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Phthalate Metabolites Were Related to the Risk of High-Frequency Hearing Loss: A Cross-Sectional Study of National Health and Nutrition Examination Survey

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Background: Phthalate metabolites are pervasive in the environment and linked to various health issues. This study aimed to investigate the relationship between phthalate metabolites and hearing loss.

Methods: We conducted a cross-sectional study with 1713 participants based on the National Health and Nutrition Examination Survey 2015–2018. Participants were defined as speech-frequency hearing loss (SFHL) or high-frequency hearing loss (HFHL). We analyzed the baseline characteristics of participants and assessed the detection rates of phthalate metabolites in samples. Phthalate metabolites with detection rates of >85% were enrolled. Then, restricted cubic spline and multivariable logistic regression analyses were conducted to explore the association of phthalate metabolites with hearing loss. Multi-model analysis was employed to select an optimal predictive model for HFHL based on phthalate metabolites and clinical factors.

Results: Among participants, 24.518% had SFHL and 41.998% had HFHL, associated with older age, higher BMI, male, non-Hispanic white, lower physical activity levels, higher exposure to work noise, hypertension, and diabetes. Monobenzyl phthalate (MBZP) showed a positive linear association with both SFHL and HFHL. Multivariable logistic regression revealed MBZP as a significant risk factor for HFHL (odds ratio=1.339, 95% confidence interval, 1.053–1.707). According to the area under curve (AUC) values, the logistic regression model had the best diagnostic performance of HFHL, with the highest AUC values of 0.865 in the test set. In the model, gender, diabetes, and MBZP were the top predictors of HFHL.

Conclusion: The study identified a significant association between MBZP exposure and HFHL, highlighting the need to reduce phthalate exposure.

Keywords: hearing loss, phthalate metabolites, monobenzyl phthalate, machine learning models, cross-sectional

Introduction

Hearing loss is a common and heterogeneous sensory disorder that severely affects communication and quality of life.[1] The prevalence of hearing loss is increasing, and according to the World Health Organization, approximately 2.5 billion people globally will suffer from hearing loss by 2050.[2] Hearing loss is the third leading cause of disability worldwide, which can manifest in various forms, including conductive hearing loss, sensorineural hearing loss, and mixed hearing loss, impacting the perception of sounds at different frequencies.[3,4] This condition impairs the ability to understand speech, particularly in noisy environments, and can lead to social isolation, depression, and reduced overall health.[5] The causes of hearing loss are multifaceted, encompassing genetic factors, aging, birth complications, noise exposure, ototoxic medications, occupational exposures, and exposure to environmental risk factors.[6,7] Identifying risk factors for hearing loss is crucial for developing effective preventive strategies and mitigating long-term health impacts.

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Phthalates are a class of chemicals widely used in industrial production as plasticizers and stabilizers for various consumer products.[8] Phthalates are easily released into the environment and can be detected in air, dust, water, and food, resulting in ubiquitous human exposure to these substances.[9] Humans are primarily exposed to phthalates through inhalation, ingestion, and skin contact.[10] Once phthalates enter the human body, they undergo metabolism, and their metabolites can be detected in urine and other biological samples.[11] Increasing research suggests that exposure to phthalates is associated with various diseases, including endocrine disruption,[12] reproductive toxicity,[13] and cardiovascular health.[14] Fábelová et al discovered that phthalate metabolites have potential ototoxic properties.[15] However, the association of phthalate metabolites with hearing loss requires further research.

The National Health and Nutrition Examination Survey (NHANES) provides a valuable dataset for investigating the associations between environmental exposures and health outcomes in a representative sample. Based on the NHANES database, subjects with complete audiometric results and phthalate metabolites data were included and divided into speech-frequency hearing loss (SFHL) and high-frequency hearing loss (HFHL) in this study. The association of phthalate metabolites with hearing loss was explored, and an optimal predictive model for HFHL based on phthalate metabolites and clinical factors was constructed. This cross-sectional study aimed to examine how phthalate metabolites may be related to auditory health and highlight the importance of environmental contaminant monitoring.

Materials and Methods

Data Source and Study Population

NHANES as a database to evaluate the health and nutritional status of national representatives of USA civilians was the source of our study. The NHANES is a complex, multistage probability survey conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention. We merged data from the years 2015 to 2018 (n=19,225) including participants ≥18 years with complete audiometric results and phthalate metabolites data, which yielded a final sample size of 1713 individuals. NCHS Ethics Review Board approved the study and all participants signed the informed consent.

Audiometric Measurement and Definition of Hearing Loss

Audiometric measurements were conducted by highly trained examiners in a sound-isolating room at a mobile examination center. The hearing threshold for each ear was assessed at seven frequencies (500, 1000, 2000, 3000, 4000, 6000, and 8000 hz) varied between −10 and 120 dB. Testing was conducted according to a modified Hughson Westlake procedure using the automated testing mode of the audiometer. More detailed procedures are accessible from the official website (https://www.cdc.gov/nchs/nhanes/). Herein, SFHL was defined as the pure tone averages at 500, 1000, 2000, and 4000 hz ≥25 dB in either ear, while the pure tone averages at 3000, 4000, and 6000 hz ≥25 dB in either ear was used to identify HFHL.[16]

Phthalate Metabolites

High-performance liquid chromatography-electrospray ionization-tandem mass spectrometry was used for the quantitative detection in urine of the following phthalate metabolites: monobutyl phthalate (MBP), monobenzyl phthalate (MBzP), monocarboxyoctyl phthalate (MCOP), mono (3-carboxypropyl) phthalate (MCPP), monocarboxynonyl phthalate (MCNP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethylhexyl) phthalate (MEHP), monoethyl phthalate (MEP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), cyclohexane-1,2-dicarboxylic acid-mono (hydroxy-isononyl) ester (MHNCH), mono-isobutyl phthalate (MiBP), and monoisononyl phthalate (MNP).[17] The lower limit of detection (in ng/mL) for MBP, MBzP, MCOP, MCPP, MCNP, MECPP, MEHHP, MEHP, MEP, MEOHP, MHNCH, MiBP, and MNP were 0.4, 0.3, 0.3, 0.4, 0.2, 0.4, 0.4, 0.8, 1.2, 0.2, 0.4, 0.8, and 0.9, respectively. The detection rate of the above phthalate metabolites was calculated and those with a detection rate of less than 85% were excluded. Finally, this study enrolled 8 phthalate metabolites.

Covariates

Based on previous studies related to hearing loss, we downloaded the following covariates from the NHANES database: age, gender (male and female), race (Hispanic, non-Hispanic White, non-Hispanic Black, and others); marital status (live with spouse and others); the body mass index (BMI) calculated as weight (kg) / [height (m^2)]; the ratio of family income to poverty calculated according to the Department of Health and Human Services poverty guidelines; physical activity (PA) expressed as the metabolic equivalent (MET). In the NHANES, self-reported PA was evaluated using the PA questionnaire, which encompasses various categories of PA, including vigorous work-related activity (MET=8), moderate work-related activity (MET=4), walking or bicycling for transportation (MET=4), vigorous leisure-time PA (MET=8), and moderate leisure-time PA (MET=4). The value of PA was calculated as follows: PA (MET-min/wk) = MET × weekly frequency × duration of corresponding activities.[18,19] Besides, work noise, off-work noise, alcohol use, smoking status, hypertension, and diabetes were also collected. Work noise exposure was assessed by the question "Have you ever had a job exposure to loud noise". Off-work noise exposure was determined by the question "Outside of a job, have you ever been exposed to very loud noise or music for 10 or more hours a week". Smoking status was defined based on "Have you smoked at least 100 cigarettes in your entire life" and "Do you now smoke cigarettes". Diabetes was diagnosed as glycohemoglobin ≥6.5 mmol/L and hypertension was defined as a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. The random forest method was used to impute missing values for continuous variables. Alcohol use and smoking status with over 15% missing values were excluded to avoid potential bias. Other categorical variables work noise, off-work noise, marital status, gender, hypertension, diabetes, and race only had missing cases of 35, 4, 88, 0, 1, 36, and 0, which requires no processing.

Statistical Analysis

Categorical variables were expressed as numbers (percent) and analyzed by Chi-square test. Continuous variables were represented by median (P_{25}, P_{75}) and compared by the Mann–Whitney-*U* test due to the skewed distribution. To avoid collinearity, we conducted collinearity analysis and removed the factors with variance inflation factor (VIF) value >3. Log transformation on the phthalate metabolites was performed to reduce the impact of excessive magnitude differences. Restricted cubic spline (RCS) curve analysis was performed to analyze the non-linear relation between the continuous independent variable (phthalate metabolites) and the dependent variable (SFHL and HFHL). Then, multivariable logistic regression models were employed to estimate the odds ratio (OR) and 95% confidence interval (95% CI) for the associations of phthalate metabolites with hearing loss and identify other independent risk factors associated with hearing loss. Age, gender (female vs male), BMI, race (Hispanic as a reference), PA (Yes vs no), work noise exposure (Yes vs no), hypertension (Yes vs no), and diabetes (Yes vs no) were adjusted. Based on the multivariable regression results, three machine learning classifiers (XG Boost, logistic regression, and random forest) were constructed for binary classification (HFHL or not), and their predictive performance was evaluated through the area under the curve (AUC), accuracy, sensitivity, specificity, positive predictive value, negative predictive value, F1 score, and Kappa value in both training and validation sets. The training sets and validation sets are at a ratio of 8:2. P-value less than 0.05 indicates statistical significance.

Results

Characteristics of Subjects

The socio-demographic characteristics of the study subjects are demonstrated in Table 1. Our study consisted of 1713 participants, of whom 24.518% had SFHL and 41.998% had HFHL. Compared with normal controls, participants with SFHL or HFHL tended to be older and had higher BMI ($P < 0.05$). Additionally, males, non-Hispanic Whites were more likely to have SFHL or HFHL ($P < 0.05$). Participants with hearing loss spent less time in PA and were more exposed to work noise ($P < 0.05$). SFHL and HFHL participants had a higher proportion of hypertension and diabetes ($P < 0.05$). PIR was neither related to SFHL nor related to HFHL ($P > 0.05$). Those who lived with a spouse were more likely to have HFHL ($P < 0.05$) but had no significant association with SFHL ($P > 0.05$). The SFHL accounted for 17.184% and

Table 1 Baseline Characteristics of the Study Population

Characteristics		Speech-Frequency Hearing Loss			High-Frequency Hearing Loss		
		<25 dB n=1293 (75.482%)	**≥25 dB n=420 (24.518%)**	**P-value**	**<25 dB n=993 (58.002%)**	**≥25 dB n=719 (41.998%)**	**P-value**
Age (median [P_{25}, P_{75}])		41.000 [29.000, 54.000]	69.000 [60.000, 77.000]	<0.001	36.000 [26.000, 49.000]	63.000 [52.000, 73.000]	<0.001
Gender [n (%)]	Male	587 (45.398)	252 (60.000)	<0.001	412 (41.490)	426 (59.249)	<0.001
	Female	706 (54.602)	168 (40.000)		581 (58.510)	293 (40.751)	
Race (median [P_{25}, P_{75}])	Hispanic	371 (28.693)	117 (27.857)	<0.001	280 (28.197)	208 (28.929)	<0.001
	Non-Hispanic White	377 (29.157)	192 (45.714)		275 (27.694)	293 (40.751)	
	Non-Hispanic Black	329 (25.445)	60 (14.286)		257 (25.881)	132 (18.359)	
	Others	216 (16.705)	51 (12.143)		181 (18.228)	86 (11.961)	
Marital status [n (%)]	Live with spouse	608 (50.331)	230 (55.156)	0.089	445 (49.063)	392 (54.672)	0.025
	Others	600 (49.669)	187 (44.844)		462 (50.937)	325(45.328)	
BMI, kg/m^2 (median [P_{25}, P_{75}])		28.300 [24.100, 33.200]	28.900 [25.800,33.700]	0.006	27.800 [23.800, 32.900]	29.200 [25.700, 33.700]	<0.001
PIR (median [P_{25}, P_{75}])		2.150 [1.070, 4.020]	1.990 [1.190,3.640]	0.455	2.230 [1.150, 4.070]	1.930 [1.070, 3.640]	0.050
Physical activity (median [P_{25},P_{75}]		1680.000 [180.000, 5520.000]	540.000 [0.000, 3360.000]	<0.001	1800.000 [240.000, 5760.000]	780.000 [0.000, 3840.000]	<0.001
Work noise [n (%)]	Yes	377 (29.779)	179 (43.447)	<0.001	270 (27.864)	286 (40.395)	<0.001
	No	889 (70.221)	233 (56.553)		699 (72.136)	422 (59.605)	
Off-work noise [n (%)]	Yes	163 (12.636)	72 (17.184)	0.019	124 (12.513)	111 (15.481)	0.079
	No	1127 (87.364)	347 (82.816)		867 (87.487)	606 (84.519)	
Hypertension [n (%)]	No	920 (71.152)	183 (43.675)	<0.001	741 (74.622)	361 (50.279)	<0.001
	Yes	373 (28.848)	236 (56.325)		252 (25.378)	357 (49.721)	
Diabetes [n (%)]	No	1146 (90.236)	277 (68.059)	<0.001	905 (92.536)	517 (74.069)	<0.001
	Yes	124 (9.764)	130 (31.941)		73 (7.464)	181 (25.931)	

Abbreviations: BMI, body mass index; PIR, ratio of family income to poverty.

12.636% of those with vs without off-work noise exposure (P <0.05); however, no significant difference in off-work noise exposure between HFHL and non-HFHL groups was observed (P >0.05). The collinearity analysis results showed that VIF was less than 3 for all significant variables, which can avoid the problem of collinearity (Table S1).

Table 2 exhibits the detection rates of the phthalate metabolites meeting the inclusion criteria. MECPP (99.8%) had the highest detection frequency, followed by MEP (99.6%), MCOP (99.4%), MEHHP (99.4%), MEOHP, (99.2%), MBP (99.1%), MCNP (96.9%), and MBzP (96.7%). The distribution of eight phthalate metabolites in the non-SFHL vs SFHL group and non-HFHL vs HFHL group was also assessed. Except for MECPP and MEOHP, other metabolites were differentially distributed in non-SFHL and SFHL groups. Significant differences in MEP and MBZP were observed between the non-HFHL and HFHL groups (Table 3). Thus, we selected the metabolites MEP and MBZP both related to SFHL and HFHL for further investigation.

The Association of MBZP and MEP with Hearing Loss

To reveal the dose-response association of MBZP and MEP with SFHL and HFHL, RCS analysis was performed by adjusting the significant socio-demographic characteristics identified in the above univariate analysis. Age, gender, BMI, race, PA, work noise exposure, hypertension, and diabetes were adjusted. MBZP was positively linked to SFHL and HFHL with a linear association (P for non-linear >0.05) (Figure 1A and B). MEP seemingly had a negative linear relationship with SFHL and HFHL after adjusting various covariates (P for non-linear >0.05) (Figure 1C and D).

To have a deep understanding of the role of MBZP and MEP in hearing loss, we performed a multivariable logistic regression analysis upon all covariate corrections. When taking SFHL as an outcome variable, MBZP and MEP had no statistical relation. Although MEP was still not significantly linked to HFHL, MBZP elevation was a harmful feature for an increased risk of HFHL with an OR=1.339 (95% CI, 1.053–1.707). Notably, the socio-demographic parameters including age, gender, diabetes, and race were also associated with HFHL independent of other variables (all P <0.05). Older age and diabetes were harmful factors for HFHL; while female gender, non-Hispanic Whites, and other races were

Table 2 Detection Rate of Phthalate Metabolites

Abbreviations	Metabolite	LLOD (ng/mL)	Detection rate N (%)
MBP	mono-n-butyl phthalate	0.4	1697 (99.1)
MBzP	monobenzyl phthalate	0.3	1657 (96.7)
MCNP	monocarboxyononyl phthalate	0.2	1660 (96.9)
MCOP	monocarboxyoctyl phthalate	0.3	1702 (99.4)
MECPP	mono(2-ethyl-5-carboxypenty) phthalate	0.4	1709 (99.8)
MEHHP	mono(2-ethyl-5-hydroxyhexyl) phthalate	0.4	1702 (99.4)
MEOHP	mono(2-ethyl-5-oxohexyl) phthalate	0.2	1700 (99.2)
MEP	mono-ethyl phthalate	1.2	1706 (99.6)

Abbreviation: LLOD, lower limit of detection.

Table 3 Distribution of Phthalate Metabolites

Phthalate metabolites	Speech-Frequency Hearing Loss			High-Frequency Hearing Loss		
	<25 dB (n=1293)	≥25 dB (n=420)	P-value	<25 dB (n=993)	≥25 dB (n=719)	P-value
MCNP (median [P_{25}, P_{75}])	1.200 [0.800, 2.400]	1.600 [0.800, 2.900]	0.002	1.400 [0.800, 2.700]	1.600 [0.800, 3.000]	0.077
MCOP (median [P_{25}, P_{75}])	5.700 [2.800, 11.800]	6.900 [3.300, 16.400]	0.002	6.200 [3.000, 14.900]	6.800 [3.200, 15.500]	0.235
MECPP (median [P_{25}, P_{75}])	8.400 [4.600, 15.000]	8.800 [4.600, 16.700]	0.505	8.800 [4.900, 16.200]	8.600 [4.300, 16.400]	0.170
MBP (median [P_{25}, P_{75}])	9.600 [5.100, 16.700]	11.000 [5.400, 20.200]	0.043	9.900 [5.400, 18.300]	10.900 [5.100, 20.100]	0.506
MEP (median [P_{25}, P_{75}])	28.700 [11.600, 79.300]	34.900 [14.000, 102.400]	0.004	29.600 [12.200, 80.500]	35.900 [14.500, 103.700]	0.006
MEHHP (median [P_{25}, P_{75}])	5.300[2.700,9.200]	5.700 [3.000,10.800]	0.042	5.500 [3.000, 10.100]	5.700 [2.800, 10.700]	0.924
MEOHP (median [P_{25}, P_{75}])	3.500 [1.800, 6.000]	3.700 [1.800, 6.900]	0.479	3.700 [1.800, 6.600]	3.600 [1.700, 6.800]	0.586
MBZP (median [P_{25}, P_{75}])	3.100 [1.600, 7.300]	4.000 [1.500, 9.600]	0.024	3.300 [1.600, 7.400]	4.100 [1.500, 10.400]	0.017

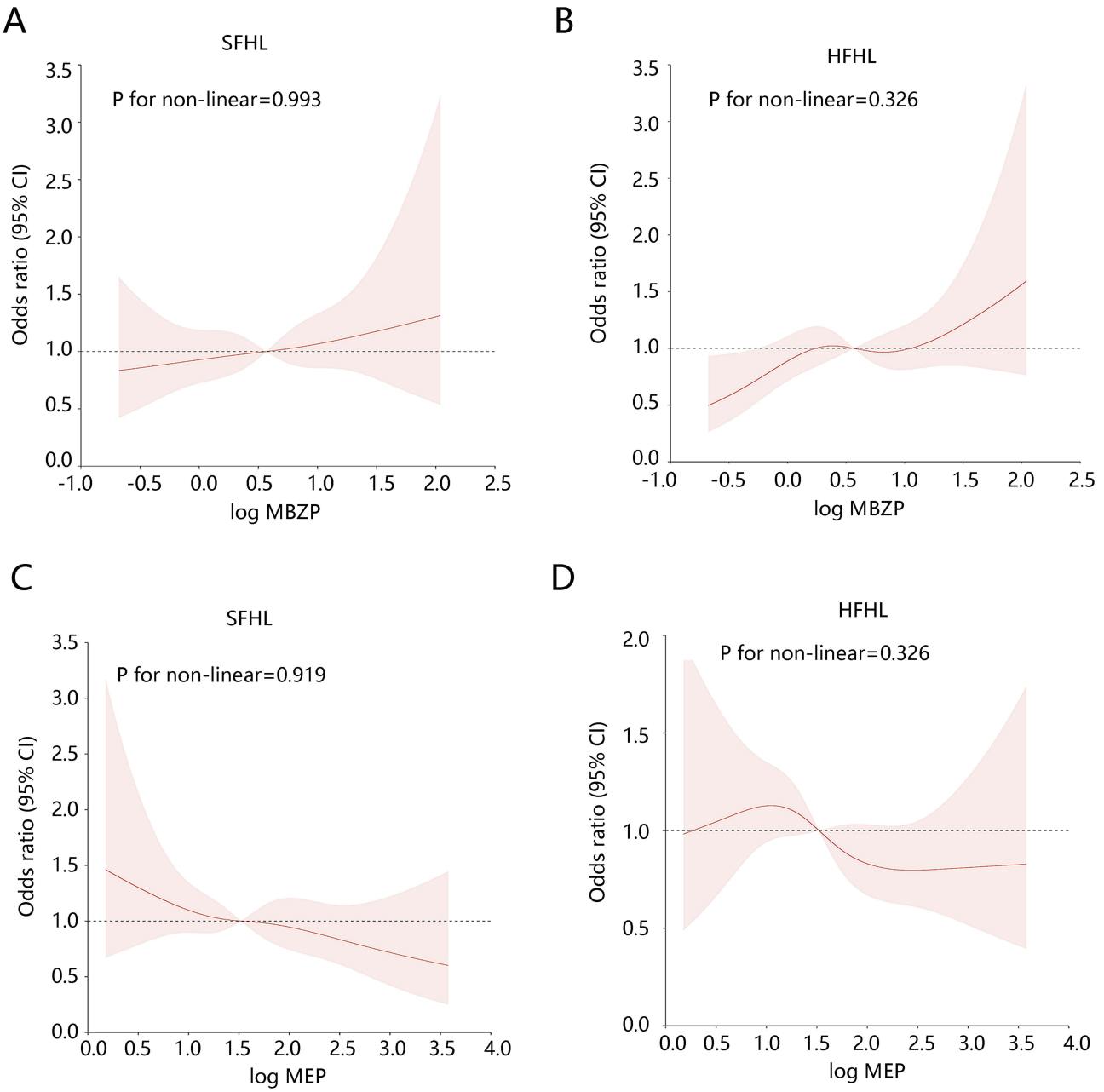

Figure 1 Restricted cubic spline analysis revealed the association of MBZP and MEP with hearing loss. The linear association of MBZP with SFHL (**A**) and HFHL (**B**). The linear association of MEP with SFHL (**C**) and HFHL (**D**).
Abbreviations: SFHL, speech-frequency hearing loss; HFHL, high-frequency hearing loss.

protective factors for HFHL (Tables 4 and 5). The findings highlighted the core value of MBZP in predicting HFHL and the role of clinical factors is also non-negligible, triggering us to construct a relevant model for clinical use.

Machine Learning Models

Following the regression analysis, we used three machine algorithms to build an MBZP-clinical model, aiming to identify the predominant influences of MBZP combined with other clinical factors on HFHL. The AUCs for the XG Boost model, logistic regression model, and random forest model in predicting HFHL were 0.971, 0.876, and 0.923, respectively in the training set (Figure 2A). In the validation set, the AUCs for the XG Boost and random forest models decreased to 0.823, and 0.857, respectively, indicating potential overfitting. However, the logistic regression model

Table 4 Association of MBZP with Hearing Loss

Characteristics	Speech-Frequency Hearing Loss		High-Frequency Hearing Loss	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age	1.113 (1.100–1.128)	<0.001	1.106 (1.095–1.118)	<0.001
Body mass index	1.022 (0.998–1.047)	0.069	1.020 (0.989–1.040)	0.058
Physical activity	0.981 (0.977–1.002)	0.206	1.001 (0.981–1.012)	0.173
Log MBZP	1.236 (0.937–1.632)	0.134	1.339 (1.053–1.707)	0.018
Work noise	0.814 (0.586–1.132)	0.219	0.872 (0.647–1.175)	0.367
Gender	0.485 (0.351–0.668)	<0.001	0.342 (0.256–0.454)	<0.001
Hypertension	1.049 (0.752–1.458)	0.778	0.778 (0.571–1.056)	0.110
Diabetes	1.637 (1.126–2.382)	0.010	1.673 (1.133–2.486)	0.010
Non-Hispanic White	0.995 (0.683–1.448)	0.978	1.033 (0.736–1.449)	0.850
Non-Hispanic Black	0.374 (0.239–0.578)	<0.001	0.462 (0.319–0.666)	<0.001
Others	0.866 (0.529–1.407)	0.565	0.618 (0.406–0.936)	0.024

Abbreviation: 95% CI, 95% confidence interval.

Table 5 Association of MEP with Hearing Loss

Characteristics	Speech-Frequency Hearing Loss		High-Frequency Hearing Loss	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age	1.112 (1.098–1.127)	<0.001	1.104 (1.093–1.116)	<0.001
Body mass index	1.025 (1.001–1.050)	0.043	1.024 (1.003–1.044)	0.021
Physical activity	0.925 (0.782–1.260)	0.186	1.310 (0.952–1.501)	0.137
Log MEP	0.914 (0.724–1.151)	0.445	0.916 (0.748–1.122)	0.398
Work noise	0.802 (0.578–1.114)	0.187	0.858 (0.638–1.155)	0.312
Gender	0.488 (0.353–0.672)	<0.001	0.347 (0.260–0.461)	<0.001
Hypertension	1.043 (0.748–1.449)	0.803	0.775 (0.569–1.050)	0.103
Diabetes	1.651 (1.136–2.402)	0.009	1.686 (1.143–2.501)	0.009
Non-Hispanic White	1.002 (0.687–1.459)	0.992	1.048 (0.747–1.471)	0.785
Non-Hispanic Black	0.401 (0.257–0.618)	<0.001	0.503 (0.348–0.723)	<0.001
Others	0.849 (0.515–1.386)	0.516	0.615 (0.403–0.934)	0.023

Abbreviation: 95% CI, 95% confidence interval.

exhibited a stable performance in predicting the outcome, achieving an AUC of 0.865 in the validation set (Figure 2B) (Table 6). These results indicated that the logistic MBZP-clinical model is optimal for predicting HFHL. Furthermore, we ranked the importance of MBZP, age, gender, diabetes, and race in the logistic regression model. The results showed that gender, diabetes, and MBZP ranked in the top three, further confirming the significance of MBZP in HFHL (Figure 2C).

Discussion

Hearing loss is a chronic non-communicable disease severely influencing people's life quality.[20] Prevention and treatment costs of hearing loss cause pressure on social economic development.[21] The current study delved into the association between phthalate metabolites and hearing loss, categorized into SFHL and HFHL. Our findings analyzed eight phthalate metabolites, among which MEP and MBZP were significantly correlated with both SFHL and HFHL. Additionally, our analysis demonstrated that MBZP is significantly associated with an increased risk of both SFHL and HFHL, indicating a dose-response relationship. MBZP emerged as a harmful factor, particularly to HFHL.

This cross-sectional study was conducted based on the NHANES database. In the included population, 24.518% had SFHL and 41.988% had HFHL. This is similar to previous studies reporting the prevalence of HFHL and SFHL among US adults aged 20–69 in 2012 at 31.1% and 14.1%, respectively, with HFHL being more prevalent than SFHL.[22]

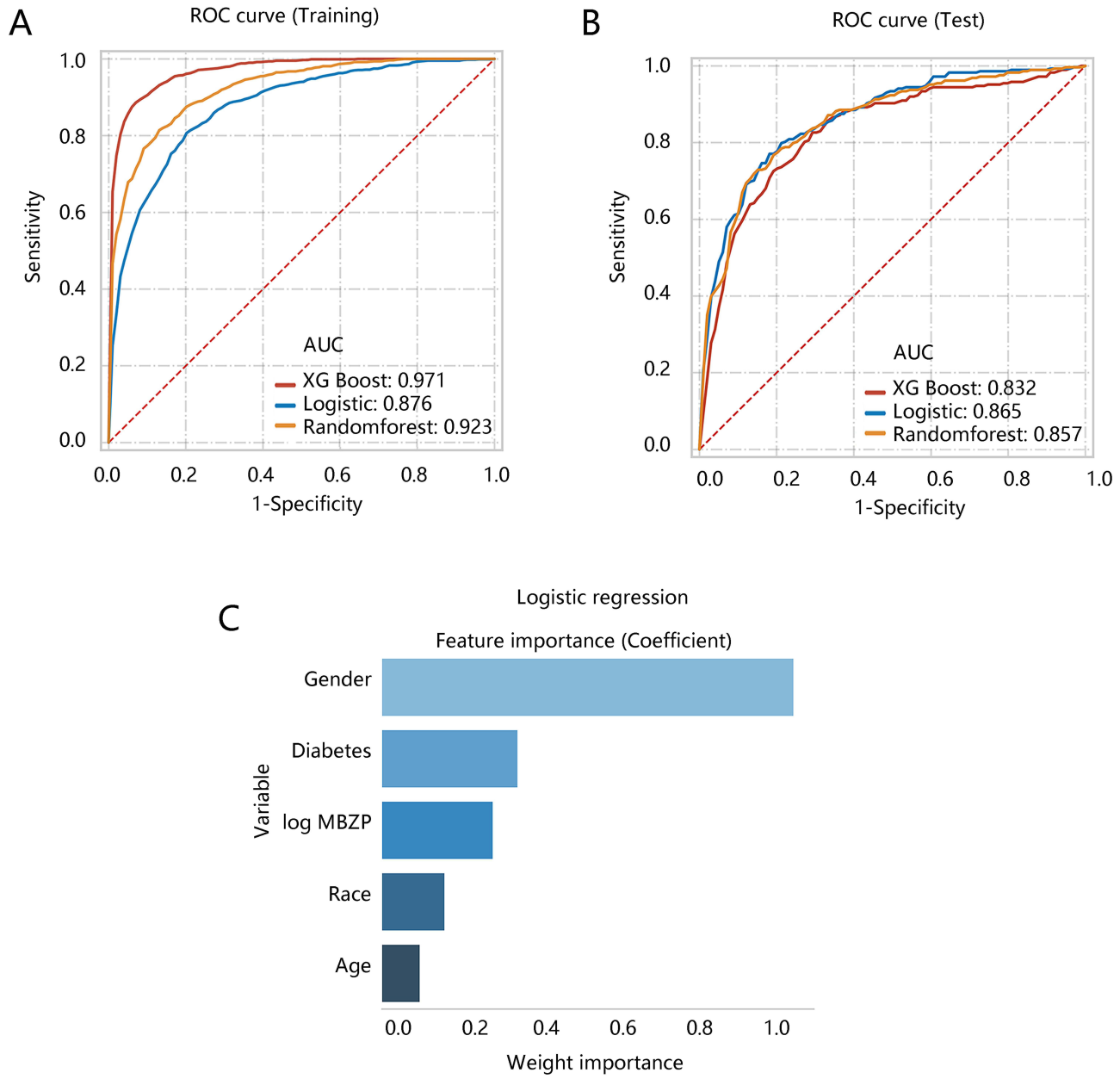

Figure 2 Optimal selection of BMZP-clinical model and feature importance rank. The predictive performance of the MBZP-clinical model for high-frequency hearing loss in the training set (**A**) and test set (**B**) to identify logistic regression as the optimal model. (**C**) The importance of the features in the logistic regression model.
Abbreviations: ROC, receiver operating characteristic curve; AUC, the area under the curve.

Phthalates, widely used as plasticizers, are increasingly drawing attention due to their health effects. Previous studies have found higher concentrations of phthalates in individuals with hearing impairments and identified them as risk factors.[23] We enrolled eight widely present phthalate metabolites (MECPP, MEP, MCOP, MEHHP, MEOHP, MBP, MCNP, and MBZP) in the included population, with detection rates exceeding 85%. Particularly, MEP and MBZP showed significant differences between the non-SFHL and SFHL groups, as well as between the non-HFHL and HFHL groups. After adjusting for socio-demographic variables and other covariates, MBZP remained positively associated with HFHL. This is consistent with Shiue's findings, where MBZP was significantly associated with hearing impairments, with higher concentrations observed in individuals who experienced tinnitus.[24]

Notably, multivariable logistic regression analysis indicated no significant association between MBZP and increased risk of SFHL, but a significant association with increased risk of HFHL (OR=1.339, 95% CI, 1.053–1.707). In most

Table 6 Predictive Performance of Three Machine Learning Classifiers in the Training and Test Sets

Model	Set	AUC (95% CI)	Accuracy	Sensitivity	Specificity	PPV	NPV	F1 Score	Kappa
XGBoost	Training	0.971 (0.963–0.978)	0.912	0.893	0.927	0.896	0.924	0.894	0.818
	Validation	0.832 (0.787–0.877)	0.763	0.788	0.760	0.727	0.791	0.755	0.516
Logistic regression	Training	0.876 (0.858–0.895)	0.802	0.818	0.792	0.734	0.859	0.774	0.598
	Validation	0.865 (0.826–0.904)	0.789	0.764	0.839	0.738	0.833	0.750	0.572
Random forest	Training	0.923 (0.909–0.937)	0.847	0.814	0.871	0.816	0.868	0.815	0.684
	Validation	0.857 (0.817–0.898)	0.792	0.764	0.833	0.763	0.814	0.763	0.573

Abbreviations: AUC (95% CI), the area under the curve (95% confidence interval); PPV, positive predictive value; NPV, negative predictive value.

forms of hearing loss, high frequencies are the first lost part of the hearing spectrum, and HFHL often precedes lower-frequency hearing loss.[25] MBZP may primarily affect early hearing issues. Further machine learning models identified MBZP as a key predictor of HFHL. These results underscore the role of MBZP in HFHL. We hypothesized that the potential mechanism by which MBZP affects HFHL involves oxidative stress. Oxidative stress, associated with the central nervous system and age-related degenerative processes, is a key factor in cochlear damage and hearing loss.[26] Increased oxidative stress levels have been observed in mice with HFHL.[27] The production of reactive oxygen species can lead to mitochondrial-mediated apoptosis of cochlear hair cells, ultimately resulting in hearing dysfunction.[28,29] In recent years, growing evidence has suggested that phthalates can induce oxidative stress. Studies have reported positive correlations between phthalate metabolites and oxidative stress biomarkers.[30] In peripheral blood mononuclear cells, phthalate metabolites, including MBZP, have been shown to increase reactive oxygen species levels.[31] These studies support our hypothesis, but the mechanism that MBZP influences HFHL through oxidative stress requires further investigation.

This study has some strengths. The study incorporated a satisfactory sample size of 1713 participants, enhancing the reliability of our findings. By adjusting for a wide range of socio-demographic and clinical variables, we were able to isolate the association of phthalate metabolites with hearing loss more effectively. Additionally, the use of machine learning models provided a nuanced understanding of the potential relevance of MBZP in HFHL. However, several limitations should be considered in this study. The data from a cross-sectional nature limited the ability to establish causal relationships between phthalate metabolites and hearing loss. Some variables, such as PA and noise exposure, were self-reported, which could introduce recall bias. The study population might not be representative of all demographic groups, potentially limiting the generalizability of our findings to other populations or regions. Although binary logistic regression was used to measure the association between independent and dependent variables by calculating the OR and 95% CI with prevalent outcomes in previous publications,[32–34] it is usually preferable to model and estimate the prevalence ratio rather than OR when diseases are not uncommon,[35] which should be considered in future verification. Future research should focus on longitudinal studies to better establish causal relationships between phthalate metabolites and hearing loss. Additionally, investigating the effects of specific phthalate compounds in larger cohorts may yield a more nuanced understanding of their health impacts.

Conclusion

In summary, our findings underscore the significant association between phthalate metabolites and hearing loss, particularly between MBZP and HFHL. The logistic regression model proved to be the most reliable in predicting HFHL, highlighting the potential of MBZP as a predictive biomarker. These findings have important implications for public health, suggesting the need for strategies to reduce phthalate exposure and address the identified risk factors to prevent hearing loss. However, the cross-sectional nature determines the association rather than causality, which should be validated in the future prospective large-scale cohort.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

The Ethics Committee of Longyan First Affiliated Hospital of Fujian Medical University deemed that this research is based on open-source data, so the need for ethics approval was waived.

Consent to Participate

Not applicable.

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Disclosure

Li-mei You and De-Chang Zhang contributed equally to this work, and should be regarded as co-first authors. The authors report no conflict of interest.

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