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RESEARCH

Association between blood ethylene oxide levels and the prevalence of periodontitis: evidence from NHANES 2013–2014

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Abstract

Background The study aimed to establish a link between blood ethylene oxide (EO) levels and periodontitis, given the growing concern about EO's detrimental health effects.

Materials and methods The study included 1006 adults from the 2013–2014 National Health and Nutrition Examination Survey (NHANES) dataset. We assessed periodontitis prevalence across groups, used weighted binary logistic regression and restricted cubic spline fitting for HbEO-periodontitis association, and employed Receiver Operating Characteristic (ROC) curves for prediction.

Results In the periodontitis group, HbEO levels were significantly higher (40.57 vs. 28.87 pmol/g Hb, $P < 0.001$). The highest HbEO quartile showed increased periodontitis risk (OR = 2.88, 95% CI: 1.31, 6.31, $P = 0.01$). A "J"-shaped nonlinear HbEO-periodontitis relationship existed (NL-P value = 0.0116), with an inflection point at ln-HbEO = 2.96 (EO = 19.30 pmol/g Hb). Beyond this, ln-HbEO correlated with higher periodontitis risk. A predictive model incorporating sex, age, education, poverty income ratio, alcohol consumption, and HbEO had 69.9% sensitivity and 69.2% specificity. The model achieved an area under the ROC curve of 0.761.

Conclusions These findings suggest a correlation between HbEO levels and an increased susceptibility to periodontitis.

Keywords Ethylene oxide · Periodontitis · NHANES · HbEO

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Introduction

Ethylene oxide (EO), also known as ethylene epoxide or oxirane, with a molecular weight of 44.05, is highly soluble in water and organic solvents, and can react with numerous compounds [1]. It's a versatile volatile organic compound widely utilized in various industries like cleaning, pharmaceuticals, and printing and dyeing. EO is a colorless, transparent liquid at low temperatures and a colorless gas with an ether-like odor at room temperature [2].

Additionally, EO is frequently used for sterilizing medical devices, fumigating food products, and manufacturing cosmetics [1, 3–5]. Strict regulations require very low residual EO levels in single-use sterile medical devices, especially face masks [5]. However, while EO offers benefits, it also has associated side effects [6, 7]. In daily life, people may encounter EO through various means, such as inhaling polluted air, vehicle emissions, tobacco smoke, or emissions from household products [2, 8–10]. Besides external sources, EO can also be internally generated through processes like gut bacterial reactions or body-wide enzymatic reactions [11, 12]. Endogenous EO concentrations range from 0.13 to 6.9 ppb [13]. EO is a metabolite derived from ethylene, and upon inhalation, it is rapidly absorbed into the bloodstream and subsequently distributed throughout the entire body [14, 15]. As a reactive compound, EO strongly interacts with nucleic acids and proteins [16], forming hemoglobin adducts called HbEO (N-(2-hydroxyethyl) valine), which are reliable indicators of EO exposure [17].

Research suggests that EO exposure may be strongly linked to concerns like inflammation, oxidative stress, insulin resistance, tumors, cardiovascular diseases, and abnormal lipid profiles [18–20]. Due to its potential harm to laboratory animals, the United States Environmental Protection Agency (USEPA) classifies EO as a carcinogen [15, 19]. Prolonged EO exposure has been associated with increased risks of various cancers, including leukemia and breast cancer, as well as neurological disorders [9, 21–23]. Additionally, extended EO exposure may increase the risk of inflammatory organ damage in rodents [24] and directly elevate oxidative stress levels in the body, potentially resulting in negative consequences related to oxidative stress [6, 25–27]. Although research has explored the link between EO exposure and various diseases, no prior investigation has examined the relationship between EO exposure and periodontitis.

Periodontitis is a persistent inflammatory disease marked by progressive destruction of the supporting tissues around teeth. It ranks as the second most common oral condition and has risen to become the 11th most prevalent disease globally [28]. Approximately 3.5 billion individuals worldwide are affected by periodontitis, making it a primary cause of tooth loss among adults aged 35 and above [29, 30]. Estimated productivity losses due to periodontitis could amount to a global cost of around $5.4 billion annually [31]. Moreover, periodontitis is recognized as a standalone risk factor for a range of conditions, including cardiovascular diseases, diabetes, and obesity [32]. The development of periodontal disease involves multiple factors, including genetics and the environment [33, 34]. Currently, there is growing concern about the potential detrimental effects of environmental exposures to substances like PM2.5 and e-cigarette vapor on periodontitis [33, 35, 36]. Hence, identifying other potential environmental factors influencing periodontitis development could provide fresh insights into prevention.

Due to the association between EO and inflammation and oxidative stress, which are potential etiological factors of periodontitis, we hypothesize that exposure to EO may be related to the occurrence of periodontitis. Therefore, our research hypothesis is that the level of HbEO may reflect the extent of EO exposure and be associated with the occurrence of periodontitis. We will utilize data from the 2013–2014 National Health and Nutrition Examination Survey (NHANES) to explore the potential relationship between HbEO levels and periodontitis.

Methods

Study participants

NHANES collects participant data through a comprehensive cross-sectional study conducted jointly by the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS). Its purpose is to assess the health and nutritional status of the U.S. civilian non-institutionalized population. This survey covers a wide range of factors, including demographics, socioeconomic status, diet, health indicators, blood chemistry, and various lab test results. The survey is conducted biennially, and except for restricted data, all relevant information is publicly available on the NCHS website (https://www.cdc.gov/nchs/nhanes/index.htm). Ethical approval was obtained, and informed consent was provided by all participants following the protocols approved by the Research Ethics Review Board of the NCHS.

The NHANES survey, which included newly released blood EO test data, spanned four cycles starting in 2013. Unfortunately, the total oral periodontal examination (FMPE) program was introduced in 2009–2010, but stopped after 2013–2014. This led to the absence of periodontitis-related data in NHANES thereafter. Therefore, this study specifically analyzed the data from 2013 to 2014.

We utilized NHANES data from the 2013-2014 survey, which initially included 10,175 participants. After exclusions for FMPE non-participation ($n = 5506$), missing EO test ($n = 3186$), and lacking periodontitis data ($n = 332$), as well as those with missing data on hypertension ($n = 0$), hyperlipidemia ($n = 0$), and diabetes mellitus (DM) ($n = 5$), we assessed various social habits. These included smoking status ($n = 0$), alcohol consumption ($n = 66$), BMI ($n = 4$), and frequency of flossing and cleaning equipment use ($n = 0$). Participants with missing socioeconomic status ($n = 70$), marital status ($n = 0$), and educational status ($n = 0$) were also excluded. The final analysis comprised 1006 participants, as illustrated in Fig. 1. Notably, our study holds a broader significance, as it effectively represents a weighted sample from the U.S. population, estimating approximately 12,762,574 individuals.

Blood ethylene oxide levels

Participants provided whole blood samples at a mobile examination center, where dedicated laboratory personnel employed a modified Edman reaction method to quantify hemoglobin oxide adducts (HbEO). Previous research has established the exceptional sensitivity of HbEO in detecting EO exposure [17, 37]. All measurements meet NCEH Laboratory Science Division quality control and quality assurance for accuracy and precision of performance standards. Detailed measurements are accessible via the following website: (https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/ETHOX_H.htm).

Evaluation of periodontitis

Following the methodology outlined by Eke et al. in 2012 and adhering to the periodontitis case definition by the U.S. Centers for Disease Control and Prevention and the American Academy of Periodontology (CDC-AAP), NHANES conducted oral periodontal examinations for participants with teeth [38]. At the Mobile Examization Center (MEC), a calibrated dentist conducted a comprehensive oral periodontal examination to ascertain the presence of periodontitis in each subject. Severity categories included mild, moderate, and severe, primarily based on periodontal probing depth (PD) and clinical attachment level (CAL). Detailed criteria can be found in Table S1. For the purposes of this cross-sectional study, the categories of mild, moderate, and severe periodontitis were aggregated for subsequent analysis.

Covariates

NHANES ensures the national representativeness of its data through the utilization of a complex probability sampling design and the application of sample weights. Given that each sample isn't uniformly chosen, the use of sampling weights significantly facilitates the generation of accurate population estimates. For the household interview, a standardized questionnaire was administered to evaluate demographic characteristics and socioeconomic status, encompassing age, sex, race, BMI, economic status, smoking status, alcohol consumption, flossing and cleaning equipment utilization, marital status, and education level. Furthermore, an assessment of the three prevalent diseases (hypertension, hyperlipidemia, and DM) was conducted in conjunction with relevant laboratory test data.

BMI was calculated by dividing a participant's weight (kg) by the square of their height (m^2). The classification was based on BMI as follows: BMI < 25 (underweight/normal), 25–30 (overweight), and > 30 (obese) [39]. Race categories included non-Hispanic white, non-Hispanic black, Hispanic, and other race (multiracial). Socioeconomic status relied on Family Poverty-to-Income Ratios (PIR) as follows: PIR < 1.3 (low-income), 1.3–3.5 (moderate-income), and > 3.5 (high-income). Smoking status had two categories: no and yes, based on the definition of a smoker (someone who smoked at least 100 cigarettes in their lifetime) [40]. Alcohol consumption was determined by consuming a minimum of 12 alcoholic beverages annually [18]. Moreover, the categorization of flossing and cleaning equipment usage as 0–1, 2–4, and ≥ 5 days a week [41]. Educational level was segmented into three categories: Less than high school, High school, and More than high school. Marital status was classified as Never married, Widowed/Divorced/Separated, and Married/Living with partner. Additionally, the presence of hypertension, hyperlipidemia, and DM was determined as yes or no, based on questionnaire responses and laboratory data, with detailed criteria outlined in Table S2.

Statistical analysis

Due to the presence of probability sampling, we incorporated specialized sample weights (WTSA2YR) in the subsequent analysis. For categorical variables reported as number (%), a chi-square test was used to compare descriptive characteristics of the study population stratified by periodontitis.

HbEO values were divided into quartiles (Q1-Q4), using the lowest quartile (Q1) as the reference group, to further assess the association between HbEO levels and periodontitis through multivariate logistic regression models. Model 1 remained unadjusted for covariates, while Model 2 was adjusted for age, sex, and race. Model 3, building upon Model 2, included additional adjustments for BMI, PIR, smoking status, alcohol consumption, marital status, education level, flossing and cleaning equipment use, DM,

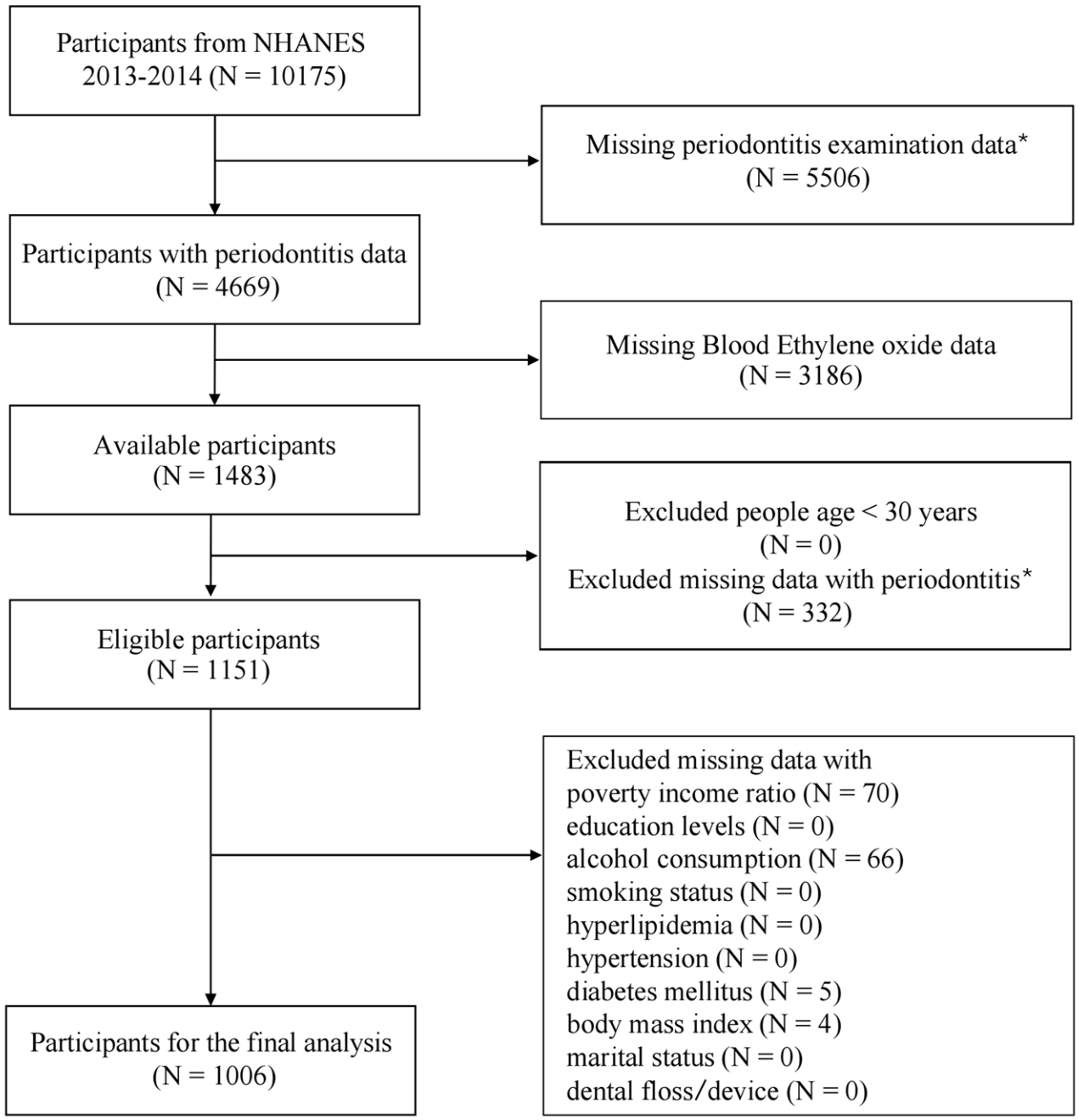

Fig. 1 Flowchart of procedures for participants selection and inclusion. * Missing periodontitis examination data (*N*=5506): The exclusion of individuals who did not undergo periodontal disease testing refers to participants who were initially not included in the assessment of their periodontal condition. Excluded missing data with periodontitis (*N*=332): The exclusion of individuals with missing periodontal disease data pertains to participants who agreed to undergo periodontal disease testing but, due to various reasons, did not participate in the actual testing, resulting in missing data for this specific variable

hyperlipidemia, and hypertension. Chan et al. emphasized that a variance inflation factor (VIF) exceeding 10 is indicative of significant collinearity issues [42]. In our study, no such severe collinearity was observed among variables including the diagnosis of HbEO, age, sex, race, BMI, PIR, educational level, marital status, smoking status, alcohol consumption, flossing and cleaning equipment use, as well as the presence of hypertension, hyperlipidemia, and DM (all variables had a VIF < 2).

We used Receiver Operating Characteristic (ROC) curve to demonstrate the predictive capabilities of various periodontitis prediction models and to evaluate the role of HbEO in these models. To ascertain whether significant disparities exist in predictive performance among the prediction models, we employed Z-tests to compare the area under the ROC curve (AUC) of each model.

Due to the non-normal distribution of HbEO values, we applied a natural logarithm transformation to achieve normality. To investigate dose-response patterns between HbEO levels and periodontitis prevalence, we examined observations at the 5th, 35th, 65th, and 95th percentiles of the HbEO distribution using restricted cubic spline (RCS) plots with four nodes. Additionally, we conducted stratified analyses to explore interactions among participants' sex, age, race, BMI, and the three common diseases (hypertension, hyperlipidemia, and DM). Statistical significance was defined as $P < 0.05$, and the analysis was conducted using R Studio (version 4.3.1) and nhanesR (version 0.9.4.3).

Results

Descriptive characteristics

In this study, a total of 1006 participants from the 2013–2014 NHANES dataset were included. Among them, based on the presence of periodontitis, there were 509 males (50.60%) and 497 females (49.40%). The prevalence of periodontitis differed significantly between male and female groups ($P = 0.015$). Among individuals with periodontitis, the prevalence was notably higher in the age ≥ 65 years (48.28%) compared to those aged 30–44 (27.74%), 45–54 (34.32%), and 55–64 (38.48%). The prevalence of periodontitis was significantly higher among non-Hispanic black (47.54%) compared to non-Hispanic white (33.01%), Hispanic (40.38%), and other race (34.73%), as illustrated in Table 1.

When HbEO levels were divided into quartiles (Q1-Q4), an ascending trend in the number of periodontitis cases was observed. Remarkably, the prevalence of periodontitis reached 58.99% when HbEO was in the highest quartile (Q4). Regarding BMI categorization, the proportions of underweight/normal, overweight, and obese participants were 26.74%, 32.11%, and 41.15%, respectively. However, the prevalence of periodontitis did not show significant differences among BMI groups ($P > 0.05$). Furthermore, participants from middle-income households (PIR = 1.3–3.5) (57.68%), those with education levels below high school (67.28%), and former alcohol consumers (52.82%) exhibited notably higher prevalence of periodontitis. Although the prevalence of periodontitis was relatively low (30.05%) for flossing 2 to 4 times per week, there was no significant difference in the prevalence of periodontitis between the three groups for flossing and cleaning equipment use. In this study, the prevalence of periodontitis in individuals with hyperlipidemia, hypertension, and diabetes was found to be 35.9%, 45.20%, and 49.2%, respectively. (Table 1)

Binary logistic regression analysis

We established three models to explore the potential relationship between HbEO levels and periodontitis. In the unadjusted model, we did not account for other covariate factors. The results revealed a significant harmful effect of HbEO at quartile 4 (3.75, 95% CI: 2.01–6.97; $P < 0.001$). In adjusted model 1, we controlled for participants' age, sex, and race, and the association remained evident (4.62, 95% CI: 1.79–11.91; $P = 0.01$). In adjusted model 2, further adjustments were made for BMI, PIR, education level, marital status, smoking status, alcohol consumption, hypertension, hyperlipidemia, DM, and flossing and cleaning equipment use. Consistent with the previous models, the relationship remained significant (2.88, 95% CI: 1.31–6.31; $P = 0.01$) (Table 2).

Receiver operating characteristic curve

The maximum model encompasses the subsequent variables: sex, age, BMI, race, PIR, marital status, education level, smoking status, alcohol consumption, hyperlipidemia, DM, hypertension, flossing and cleaning equipment use and HbEO. Although this model exhibits the largest AUC (0.771), it incorporates an excessive number of variables, thereby influencing its clinical utility. While considering the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), we endeavored to identify a balanced point between goodness of fit and the count of parameters to construct candidate model [43, 44]. When evaluating models containing only five or fewer variables, all predictive models demonstrate a notable reduction in predictive performance in comparison to the comprehensive maximum model. However, when six variables are included in the prediction model, the candidate model demonstrates predictive performance akin to that of the comprehensive model. The candidate model comprises sex, age, education level, PIR, alcohol consumption, and HbEO. The AUC of the candidate model (0.761) closely mirrors that of the maximum model (0.771), with a non-significant difference observed in the Z-test for AUC comparison between the two models ($Z = 1.581$, $P = 0.114$), as illustrated in Fig. 2. Detailed information about the candidate model can be found in Supplementary Information Table S3. Upon removing HbEO from the candidate model, the resulting predictive model's AUC notably decreases in comparison to the candidate model

Table 1 Descriptive characteristics of the study population stratified by periodontitis

Characteristic	Total	No Periodontitis	Periodontitis	*P*-values
	(*N* = 1006)	(*N* = 568)	(*N* = 438)	
HbEO Q4, n (%)				< 0.001
1	253 (25.15)	164 (72.25)	89 (27.75)	
2	253 (25.15)	172 (77.70)	81 (23.30)	
3	248 (24.65)	138 (60.59)	110 (39.41)	
4	252 (25.05)	94 (41.01)	158 (58.99)	
Age, n (%)				0.002
30–44	373 (37.08)	253 (72.26)	120 (27.74)	
45–54	198 (19.68)	119 (65.68)	79 (34.32)	
55–64	216 (21.47)	106 (61.52)	110 (38.48)	
>=65	219 (21.77)	90 (51.72)	129 (48.28)	
Sex, n (%)				0.015
Female	497 (49.40)	323 (69.92)	174 (30.08)	
Male	509 (50.60)	245 (59.10)	264 (40.90)	
Race/Ethnicity, n (%)				0.051
Non-Hispanic white	458 (45.53)	277 (66.99)	181 (33.01)	
Non-Hispanic black	193 (19.19)	88 (52.46)	105 (47.54)	
Hispanic	212 (21.07)	116 (59.62)	96 (40.38)	
other race	143 (14.21)	87 (65.27)	56 (34.73)	
BMI, n (%)				0.077
Underweight/Normal	269 (26.74)	160 (71.10)	109 (28.90)	
Overweight	323 (32.11)	180 (65.34)	143 (34.66)	
Obese	414 (41.15)	228 (59.33)	186 (40.67)	
Marital status, n (%)				0.022
Married/Living with Partner	635 (63.12)	377 (67.54)	258 (32.46)	
Never married	133 (13.22)	69 (53.10)	64 (46.90)	
Widowed/Divorced/Separated	238 (23.66)	122 (60.62)	116 (39.38)	
PIR, n (%)				< 0.001
<1.3	338 (33.60)	172 (57.30)	166 (42.70)	
1.3–3.5	306 (30.42)	126 (42.32)	180 (57.68)	
>3.5	362 (35.98)	270 (79.24)	92 (20.76)	
Education levels, n (%)				< 0.001
Less than high school	83 (8.25)	25 (32.72)	58 (67.28)	
High school	321 (31.91)	145 (49.82)	176 (50.18)	
More than high school	602 (59.841)	398 (72.90)	204 (27.10)	
Alcohol consumption, n (%)				0.017
Never	141 (14.02)	79 (66.55)	62 (33.45)	
Former	159 (15.81)	67 (47.18)	92 (52.82)	
Mild	363 (36.08)	218 (69.72)	145 (30.28)	
Moderate	163 (16.20)	104 (68.08)	59 (31.92)	
Heavy	180 (17.89)	100 (60.75)	80 (39.25)	
Smoking status, n (%)				< 0.001
No	561 (55.76)	362 (73.47)	199 (26.53)	
Yes	445 (44.24)	206 (52.80)	239 (47.20)	
Hyperlipidemia, n (%)				0.766
No	270 (26.84)	152 (65.32)	118 (34.68)	
Yes	736 (73.16)	416 (64.07)	320 (35.92)	
Hypertension, n (%)				< 0.001
No	554 (55.07)	361 (71.56)	193 (28.44)	
Yes	452 (44.93)	207 (54.80)	245 (45.20)	
Diabetes mellitus, n (%)				0.014
No	751 (74.65)	447 (68.12)	304 (31.88)	
Yes	255 (25.35)	121 (50.77)	134 (49.23)	
Flossing, n (%)				0.097

Table 1 (continued)

Characteristic	Total	No Periodontitis	Periodontitis	*P*-values
	(*N* = 1006)	(*N* = 568)	(*N* = 438)	
0–1 days a week	361 (35.89)	176 (58.44)	185 (41.56)	
2–4 days a week	261 (25.94)	167 (69.95)	94 (30.05)	
>=5 days a week	384 (38.17)	225 (65.21)	159 (34.79)	

Abbreviations HbEO, hemoglobin adduct of ethylene oxide; BMI, body mass index; PIR, poverty income ratio

P-value by chi-square test for classified variables

Table 2 Adjusted association of HbEO with periodontitis

Exposure	Unadjusted model	Adjust 1	Adjust 2
	Odds ratio (95% CI) associated with periodontitis		
HbEO			
Q1	1 (Ref)	1 (Ref)	1 (Ref)
Q2	0.75 (0.32, 1.76); 0.47	0.69 (0.24, 2.03); 0.42	0.63 (0.23, 1.70); 0.34
Q3	1.69 (0.95, 3.03); 0.07	1.37 (0.72, 2.61); 0.26	1.20 (0.75, 1.94); 0.42
Q4	3.75 (2.01, 6.97); <0.001	4.62 (1.79, 11.91); 0.01	2.88 (1.31, 6.31); 0.01

Unadjusted model: Non-adjusted model

Adjust 1: Adjust for age, sex, race

Adjust 2: Adjust for age, sex, race, body mass index, poverty income ratio, education levels, marital status, smoking status, alcohol consumption, hyperlipidemia, hypertension, diabetes mellitus and flossing

(Ref): indicates the reference group, which corresponds to Q1 [9.28, 24.21]. Results and *P*-values for other quartiles (Q2, Q3, Q4) are relative to the reference group Q1. The specific values of quartiles are as follows: Q1 [9.28, 24.21]; Q2 (24.21,34.05]; Q3 (34.05,59.99]; Q4 (59.99,1781.19]

Abbreviations HbEO, hemoglobin adduct of ethylene oxide; CI, confidence interval

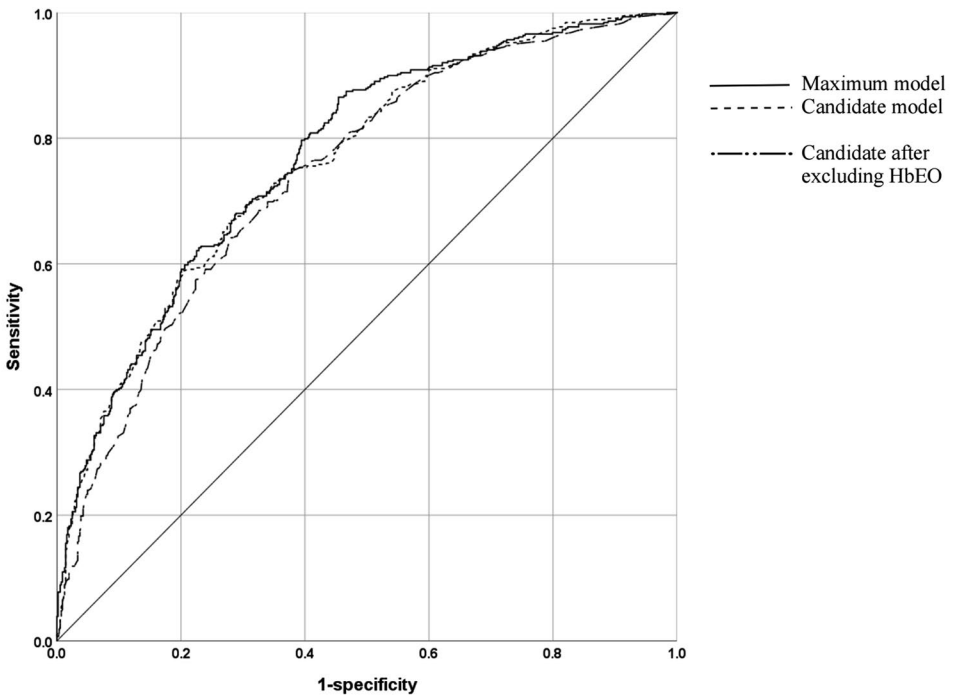

Fig. 2 Three predictive models, including the maximum, candidate, and candidate after excluding HbEO, were evaluated using receiver operating characteristic (ROC) curves. The Z-test for the area under the ROC curve (AUC) showed no significant difference in predictive performance between the maximum and candidate models for periodontitis (Z = 1.581, *P* = 0.114). However, there was a significant difference in predictive performance between the candidate and candidate after excluding HbEO models (Z = 2.470, *P* = 0.014)

(0.743 vs. 0.761, Z = 2.470, $P = 0.014$). This finding highlights the beneficial influence of HbEO in improving the diagnostic accuracy of the periodontitis prediction model.

Nonlinear relationships exploration

We further investigated potential nonlinear associations. In this regard, we employed RCS regression models to account for potential nonlinearity in the relationship between natural logarithm-transformed EO (ln-HbEO) levels and periodontitis risk. The results revealed a "J"-shaped nonlinear relationship between ln-HbEO and periodontitis (NL-*P* value = 0.0116) after adjustment for all confounders. The inflection point occurred at an ln-HbEO value of 2.96 (EO = 19.30 pmol/g Hb). Beyond this point, as ln-HbEO levels increased, the risk of periodontitis also increased (Fig. 3).

Subgroup analyses

After conducting subgroup analyses based on sex, age, race, BMI, DM, hypertension, and hyperlipidemia, we did not find any significant interactions among the subgroups ($P > 0.05$). The impact of HbEO on periodontitis remained consistent across these subgroups, as depicted in Fig. 4. Notably, the relationship between HbEO and periodontitis was particularly pronounced in male, those aged 30–44 and 55 years and older, Non-Hispanic White and other race, underweight/normal, and those with hyperlipidemia participants. In subgroup analysis, whether among smokers, individuals with a BMI < 25, or patients with hyperlipidemia, the correlation between HbEO and periodontitis remains significant after stratification.

Discussion

Our study aimed to investigate the potential link between EO exposure and periodontitis. We considered several covariates, including age, sex, race, BMI, marital status, PIR, education level, alcohol consumption, smoking status, hyperlipidemia, hypertension, DM, flossing and cleaning equipment use, and HbEO levels. From what we understand, this is the first study that verifies a potential significant positive association between EO exposure and periodontitis. We utilized a nationally representative sample from the US population in 2013–2014, resulting in a final cohort of 1006 participants after assessing inclusion and exclusion criteria.

The results of the study showed that median HbEO levels were significantly higher in periodontitis patients than in the non-periodontitis group (40.57 pmol/g Hb vs. 28.87 pmol/g Hb, $P < 0.0001$). Notably, even after adjusting for all confounders, the odds ratio (OR) associated with periodontitis in people taking probiotics was 2.88 (95%CI 1.31–6.31, $P = 0.01$) for high EO exposure (Q4) compared with low EO exposure (Q1). What's more, a non-linear association of the "J" type was observed between HbEO and the prevalence of periodontitis (NL-*P* value = 0.0116). This shows that the body may have some tolerance to EO exposure (19.30-55.99 pmol/g Hb), and after this point (EO = 19.3 pmol/g Hb), the prevalence of periodontitis increases with EO exposure.

In our study participants, we observed a higher prevalence of periodontitis in men compared to women. The

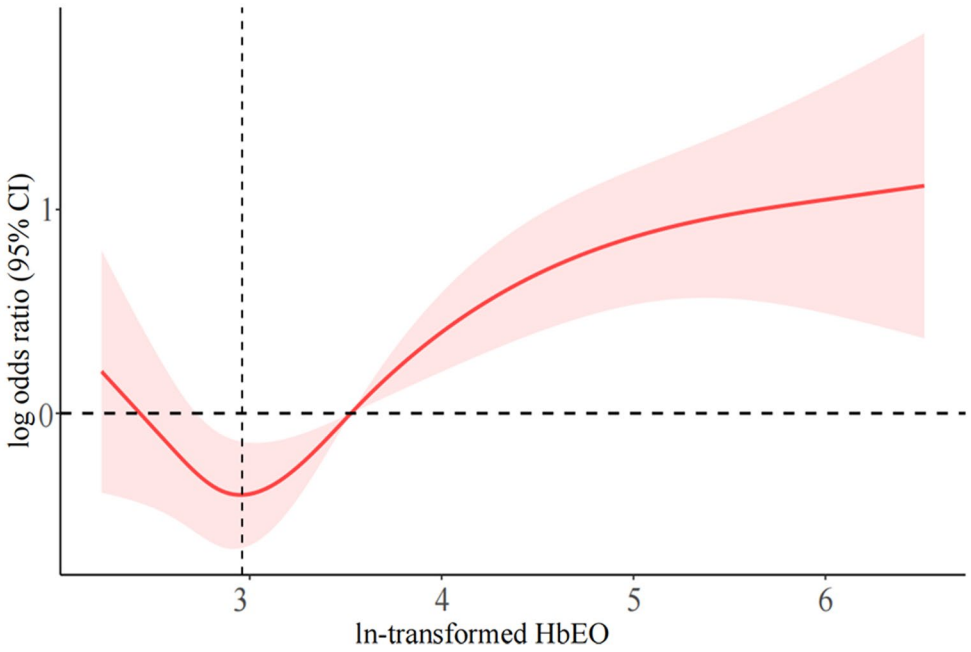

Fig. 3 The full-adjusted relationship between ln-transformed HbEO and periodontitis using Restricted Cubic Spline. The solid line represents the fitted nonlinear curve. The area adjacent to the solid line represents the 95% confidence interval. *Abbreviations* HbEO, hemoglobin adduct of ethylene oxide; CI, confidence interval

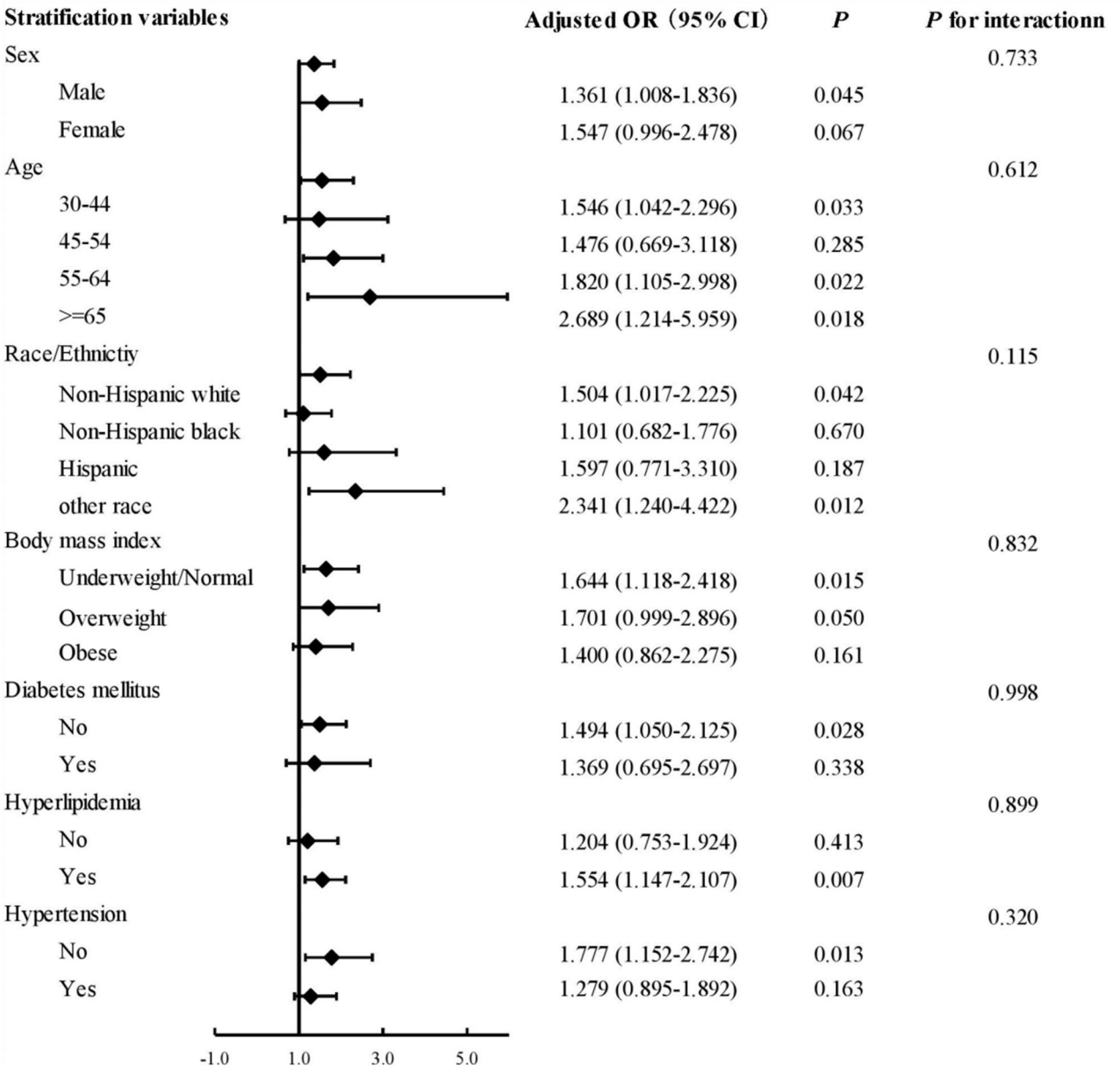

Fig. 4 The odds ratio of periodontitis in participants exposed to probiotics compared to those not exposed was examined, performing subgroup analysis. All analyses were adjusted for age, sex, race, body mass index, poverty income ratio, education, marital status, smoke, alcohol, hyperlipidemia, hypertension, diabetes mellitus, and prebiotics, but not for the specific stratification variables of interest

lowest incidence of periodontitis was found among the non-Hispanic white population. Additionally, there was a notable increase in periodontitis prevalence with increasing age. However, we did not detect a significant difference in periodontitis prevalence among individuals categorized as underweight/normal weight, overweight, and obese. We acknowledge the discrepancy between our findings and previous reports regarding the association between obesity and periodontitis [45]. However, there are also studies indicating that the prevalence of periodontitis does not increase with increasing BMI, which is consistent with our findings [46–48]. We speculate that the complexity of the relationship between obesity and periodontitis may explain this inconsistency. Additionally, differences in study populations, designs, and definitions of periodontitis may contribute to the variation in results. Periodontitis was less prevalent among individuals from higher-income households (PIR > 3.5), those with higher education levels, non-smokers, and those without diabetes or hypertension. These findings align with prior NHANES-based research,

underscoring the importance of considering these covariates when investigating EO exposure [43, 49–51].

Tüornqvist et al. established that HbEO accurately represents cumulative EO exposure in the four months leading up to measurement [52]. In our study, the prevalence of periodontitis in the smoking group was notably high at 47.20%, indicating significant harm associated with smoking in relation to periodontitis. It's important to note that research by Jain has highlighted smoking as one of the most prevalent means by which the general population is exposed to EO [9]. After stratifying our data by smoking habits, we similarly observed a closer association between EO exposure and periodontitis within the smoking group (1.329, 95% CI 1.044–1.693, $P=0.024$ vs. 1.632, 95% CI 0.822–3.239, $P=0.148$). Hence, cumulative EO exposure appears to be a significant environmental pollution factor in the development of periodontitis. In line with our hypothesis, scholar Yu has also proposed that smokers, who are also EO-exposed individuals, may adopt unhealthy dietary habits due to insulin resistance, resulting in abnormal fat breakdown and a decrease in BMI [7]. Similarly, our study confirmed this association, showing a significant positive correlation (1.644, 95%CI 1.118–2.418, $P=0.015$) between EO exposure and the prevalence of periodontitis in individuals with underweight/normal (BMI < 25). Research by Zhu and colleagues has indicated a potential link between HbEO and abnormal blood lipid levels [25]. Moreover, lipid abnormalities can contribute to periodontal damage either directly through involvement in systemic inflammatory pathways or indirectly through factors like glycosylated hemoglobin (HbA1c) and obesity [53]. In our stratified analysis of hyperlipidemia, we observed that within the hyperlipidemia group, an increase in EO exposure corresponded to an increased prevalence of periodontitis, and this association was statistically significant. Our subgroup analyses further support the hypothesis that EO's impact on lipid profiles, inflammation, and metabolism plays a role in periodontitis development.

EO's hydrolytic metabolism generates ethylene glycol, used in antifreeze and related products [20, 54]. Ethylene glycol can bind with glutathione (GSH), leading to S-carboxymethyl GSH and S-carboxymethyl homocysteine formation. This disrupts sulfhydryl (-SH) group production, reducing GSH levels, and causing oxidative stress damage [51], which can contribute to periodontitis [55].

Both EO and its metabolites have potential hazards, stimulating mucous membranes, cells, and the central nervous system [56, 57]. Growing evidence indicates that EO exposure may play a role in conditions like asthma, chronic obstructive pulmonary disease, cardiovascular diseases, and lipid abnormalities by activating inflammation [25, 27, 58, 59]. Thus, we propose that EO exposure, even before contributing to systemic chronic inflammatory disease [60–62], may have affected oral health, although it has received less attention.

The American Academy of Periodontology (AAP) underscores the significance of conducting risk assessments in the evaluation of periodontal health [63]. As predictive models related to periodontitis continue to emerge, it becomes increasingly crucial to further our understanding of early risk factors for periodontal disease, such as age, gender, BMI, obesity, smoking, diabetes, and oral hygiene practices, and their impact on oral health and quality of life for individuals. Our study results indicate that EO exposure positively influences the diagnostic performance of periodontitis prediction models. Nevertheless, it's important to acknowledge that there is a modest enhancement of 1.8% (AUC: 0.743 vs. 0.761) when taking EO exposure into account compared to a prediction model that excludes it.

This study has limitations. Firstly, it used a cross-sectional design, requiring further prospective research to confirm the causal link between these variables. Secondly, like other epidemiological studies, unmeasured other confounding factors such as sleep patterns, eating habits and neuropsychiatric status may impact the results. Future research should consider including a broader range of potential influencing factors to enhance the understanding of the findings.

Conclusion

Our study found a link between blood EO levels and periodontitis prevalence. Particularly, when EO exposure exceeds 19.30 pmol/g Hb, periodontitis prevalence consistently rises. This discovery is noteworthy, highlighting the need for attention to this issue and providing fresh insights into addressing oral health challenges arising from environmental pollution. However, our study's design requires further validation through prospective longitudinal cohort studies.

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Author contributions XY drafted the manuscript and conducted statistical analysis. TYJ, RZY, and Li Linke conducted statistical analysis and contributed to the writing of the methods section. LYJ and XJ were responsible for guiding and reviewing this article. All authors have read and approved the final manuscript.

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Data availability The NHANES dataset is publicly available online, accessible at cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate All the data used in our study were obtained from the National Health and Nutrition Examination Survey (NHANES). NHANES is a nationally representative cross-sectional study conducted under the direction of the National Center for Health Statistics (NCHS) to assess the health and nutrition status of the non-institutionalized population of the United States using a complex, multistage, and probabilistic sampling design. All of the surveys were authorized by the NCHS Ethics Review Board before being conducted, and all participants signed informed consent forms. More information is available at http://www.cdc.gov/nchs/nhanes/.

Consent for publication Not applicable.

Competing of interests None of the authors have any potential conflicts of interest.

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