Finally, considering that coffee consumption, as a dietary habit, has the potential to change over time, we only analyzed coffee consumption once using a 24-h dietary recall, which may not reflect usual intake for all participants.

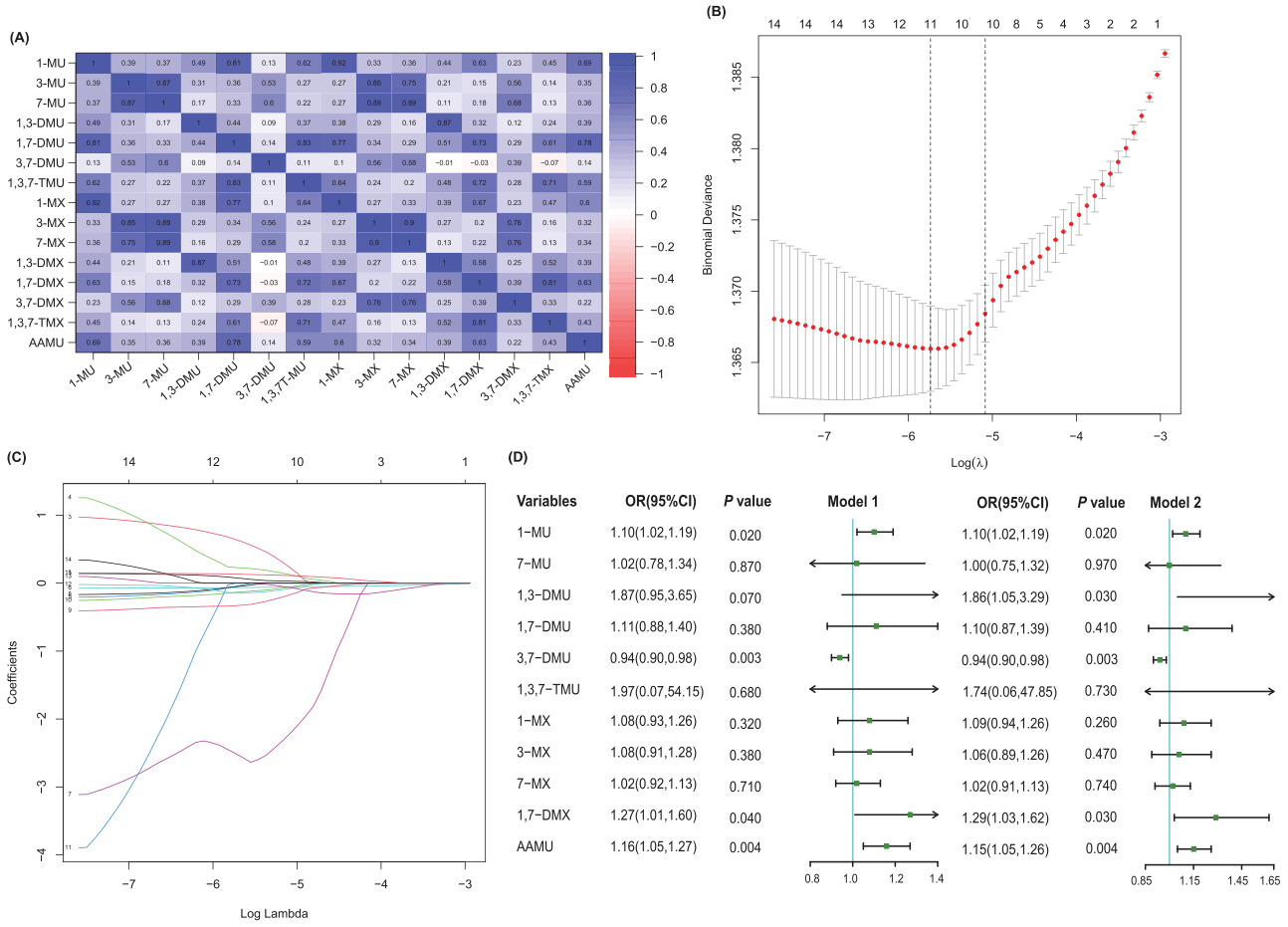

FIGURE 3 (A) Heatmap of metabolite–metabolite correlation. (B) Selection of optimal parameter (λ) in least absolute shrinkage and selection operator (LASSO) model. Eleven metabolites were selected when $\log(\lambda) = -5.74$. (C) LASSO coefficient profiles of 15 caffeine metabolites. (D) Forest plot for association between caffeine metabolites and periodontitis. AAMU, 5-actlyamino-6-amino-3-methyluracil; DMU, dimethyluric acid; DMX, dimethylxanthine; MU, methyluric acid; MX, methylxanthine; OR, odds ratio; TMU, trimethyluric acid; TMX, trimethylxanthine.

Therefore, prospective cohort studies with repeated measurements are still required to validate the results of the present research.

5 | CONCLUSION

In summary, the present study provided preliminary evidence that coffee consumption (especially certain types of coffee) may be associated with periodontitis and its severity. The present findings also suggested a positive association between urinary caffeine metabolites (1-MU, 1,3-DMU, 3,7-DMU, 1,7-DMX, and AAMU) and periodontitis. Future studies are warranted to corroborate the present findings and clarify the mechanisms involved.

AUTHOR CONTRIBUTIONS

Qiansi Chen: Contributed to conception, design, data acquisition and interpretation, performed all statistical analyses, drafted and critically revised the manuscript. Ruiyang Ge: Contributed to conception, design, data acquisition and interpretation, performed all statistical analyses, drafted and critically revised the manuscript. Yuxuan Wu: Contributed to conception, design, data acquisition and interpretation, drafted and critically revised the manuscript. Yuying Wu: Contributed to conception, design, data acquisition and interpretation, drafted, and critically revised the manuscript. Han Yang: Contributed to data acquisition and interpretation, performed partial statistical analyses, and critically revised the manuscript. Yiming Yu: Contributed to data acquisition and interpretation, performed partial statistical analyses, and critically revised the manuscript. Qingrong Deng: Contributed to conception, design, and critically revised the manuscript. Baochang He: Contributed to conception, design, and critically revised the manuscript. Fuhua Yan: Contributed to conception, design, and critically revised the manuscript. Yanfen Li: Contributed to conception, design, provided

professional advice, and critically revised the manuscript. Fa Chen: Contributed to conception, established the general idea of the design, proposed a professional statistical analysis, and critically revised the manuscript. All authors gave their final approval and agreed to be accountable for all aspects of the work.

ACKNOWLEDGMENTS

This research was supported by the High-Level Talents Research Start-up Project of Fujian Medical University, Fujian, China (no. XRCZX2018001) and Joint Funds for the Innovation of Science and Technology of Fujian Province, Fujian, China (no. 2021Y9015).

CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in NHANES at: https://www.cdc.gov/nchs/nhanes/index.htm.

ETHICS STATEMENT

The NCHS Research Ethics Review Board reviewed and approved NHANES, and all participants provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Chen Q, Ge R, Wu Y, et al. The associations of coffee consumption, coffee types, and caffeine metabolites with periodontitis: Results from NHANES 2009–2014. *J Periodontol*. 2023;1-11. https://doi.org/10.1002/JPER.23-0322