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Association between the Endothelial Activation and Stress Index and Hearing Loss: A Cross-Sectional Analysis Based on the National Health and Nutrition Examination Survey (NHANES) 2015-2018

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Abstract: Purpose: To investigate the association between the endothelial activation and stress index (EASIX) and hearing loss (HL), and to further analyze its dose–response relationship and differences across subgroups. Methods: Data were obtained from the 2015–2016 and 2017–2018 cycles of the National Health and Nutrition Examination Survey (NHANES), and a total of 5,707 participants with completed audiometric examinations and complete laboratory data were included. EASIX was calculated as LDH (U/L) × Cr (mg/dL) / PLT (10^9/L). Hearing loss was defined as a pure-tone average (PTA) ≥ 25 dB HL at seven frequencies (0.5, 1, 2, 3, 4, 6, and 8 kHz) in the worse ear; low-frequency hearing loss (LFHL) and high-frequency hearing loss (HFHL) were defined using 0.5–2 kHz and 3–8 kHz, respectively. Multivariable linear regression and logistic regression were used to analyze the associations of EASIX with hearing thresholds and the risk of hearing loss, and generalized additive models were used to explore dose–response relationships. Results: In the fully adjusted model, participants in the highest EASIX quartile (Q4) had an average hearing threshold 5.3 dB HL higher than those in the lowest quartile (Q1) ($\beta = 5.3$, 95% CI 3.9–6.6, $P < 0.001$). Consistent with this finding, the Q4 group also showed a 2.6-fold higher risk of high-frequency hearing loss (HFHL) compared with the Q1 group (OR = 2.6, 95% CI 2.0–3.5, $P < 0.001$), along with a significantly elevated risk of low-frequency hearing loss (LFHL) (OR = 1.7, 95% CI 1.1–2.6, $P = 0.026$). Further dose–response analysis revealed a nonlinear relationship between EASIX and hearing threshold, with a breakpoint at approximately 1.12. In addition, subgroup analyses indicated that age, sex, diabetes, and hypertension each modified the association (all P for interaction < 0.01), with the strongest effects observed among participants without diabetes or hypertension. Conclusion: EASIX was positively associated with hearing loss, and the relationship was most evident in participants without diabetes or hypertension. As a simple, inexpensive composite measure of endothelial dysfunction, EASIX may help flag people at elevated risk of hearing loss.

Keywords: Endothelial Activation and Stress Index; Hearing Loss; NHANES; Cross-sectional Study; Biomarker.

1. Introduction

Rapid population aging has made hearing loss (HL) a pressing public health concern. HL is most common among older adults, but its prevalence has also been climbing in younger age groups, so the condition now affects people across the whole life span. According to the World Report on Hearing, nearly 2.5 billion people will have some degree of HL by 2050. The associated disability is substantial: HL currently accounts for roughly 43.4 million years lived with disability (YLD) worldwide and is the third leading cause of YLD, behind low back pain and migraine [1].

The pathogenesis of HL remains incompletely understood and is currently considered to involve impaired inner ear microcirculation, immune factors, viral infection, infectious diseases, psychological factors, and noise exposure [2]. Given that HL is generally irreversible, early identification of relevant risk factors and timely intervention are of critical importance.

In recent years, the theory of inner ear microcirculatory impairment and vascular pathology has become a new research focus. The endothelial activation and stress index (EASIX) is a promising integrative biomarker composed of three routine laboratory parameters—lactate dehydrogenase (LDH), creatinine (Cr), and platelet count (PLT)—that is used to assess endothelial dysfunction and systemic inflammatory status [3]. EASIX has been applied in research on endothelial complications associated with hematopoietic stem cell transplantation [4] and cardiovascular disease (e.g., chronic heart failure) [5]. Owing to its easy accessibility and cost-effectiveness, EASIX is expected to be incorporated into clinical practice for the assessment of endothelial function.

However, the association between EASIX and HL has not been adequately explored. Therefore, this study aimed to analyze the association between EASIX and HL using the NHANES database, and to further investigate its dose–response relationship and differences across subgroups.

2. Materials and Methods

2.1. Study Design and Population

We pooled two consecutive cycles of NHANES (2015–2016 and 2017–2018). NHANES draws its sample through a multistage, stratified design that is intended to represent the health status of the U.S. population. To enter the present analysis, participants had to complete the audiometric examination and have usable results for LDH, Cr, and PLT. Of the 29,196 people in the initial sample, 22,324 lacked a complete audiometric record and a further 1,165 had missing LDH, PLT, or Cr values; 5,707 participants remained for analysis (Figure 1).

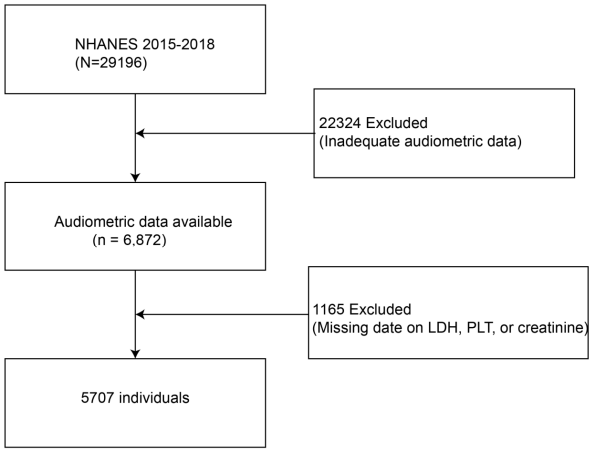


Figure 1. Flowchart of participant selection

Data were derived from the NHANES 2015–2018 cycles. The initial sample comprised 29,196 participants. After excluding 22,324 participants without complete audiometric data, 6,872 remained; after further excluding 1,165 participants with missing LDH, PLT, or Cr data, 5,707 participants were included in the final analysis.

2.2. Study Variables

2.2.1. Endothelial Activation and Stress Index (EASIX)

EASIX was computed as LDH (U/L) × Cr (mg/dL) / PLT (10^9/L). We then split the cohort into four groups by EASIX quartile: Q1 (0.08–0.32), Q2 (0.32–0.45), Q3 (0.45–0.62), and Q4 (0.62–11.52).

2.2.2. Hearing Loss

All audiometric examinations were performed by standardized trained examiners in dedicated sound-isolated booths in the Mobile Examination Center (MEC), and hearing thresholds were measured at seven frequencies (0.5, 1, 2, 3, 4, 6, and 8 kHz) in both ears. Because this study aimed to examine the organic damage to the cochlea induced by systemic endothelial stress exposure, and with reference to previous studies of risk factors for hearing loss based on the NHANES database, the ear with the worse thresholds (the worse ear) was selected, and the PTA was calculated as the mean of hearing thresholds across the seven frequencies; worse-ear PTA ≥ 25 dB HL was defined as hearing loss. LFHL (500, 1,000, and 2,000 Hz) and HFHL (3,000, 4,000, 6,000, and 8,000 Hz) were further defined and analyzed separately. It should be noted that the outcome definition used in this study focuses on organic cochlear damage and is not fully equivalent to the World Health Organization (WHO) standard, which uses the better-hearing ear to assess hearing disability and impairment of social communication function.

2.2.3. Covariates

Confounders that might affect both EASIX and hearing loss were included in the analyses: age, sex, race/ethnicity, education level, body mass index (BMI), hypertension (self-reported physician diagnosis), diabetes (self-reported physician diagnosis), smoking (≥ 100 cigarettes over the lifetime), estimated glomerular filtration rate (eGFR), sleep duration, total cholesterol, and triglycerides. These variables were obtained through standardized questionnaires, physical examination, or laboratory testing. The proportion of missing values for each covariate was low, and complete-case analysis was used in the regression models.

2.3. Statistical Analysis

All analyses were run in R (version 4.5.0) with EmpowerStats, and statistical significance was set at a two-sided α of 0.05. Because the data come from a cross-sectional survey, the models are intended to describe associations; causal interpretation is not warranted.

To account for the combined 2015–2018 cycles and the NHANES sampling scheme, survey weights (WTMEC2YR) were applied together with the primary sampling units (SDMVPSU) and strata (SDMVSTRA), following CDC recommendations. Categorical variables are summarized as weighted percentages; continuous variables as medians with interquartile ranges. Quartile comparisons relied on the chi-square test (categorical) and the Kruskal–Wallis test (continuous).

Two outcome types were modeled. For PTA, a continuous measure, we used multivariable linear regression; for hearing loss, a binary outcome, we used logistic regression. Adjustment proceeded in three steps: Model 1 included no covariates; Model 2 controlled for sex, race/ethnicity, age, and education; Model 3 added total cholesterol, triglycerides, diabetes, hypertension, sleep duration, smoking, BMI, and eGFR.

We examined the shape of the EASIX–PTA relationship with generalized additive models (GAMs) and smooth curve fitting, and used two-piecewise linear (piecewise) regression to estimate the breakpoint. Subgroup models were run for age, sex, diabetes, and hypertension; a multiplicative interaction term between EASIX and each stratifying variable was included to test effect modification.

3. Results

3.1. Participant Characteristics

A total of 5,707 participants were included in this study, of whom 1,291 (22.6%) met the definition of hearing loss. Participants were divided into four groups according to EASIX quartiles: Q1 (0.08–0.32), Q2 (0.32–0.45), Q3 (0.45–0.62), and Q4 (0.62–11.52). As shown in Table 1, age, sex, race/ethnicity, the prevalence of hypertension and diabetes, eGFR, and hearing thresholds differed significantly across EASIX quartiles (all $P < 0.05$). Compared with the Q1 group, participants in the Q4 group were older, had a higher proportion of men, and had higher prevalence of hypertension and diabetes. In addition, eGFR decreased progressively with increasing EASIX ($P < 0.001$). The prevalence of both HFHL and LFHL increased significantly with increasing EASIX (both P for trend < 0.001).

Categorical data are presented as weighted percentages and continuous data as medians (interquartile ranges). Group comparisons used the chi-square test for categorical variables and the Kruskal–Wallis test for continuous variables. BMI, body mass index; eGFR, estimated glomerular filtration rate; HFHL, high-frequency hearing loss; LFHL, low-frequency hearing loss; PTA, pure-tone average.

3.2. Association Between EASIX and Hearing Thresholds (PTA)

To characterize the EASIX–PTA relationship, hearing thresholds were regressed on EASIX quartiles (Table 2). Higher quartiles predicted higher PTA in each of the three models. After full adjustment, hearing thresholds in Q2, Q3, and Q4 exceeded those in Q1 by 1.4 (95% CI 0.3–2.5; P =

0.014), 2.3 (95% CI 1.1–3.5; P < 0.001), and 5.3 dB HL (95% CI 3.9–6.6; P < 0.001), respectively. The rise was monotonic and the linear trend across quartiles was significant (P < 0.001).

Table 1. Baseline characteristics of participants according to EASIX quartiles

Characteristic	Q1 (0.08–0.32) N=1427	Q2 (0.32–0.45) N=1426	Q3 (0.45–0.62) N=1427	Q4 (0.62–11.52) N=1427	P-value
Age(years)	37.00 (25.57 ,51.00)	41.00 (25.00 ,54.00)	47.00(30.00,61.00)	58.00(35.00,71.00)	<0.0001
Gender(%)					<0.0001
Male	18.03 (12.80,24.79)	43.00 (37.09,49.32)	60.61 (55.97 ,65.06)	72.52 (68.08,76.56)	
Female	81.97 (75.21,87.20)	56.90 (50.68,62.91)	39.39 (34.94 ,44.03)	27.48 (23.44,31.92)	
Race(%)					<0.0001
Mexican American	16.09 (10.18 ,24.49)	8.41 (5.23, 13.26)	7.27 (4.91 , 10.64)	4.53 (3.00,6.81)	
Other Hispanic	8.86 (5.70 , 13.53)	7. 11 (4.74, 10.53)	5.93 (3.79 ,9. 17)	4.89 (3.44,6.92)	
Non-Hispanic white	53.72 (44.92 ,62.29)	64.02 (56.15 ,71.20)	67.05 (59.13,74. 12)	68.16 (61.02,74.53)	
Non-Hispanic black	9.91 (6.66, 14.49)	9.84 (6.77, 14.08)	10.45 (6.64, 16.07)	14.73 (9.91,21.34)	
Other/multiracial	11.43 (8.16, 15.78)	10.63 (8.31, 13.50)	9.30 (6.78, 12.62)	7.68 (6.01,9.77)	
Education level, *n* (%)					0.6450
Less than 9th grade	7.60 (4.43, 12.74)	5.65 (3.47,9.07)	4.44 (2.76,7.06)	4.34 (2.04,9.01)	
9- 11th grade	8.03 (5.15, 12.30)	6.53 (4.65 ,9.08)	11.12 (7.79, 15.64)	8.45 (5.53, 12.71)	
High school graduate	21.01 (16.23,26.74)	21.57 (17.19 ,26.72)	23.18 (17.50,30.03)	22.51 (18.25,27.44)	
Some college	32.68 (26.72,39.27)	31.30 (25.31 ,37.99)	29.54 (23.10 ,36.90)	31.10 (26.24,36.42)	
College graduate	30.68 (21.38 ,41.88)	34.94 (26.16 ,44.88)	31.73 (23.45 ,41.34)	33.60 (27.33,40.49)	
Smoke status (%)					0.0554
Yes	40.76 (33.76,48. 16)	41.05 (34.82 ,47.57)	49.46 (44.23 ,54.70)	42.59 (36. 14,49.29)	
No	59.24 (51.84,66.24)	58.95 (52.43 ,65. 18)	50.54 (45.30 ,55.77)	57.41 (50.71 ,63.86)	
Diabetes (%)					0.0005
Yes	9.31 (7.64, 11.31)	6.59 (4.06 , 10.54)	9.99 (6.73 , 14.58)	16. 11 (12.84,20.03)	
No	90.69 (88.69,92.36)	93.41 (89.46 ,95.94)	90.01 (85.42 ,93.27)	83.89 (79.97,87. 16)	
Hypertension (%)					0.0002
Yes	20.67 (15.85,26.48)	26.70 (21.61,32.49)	31.29 (26.14,36.94)	40.20 (32.65,48.24)	
No	79.33 (73.52,84. 15)	73.30 (67.51,78.39)	68.71 (63.06,73.86)	59.80 (51.76,67.35)	
HFHL (%)					<0.0001
Yes	15.41 (11.67,20.07)	21.19 (16.20,27.21)	32.92 (28.52,37.64)	48.97 (41.44,56.55)	
No	84.59 (79.93,88.33)	78.81 (72.79,83.80)	67.08 (62.36,71.48)	51.03 (43.45,58.56)	
LFHL(%)					<0.001
Yes	3.58 (2.26,5.63)	4.42(2.67,7.24)	9.10(6.14,13.29)	16.88 (13. 19,21.35)	
No	96.42(94.37 ,97.74)	95.58（92.76,97.33)	90.90 (86.71,93.86)	83.12 (78.65,86.81)	
BMI	28.83 (28.02,29.65)	28.56(27.72，29.40)	29.01(28.16,29.86)	29.13(28.48,29.78)	0.8109
Sleep hours	7.82 (7.72 ,7.92)	7.73 (7.61,7.85)	7.66 (7.56 ,7.77)	7.76 (7.60,7.92)	0.1615
eGFR	113.15(102.38,124.66)	101.55 (90.64 ,113.69)	92.22 (79.59,105.73)	79.87 (64.24,93.61)	<0.001
Triglycerides,mmol/L	1.34 (1.24 ,1.45)	1.39 (1.27, 1.51)	1.37 (1.29, 1.44)	1.42 (1.34, 1.50)	0.6796
PTA	11.70 (10.41,13.00)	13.80 (11.97, 15.63)	18.65 (17.12,20. 17)	23.55 (21.20,25.91)	<0.0001

Table 2. Association between EASIX quartiles and hearing thresholds (PTA) assessed by multiple linear regression

EASIX quartile	Model 1 β (95% CI) P value	Model 2 β (95% CI) P value	Model 3 β (95% CI) P value
Q1	1-Reference	1-Reference	1-Reference
Q2	2.0 (1.0, 3.1) <0.001	2.3 (1.2, 3.4) <0.001	1.4 (0.3, 2.5) 0.014
Q3	5.7 (4.6, 6.8) <0.001	4.7 (3.5, 5.8) <0.001	2.3 (1.1, 3.5) <0.001
Q4	12.5 (11.4, 13.6) <0.001	8.6 (7.5, 9.8) <0.001	5.3 (3.9, 6.6) <0.001
P for trend	<0.001	<0.001	<0.001

Model 1 was unadjusted; Model 2 adjusted for sex, race/ethnicity, age, and education; Model 3 was further adjusted for total cholesterol, triglycerides, diabetes, hypertension, sleep duration, smoking, BMI, and eGFR.

3.3. Association Between EASIX and Different Types of Hearing Loss

HFHL became more likely as EASIX rose. In the unadjusted analysis, the ORs for Q2, Q3, and Q4 relative to Q1 were 1.7 (95% CI 1.4–2.0), 2.6 (95% CI 2.1–3.1), and 6.0 (95% CI 5.0–7.2), respectively (all P < 0.001). Full adjustment attenuated these estimates but they remained significant for each quartile: 1.5 (95% CI 1.2–1.9, P = 0.004) for Q2, 1.6 (95% CI 1.2–2.0, P < 0.001) for Q3, and 2.6 (95% CI 2.0–3.5, P < 0.001) for Q4 (Table 3).

Table 3. Association between EASIX quartiles and high-frequency hearing loss (HFHL) assessed by logistic regression

EASIX quartile	Model 1	Model 2	Model 3
	OR(95% CI)P value	OR(95% CI)P value	OR(95% CI)P value
Q1	1-Reference	1-Reference	1-Reference
Q2	1.7(1.4,2.0) <0.001	1.7(1.4, 2.1) <0.001	1.5(1.2,1.9) 0.004
Q3	2.6(2.1,3.1) <0.001	2. 1(1.7,2.7) <0.001	1.6(1.2, 2.0) <0.001
Q4	6.0(5.0,7.2) <0.001	4.2(3.4,5.3) <0.001	2.6(2.0,3.5) <0.001
P for trend	<0.001	<0.001	<0.001

Model 1 was unadjusted; Model 2 adjusted for sex, race/ethnicity, age, and education; Model 3 was further adjusted for total cholesterol, triglycerides, diabetes, hypertension, sleep duration, smoking, BMI, and eGFR.

Similarly, EASIX was also significantly and positively associated with low-frequency hearing loss (LFHL). However, the effect estimates were smaller than those observed for HFHL (Table 4). In the fully adjusted Model 3, the ORs for the Q3 and Q4 groups were 1.6 (95% CI 1.1–2.4, P = 0.024) and 1.7 (95% CI 1.1–2.6, P = 0.026), respectively. The Q2 group did not reach statistical significance (OR = 1.1, 95% CI 0.7–1.6, P = 0.675). These findings suggest that elevated EASIX may preferentially affect high-frequency auditory function. Its effect on LFHL appears to be relatively weaker.

Table 4. Association between EASIX quartiles and low-frequency hearing loss (LFHL) assessed by logistic regression

EASIX quartile	Model 1	Model 2	Model 3
	OR(95% CI)P value	OR(95% CI)P value	OR(95% CI)P value
Q1	1-Reference	1-Reference	1-Reference
Q2	1.3 (0.9,1.8) 0.170	1.3 (0.9,1.9) 0.240	1.1 (0.7,1.6) 0.675
Q3	2.7 (2.0,3.7) <0.001	2.2 (1.5,3.1) <0.001	1.6 (1.1,2.4) 0.024
Q4	5.4 (4.0,7.3) <0.001	2.7 (1.9, 3.9) <0.001	1.7 (1.1,2.6) 0.026
P for trend	<0.001	<0.001	<0.001

Model 1 was unadjusted; Model 2 adjusted for sex, race/ethnicity, age, and education; Model 3 was further adjusted for total cholesterol, triglycerides, diabetes, hypertension, sleep duration, smoking, BMI, and eGFR.

3.4. Dose–Response Relationship Between EASIX and Hearing Loss

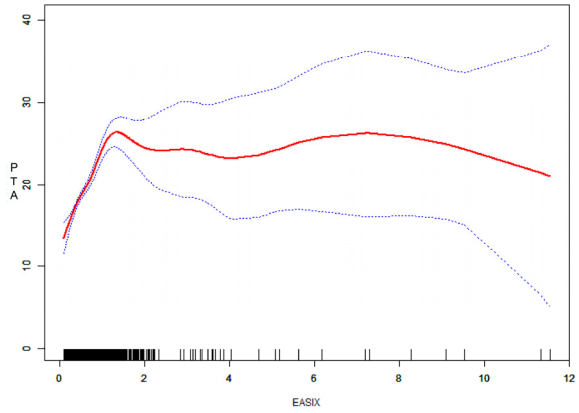


Figure 2. Threshold effect analysis for the association between EASIX and hearing thresholds (PTA)

Generalized additive models and smooth curve fitting were used to explore the shape of the association between EASIX and hearing thresholds. After adjusting for all covariates, the analysis revealed a nonlinear dose–response relationship. Piecewise regression identified a breakpoint at 1.12. When EASIX was below 1.12, higher EASIX was significantly associated with elevated hearing thresholds (β = 11.27 dB HL, 95% CI 9.23–13.32, P < 0.001). In contrast, when EASIX was at or above 1.12, no significant association was observed (β = −0.32 dB HL, 95% CI −1.27 to 0.63, P = 0.513). This pattern suggests a possible saturation effect. However, because relatively few participants had high EASIX values, the results for this range should be interpreted with caution (Figure 2).

3.5. Subgroup Analyses

To see whether these findings were consistent across populations, the analysis was repeated within subgroups defined by age, sex, diabetes, and hypertension (Table 5). The EASIX–threshold link differed by age (P for interaction < 0.01): a significant association appeared only among participants aged ≤60 years (β = 1.0, 95% CI 0.1–1.9), whereas the estimate for those older than 60 was 0.3 (95% CI −1.2 to 1.9). Sex also modified the link (P for interaction < 0.01), with coefficients of 2.4 (95% CI 1.4–3.4) in men and 1.9 (95% CI 0.5–3.3) in women. Metabolic status showed the largest contrast: among participants free of diabetes, hearing thresholds rose 3.7 dB HL per unit increase in EASIX (95% CI 2.6–4.7; P < 0.001), against essentially no change in diabetic participants (β = 0.1, 95% CI −1.2 to 1.3). The corresponding values for hypertension were 3.8 (95% CI 2.5–5.1) in normotensive and 0.9 (95% CI −0.2 to 1.9) in hypertensive participants, with both interaction terms significant (P < 0.01; Table 5).

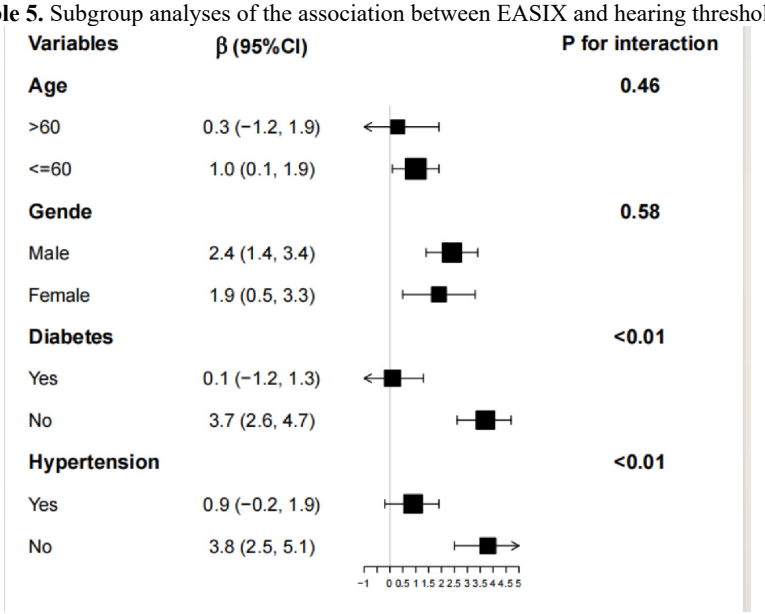
β, regression coefficient; CI, confidence interval. Each subgroup model was adjusted as in Model 3 except for the variable used to define the subgroup. P for interaction was obtained from models containing an EASIX × subgroup product term.

4. Discussion

Our study found a clear positive association between EASIX and hearing loss. This association remained robust even after adjustment for multiple confounders. Compared with participants in the lowest quartile (Q1), those in the highest quartile (Q4) had average hearing thresholds that were 5.3 dB HL higher (95% CI 3.9–6.6, P < 0.001). The risk of high-frequency hearing loss was 2.6 times higher in the Q4 group than in the Q1 group (OR = 2.6, 95% CI 2.0–3.5, P < 0.001). The risk of low-frequency hearing loss also increased

significantly (OR = 1.7, 95% CI 1.1–2.6, P = 0.026). A nonlinear dose–response relationship was observed, with a breakpoint at 1.12. Notably, the association was stronger among participants without diabetes or hypertension. This pattern suggests that metabolic status may play a role in hearing decline.

Table 5. Subgroup analyses of the association between EASIX and hearing thresholds



Previous studies have shown that EASIX is significantly associated with adverse outcomes in various conditions, including functional outcomes and mortality after acute ischemic stroke and 28-day mortality in patients with sepsis [6, 7]. In terms of effect sizes (OR or hazard ratio [HR]), most studies reported values ranging from 1.3 to 2.0; for example, similar risk ranges were observed in patients undergoing hematopoietic stem cell transplantation and in those with chronic heart failure [4, 5]. The present study extends the application of EASIX to the field of hearing loss, in which an OR of 2.6 for HFHL was observed. Of note, differences in population characteristics, outcome definitions, and adjusted variables across studies warrant caution when directly comparing effect sizes. Our results may suggest that EASIX is a cross-organ, general marker of endothelial dysfunction and that the auditory system may be relatively sensitive to endothelial–microcirculatory damage; however, this hypothesis requires further verification.

Why EASIX and hearing loss might travel together can be approached through its three components, although the mechanisms discussed below remain speculative. Cr reflects renal function, and the kidney and inner ear resemble each other in embryologic origin, gene expression, ultrastructure (for example basement membrane antigenicity), and ion-transport machinery, including ClC-K, KCNQ1/KCNE1, and the Na^+–K^+–$2Cl^-$ cotransporter[8] [9]. Our data fit this picture loosely: eGFR fell as EASIX rose and moved in step with hearing thresholds. Because eGFR is itself computed from Cr, however, that correlation is partly built in, so this line of evidence offers only indirect support. LDH tells a similar story. Higher LDH usually signals cellular damage and metabolic stress, and the cochlea is a metabolically demanding organ that tolerates ischemia and hypoxia poorly [10]. In sudden sensorineural hearing loss (SSNHL), circulating inflammatory biomarkers such as CRP and TNF-α have been linked to both its diagnosis and prognosis [11]. Platelets complete the picture. Direct evidence linking platelet count to hearing loss is limited, yet markers of platelet activation such as mean platelet volume are elevated in vascular forms of hearing loss, particularly pan-frequency SSNHL. This raises the possibility that microthrombi contribute to cochlear microcirculatory failure, with platelet consumption reflected in the counts captured by EASIX [12]. Read together, these observations suggest EASIX is not a single-pathway marker. By capturing renal load (Cr), metabolic stress (LDH), and a tendency toward microthrombotic consumption (PLT) at the same time, it may give a broader read on the endothelial–microcirculatory risk that underlies hearing loss.

Several strengths deserve mention. The sample is large and nationally representative, and the complex sampling design and survey weights were incorporated into every analysis, which should support generalizability. To our knowledge this is also the first systematic examination of EASIX across different types of hearing loss; progressive adjustment in multiple models strengthened the results, and the dose–response and subgroup analyses add useful context for future research.

The limitations are equally important. Because the design is cross-sectional, causality cannot be inferred, and reverse causation is conceivable if hearing loss itself alters lifestyle in ways that shift EASIX components. Selection bias is another concern: roughly 76% of audiometric records were incomplete, and we did not restrict age, so the very wide age span limits extrapolation to any particular age group. We also lacked data on ototoxic drug use, occupational or environmental noise exposure, and family history of hearing loss, so residual confounding cannot be excluded. The many subgroup tests were not corrected for multiple comparisons, and some positive findings may reflect chance and should be read as exploratory. EASIX was measured only once, leaving its long-term dynamics unexamined. Its strongly right-skewed distribution, with few observations in the high range, also argues for caution when interpreting the upper segment of the threshold analysis. Because LDH, Cr, and PLT were not modeled separately, a single component driving the association cannot be ruled out. Finally, participants were mostly U.S. residents of non-Hispanic White origin, and

transferring these results to other racial or ethnic groups, regions, or healthcare systems requires care.

Future prospective cohort studies, Mendelian randomization studies, and basic experiments are needed to verify the causal relationship and to clarify the underlying pathophysiological mechanisms.

5. Conclusion

This study found that EASIX was significantly positively associated with hearing loss, particularly in participants without diabetes or hypertension. As a simple composite indicator integrating renal function, cellular damage/metabolic stress, and platelet consumption, EASIX may serve as a potential biomarker for endothelial dysfunction-related hearing loss. Future prospective cohort studies and basic experiments are still needed to further verify the causal relationship and elucidate the underlying pathophysiological mechanisms.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data are publicly available from the NHANES database (https://www.cdc.gov/nchs/nhanes/).

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