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Interaction between Noise Exposure and Phenotypic Age Acceleration in Hearing Loss: An NHANES Study

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Abstract: Hearing loss is a growing public health burden, and aging and occupational noise exposure are two major contributors. This cross-sectional study examined whether phenotypic age acceleration interacts with occupational noise exposure in relation to hearing loss. We included 2,014 adults from the National Health and Nutrition Examination Survey 2005–2010, representing 16,596,487 non-institutionalized U.S. adults after survey weighting. Hearing loss was defined as concordant objective audiometric impairment and self-reported hearing difficulty. Phenotypic age acceleration was derived from the residual of phenotypic age regressed on chronological age. After adjustment for sex, race, body mass index, diabetes, and hypertension, occupational noise exposure was associated with higher odds of hearing loss (OR = 2.35, 95% CI: 1.56–3.43; $p < 0.001$), as was accelerated phenotypic aging (OR = 2.05, 95% CI: 1.53–2.67; $p < 0.001$). These associations remained after additional adjustment for chronological age. In the weighted joint analysis, participants with both occupational noise exposure and accelerated phenotypic aging had the highest odds of hearing loss (OR = 5.51, 95% CI: 3.31–9.28). In an unweighted sensitivity analysis, the joint-exposure OR was 12.98 (95% CI: 6.10–27.60), with positive additive interaction indices (RERI = 7.79, AP = 0.60, SI = 2.90). Mediation analysis showed no significant indirect effect through phenotypic age acceleration (mediation proportion = 0.34%; $p = 0.19$). These findings suggest that occupational noise exposure and accelerated biological aging may jointly increase hearing loss risk.

Keywords: Phenotypic Age Acceleration; Noise; Hearing Loss; Interaction

1. Introduction

Issues related to hearing loss (HL) are a fast-growing public health issue. Also, it causes various socioeconomic problems. For instance, loss of good employment, reduced income, and lesser educational attainment [1–3]. It is also connected to a lower quality of life, including dementia risk. Hearing loss that is anatomically classified as conductive, sensorineural, or mixed is predominantly sensorineural globally. Changes brought on by ageing and

exposure to noise are major modifiable risk factors throughout life [4,5]. It is therefore necessary to study their cumulative panel effects on hear.

The progressive and multifactorial hearing impairment which occurs with age, known as presbycusis, is said to be caused by degeneration of cochlear hair cells, spiral ganglion neurons, stria vascularis and central auditory pathways. Consequently, sound detection as well as frequency discrimination gets impaired due to the occurrence of these structural and functional changes. Moreover, understanding speech also becomes hard, particularly in challenging listening conditions. Hearing loss due to noise, on the other hand, mainly refers to repeated or excessive exposure to sound causing mechanical and metabolic damage in the cochlea. Acoustic exposure usually affects first the high-frequency regions and can result in outer hair cell damage, synaptic dysfunction, oxidative stress, mitochondrial injury, inflammation, and irreversible elevation of the auditory threshold. Although traditionally considered diverse contributors to acquired hearing loss, there is now considerable evidence that age-related and noise-related hearing impairment share common biological pathways. This could include oxidative stress, chronic inflammation, mitochondrial dysfunction, microvascular impairment and apoptotic cochlear cell death. The common mechanisms open avenues to examine whether occupational noise exposure and accelerated biological aging contribute to shared hearing loss [6].

Both NIHL and presbycusis have been well-studied, but their interaction is not. Findings from a population study done in 2020 (n = 1213) indicate that noise exposure results in an acceleration of the onset of presbycusis by at least 20 years [7], a later study done with animals confirmed RAGE signaling [8]. Aging makes one vulnerable to NIHL [9], large epidemiological studies assessing noise induced acceleration of age-related hearing loss are rare. It is crucial to assess whether noise and aging have multiplicative, rather than merely additive, effects.

To cover this gap, we carried out systemic analyses of noise-aging-HL relationships using large cross-sectional datasets [10,11]. We used Phenotypic Age Acceleration (PhenoAgeAccel) as our aging measure. This is a novel composite biomarker that incorporates various physiological parameters to quantify biological aging. Our analysis sheds light on joint impacts of noise and biological age and which gives mechanistic insights into the multifactorial HL origin and targeted prevention. This article provides results that are original and not published elsewhere.

2. Materials and Methods

2.1. Study Population

The National Center for Health Statistics (NCHS) of the CDC conducts the NHANES survey using a multi-stage, stratified sampling technique to estimate the health and nutritional status of the civilian non-institutionalized population of the United States. We collected a dataset comprised of 85,750 participants from the consecutive cycles of NHANES 2005–2006, 2007–2008, and 2009–2010. We excluded participants with incomplete information on hearing, noise, PhenoAgeAccel, or covariates. Thus, the final sample size included 2,014 participants (**Figure 1**). The authorisation was given to obtain and analyse all data above. According to the NHANES dataset is publicly available and ethical approved. Complex design involves many sub-stages and probability samples. The analyses were weighted by surveys and they were carried out as per NHANES analytic guidelines. As 3 consecutive two-year cycles of data have been combined, 6-year weights have been constructed. A 6-year weight was obtained by dividing the corresponding two-year sample weight by 3. The NHANES strata variable SDMVSTRA and primary sampling unit variable SDMVPSU were used to specify the complex survey design. The combined sample weights, strata, and primary sampling units were utilized in weighted descriptive analyses and weighted logistic regression models.

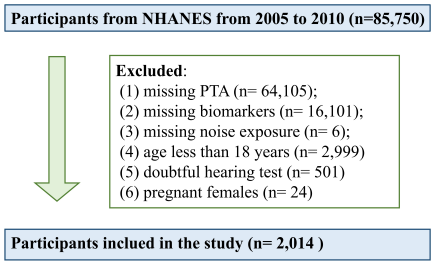

Figure 1. Research population inclusion and exclusion criteria.

All available cases were analysed. We excluded participants with missing data on audiometric assessment, phenotypic aging biomarkers, occupational noise exposure and covariates. The exclusion process is depicted in **Figure 1**. The reason for exclusion differed from participant to participant and did not permit a comparison of key variables. Furthermore, the underlying assumptions required for a reliable comparison are not met.

2.2. Audiometric Measurement

Trained examiners conducted audiometric measurement at mobile examination centre. The PTA of both ears was measured with Interacoustics Model AD226 Audiometer and TDH-49P headphones and Etymotic Ear Tone 3A insert earphones.

In this study, the primary outcome was defined as concordant hearing loss, which required both objective audiometric hearing loss and self-reported hearing difficulty. Objective hearing loss as measured in the audiometric testing was defined as a pure-tone average ≥20 dB at 0.5, 1, 2 and 4 kHz. The chosen speech-frequency PTA definition captures clinically relevant hearing impairment related to communication function, rather than a specific diagnosis of noise-induced hearing loss. A self-reported hearing difficulty was defined as response of "a little trouble," "moderate hearing trouble," "a lot of trouble," or "deaf" on the NHANES hearing questionnaire. Participants who had differing objective and subjective hearing status were excluded from the primary analysis. This definition was selected for its ability to improve outcome specificity and to define hearing loss which conveys effective dysfunction and associated physiological evidence.

2.3. Noise and PhenoAgeAccel

The occupational exposure to noise was assessed with the NHANES questionnaire item "Ever had job exposure to loud noise? Those who responded positively were deemed to have occupational noise exposure. Night-shift assignments were classified as "exposed." This indicator of self-reported lifetime occupational exposure was treated as a binary variable and not as a quantitative variable for noise intensity, duration, cumulative dose or frequency of exposure.

Using nine conventional clinical chemical biomarkers a measure of biological age namely PhenoAge was computed [12]. The formula to calculate PhenoAge is the following.

$$\text{PhenoAge} = 141.5 + \frac{\text{Ln}[-0.00553 \times \text{Ln}(1 - \text{risk})]}{0.09165}$$

where

$$\text{risk} = 1 - \exp\left(\frac{-1.51714 \times \exp(\text{xb})}{0.0076927}\right)$$

The coefficients and intercepts for the two prognostic models described above are $\beta 0 = -19.907$ and $\beta 0 + \beta d1$ for the first and second model, respectively, where $\beta d1$ is the coefficient of the interaction variable (e.g., body mass index) for the first and second model.

The derivation of PhenoAgeAccel followed a residual-based approach. The PhenoAge was regressed on Chronological age using a linear regression model, and the residual from this model was defined as PhenoAgeAccel. Consequently, phenoageaccel is the gap between the phenotypic age observed on an individual and the one predicted by age. We classified participants as either having accelerated phenotypic aging or not having accelerated phenotypic aging based on their PhenoAgeAccel results. Participants with PhenoAgeAccel > 0 were classified as having accelerated phenotypic aging, whereas those with PhenoAgeAccel ≤ 0 were classified as not having accelerated phenotypic aging. This classification of exposure as present or absent was utilized to create the joint exposure variable for the analysis of additive interaction.

2.4. Covariates

Variables such as chronological age, sex, race, BMI, diabetes, and hypertension were included as covariates. Race categories described Mexican American, Non-Hispanic White, Non-Hispanic Black, Other Hispanic, and other race. The World Health Organization (WHO) expert committee has classified BMI into two categories; ≤25 and >25 with reference (more on WHO standard can be found at https://www.who.int/zh/news-room/fact-sheets/detail/obesity-and-overweight. As per the answers in the questionnaire and a diagnosis of glycohemoglobin HbA1c

≥6.5(%), diabetes was diagnosed. Hypertension was defined based on questionnaire responses, blood pressure measurements, and use of antihypertensives.

2.5. Statistical Analysis

For the joint exposure analysis, we classified participants into four groups based on whether they had experienced exposure to occupational noise, accelerated phenotypic aging, neither exposure, exposure to occupational noise only, as well as to accelerated phenotypic aging only. Participants who were not exposed were used as reference. Survey-weighted logistic regression, which accounted for the NHANES sampling weights, strata, and primary sampling units, was used for the primary joint association analysis. Also, we performed an unweighted logistic regression model as a sensitivity analysis to estimate indices of additive interaction.

The relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP) and synergy index (SI) were used to assess additive interaction. These indices were calculated from the same unweighted logistic regression model as the reported unweighted odds ratios, using unrounded model-based estimates. The authors calculated the relative excess risk due to interaction (RERI), attributable proportion (AP) and synergy index (SI) using the following formulae: RERI = OR11 − OR10 − OR01 + 1; AP = RERI/OR11; and SI = (OR11 − 1)/[(OR10 − 1) + (OR01 − 1)], where: OR11 = both occupational noise exposure and accelerated phenotypic aging; OR10 = accelerated phenotypic aging only; and OR01 = occupational noise exposure only. The delta method, which relies on the variance-covariance matrix generated from the fitted model, was used to estimate the 95% confidence intervals for the RERI, AP, and SI measures.

The means and standard deviations (SDs) of continuous variables were determined and compared by *t*-test among groups. The categorical variables were described in weighted percentages, and the difference among the groups was assessed by chi-square. HL's PhenoAgeAccel and noise were investigated with logistic regression analysis. PhenoAgeAccel measures biological aging. Using NHANES data, we analyzed different indicators of additive interaction of noise and aging for HL, including relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (SI). If the confidence interval of RERI and AP contains 0 and the confidence interval of S contains 1 that shows no additive interaction. Since the additive interaction indices were obtained using logistic regression analysis, RERI, AP and SI should be seen as odds-based interaction measures.

An exploratory mediation analysis was conducted on whether PhenoAgeAccel statistically mediated the relationship between exposure to occupational noise and concordant hearing loss. We treated occupational noise exposure as the exposure, PhenoAgeAccel as the mediator and concordant hearing loss as the outcome. The model for mediation was adjusted for the sex, race, BMI, diabetes and hypertension. Survey weights were not included in the mediation analysis. The confidence intervals were estimated at the 95% level using bootstrap sampling with 500 repetitions. Since all variables are cross-sectionally measured, the mediation analysis will be exploratory and not interpreted as causal mediation evidence. All analyses were performed using R software, with a two-sided *p*-value less than 0.05 considered statistically significant.

3. Results

3.1. Basic Characteristics

The final analytic sample included 2,014 eligible participants from three consecutive NHANES cycles between 2005 and 2010, including 1,281 participants without concordant hearing loss and 733 participants with concordant hearing loss. After application of survey weights, the analytic sample represented 16,596,487 non-institutionalized U.S. adults. Baseline characteristics according to hearing loss status are shown in **Table 1**.

Table 1. The baseline information of the subjects.

Variable	Control (n = 1281)	HL (n = 733)	*p* Value
Age, year	39.18 (1.64)	77.04 (0.25)	<0.001
PhenoAge	34.39 (1.59)	76.07 (0.35)	<0.001
PhenoAgeAccel			<0.001
no	1,059 (82.67)	434 (59.21)	
yes	222 (17.33)	299 (40.79)	
Noise exposure history			<0.001
no	1,059 (82.67)	400 (54.57)	

Table 1. *Cont.*

Variable	Control (n = 1281)	HL (n = 733)	*p* Value
yes	222 (17.33)	333 (45.43)	
Sex			0.09
female	649 (50.66)	294 (40.11)	
male	632 (49.34)	439 (59.89)	
Race			<0.001
mexican American	287 (22.40)	63 (8.59)	
non-Hispanic Black	355 (27.71)	63 (8.59)	
non-Hispanic White	493 (38.49)	571 (77.90)	
other Hispanic	85 (6.64)	18 (2.46)	
other Race	61 (4.76)	18 (2.46)	
BMI, kg/m^2			<0.001
less than or equal to 25	615 (48.01)	215 (29.33)	
more than 25	645 (50.35)	498 (67.94)	
missing	21 (1.64)	20 (2.73)	
Diabetes			<0.001
no	1,190 (92.90)	546 (74.49)	
yes	91 (7.10)	187 (25.51)	
Hypertension			<0.001
no	936 (73.07)	204 (27.83)	
yes	345 (26.93)	529 (72.17)	
Hearing aid			<0.001
no	1,279 (99.84)	452 (61.66)	
yes	2 (0.16)	281 (38.34)	

Note: Values are presented as unweighted numbers and weighted percentages unless otherwise indicated. The unit of age is years, and the unit of BMI is kg/m^2. A *p*-value of less than 0.05 is considered statistically significant. Control (n = 1,281) means 1,281 individuals without hearing loss, while HL (n = 733) means 733 individuals with hearing loss. Abbreviations: HL, Hearing loss; PhenoAge, Phenotypic age; PhenoAgeAccel, Phenotypic age acceleration.

Participants with concordant hearing loss were substantially older than those without concordant hearing loss, with a mean age of 77.04 years compared with 39.18 years in the control group ($p < 0.001$). The hearing loss group also had a higher mean PhenoAge than the control group (76.07 vs. 34.39 years, $p < 0.001$). Accelerated phenotypic aging was more frequent among participants with concordant hearing loss than among controls (40.79% vs. 17.33%, $p < 0.001$). Similarly, a history of occupational noise exposure was reported more often in the hearing loss group than in the control group (45.43% vs. 17.33%, $p < 0.001$).

Differences were also observed in demographic and cardiometabolic characteristics. Male participants accounted for 59.89% of the hearing loss group and 49.34% of the control group, although the sex distribution did not reach statistical significance ($p = 0.09$). Non-Hispanic White participants were more common among those with concordant hearing loss than among controls (77.90% vs. 38.49%, $p < 0.001$). Participants with concordant hearing loss were also more likely to have a BMI greater than 25 kg/m^2 (67.94% vs. 50.35%, $p < 0.001$), diabetes (25.51% vs. 7.10%, $p < 0.001$), and hypertension (72.17% vs. 26.93%, $p < 0.001$). Hearing aid use was also more frequently reported in the hearing loss group than in the control group (38.34% vs. 0.16%, $p < 0.001$). Overall, these baseline findings indicate that concordant hearing loss was associated with older chronological age, higher biological aging burden, more frequent occupational noise exposure, and a greater prevalence of cardiometabolic comorbidities.

3.2. Association of Aging and Noise for HL

To assess the independent associations of occupational noise exposure and accelerated phenotypic aging with concordant hearing loss (see **Table 2**), weighted logistic regression was used. In the unadjusted analysis, the odds of concordant hearing loss was significantly higher in individuals with occupational noise exposure compared with people without occupational noise exposure (OR = 3.25, 95% CI: 2.37–4.47; $p < 0.001$). Likewise, participants showing accelerated signs of aging had increased risk of concordant hearing loss compared to those without such accelerated aging (OR = 3.17, 95% CI: 2.59–3.89; $p < 0.001$). Results suggested that concordant (B) hearing loss had a strong relationship with accelerated phenotypic aging and occupational noise exposure before covariate adjustment.

After adjusting for sex, race, BMI, diabetes and hypertension, both associations were attenuated but remained significant. The odds of finding concordant hearing loss—i.e., finding a loss at both the 3 kHz and 6 kHz frequencies—are more than 2-fold higher (OR = 2.35, 95% CI: 1.56–3.43; $p < 0.001$) in those exposed to occupational noise. Accelerated phenotypic aging was also independently associated with higher odds (OR = 2.05, 95% CI: 1.53–2.67; $p <$

0.001) of finding that same concordance. To address the possible confounding effect of chronological age, we conducted an additional model with further adjustment for chronological age. The findings were essentially the same. The association between occupational noise exposure and hearing loss remained (OR = 2.21, 95% CI: 1.56–3.57; $p < 0.001$). Likewise, the association between accelerated phenotypic aging and hearing loss remained (OR = 2.03, 95% CI: 1.47–2.59; $p < 0.001$). Our findings imply that both occupational noise exposure and accelerated phenotypic aging are independently related to concordant hearing loss, by themselves though enhances hearing loss further not too much by age.

Table 2. The association between noise and aging by logistic regression.

Noise and Aging	Crude Model		Model 1		Model 2	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Noise						
no	Ref.		Ref.		Ref.	
yes	3.25 (2.37, 4.47)	<0.001	2.35 (1.56, 3.43)	<0.001	2.21 (1.56, 3.57)	<0.001
Aging						
no	Ref.		Ref.		Ref.	
yes	3.17 (2.59, 3.89)	<0.001	2.05 (1.53, 2.67)	<0.001	2.03 (1.47, 2.59)	<0.001

Note: Model 1 was adjusted for sex, race, BMI, diabetes, and hypertension. Model 2 was additionally adjusted for chronological age. For each exposure variable, participants without occupational noise exposure or without accelerated phenotypic aging were used as the reference group. A two-sided *p* value < 0.05 was considered statistically significant.

3.3. Subgroup Analysis of the Association of Aging and Noise for HL

Exploratory subgroup analyses were performed to evaluate whether the associations of occupational noise exposure and accelerated phenotypic aging with concordant hearing loss were consistent across sex, race, BMI, diabetes, and hypertension strata (**Table 3**). In sex-stratified analyses, occupational noise exposure was significantly associated with concordant hearing loss among males (OR = 2.67, 95% CI: 1.79–3.95; $p < 0.001$), but not among females (OR = 1.35, 95% CI: 0.74–2.37; $p = 0.33$). A similar pattern was observed for accelerated phenotypic aging, which was significantly associated with concordant hearing loss among males (OR = 2.65, 95% CI: 1.69–4.11; $p < 0.001$), whereas the association among females did not reach statistical significance (OR = 1.46, 95% CI: 0.91–2.32; $p = 0.12$).

Table 3. Subgroup analysis for the association of HL with noise and aging.

Variables	Noise		Aging	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Sex				
female	1.35 (0.74, 2.37)	0.33	1.46 (0.91, 2.32)	0.12
male	2.67 (1.79, 3.95)	<0.001	2.65 (1.69, 4.11)	<0.001
Race				
non-Hispanic Black	1.74 (0.74, 4.03)	0.2	3.51 (1.63, 7.51)	0.001
non-Hispanic White	2.31 (1.59, 3.44)	<0.001	2.12 (1.34, 3.11)	<0.001
mexican American	2.27 (0.88, 5.89)	0.09	1.27 (0.49, 3.32)	0.63
other Hispanic	4.11 (0.10, 173)	0.46	0 (0.00, 18.00)	0.87
other Race	1.02 (0.15, 6.82)	0.98	0.9 (0.14, 5.80)	0.91
BMI				
less than or equal to 25	1.19 (0.66, 2.16)	0.57	2.27 (1.27, 4.07)	0.01
more than 25	2.64 (1.80, 3.86)	<0.001	1.93 (1.32, 2.81)	<0.001
Diabetes				
no	2.43 (1.70, 3.48)	<0.001	2.42 (1.67, 3.51)	<0.001
yes	1.22 (0.59, 2.52)	0.58	1.08 (0.58, 2.02)	0.8
Hypertension				
no	2.1 (1.24, 3.54)	0.01	2.18 (1.21, 3.93)	0.01
yes	1.93 (1.29, 2.89)	0.002	1.89 (1.30, 2.75)	<0.001

Note: The model was adjusted by all covariates except itself.

Across racial subgroups, occupational noise exposure was significantly associated with concordant hearing loss among non-Hispanic White participants (OR = 2.31, 95% CI: 1.59–3.44; $p < 0.001$), while the estimates were not statistically significant among non-Hispanic Black participants, Mexican American participants, other Hispanic participants, or participants of other races. Accelerated phenotypic aging was significantly associated with concordant hearing loss among non-Hispanic Black participants (OR = 3.51, 95% CI: 1.63–7.51; $p = 0.001$) and non-Hispanic

White participants (OR = 2.12, 95% CI: 1.34–3.11; $p < 0.001$), but not in the other racial subgroups.

In BMI-stratified analyses, occupational noise exposure was significantly associated with concordant hearing loss among participants with BMI >25 kg/m^2 (OR = 2.64, 95% CI: 1.80–3.86; $p < 0.001$), but not among participants with BMI ≤25 kg/m^2 (OR = 1.19, 95% CI: 0.66–2.16; $p = 0.57$). In contrast, accelerated phenotypic aging was associated with concordant hearing loss in both BMI categories, with ORs of 2.27 (95% CI: 1.27–4.07; $p = 0.01$) among participants with BMI ≤25 kg/m^2 and 1.93 (95% CI: 1.32–2.81; $p < 0.001$) among those with BMI >25 kg/m^2.

When stratified by diabetes status, occupational noise exposure and accelerated phenotypic aging were both significantly associated with concordant hearing loss among participants without diabetes. The corresponding ORs were 2.43 (95% CI: 1.70–3.48; $p < 0.001$) for occupational noise exposure and 2.42 (95% CI: 1.67–3.51; $p < 0.001$) for accelerated phenotypic aging. However, neither association was statistically significant among participants with diabetes. In analyses stratified by hypertension status, both occupational noise exposure and accelerated phenotypic aging were significantly associated with concordant hearing loss regardless of hypertension status. Among participants without hypertension, the ORs were 2.10 (95% CI: 1.24–3.54; $p = 0.01$) for occupational noise exposure and 2.18 (95% CI: 1.21–3.93; $p = 0.01$) for accelerated phenotypic aging. Among participants with hypertension, the corresponding ORs were 1.93 (95% CI: 1.29–2.89; $p = 0.002$) and 1.89 (95% CI: 1.30–2.75; $p < 0.001$), respectively.

Overall, these exploratory subgroup analyses showed that the positive associations of occupational noise exposure and accelerated phenotypic aging with concordant hearing loss were generally observed across several participant subgroups, particularly among males, non-Hispanic White participants, participants with BMI > 25 kg/m^2, participants without diabetes, and participants with or without hypertension. However, some subgroup estimates were imprecise, especially in racial subgroups with small sample sizes, as reflected by wide confidence intervals. Therefore, these findings should be interpreted as exploratory and hypothesis-generating rather than as definitive evidence of effect modification.

3.4. Interaction Effects of Noise and Aging for HL

In the survey-weighted joint association analysis, the participants were characterized in four groups according to occupational noise exposure and accelerated phenotypic aging status. Reference was the group of participants without both exposures. There was only a greater odds of concordant hearing loss (OR = 2.02, 95% CI: 1.40–2.92) in reference group participants with accelerated phenotypic aging than those without. There was also a greater odds of concordant hearing loss (OR = 2.15, 95% CI: 1.49–3.08) in participants with only occupational noise exposure. Importantly, those who had occupational noises as well as phenotypic aging accelerated had the maximum odds of concordant hearing loss (OR = 5.51; 95% CI: 3.31–9.28). This implies that the presence of both factors was linked with a higher burden of hearing loss.

A logistic regression model was run without weights to check for additive interaction as a sensitivity analysis (**Table 4**). Using this unweighted model, the odds ratios were 3.01 (95% CI: 1.35–4.52) for phenotypic accelerated aging only, 3.19 (95% CI: 1.38–4.67) for only occupational noise exposure, and 12.98 (95% CI: 6.10–27.60) in the case of participants suffering both. The additive interaction indices derived from the same unweighted model indicated a positive interaction between occupational noise exposure and accelerated phenotypic aging on the odds scale. The RERI was 7.79 (95% CI: 3.15–12.44) indicating excess odds beyond the sum of the individual exposure associations. The AP was 0.60 (95% CI: 0.45–0.76), indicating that approximately 60% of the odds among those with both exposures was due to an interaction on the odds scale. The SI was 2.90 (95% CI: 1.87–4.49) supporting a positive additive pattern. The results suggest that occupational noise exposure and accelerated phenotypic aging may contribute to concordant hearing loss in conjunction with each other. However, estimates from the interactions should be interpreted with caution since these came from unweighted logistic regression sensitivity analysis.

Table 4. Joint association and interaction analysis.

Noise and Aging	Weighted Model	Unweighted Model	Unweighted Interaction Analysis		
	OR (95% CI)	OR (95% CI)	RERI (95% CI)	AP (95% CI)	SI (95% CI)
none	Ref.	Ref.	-	-	-
only aging	2.02 (1.40, 2.92)	3.01 (1.35, 4.52)	-	-	-
only noise	2.15 (1.49, 3.08)	3.19 (1.38, 4.67)	-	-	-

Table 4. *Cont.*

Noise and Aging	Weighted Model	Unweighted Model	Unweighted Interaction Analysis		
	OR (95% CI)	OR (95% CI)	RERI (95% CI)	AP (95% CI)	SI (95% CI)
both	5.51 (3.31, 9.28)	12.98 (6.10, 27.60)	7.79 (3.15, 12.44)	0.60 (0.45, 0.76)	2.90 (1.87, 4.49)

Note: Participants without occupational noise exposure and without accelerated phenotypic aging were used as the reference group. The survey-weighted model incorporated NHANES sampling weights, strata, and primary sampling units. The unweighted logistic regression model was additionally performed as a sensitivity analysis. RERI, AP, and SI were calculated from the same unweighted logistic regression model as the displayed unweighted odds ratios, using unrounded model-based estimates. Models were adjusted for sex, race, BMI, diabetes, and hypertension.

3.5. The Association between Noise and Aging

In order to determine if PhenoAgeAccel statistically mediated the relationship between occupational noise exposure and concordant hearing loss, we examined the association between occupational noise exposure and accelerated phenotypic ageing first. Following the adjustment for sex, race, body mass index (BMI), diabetes, and hypertension, there was no significant association between occupational noise exposure and accelerated phenotypic aging (odds ratio OR = 1.13; 95% CI: 0.87–1.47; $p = 0.376$) (**Table 5**). Exploratory mediation analysis showed that the indirect effect of occupational noise on hearing concordance via PhenoAgeAccel was not significant (mediation proportion = 0.34%; $p = 0.19$) (**Figure 2**). Due to occupational noise exposure, PhenoAgeAccel, and concordant hearing loss were measured cross-sectionally, this should only be interpreted as no statistical evidence for mediation in the current dataset and not as conclusive evidence against a potential mediating role by biological ageing.

Table 5. The association between noise and aging.

Noise	Crude Model		Adjusted Model	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
no	ref		ref	
yes	1.73 (1.40, 2.13)	<0.001	1.13 (0.87, 1.47)	0.376

Note: Model was adjusted by covariates including sex, race, BMI, diabetes, and hypertension.

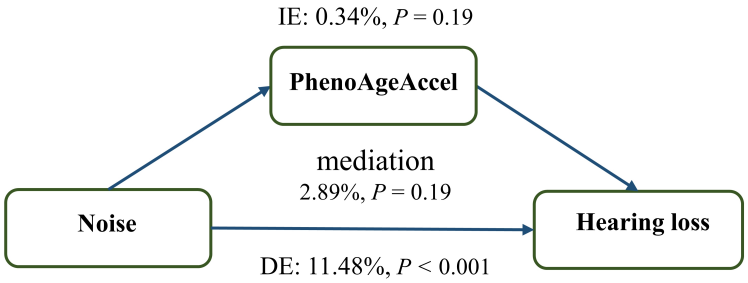

Figure 2. Mediation analysis between noise exposure and hearing loss.

4. Discussion

The main causes of sensorineural hearing loss (SNHL) are aging and noise. Noise exposure is the most common preventable cause. The aging process is heterogeneous and complex, characterized by impaired sensing of nutrients; inflammation; dysbiosis; telomere shortening. Our study offers unprecedented systematic evidence that exposure to noise and aging interact synergistically in the case of hearing damage. Research conjoined with sonic effects suggests conventional estimates have severely underplayed the irreversible damage caused by noise to hearing. Hence, noise-reduction techniques may actually do a much better job at hearing preservation than expected.

Although aging is a biological process that cannot be altered, there is substantial evidence that modifiable factors may accelerate or decelerate it [13–15]. Our results show that delaying biological aging may reduce its interactions with noise exposure, which has therapeutic value. This is particularly pertinent to groups of workers who have no choice but to be exposed to noise, like workers employed in noisy settings like entertainment and manufacturing. To protect these individuals' hearing, the plan must include the following: 1) maximum noise control measures, 2) physiological stress reduction, and 3) antioxidant-rich diet and lifestyle [16,17].

The pathophysiological relationship between noise and aging involves several mechanisms. Inflammatory cascades likely represent a shared mechanism in noise-induced and age-related neuronal damage and hearing loss according to evidence [18, 19]. The localized release of inflammatory mediators and infiltration of immune cells initiate cochlear inflammation rapidly following acoustic trauma [20]. Simultaneously, inflammation in the elderly is associated with changes to macrophage morphology and density within the cochlea affected by presbycusis [21]. Another important converging mechanism is oxidative stress. The exposure to noise causes an acute overproduction of reactive oxygen species (ROS). This reaches a peak around 7–10 days after the noise exposure and then gradually declines. This finding indicates a potential therapeutic window [22]. The antioxidant capacity decreases with age and this, together with cochlear microvascular insufficiency, further increases the production of ROS. The signaling of downstream ROS propagates inflammatory as well as apoptotic disintegration pathways creating a cycle of pathology that self-propagates. We propose that noise exposure leads to inflammatory and oxidative damage in the aged cochlea, resulting in cumulative compound injury.

Recent studies show that exposure to noise may accelerate biological ageing [23], this is consistent with our univariate tests. Thus, we hypothesized noise might mediate hearing loss through aging. An exploratory mediation analysis was conducted to determine whether PhenoAgeAccel mediated the association between occupational noise and concordant hearing loss. There was no statistically significant indirect effect. However, we could not establish temporal ordering because occupational noise exposure, PhenoAgeAccel, and hearing loss was measured at one-time point. Hence, this result should be interpreted only as a lack of statistical evidence for mediation in this cross-sectional dataset, rather than as evidence that biological aging may not mediate the relationship.

Based on exploratory subgroup analyses, the connection between occupational exposure to noise and accelerated phenotypic aging with concordant hearing loss may differ according to participant characteristics like in males. This is consistent with established epidemiological data that show male predominance [24] or increased severity [25] in NIHL and ARHL. Nevertheless, numerous subgroup estimates relied on small sample sizes and warrant careful interpretation. As a result, we drew no strong subgroup-specific conclusions, and larger studies are needed to evaluate potential effect modification by sex, race and other demographic factors.

Objective hearing loss, defined as PTA frequencies, may have limited sensitivity for early noise-related auditory damage. We measured objective hearing loss by calculating the average threshold measured at these frequencies: 0.5, 1, 2 and 4 kHz. This tests for speech-frequency hearing loss and is likely to be relevant to the communication-related burden of hearing loss. Nevertheless, the initial effect of noise-induced hearing loss is in the higher frequencies, 3, 4 and 6 kHz. As a result, we may underestimate the early or typical high-frequency NIHL. Future studies should consider the evaluation of low/mid and high-frequency PTA patterns separately.

While this study shows an interaction between noise exposure and aging, certain limitations should be noted. To begin with, complete-case design might have introduced selection bias. A large number of participants were missing audiometric data, biological aging biomarkers, occupational noise exposure or covariates. Due to heterogeneous exclusions and the absence of several key variables among the excluded participants, we could not perform a fully comparable baseline analysis between included and excluded participants. As a result, the final analytic sample may vary from the initial NHANES population, warranting caution in interpretation of the results. Second, due to the cross-sectional design, causal inference is impossible, so longitudinal verification is needed. Future investigations will involve conducting targeted cohort studies with independent data collection to further inform noise-aging interactions in acquired SNHL. Additionally, due to limitations of our database, it was not possible for us to accurately categorize the cause of hearing loss 30. There is strong epidemiologic evidence however that NIHL and ARHL are the most common forms [26]. The definition of outcome may have inflicted selection bias. Our primary outcome was defined as concordant hearing loss, requiring objective audiometric impairment (i.e., hearing loss on audiometry) as well as self-reported difficulty (i.e., any trouble hearing). A more stringent definition may increase specificity and capture clinically meaningful hearing impairment, however, this may reduce sensitivity and exclude participants with discordant subjective-objective hearing status. The perception of hearing subjects may be influenced by education, occupation, cognition, health awareness and so on. Consequently, we believe that our results should be considered more applicable to concordant, clinically significant hearing loss than all audiometric hearing loss. Also, exposure to noise was assessed with a single self-report questionnaire item on lifetime occupational loud-noise exposure. The binary measure failed to consider intensity, duration, frequency, cumulative dose, time since exposure, use of hearing protection, occupation, and recreational noise exposure. Hence, we might have

had exposure misclassification, and we could not study dose response or duration response. Consequently, we interpret occupational noise exposure as a crude measure of prior exposure to loud noises rather than an accurate measure of noise burden. There is a need for future research using quantitative assessments of noise exposure with information on occupational and recreational exposure. To create the combined exposure variable and estimate the additive interaction indices, PhenoAgeAccel was divided into two groups: >0 and ≤0. Though this method is epidemiologically interpretable, it may have led to information loss and may not investigate dose-response or nonlinear associations between biological aging and hearing loss. Future research should estimate PhenoAgeAccel as a continuous variable, by quantiles, and flexible modeling such as restricted cubic splines. Odds ratios from logistic regression were used to estimate indices. Because hearing loss was relatively common, odds ratios might not equal risk ratios and thus, RERI, AP and SI based on the odds ratio might overestimate additive interaction on the risk scale. Thus, one should interpret these indices as odds-based measures rather than direct estimators of risk-ratio or risk-difference based interaction. The verification of these findings with log-binomial regression, Poisson regression with robust variance or marginal standardization in future studies may be important. Subgroup analyses should be interpreted cautiously. Some strata groups had small sample sizes, which may have resulted in unstable estimates and wide confidence intervals. Hence, subgroup findings are exploratory and hypothesis-generating. We did not reach a conclusion suggesting a sex-specific additive interaction because the re-analysis did not provide formal sex-interaction testing, nor complete sex-stratified joint ORs, RERIs, APs, SIs or sample size estimates.

5. Conclusion

Individuals exposed to occupational noise and those with accelerated phenotypic aging had increased likelihood of consistent hearing loss. Findings from odds-based additive interaction analyses pointed to a possible positive interaction, but caution is advised in interpreting this result as OR-based interaction indices may exaggerate risk-scale interaction when the outcome is common.

Author Contributions

Resources, validation, project administration, supervision, conceptualization, writing—review and editing, T.L. and X.Y.; writing—original draft, methodology, software, formal analysis, investigation, data curation, J.D., S.X., C.W., and C.Z.; investigation, visualization, X.Y. and J.D. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement

The participants provided their written informed consent to participate in this study.

Data Availability Statement

All data used in the study can be obtained from the public database National Health and Nutrition Examination Survey (NHANES).

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AI Use Statement

No artificial intelligence tools were used in the design, data analysis, writing, or figure generation of this manuscript. The authors assume full responsibility for the accuracy and integrity of all content.

Abbreviations

Abbreviation	Full Name
AP	Attributable Proportion
CI	Confidence Interval
HL	Hearing Loss
NHANES	National Health and Nutrition Examination Survey
NIHL	Noise-Induced Hearing Loss
OR	Odds Ratio
PhenoAgeAccel	Phenotypic Age Acceleration
PTA	Pure-Tone Audiometry
RERI	Relative Excess Risk Due to Interaction
SI	Synergy Index
SNHL	Sensorineural Hearing Loss

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