METALS, NOISE, DIET, AND HEARING LOSS

By

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ABSTRACT

Hearing loss is one of the most common chronic health disabilities experienced by older adults, and the prevalence of hearing loss tends to increase dramatically with advancing age. Therefore, identification of modifiable risk factors as well as protective factors is important to lessening the burden of disease associated with hearing loss.

The overall aims of this thesis are to assess the impact on hearing loss in the general population of occupational noise exposure, one of the most important known risk factors, and to also assess the potential impacts of exposure to cadmium and lead. This thesis also aimed to assess the potential protective effect of dietary intake, and to investigate whether those dietary intakes lower susceptibility for risk factors on hearing loss.

We examined over 3,500 adults of 20 to 69 years of age from the National Health and Nutrition Examination Survey (NHANES) 1999-2004. Our results support the hypothesis that occupational noise exposure increases the risk of hearing loss across various occupations, after controlling for potential confounding factors. Utilization of an occupational noise exposure assessment tool using the Occupational Information Network (O*NET) database allowed us to perform epidemiologic studies of occupational noise exposure in the general population. Our results also support the hypothesis that environmental cadmium and lead exposures increase the risk of hearing loss among

adults, particularly those less exposed to noise. Moreover, we found that higher intake of β-carotene, calcium, and an antioxidant composite of β-carotene plus vitamin C reduces the risk of hearing loss, and that higher antioxidant intake acts in synergy in combination with higher calcium and/or magnesium intake to reduce the risk of hearing loss. In particular, those dietary intakes were observed to lower individual susceptibility to the impact of noise on hearing loss, but not likely to affect susceptibility to cadmium and lead exposure in human population.

Overall, this thesis provides evidence of the hazardous effects of noise and heavy metals exposures and the protective effect of dietary intake on hearing loss in the general population. Our findings provide preliminary evidence for public health strategies for the prevention and therapeutic treatment of hearing loss.

CHAPTER I.

Introduction

1. Hearing Loss

Hearing loss is one of the leading chronic health disabilities experienced by older adults.[1] More than 35 million Americans 18 years and older suffer from hearing loss, and the number of people with hearing loss increased dramatically with advancing age.[2]

Hearing loss affects communication ability, thereby it is associated with social isolation, educational opportunities, and job productivity, as well as economic success; [3, 4]; besides the cost of medical treatment or hearing aids, the hearing impaired person are likely to be low income or unemployed (Average loss of income from underemployment per hearing impaired person was $9,741 in 1999 in US economy [5].)

In addition to aging, environmental factors such as noise and ambient ototoxic chemicals are important determinants of hearing loss, and a growing prevalence of those environmental factors tends to promote the incidence of hearing loss. Therefore, identification of both novel risk factors, particularly those that are preventable, and protective factors, those that may beneficially interact with traditional risks, is important.

2. Noise and Hearing Loss

Noise is one of the most important risk factor of hearing loss including acute trauma and chronic exposure. Recent reviews report that noise exposure increases mitochondrial activity and free radical formation, reduces cochlear blood flow, causes excitotoxic neural swelling, and induces both necrotic and apoptotic cell death in the organ of Corti in inner ear [6-9]. While hearing loss could occur purely by noise induction, it usually occurs from a combination of different factors.

Occupational noise exposure has been associated with hearing loss, especially among workers with high noise exposure levels.[10-14] Approximately 16% of hearing impairment worldwide is attributed to occupational noise.[10, 15, 16] In the U.S., about 5-30 million workers are exposed to noise levels at work that put them at risk of hearing loss.[17] Although previous epidemiologic studies have consistently shown a positive association between occupational noise exposure and hearing loss, few studies have been able to measure cumulative personal noise exposure in the general population. Several studies conducted in the U.S. and Europe reported an association between estimated-noise exposure and hearing loss [11, 15, 18], using job-exposure matrix (JEM) of occupation and/or industry classifications. However, such studies are limited to occupations and industries with high noise exposures, which preclude studies of the health effect of occupational noise exposure in the general population.

3. Heavy Metals and Hearing loss

Cadmium and lead are known risk factors for hearing loss. Experimental studies suggested that cadmium and lead exposures also are associated with free radical formation, which result in hearing loss [19-24]. Lead exposure, even at low levels, induces degeneration in the inner ear receptor cells and latency in auditory nerve conduction velocity [19-22]; cadmium exposure causes apoptosis and destroyed arrangement in inner ear receptor cells causing an elevation of auditory thresholds [23, 24].

Although present environmental cadmium and lead levels have no known adverse health consequence, long-term environmental exposures or past high level exposure experiences are still in a significant public health concern [25].

In the general population, the primary sources of cadmium exposure are cigarette smoke, contaminated food intake (shellfish, offal, vegetables), and ambient air particularly in urban areas, occupational settings, and contaminated agricultural region [26]. Primary historical sources of lead exposure (gasoline, solder, paint) have been phased out and environmental lead exposure has decreased considerably in the U.S. [27, 28]. However, environmental exposure to low levels of both metals is widespread [27, 29], and they accumulate in the body resulting in chronic disease [28, 30, 31], in part, likely contributing to inducing hearing loss, in general population.

Nevertheless, no epidemiologic research has been conducted on cadmium. Epidemiologic researches of lead have been limited on occupationally high exposed workers [32-34] and relatively vulnerable children and youth [35, 36]. One recent study has reported an association with lead in elderly men [4]; many studies, however, have been limited by the difficulty in controlling traditionally important risk factors including

noise exposure, in assessing the association between low level lead and cadmium exposures and hearing loss.

4. Diet and Hearing loss

The major clinical issue of whether diet could affect hearing loss came with the knowledge that noise-stress-induced metabolic activity , which in turn induces free radicals formation in inner ear is a key mechanism in hearing loss [9, 37-40]. This new understanding indicates antioxidants may be effective to prevent noise-induced hearing loss. In fact, animal experiments observed that antioxidants of β-carotene (metabolized to vitamin A in vivo), vitamin C and E respectively reduce free radicals formation and have therapeutic effect on hearing loss [37, 39, 41-47].

Despite the theoretical and biological evidences, the associations of dietary β-carotene, vitamin C and E with hearing loss were inconsistent in human-based epidemiologic studies [48-52]. A recent animal study indicates that although neither those antioxidants nor magnesium agent individually may have reliable reduction on hearing loss, together these antioxidants the mineral magnesium may act in synergistically to effectively prevent hearing loss [53]. One effect of magnesium is to reduce noise–induced vasoconstriction that occurs with free radical formation [9, 54-56]. Interestingly, calcium intake may act similarly to prevent hearing loss, with combined intakes of antioxidants, because excess calcium at in inner ear hair cells surface also is known to protect hearing loss by antibiotics [57-60]. A human case study, however, did not observe that, calcium supplementation protects against hearing loss [61].

5. Overall Aims

The overall aims of this thesis are to identify novel risk factors and potential protective factors that modulate hearing loss, thereby providing preliminary results for public health strategies to effectively prevent or delay hearing loss

The first study of this thesis introduced a quantitative occupational noise exposure assessment tool using the Occupational Information Network (O*NET) database and evaluated its applicability for epidemiologic research using data from the National Health and Nutrition Examination Survey (NHANES) 1999-2004 in the general US population.

The primary purpose of the second study of this thesis is to explore the effect of environmental cadmium and lead exposure on hearing loss in the U.S. general population, while controlling for noise exposure and other major factors contributing to hearing loss. Furthermore, the second study investigates their interactive effect of cadmium and lead exposure with noise exposure on hearing loss.

The aims of third study of this thesis is to identify whether higher intakes of dietary antioxidants (β-carotene, vitamins C and E), calcium and magnesium, and their combinations are beneficially associated with attenuation in hearing loss among adults.

The fourth study of this thesis hypothesized that higher intakes of dietary antioxidants, calcium and magnesium would reduce individual susceptibility to noise-, cadmium-, and lead-induced hearing impairment.

6. Thesis Overview

This thesis identified potential risk factors on hearing loss in Chapter II and III, and protective factors on hearing loss in Chapter IV, and the implications of these finding (Chapter II and III) for public health policy, Chapter IV.

Figure I-1 shows the overview of this thesis. In Chapter II, this thesis defines occupation noise exposure as one of the most important risk factors. In Chapter III, this thesis identifies cadmium and lead exposures as risk factors and their interaction with noise exposure, as identified in Chapter II. In Chapter IV, dietary intakes of antioxidants, calcium, and magnesium, potential protective factors, are reported. Finally, given inevitable noise and metals exposures of Chapter II and III, Chapter V investigated how and how dietary intake factors of Chapter IV affect susceptibility for those exposures on hearing loss in human population.

Table I-1 presents the list of variables that used in this thesis.

Variables	Unit	Description
Interest		
Occupational Noise	.	O*NET score: 1 < Noise scale < 5
Cadmium	µg/L	Blood cadmium level
Lead	µg/dL	Blood lead level
Diet *(β-carotene, vitamins C and E, calcium and magnesium)*	Mg	24-hour dietary recall
Antioxidants composite score	.	Sum of percentile rank scores of each antioxidant: β-carotene and vitamin C (and vitamin E)
Outcome		
Hearing Thresholds	dB	.
Hearing Loss	Y/N	Hearing Thresholds > 25 dB
Noise Notch	Y/N	Hearing threshold at 3,4, and/or 6 kHz is at least 10 dB greater than at 1 or 2 kHz and at least 10 dB greater than at 6 or 8 kHz
Covariates		
Age	year	.
BMI	Kg/m^2	Body mass index
Sex	.	Male/Female
Race ethnicity	.	Non-Hispanic White Non-Hispanic Black Mexican American Other
Education	.	< High School High School > High School
Ototoxic medication	Y/N	Medications of aminoglycoside, loop diuretics, antineoplastic drugs, or nonsteroidal anti-inflammatory drugs
Smoking pack-years	.	Never <20 ≥20
Hypertension	Y/N	Self-reported physician diagnosis, use of antihypertensive medication, systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90 mm Hg at the time of examination
Diabetes mellitus	Y/N	Self-reported either previous physician diagnosis or use of antihyperglycemic medication
Firearm noise	Y/N	Ever been exposed outside of work, to the noise of a firearm for a mean of at least once a month for 1-year
Recreation noise	Y/N	Ever been exposed outside of work to loud noise

Table I-1. List of variables in this thesis

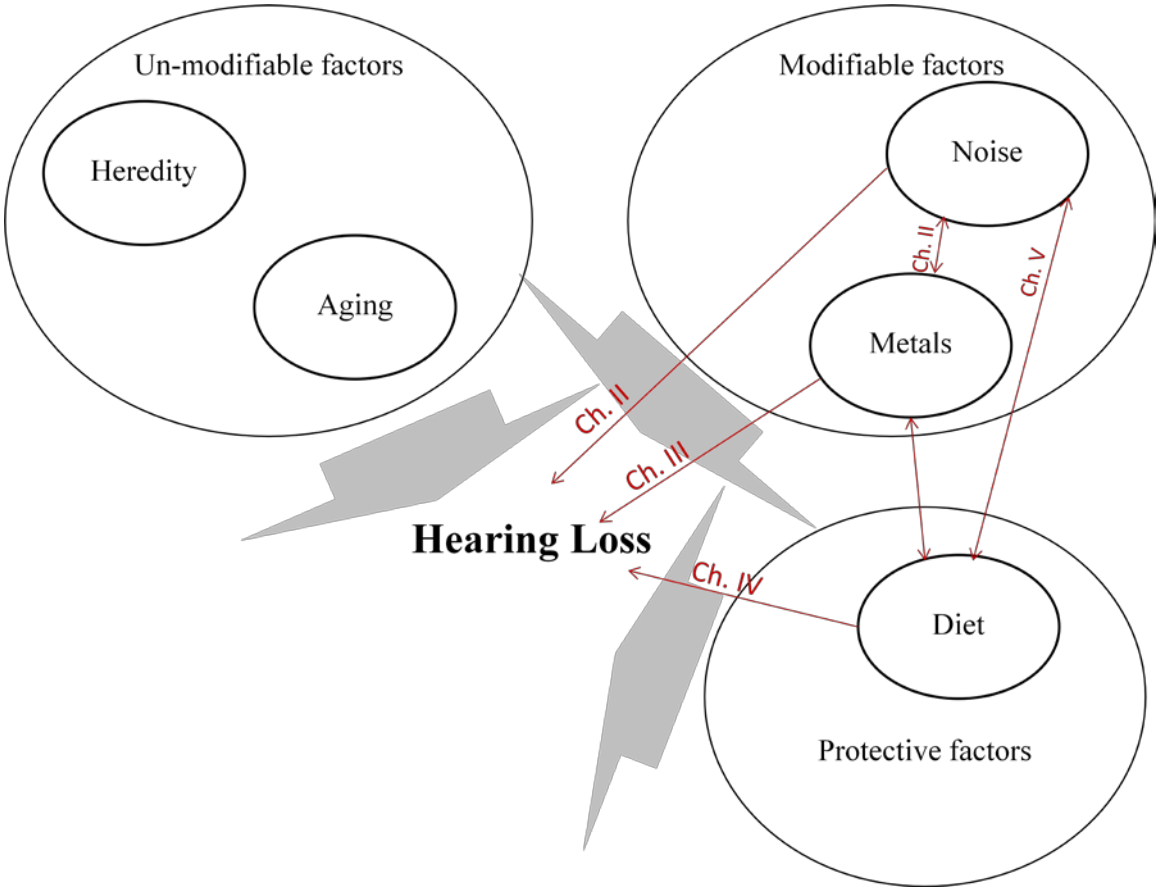

Figure I-1. Overview of the thesis.

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CHAPTER II.

Occupational Noise Exposure Assessment using O*NET and Its Application to a Study of Hearing Loss: the National Health and Nutrition Examination Survey, 1999 to 2004

ABSTRACT

Objectives: Although occupational noise is a well-known risk factor for hearing loss, little epidemiologic evidence has been reported on its association with hearing loss in the general population, in part, because of the difficulty in exposure assessment. This study introduced a quantitative occupational noise exposure assessment tool using the Occupational Information Network (O*NET) database and evaluated its applicability for epidemiologic research using data from the National Health and Nutrition Examination Survey (NHANES) 1999-2004.

Methods: The O*NET noise exposure data was assessed by questionnaires across numerous occupations, asking the frequency of exposure to sounds and noise levels that are distracting and uncomfortable (with 5 possible responses from "never" to "every day"). Means of the O*NET noise scores were computed to correspond to NHANES occupational categories and assigned to 3,828 adults aged 20 to 69 years who participated in the 1999-2004 NHANES. Pure-tone averages (PTA) of hearing thresholds at 0.5, 1, 2 and 4 kHz were computed, and hearing loss was defined as a PTA greater than 25 dB in

either ear. Linear and logistic regression models with either continuous or quintiles of the O*NET noise scores were fit on log-transformed PTA and binary hearing loss, respectively.

Results: Noise scores ranged from 1.80 to 4.37 with mean±standard error of 3.06±0.02. After controlling for potential confounders, the highest (v. lowest) noise score quintile had a 22.5% (95% confidence interval (CI), 11.0%, 35.2%) increase in PTA, and there was a linear dose-dependent trend across the quintiles of noise scores (p-trend<0.0001). The adjusted odds ratio for hearing loss comparing the highest with the lowest noise score quintiles was 2.1 (95% CI, 1.2, 3.6).

Conclusions: This study suggests the O*NET noise score is a useful tool for examining occupational noise-induced health effects in the general population in the absence of actual occupational noise exposure assessment data.

INTRODUCTION

Hearing loss is one of the leading chronic health disabilities experienced by older adults.[1] More than 35 million Americans 18 years and older suffer from hearing loss, and the number of people with hearing loss tends to increase dramatically with advancing age.[2] In addition to aging, noise is one of the most important determinants of hearing loss. While hearing loss could occur purely by noise induction, it usually occurs from a combination of different factors.

Occupational noise exposure has been associated with hearing loss, especially among workers with high noise exposure levels.[3-7] Approximately 16% of hearing impairment worldwide is attributed to occupational noise.[7-9] In the U.S., about 5-30 million workers are exposed to noise levels at work that put them at risk of hearing loss.[10]

Hearing loss can be diagnosed through review of an audiogram, regardless of whether the hearing loss is caused by noise or other factors, such as aging.[11, 12] Noise-induced hearing loss usually begins at 3, 4, or 6 kHz (higher frequencies). With noise induced hearing loss, thresholds at these frequencies are higher (indicating hearing loss) than at frequencies of 0.5 and 1 kHz (lower frequencies) and at 8 kHz (recovery), which is named a noise notch.[12, 13] In contrast, the audiogram of age-related hearing loss shows substantial down-sloping (higher thresholds) in higher frequencies.[11, 13] The association between noise exposure and noise notch allows us to observe the distinct effect of noise exposure on noise-induced hearing loss, while excluding the effect of changes in hearing ability by other factors.

Although previous epidemiologic studies have consistently shown a positive association between occupational noise exposure and hearing loss, few studies have been able to measure cumulative personal noise exposure in the general population. Occupation and/or industry classifications can be used through job-exposure matrix (JEM),[14, 15] and several studies conducted in the U.S. and Europe reported an association between JEM-estimated noise exposure and hearing loss.[6, 8, 16] However, such JEMs are limited to occupations and industries with high noise exposures, which preclude studies of the health effect of occupational noise exposure in the general population.

Recent studies have reported that the Occupational Information Network (O*NET) has the potential to serve as JEM for select environmental factors, applying it to national health surveys to examine associations with health outcomes.[17, 18] This study used the O*NET database as a surrogate measure for occupational noise exposure estimates. The O*NET is the survey-based database system generated by the U.S. Department of Labor providing information on skills, abilities, knowledge, work activities, and interests across occupational groups.[19] Data were collected through questionnaires from employees selected in every occupation group coded as the Standardized Occupation Codes (SOC) and were scored by mean scales in each SOC group. Because a question about occupational noise exposure is included in the questionnaire, mean scores of such a question may provide quantitative measures of occupational noise exposure in all occupation groups, those occupations with high noise exposure as well as those with low exposure. This allows us to evaluate the potential health effects of noise within various occupational groups of the general population. An

important limitation of this approach is the fact that it cannot be validated as a method of assessing occupational exposure without being compared to direct measurements of workplace noise in each occupation. Nonetheless, if the O*NET noise estimates have a significant association with hearing loss in a well-defined population with a wide range of occupation groups, the applicability of this method may be confirmed.

The aims of this study are to introduce a quantitative occupational noise exposure assessment tool using O*NET and to evaluate its applicability using data from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2004 in the general US population.

MATERIALS AND METHODS

O*NET Noise Exposure Assessment

The O*NET is a publicly available online database that describes occupational features across SOC taxonomy. This study used the recent version "O*NET 12.0" available at the O*NET website (www.onetcenter.org/database.html#download) or the National Crosswalk Service Center (www.xwalkcenter.org). We extracted the data of the occupational noise scale scores as the element name "Sounds, Noise Levels are Distracting, etc" (element ID IV.C.2.b.1.a) across 801 SOC groups. Occupational noise exposure was scored by frequency-type answers to the question, "In your current job, how often are you exposed to sounds and noise levels that are distracting and uncomfortable?".[20] Five responses are possible, "Never (1)", "Once a year or more but not every month (2)", "Once a month or more but not every week (3)", "Once a week or

more but not every day (4)", and "Every day (5)".[21] An example of the O*NET database structure (O*NET SOC code, noise estimates, standard error, and survey sample size) is presented in Table II-1. We used the mean of responses in each 801 SOC occupation as a proxy measure of occupational noise exposure. For example, the category ‘accountants’ (SOC: 13-2011.01) has the mean score of 1.49 (standard error (SE)=0.24), whereas the category ‘construction carpenters’ (SOC: 47-2031.01) has 4.17 (SE=0.26). If the score is closer to 5, most workers in that job category are exposed daily to 'distracting and uncomfortable noise levels'. Likewise, if the score is close to 1, workers in that category are almost never exposed to such noise levels. The mean O*NET noise scores, therefore, represent the probability of a worker in a certain job category being exposed to ‘distracting and uncomfortable sounds and noise’, and do not reflect the loudness of sound wave (such as decibels).

Application of the O*NET Noise Estimates to a Hearing Loss Study

Study Population. The NHANES, conducted by the National Center for Health Statistics (NCHS) since the early 1960s, is an ongoing series of cross-sectional surveys designed to assess health and nutritional status in the civilian, non-institutionalized US population.

In NHANES 1999 to 2004, half of the subjects aged 20 to 69 years were randomly selected to participate in the Audiometry Examination Component. Subjects were excluded if they used hearing aids that were not able to be removed for testing or had sufficient ear pain at the time of the exam that they could not tolerate

headphones.[22] The eligible sample size was 5742 participants; 1,807 in 1999–2000, 2,046 in 2001–2002, and 1,889 in 2003–2004.

Audiometric Measures. Audiometry examination was performed in a sound-isolated room in the mobile examination center by health technicians trained by a NIOSH (National Institute for Occupational Safety and Health) certified audiologist. Instrumentation for the Audiometry Component included an Interacoustics Model AD226 audiometer with standard TDH-39 headphones and Etymotic EarTone 3A insert earphones.[22] Pure-tone air conduction hearing thresholds were obtained on both ears at frequencies of 0.5, 1, 2, 3, 4, 6, and 8 kHz across an intensity range of −10 to 120 decibels (dB). Participants with missing value at one or more frequencies were excluded from analysis. Procedural details in collecting the audiometric data have been described elsewhere.[22, 23]

We computed hearing thresholds (dB) at speech frequencies as a pure tone average (PTA) of 0.5, 1, 2 and 4 kHz, and the hearing thresholds at high frequencies as a pure tone average (high-PTA) of 3, 4, and 6 kHz [24] According to classification by the World Health Organization, hearing loss is defined as PTA greater than 25 dB in either ear.[24, 25] Noise notch was defined as the hearing threshold at 3,4, and/or 6 kHz at least 10 dB greater than at 1 or 2 kHz and at least 10 dB greater than at 6 or 8 kHz.[11, 12]

Of the initial sample of 5742 participants eligible for inclusion in the audiometry examination, 324 (6%) were excluded from analysis because a test was not performed at all and 152 (3%) were excluded because tests have missing values at one or more frequencies. As an additional measure of reliability of participant responses, all audiograms tested the 1 kHz frequency twice in each ear.[22] Three participants were

excluded because there was more than 10 dB difference between the 1-kHz test-retest thresholds.[24] An additional 452 participants were excluded because of unilateral hearing loss defined as more than 10 dB difference between the PTAs of left and right ears. Therefore, audiometric results for 4811 participants were included for analysis in the present study.

Occupational Noise Estimates. Participant occupation information was obtained from the Occupation Questionnaire which contains personal interview data on employment and variables relating to the work environment, such as workplace noise exposure history.[26] We used the participant's longest job as a measure of past noise exposure. The longest job information was obtained by asking the question directly: "What kind of work were you doing the longest?".[27] Occupation data were then coded by trained coders using the U.S. Census Bureau's Census 1990 or 2000 indexes of Occupation which are the 3-digit NCHS (National Center for Health Statistics) Occupational Classification Source Codes. [28] In the publicly-available NHANES data, these codes were collapsed into 41 occupation categories.[27] Of the 4811 participants with available audiometric measurements, 4547 had information available on their longest job —2498 participants who answered their longest job plus an additional 2049 participants who answered their longest job was the same as their current job and for whom the current job code was assigned as their longest job. To link the O*NET noise estimates to the 41 occupation categories, we grouped the 801 O*NET SOCs available into the corresponding NHANES occupation categories and computed the averages of the O*NET noise scores in each category. Because military occupations were not included in the O*NET survey, we could not generate an O*NET noise score for the military

occupation group and so resulted in 40 occupation groups for analysis. After linking O*NET noise estimates to occupation categories, we assigned an average noise score to each participant. Of 4547 participants with available longest job information, we excluded 66 participants whose longest jobs were not coded to any of the 41 occupation groups and 59 participants who had military occupation, yielding 4422 participants available for statistical analyses.

We also computed the weighted averages of O*NET noise scores for the 40 NHANES occupation groups, accounting for the SEs of the noise scores in each O*NET SOC group and which reflect the precision of the O*NET survey data (see Table II-1). Because SEs were not available for 58 out of 801 SOCs, we used the unweighted averages as our primary index of occupational noise and examined the weighted ones as a sensitivity analysis. The unweighted and weighted average O*NET scores for 40 occupation categories are presented in Table II-2.

The characteristics between participants with and without the longest job information were similar in terms of prevalence of hearing loss, age, body mass index (BMI), and the status of hypertension and diabetes. Compared to included participants, excluded participants were less likely to be male, Non-Hispanic White and smokers, less educated, and less exposed to occupational noise (see Table II-3).

Demographic and Hearing-Related Variables. Other demographic and hearing-related variables were obtained from the NHANES questionnaires. Body mass index (BMI) was calculated as weight in kilograms/height in meters squared (missing for 49 participants). Use of ototoxic medication was counted when participants reported medications of aminoglycoside, loop diuretics, antineoplastic drugs, or nonsteroidal anti-

inflammatory drugs (missing for 5 participants). Smoking pack-years were computed and grouped into nonsmokers, smokers less than 20 pack-years, or smokers more than 20 pack-years (missing for 392 participants). Hypertension was defined as self-reported physician diagnosis, use of antihypertensive medication, systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90 mm Hg at the time of examination (missing for 189 participants). Diabetes mellitus was defined as those who self-reported either previous physician diagnosis or use of antihyperglycemic medication (missing for 2 participants).

Non-occupational noise exposures were determined by audiometry questionnaires asking if the subject had ever been exposed outside of work to the noise of a firearm for a mean of at least once a month for 1-year (missing for 5 participants) and if the subject had ever been exposed outside of work to loud noise (e.g., power tools or loud music) for a mean of at least once a month for 1-year (missing for 6 participants).

Our study sample was limited to adults who had complete information on these important covariates, and therefore, a total of 3828 participants were available for data analyses.

Statistical Analysis. All statistical analyses were performed using SAS survey procedures (SAS 9.2) and the R survey package (R 2.9.1) to account for the complex survey design of the NHANES.[1, 29] Sample weights for the combined 6-year sample were used per NCHS recommendations in order to provide annual national estimates, which accounted for the unequal probabilities of selection due to oversampling and non-response.[24]

Linear regressions were used for continuous hearing thresholds in each frequency

and PTA. Hearing threshold outcomes were log-transformed to normalize distributions. Eighty subjects (2.1%) with better-than-normal hearing had zero or negative hearing thresholds. We excluded these subjects to better interpret regression results of log-transformed thresholds in our primary linear regression analyses. Linear regressions including all available subjects were considered in sensitivity analyses to evaluate the effect of the exclusion. In sensitivity analyses, a constant 6 was added before log-transformation to make all hearing threshold values positive and the resulting data as normal as possible. We examined the O*NET noise score as a continuous variable and in quintiles. For the latter, we tested for linear trend across quintiles using ordinal terms. For dichotomous hearing loss and noise notch outcomes, we determined the odds ratio (OR) and 95% confidence interval (CI) using logistic regression models. In multiple regression analyses, we identified *a priori* those covariates that needed to be controlled for, based on biological consideration and the current state of the literature: age (years), sex, race/ethnicity, BMI (kg/m^2), cigarette smoking (pack-years), ototoxic medication, hypertension, diabetes mellitus, firearm noise exposure, and recreation noise exposure.[30] We fit age and age-squared to capture nonlinear effects of age. To identify influence of potential confounders, we developed sequential models: a) age, sex and race/ethnicity-adjusted; b) additionally adjusted for BMI, ototoxic medication, cigarette smoking, current diagnosis of hypertension, and current diagnosis of diabetes; c) additionally adjusted for recreational noise and firearm noise exposures.

RESULTS

O*NET Noise Exposure Assessment

Table II-2 shows the unweighted and weighted averages of O*NET noise scores by 40 occupation groups. “Private household occupations” had the lowest noise score in both unweighted (1.80) and weighted averages (2.02), whereas “Extractive and precision production occupations” and “Other transportation and material moving occupations” were highest in unweighted (4.37) and weighted (4.63) averages, respectively. We used the unweighted scores in all subsequent analyses.

Application to Hearing Loss Study

General Characteristics. Table II-4 shows descriptive characteristics of study participants. Overall, 456 subjects (11.9%) had a mild or greater hearing loss. After accounting for sampling weights, cluster and strata of the NHANES complex design, the mean of O*NET noise scores in the entire population was 3.06 (SE=0.02) and subjects with hearing loss had a significantly higher noise score than those without hearing loss (3.26 (SE=0.04) vs. 3.04 (SE=0.02)). The means of O*NET scores in the entire population and for subjects with and without hearing loss which were not considered sampling weights were 3.09 (standard deviation (SD)=0.60), 3.26 (SD=0.65), and 3.07 (SD=0.59), respectively. Distributions of the O*NET noise scores in the NHANES participants are shown in Figure II-1. Subjects with hearing loss were older (54.8 vs. 40.4 years), more likely to be male (66% vs. 46%), Non-Hispanic White (80% vs. 71%) and ever smoker (59% vs. 46%), used ototoxic medication (24% vs. 15%), less educated (percentage of greater than high school diploma 43% vs. 60%), more likely to be exposed to occupational noise (45% vs. 32%) and firearm noise (13% vs. 7%), and more likely to

have hypertension (43% vs. 21%) and diabetes (12% vs. 3%) than those without hearing loss.

Table II-5 presents the distributions of participant characteristics by quintiles of the O*NET noise scores. Subjects with higher occupational noise were more likely to be male and of race/ethnicity other than Non-Hispanic White, more likely to have higher hearing thresholds, less educated, and more likely to be exposed to firearm and recreational noises than those with lower occupational noise.

Occupational Noise Exposure and Hearing Thresholds. Table II-6 shows percent changes in PTA in associations with the O*NET score as a continuous variable and in quintiles in various covariate-adjusted models. An increase in occupational noise exposure either as a continuous variable or in quintiles was significantly associated with higher (poorer) hearing thresholds. In the fully adjusted model (Model C), subjects in the highest noise quintile had 22.5% (95% CI=11.0% to 35.2%) higher hearing thresholds than those in the lowest quintile. A unit increase in the O*NET noise score was associated with a 15.4% (95% CI=9.7 to 21.5%) increase in hearing thresholds in the fully adjusted model. The same trends were also observed in PTA at high frequencies, (see Table II-7) and all individual frequencies (see Figure II-2). Table II-6 was designed to show results from the linear regression of log-transformed PTA with the O*NET score, which excludes the subjects with zero and negative hearing thresholds (2.09 %) for better interpretation of log-transformation. Table II-8, Panel A vs. B., compares results in subjects with only positive hearing thresholds with results in all available subjects. Panel A was designed to show results from the linear regression of log-transformed (PTA+6) with the O*NET score in all available subjects, whereas panel B was designed to show

results from the linear regression of log-transformed (PTA+6) with the O*NET score in subjects with only positive hearing thresholds, the same subjects as Table II-6. From the comparison of Table II-8, panel A vs. B, linear regression in subjects with only positive hearing thresholds showed consistent patterns to those of linear regression in all available subjects.

Occupational Noise Exposure and Hearing Loss and Noise Notch. Table II-9, Panel A shows the association between O*NET noise score and the risk of hearing loss in different covariate-adjusted models. There were significant dose-dependent relationships in all models, and further adjustment for potential confounders including ototoxic medication, cigarette smoking, hypertension, diabetes, recreation noise and firearm noise did not change the result. The fully adjusted OR for hearing loss comparing the highest versus the lowest quintiles was 2.07 (95% CI=1.18 to 3.63).

Table II-9, Panel B shows odds ratio for risk of the noise notch by quintiles of O*NET noise score. The association showed a statistically significant dose-dependent relationship, and the increase pattern in the risk of noise notch in association with O*NET noise score explains better the dose-dependent relationship between occupational noise and hearing loss than that in the odds ratio of the risk of hearing loss by the O*NET noise score in panel A. The fully adjusted OR for noise notch comparing the highest versus the lowest quintiles was 1.51 (95% CI=1.09 to 2.09).

As a sensitivity analysis, we also examined associations with the weighted O*NET noise scores. Overall associations were similar to those with unweighted scores (Tables II-10 and II-11).

DISCUSSION

The present study introduces a new occupational noise exposure assessment tool using the O*NET database, evaluating its applicability to an examination of noise-related adverse health effects in the general population using hearing loss, a well-established noise-induced health outcome.

Our findings suggest that the use of O*NET scores may provide enough variation in the proxy measure of occupational noise exposure so that it can be applied for the general population with a wide range of occupation groups. It should be noted that this study did not attempt to validate the O*NET scores as a surrogate for personal occupational noise exposure levels. Rather, we evaluated an applicability of the O*NET scores as a proxy measure in association with occupational noise-related health effects in the general population, given available job title information. We found a significant dose-response relationship of O*NET noise scores with hearing loss and noise notch in NHANES, confirming that O*NET scores would be useful for examining noise-related health effects in the absence of personal occupational noise exposure data. Our results also extend evidence of noise-induced hearing loss in workers with extremely high noise exposure to the general population with low noise exposure, reinforcing occupational noise as an important risk factor for hearing loss.

In fact, we ran regression analyses dealing with O*NET scores as a continuous variable and estimated the beta coefficients corresponding to a one-unit increase in O*NET scores. The OR for risk of hearing loss corresponding to a one-unit increase in O*NET scores (range between 1 to 5) was 1.65 (95% CI=1.28 to 2.13) in a multivariable-

adjusted model. A significant dose-dependent relationship with O*NET scores was retained in sequential models after adjusting for socioeconomic factors, non-occupational noise exposures, and other potential risk factors. This suggests that the association between occupational noise exposure and hearing loss is independent of such risk factors. This increased risk is roughly equivalent to 20 or more pack-years of smoking (OR=1.54), diabetes (OR=1.66), and recreational noise exposure (OR=1.62) (see Table II-12). The estimated effect size of O*NET score is also similar to the effects of 5 years of aging (OR=1.69) when age is fit linearly.

It is difficult to compare our findings to other studies because there are no studies of dose-response relationship between occupational noise exposure and hearing loss in the general population with low- to high-exposure as a continuous variable. A few previous investigations of noise and hearing loss have been made across crude occupational groups in the general population. In one such study, over 3,500 older adults in Beaver Dam, Wisconsin, were examined for hearing loss in 6 occupation categories. A statistically significant increased risk of hearing loss was found in service (OR=1.85, 95% CI=1.40 to 2.43), operations/fabricators (OR=1.99, 95% CI=1.53 to 2.59), and production (OR=3.48, 95% CI=2.53 to 4.79), compared to management as a reference group.[6] Another study mailed a questionnaire over 22,000 adults of working age across Britain and examined the association between years worked in a noisy job and self-reported hearing difficulty. That study found an increase in hearing difficulty by years worked in a noisy job and a statistically significant increased risk of hearing loss in 5-10 years (prevalence ratio (PR)=3.0, 95% CI=1.5 to 6.1) and over 10 years (PR=3.8, 95% CI=2.4 to 6.2), compared to non-exposed group.[16] Our findings are broadly compatible with

these studies and confirm the evidence of increased risk of hearing loss with increase in occupational noise exposure in the general population.

In addition to its relationship with hearing loss, the O*NET occupational noise score had a strong dose-dependent relationship with noise notch. The presence of noise notch is one diagnostic in determining that hearing loss is noise-induced rather than the effect by other factors such as aging.[11, 12] The ORs of the risk of noise notch increased gradually across the O*NET noise score quintiles (ORs 1 (ref), 0.96, 0.79, 1.35, and 1.51). This suggests that the O*NET occupational noise could be a good proxy for occupational noise exposure.

The main strengths of this study include a) the use of representative samples of the US general population, including oversampled minority populations, which enables the observed results to be generalizable; b) the adjustment for various potential confounding factors of the association between occupational noise and hearing loss, especially noise exposure other than workplace noise, such as firearm and recreational noise, and use of ototoxic medication; c) the use of NHANES data conducted with strict quality control procedures.

This study has several limitations that should be considered. Because the O*NET database we used is based on the frequency of exposure to sounds and noise levels considered distracting and uncomfortable rather than on actual noise measurements, exposure misclassification may exist. Moreover, the O*NET data is classified only by occupation groups and does not account for variations in noise exposure from different industry groups or different job task groups within the same occupation classification. The assumption that jobs with the same title have similar occupational noise exposure

could also lead to misclassification of exposure. Misclassification might also have occurred when 801 O*NET occupation groups were combined into 40 NHANES occupation groups. Because the O*NET survey is totally independent of the audiometry tests in NHANES, however, such exposure misclassification is likely to be non-differential and lead to a true association towards the null.

Although our study showed that as an exposure proxy, longest job is better than current job in predicting occupational noise-induced hearing loss, we could not account for the job history nor the duration of each job. Because the reported longest job is more likely to be related to hearing loss, however, the bias would be non-differential. Collecting information on full job history and duration would improve validity and reliability of any noise exposure assessment using O*NET.

Although we examined three cycles of the NHANES data, which offers significant power, causal inferences may not be made because of the cross-sectional nature of the NHANES data. Nevertheless, use of the longest job may be temporally relevant to current audiometry test results.

One might argue that there is selection bias in that the association between occupational noise and hearing loss is different for subjects included in our analysis who provided information on their longest job and those excluded due to no longest job information. We found that the prevalence of noise notch for included subjects was significantly different from the prevalence for excluded subjects and that included subjects were more likely than excluded subjects to have been exposed to loud job noise for at least 3 months on all previous jobs (Table II-3). Most of the excluded subjects had never worked (75%), are currently housewives (67%, all female), disabled people with no

job history (10%) and students (8%). Although our results cannot be generalized to the non-included people (housewives, students, and the disabled), we believe that the observed associations are valid to conclude noise exposure at workplaces as an important risk factor for hearing loss and that the selection bias is unlikely.

In summary, the present study supports the hypothesis that occupational noise exposure increases the risk of hearing loss across various occupations. Utilization of the O*NET noise exposure data would allow us to perform epidemiologic studies of occupational noise exposure in the general population and to better understand the health effects of occupational noise exposure.

Table II-1. A sample of the structure of the O*NET noise estimates index (Each row is composed of O*NET-SOC code, O*NET-SOC title, interest element name, mean score of interest element, and standard error of mean score, data sample size).

O*NET SOC Code[a]	O*NET SOC Title	Element Name	Mean Score	S.E.	N
11-1011.00	Chief Executives	Sounds, Noise Levels Are Distracting or Uncomfortable	2.37	0.60	27
11-1021.00	General and Operations Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	3.19	0.49	38
11-2011.00	Advertising and Promotions Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	1.63	0.38	36
11-2021.00	Marketing Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	1.77	0.32	15
11-2022.00	Sales Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	2.95	0.51	17
11-2031.00	Public Relations Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	1.88	0.34	26
11-3011.00	Administrative Services Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	2.77	0.36	30
11-3021.00	Computer and Information Systems Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	3.51	0.38	28
11-3031.01	Treasurers and Controllers	Sounds, Noise Levels Are Distracting or Uncomfortable	2.84	0.40	42
11-3031.02	Financial Managers, Branch or Department	Sounds, Noise Levels Are Distracting or Uncomfortable	1.86	0.58	15
11-3040.00	Human Resources Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	2.79	0.45	25
11-3041.00	Compensation and Benefits Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	2.23	0.32	30
11-3042.00	Training and Development Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	2.56	0.81	17
11-3051.00	Industrial Production Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	2.99	0.53	18
11-3061.00	Purchasing Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	3.30	0.42	26
11-3071.01	Transportation Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	3.40	0.34	27
11-3071.02	Storage and Distribution Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	3.06	0.42	18
11-9011.01	Nursery and Greenhouse Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	3.41	0.47	24
11-9011.02	Crop and Livestock Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	2.07		29
11-9011.03	Aquacultural Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	3.45		31
11-9012.00	Farmers and Ranchers	Sounds, Noise Levels Are Distracting or Uncomfortable	3.48	0.27	24
11-9021.00	Construction Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	3.32	0.26	21
11-9031.00	Education Administrators, Preschool and Child Care Center/Program	Sounds, Noise Levels Are Distracting or Uncomfortable	2.77	0.45	21
11-9032.00	Education Administrators, Elementary and Secondary School	Sounds, Noise Levels Are Distracting or Uncomfortable	2.96	0.17	134
11-9033.00	Education Administrators, Postsecondary	Sounds, Noise Levels Are Distracting or Uncomfortable	2.26	0.11	197
11-9041.00	Engineering Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	3.49	0.41	18
11-9051.00	Food Service Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	3.00	0.38	64
11-9061.00	Funeral Directors	Sounds, Noise Levels Are Distracting or Uncomfortable	1.94	0.16	88
11-9071.00	Gaming Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	3.91	0.42	30
11-9081.00	Lodging Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	2.45	0.41	23
11-9111.00	Medical and Health Services Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	3.02	0.42	20
11-9121.00	Natural Sciences Managers	Sounds, Noise Levels Are Distracting or Uncomfortable	3.18	0.30	24
11-9131.00	Postmasters and Mail Superintendents	Sounds, Noise Levels Are Distracting or Uncomfortable	2.23	0.34	32

[a]O*NET-SOC code are available for 801 SOC.; The element ID "4.C.2.b.1.a" is "Sounds, noise levels are distracting or uncomfortable."; Data value (mean score of interest agent) is available between 1 to 5.

Table II-2. Unweighted and weighted averages of O*NET occupational noise scores by 40 NHANES occupation groups.

NHANES code	NHANES occupation group	O*NET noise score	
		Unweighted average	Weighted average[a]
1	Executive, administrators, and managers	2.65	2.64
2	Management related occupations	2.87	2.83
3	Engineers, architects and scientists	2.77	2.84
4	Health diagnosing, assessing and treating occupations	2.45	2.23
5	Teachers	2.50	2.48
6	Writers, artists, entertainers, and athletes	2.73	2.72
7	Other professional specialty occupations	2.48	2.46
8	Technicians and related support occupations	3.12	3.16
9	Supervisors and proprietors, sales occupations	2.68	2.96
10	Sales representatives, finance, business, & commodities ex. retail	2.41	2.29
11	Sales workers, retail and personal services	2.70	2.85
12	Secretaries, stenographers, and typists	2.68	2.67
13	Information clerks	2.74	2.66
14	Records processing occupations	2.80	2.82
15	Material recording, scheduling, and distributing clerks	3.34	3.37
16	Miscellaneous administrative support occupations	2.59	2.50
17	Private household occupations	1.80	2.02
18	Protective service occupations	3.51	3.63
19	Waiters and waitresses	2.84	2.84
20	Cooks	2.84	2.84
21	Miscellaneous food preparation and service occupations	2.84	2.84
22	Health service occupations	2.73	2.58
23	Cleaning and building service occupations	3.33	3.91
24	Personal service occupations	2.83	2.69
25	Farm operators, managers, and supervisors	3.25	3.48
26	Farm and nursery workers	3.16	3.22
27	Related agricultural, forestry, and fishing occupations	3.61	4.16
28	Vehicle and mobile equipment mechanics and repairers	4.34	4.59
29	Other mechanics and repairers	3.60	3.91
30	Construction trades	3.95	4.23
31	Extractive and precision production occupations	4.37	4.63
32	Textile, apparel, and furnishings machine operators	3.24	3.78
33	Machine operators, assorted materials	3.94	4.44
34	Fabricators, assemblers, inspectors, and samplers	3.63	4.16
35	Motor vehicle operators	3.23	3.56
36	Other transportation and material moving occupations	4.26	4.75
37	Construction laborers	4.09	4.09
38	Laborers, except construction	3.93	3.93
39	Freight, stock, and material movers, hand	3.93	3.93
40	Other helpers, equipment cleaners, hand packagers and laborers	3.67	3.73

[a]Weighted average was defined as $\sum_{i=1}^{P} \frac{(O * \text{NET score}i)\text{SE}i}{\sum_{i=1}^{P}(1/\text{SE}i)}$ where i is an individual job title in O*NET Standard Occupation Classification (SOC) and P is the total number of O*NET SOCs classified within the NHANES occupation group.

Table II-3. Participants characteristics by longest job information status (N=4058[a])

Characteristic	Longest job information (N=3828)	No Longest job infomation (N=230)	*P-value*
O*NET noise[b]	3.06 (± 0.02)	.	.
O*NET noise[b] *(Weighted)*	3.15 (± 0.02)	.	.
Age *(y)*	41.96 (± 0.27)	40.62 (± 1.73)	*0.4454*
Body mass *(index:wtkg/htm)*	28.04 (± 0.15)	28.37 (± 0.65)	*0.6200*
Hearing Thresholds *(dB)*			
PTA at speech frequencies[c]	12.72 (± 0.24)	12.16 (± 0.67)	*0.3972*
0.5 kHz	11.64 (± 0.23)	12.52 (± 0.78)	*0.2652*
1 kHz	9.59 (± 0.22)	9.81 (± 0.78)	*0.7846*
2 kHz	10.90 (± 0.29)	10.21 (± 0.74)	*0.3725*
3 kHz	14.25 (± 0.33)	12.67 (± 0.91)	*0.0864*
4 kHz	18.74 (± 0.42)	16.11 (± 0.87)	*0.0035*
6 kHz	24.56 (± 0.43)	22.72 (± 1.05)	*0.0825*
8 kHz	23.58 (± 0.31)	22.79 (± 1.00)	*0.4020*
Hearing Loss[d] *(PTA>25dB, %)*	11.1	9.0	*0.3777*
Noise Notch[e] *(%)*	17.6	11.8	*0.0318*
Sex *(Male %)*	48.5	27.2	*<.0001*
Race ethnics (%)			*0.0039*
Non-Hispanic White	72.3	60.7	
Non-Hispanic Black	10.7	12.2	
Mexican American	6.7	10.7	
Other	10.3	16.4	
Ototoxic medication *(Current use %)*	15.9	12.5	*0.2978*
Cumulative cigarette packyears (%)			*0.0062*
Never	53.6	64.8	
<20	33.9	25.7	
≥20	12.4	9.5	
Current dx of hypertension *(%)*	23.1	19.8	*0.2575*
Current dx of diabetes mellitus *(%)*	4.3	4.3	*0.9813*
Noise Exposure at firearm *(Exposed %)*	7.4	4.3	*0.1052*
Noise Exposure at recreation *(Exposed %)*	25.9	21.1	*0.1861*
Noise Exposure at Job[f] *(Exposed %)*	33.0	9.4	*<.0001*

Continuous variables: survey t-test, age-adjusted

Categorical variables: 2*2 table or 2*C table : survey X_square (Rao-Scott Chi-Square Test)

[a]Participants (N=4058) are the individuals having all interest variables in this study.: hearing thresholds, hearing loss, age, BMI, sex, race ethnicity, ototoxic medication, cumulative cigratte packyears, hypertension, diabetes mellitus, firearm noise Exposure, and recreation noise exposure

[b]O*NET noise score (1 < Noise scale < 5)

[c]PTA at speech frequencies (Pure tone means at 0.5, 1, 2, 4 KHz)

[d]Hearing Loss (PTA at speech frequencies > 25 dB)

[e]Noise Notch (Hearing threshold at 3,4, and/or 6 kHz is at least 10 dB greater than at 1 or 2 kHz and at least 10 dB greater than at 6 or 8 kHz.)

[f]Noise Exposure at Job (Questionnaire: Loud job noise, ever exposed, 3 months?)

Table II-4. Participants characteristics by hearing loss status (N=3828[a]).

Characteristic	All participants (N=3828)	Not Hearing Loss (N=3372)	Hearing Loss[b] (N=456)	*P-value*[c]
O*NET noise[d]	3.06 (± 0.02)	3.04 (± 0.02)	3.26 (± 0.04)	*<.0001*
O*NET noise[d] *(Weighted)*	3.15 (± 0.02)	3.12 (± 0.02)	3.39 (± 0.05)	*<.0001*
Age *(y)*	41.96 (± 0.27)	40.35 (± 0.27)	54.81 (± 0.67)	*<.0001*
Body mass index *(wtkg/htm)*	28.04 (± 0.15)	28.05 (± 0.15)	28.02 (± 0.36)	*0.9266*
Pure tone average hearing thresholds[e] *(dB)*	12.72 (± 0.24)	10.96 (± 0.16)	27.00 (± 0.70)	*<.0001*
Noise notch[f] *(%)*	17.6	16.8	23.7	*<.0001*
Sex *(Male %)*	48.5	46.3	66.2	*<.0001*
Race ethnicity (%)				*<.0001*
Non-Hispanic White	72.3	71.3	80.1	
Non-Hispanic Black	10.7	11.5	4.9	
Mexican American	6.7	7.1	3.6	
Other	10.3	10.2	11.3	
Ototoxic medication *(current use %)*	15.9	14.8	24.4	*0.0013*
Cumulative cigarette pack-years (%)				*<.0001*
Never	53.6	55.3	40.6	
<20	33.9	34.7	27.5	
≥20	12.4	10.0	31.9	
Hypertension *(%)*	23.1	20.6	43.2	*<.0001*
Diabetes mellitus *(%)*	4.3	3.4	11.5	*<.0001*
Noise exposure at firearm *(exposed %)*	7.4	6.6	13.2	*0.0010*
Noise exposure at recreation *(exposed %)*	25.9	25.4	29.6	*0.1341*
Noise exposure at job[g] *(exposed %)*	33.0	31.5	45.4	*<.0001*

[a]Participants (N=3828) are the individuals having all interest variables in this study: hearing thresholds, hearing loss, noise, age, body mass index, sex, race ethnicity, ototoxic medication, cumulative cigarette pack-years, hypertension, diabetes mellitus, firearm noise exposure, and recreation noise exposure.

[b]Hearing loss was defined as pure tone average at speech frequencies > 25 dB.

[c]Survey *t*-test (age-adjusted) for continuous variables and survey (Rao-Scott) Chi-square test for categorical variables were used.

[d]O*NET noise score (1 < Noise scale < 5).

[e]Pure tone average at speech frequencies at 0.5, 1, 2, and 4 kHz.

[f]Noise notch (Hearing threshold at 3,4, and/or 6 kHz is at least 10 dB greater than at 1 or 2 kHz and at least 10 dB greater than at 6 or 8 kHz).

[g]Noise exposure at job was defined as ever exposure to loud noise at work for at least 3 months.

Table II-5. Characteristics of study population by noise exposure quintile at longest job.

	O*Net noise exposure scores at longest job					
(N=3828)	Quintile 1 (1.795-2.588) (N=695)	Quintile 2 (2.653-2.729) (N=830)	Quintile 3 (2.737-2.868) (N=731)	Quintile 4 (3.121-3.631) (N=805)	Quintile 5 (3.667-4.368) (N=767)	*p-Trend*
PTA Hearing Thresholds [a] *(dB)*	11.0 (± 0.4)	11.9 (± 0.3)	11.7 (± 0.3)	13.5 (± 0.4)	15.9 (± 0.6)	*<.0001*
Age *(y)*	43.8 (± 0.5)	41.8 (± 0.5)	40.9 (± 0.5)	42.0 (± 0.6)	41.4 (± 0.6)	*0.0066*
Hearing Loss [b] (%)	8.8	8.7	8.5	12.8	17.8	*<.0001*
Noise Notch [c] (%)	13.8	14.2	11.8	22.4	27.0	*<.0001*
Sex *(Male %)*	28.2	37.9	36.1	63.2	81.0	*<.0001*
Race ethnicity (%)						*0.0041*
Non-Hispanic White	76.25	75.40	75.16	64.82	68.63	
Non-Hispanic Black	10.09	10.30	9.70	13.81	10.12	
Mexican American	4.02	4.66	4.73	10.69	9.98	
Other	9.64	9.63	10.41	10.68	11.27	
Noise Exposure at firearm *(Exposed %)*	3.0	7.0	4.3	10.2	12.8	*<.0001*
Noise Exposure at recreation *(Exposed %)*	18.9	24.2	21.6	28.9	36.6	*<.0001*

[a] PTA (pure tone average) at speech frequencies at 0.5, 1, 2, 4 kHz, age-adjusted.
[b] Hearing loss (PTA at speech frequencies > 25 dB)
[c] Noise notch (Hearing threshold at 3,4, and/or 6 kHz is at least 10 dB greater than at 1 or 2 kHz and at least 10 dB greater than at 6 or 8 kHz.)

Table II-6. Percent change (95% CIs) of hearing thresholds (dB) by noise exposure levels at longest job.

Variables	No.	Model A[a]		Model B[b]		Model C[c]	
O*NET Noise (unit score)[d]		18.41	(12.23, 24.93)	16.01	(10.09, 22.25)	15.43	(9.70, 21.45)
O*NET Noise Quintile							
Quintile 1 (1.795-2.588)	680	0	(Reference)	0	(Reference)	0	(Reference)
Quintile 2 (2.653-2.729)	807	2.90	(-5.61 12.17)	1.89	(-6.30, 10.78)	1.44	(-6.71, 10.31)
Quintile 3 (2.737-2.868)	711	0.72	(-8.98, 11.45)	-0.81	(-10.30, 9.68)	-0.90	(-10.40, 9.61)
Quintile 4 (3.121-3.631)	793	17.24	(6.20, 29.42)	14.02	(3.32, 25.82)	13.27	(2.87, 24.72)
Quintile 5 (3.667-4.368)	757	27.97	(15.99, 41.20)	23.66	(11.90, 36.66)	22.48	(10.99, 35.15)
P-Trend		<.0.0001		<.0.0001		<.0.0001	

[a]Model A was adjusted for age, age^2, sex, and race/ethnicity.

[b]Model B: Model A + further adjusted for body mass index, ototoxic medication, cumulative cigarette pack-years, current dx of hypertension, and current dx of diabetes.

[c]Model C: Model B + further adjusted for recreation noise and firearm noise.

[d]Percent change in hearing thresholds for one unit score increase.

Table II-7. Percent change (95% CIs) of hearing thresholds (dB) at high frequencies by noise exposure levels at longest job.

Variables	No.	Model A[a]		Model B[b]		Model C[c]	
O*NET Noise (unit score)[d]		19.68	(12.97, 26.79)	17.01	(10.44, 23.98)	16.16	(9.89, 22.79)
O*NET Noise Quintile							
Quintile 1 (1.795-2.588)	675	0	(Reference)	0	(Reference)	0	(Reference)
Quintile 2 (2.653-2.729)	809	0.59	(-6.34, 8.04)	-0.38	(-6.97, 6.67)	-1.11	(-7.63, 5.87)
Quintile 3 (2.737-2.868)	712	-2.20	(-10.46, 6.83)	-3.87	(-11.92, 4.91)	-4.04	(-12.07, 4.72)
Quintile 4 (3.121-3.631)	786	13.83	(3.96, 24.64)	10.84	(1.16, 21.44)	9.65	(0.23, 19.96)
Quintile 5 (3.667-4.368)	760	28.01	(15.39, 42.01)	23.10	(10.75, 36.84)	21.33	(9.52, 34.43)
P-Trend		<.0.0001		0.0003		0.0004	

[a]Model A was adjusted for age, age^2, sex, and race/ethnicity.

[b]Model B: Model A + further adjusted for body mass index, ototoxic medication, cumulative cigarette pack-years, current dx of hypertension, and current dx of diabetes.

[c]Model C: Model B + further adjusted for recreation noise and firearm noise.

[d]Percent change in hearing thresholds for one unit score increase.

Table II-8. Percent change (95% CIs) of hearing thresholds +6 (dB) by noise exposure levels at longest job in entire subjects and subjects with only positive hearing thresholds

Variables	No.	Regression Model[a]	
A. Entire subjects (3828 subjects)			
O*NET Noise (unit score)[b]		9.01	(5.47, 12.67)
O*NET Noise Quintile			
Quintile 1 (1.795-2.588)	695	0	(Reference)
Quintile 2 (2.653-2.729)	830	1.76	(-2.74, 6.47)
Quintile 3 (2.737-2.868)	731	0.48	(-5.06, 6.36)
Quintile 4 (3.121-3.631)	805	6.97	(1.35, 12.92)
Quintile 5 (3.667-4.368)	767	13.93	(6.67, 21.68)
P-Trend		0.0001	
B. Subjects with only positive hearing thresholds (3748 subjects)			
O*NET Noise (unit score)[b]		9.27	(6.06, 12.58)
O*NET Noise Quintile			
Quintile 1 (1.795-2.588)	680	0	(Reference)
Quintile 2 (2.653-2.729)	807	1.83	(-2.30, 6.13)
Quintile 3 (2.737-2.868)	711	0.01	(-5.31, 5.64)
Quintile 4 (3.121-3.631)	793	7.54	(2.07, 13.30)
Quintile 5 (3.667-4.368)	757	14.00	(7.69, 20.68)
P-Trend		<.0001	

[a]Regression model was adjusted for age, age^2, body mass index, sex, race/ethnicity, ototoxic medication, cumulative cigarette pack-years, hypertension, diabetes, recreation noise and firearm noise.
[b]Percent change in hearing thresholds for one unit score increase.

Table II-9. Odds ratios (ORs) (95% CIs) of hearing loss and noise notch by noise exposure levels at longest job.

Variables		Model A[a]	Model B[b]	Model C[c]
A. ORs of hearing loss	Hearing loss No./ Participants No.			
O*NET Noise (unit score)[d]		1.74 (1.35, 2.26)	1.68 (1.30, 2.18)	1.65 (1.28, 2.13)
O*NET Noise Quintile				
Quintile 1 (1.795-2.588)	65/695	1 (Reference)	1 (Reference)	1 (Reference)
Quintile 2 (2.653-2.729)	76/830	1.04 (0.62, 1.72)	1.01 (0.60, 1.69)	0.99 (0.59, 1.65)
Quintile 3 (2.737-2.868)	67/731	1.14 (0.64, 2.03)	1.10 (0.62, 1.96)	1.09 (0.61, 1.95)
Quintile 4 (3.121-3.631)	112/805	1.61 (0.96, 2.70)	1.50 (0.89, 2.52)	1.43 (0.87, 2.36)
Quintile 5 (3.667-4.368)	136/767	2.30 (1.32, 4.01)	2.14 (1.22, 3.75)	2.07 (1.18, 3.63)
P-Trend		0.001	0.0019	0.0026
B. ORs of noise notch	Noise notch No./ Participants No.			
O*NET Noise (unit score)[d]		1.45 (1.20, 1.76)	1.43 (1.18, 1.73)	1.41 (1.17, 1.70)
O*NET Noise Quintile				
Quintile 1 (1.795-2.588)	101/695	1 (Reference)	1 (Reference)	1 (Reference)
Quintile 2 (2.653-2.729)	119/830	0.98 (0.67, 1.42)	0.97 (0.67, 1.42)	0.96 (0.66, 1.40)
Quintile 3 (2.737-2.868)	77/731	0.80 (0.58, 1.11)	0.80 (0.58, 1.10)	0.79 (0.57, 1.09)
Quintile 4 (3.121-3.631)	168/805	1.40 (1.05, 1.87)	1.37 (1.02, 1.84)	1.35 (1.00, 1.81)
Quintile 5 (3.667-4.368)	190/767	1.60 (1.16, 2.20)	1.55 (1.12, 2.14)	1.51 (1.09, 2.09)
P-Trend		0.0016	0.0032	0.0045

[a]Model A was adjusted for age, age^2, sex, and race/ethnicity.

[b]Model B: Model A + further adjusted for body mass index, ototoxic medication, cumulative cigarette pack-years, current dx of hypertension, and current dx of diabetes.

[c]Model C: Model B + further adjusted for recreation noise and firearm noise.

[d]Percent change in hearing thresholds for one unit score increase.

Table II-10. Percent change (95% CIs) of hearing thresholds (dB) by weighted noise exposure levels at longest job

Variables	No.	Regression Model[a]	
Weighted O*NET Noise (unit score)[b]		12.78	(8.28, 17.46)
Weighted O*NET Noise Quintile			
Quintile 1 (2.020-2.578)	817	0	(Reference)
Quintile 2 (2.637-2.821)	700	-4.23	(-11.72, 3.89)
Quintile 3 (2.832-2.963)	739	1.24	(-7.39, 10.69)
Quintile 4 (3.157-3.930)	796	11.37	(1.84, 21.78)
Quintile 5 (4.090-4.748)	776	21.45	(10.28, 33.75)
P-Trend		<.0.0001	

[a]Regression model was adjusted for age, age^2, body mass index, sex, race/ethnicity, ototoxic medication, cumulative cigarette pack-years, hypertension, diabetes, recreation noise and firearm noise.
[b]Percent change in hearing thresholds for one unit score increase.

Table II-11. ORs (95% CIs) of hearing loss and noise notch by weighted noise exposure levels at longest job

Variables		Regression Model[a]	
A. ORs of hearing loss	Hearing Loss No./ Participants No.		
Weighted O*NET Noise (unit score)[b]		1.49	(1.21, 1.84)
Weighted O*NET Noise Quintile			
Quintile 1 (2.020-2.578)	78/817	1	(Reference)
Quintile 2 (2.637-2.821)	64/700	0.88	(0.50, 1.55)
Quintile 3 (2.832-2.963)	66/739	0.95	(0.54, 1.69)
Quintile 4 (3.157-3.930)	105/796	1.29	(0.79, 2.12)
Quintile 5 (4.090-4.748)	143/776	1.92	(109, 3.41)
P-Trend		0.0064	
B. ORs of noise notch	Noise notch No./ Participants No.		
Weighted O*NET Noise (unit score)[b]		1.35	(1.14, 1.60)
Weighted O*NET Noise Quintile			
Quintile 1 (2.020-2.578)	118/817	1	(Reference)
Quintile 2 (2.637-2.821)	89/700	0.81	(0.59, 1.11)
Quintile 3 (2.832-2.963)	90/739	0.91	(0.67, 1.23)
Quintile 4 (3.157-3.930)	166/796	1.27	(0.95, 1.71)
Quintile 5 (4.090-4.748)	192/776	1.54	(1.13, 2.11)
P-Trend		0.0005	

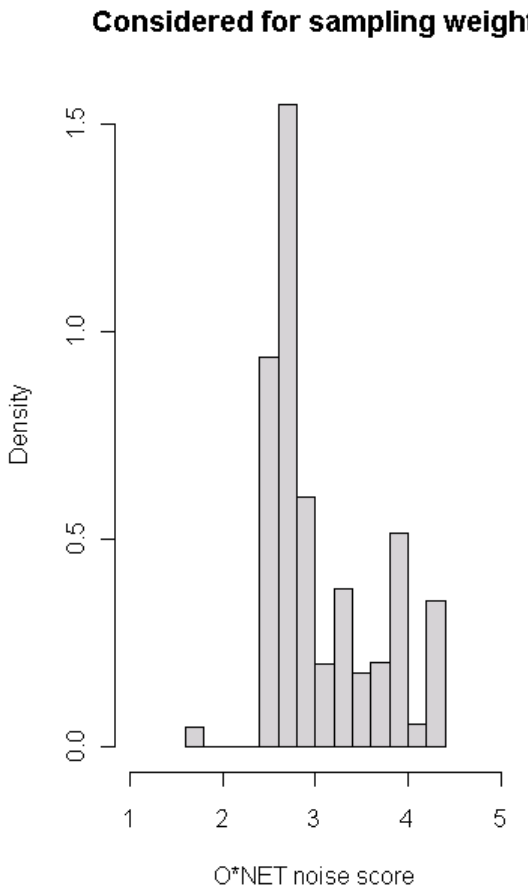
[a]Regression model was adjusted for age, age^2, body mass index, sex, race/ethnicity, ototoxic medication, cumulative cigarette pack-years, hypertension, diabetes, recreation noise and firearm noise.
[b]Percent change in hearing thresholds for one unit score increase.

Table II-12. ORs (95% CIs) of hearing loss by contribution of different variables in a multiple logistic regression

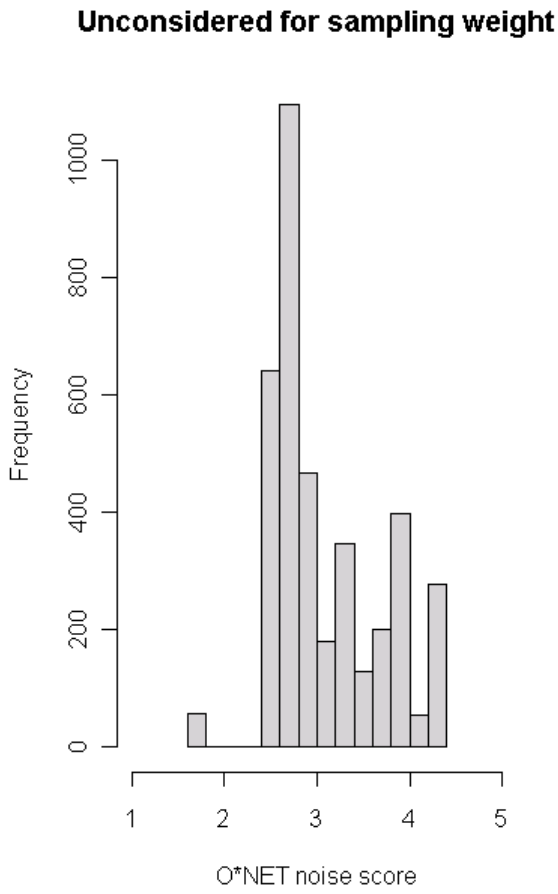
Variables	Hearing Loss No./ Participants No.	Regression Model[a]	
All	456/3828		
O*NET noise *(unit score change)*		1.65	(1.28, 2.13)
Age *(unit year change)*		1.07	(0.98, 1.18)
Age^2 *(unit year change)*		1.00	(1.00, 1.00)
Body mass index *(10 wtkg/htm change)*		0.99	(0.97, 1.02)
Sex			
Female	147/2043	1	(Reference)
Male	309/1785	0.49	(0.37, 0.64)
Race ethnicity			
Non-Hispanic White	261/1880	1	(Reference)
Non-Hispanic Black	59/794	0.41	(0.28, 0.59)
Mexican American	94/827	0.71	(0.53, 0.97)
Other	42/327	1.31	(0.80, 2.15)
Ototoxic medication			
No	343/3243	1	(Reference)
Yes	113/585	1.06	(0.79, 1.41)
Cumulative cigarette packyears			
Never	184/2177	1	(Reference)
<20	145/1227	0.96	(0.65, 1.42)
≥20	127/424	1.54	(1.11, 2.15)
Current dx of hypertension			
No	242/2809	1	(Reference)
Yes	214/1019	1.12	(0.84, 1.49)
Current dx of diabetes mellitus			
No	389/3603	1	(Reference)
Yes	67/225	1.66	(0.99, 2.77)
Noise Exposure at firearm			
No	406/3593	1	(Reference)
Yes	50/235	1.41	(0.89, 2.23)
Noise Exposure at recreation			
No	343/2948	1	(Reference)
Yes	113/880	1.62	(1.21, 2.17)

[a]Regression model was adjusted for age, age^2, body mass index, sex, race/ethnicity, ototoxic medication, cumulative cigarette pack-years, hypertension, diabetes, recreation noise and firearm noise.

Figure II-1. Distribution of O*NET noise scores of participants in NHANES, considered for sampling weights and unconsidered for sampling weights

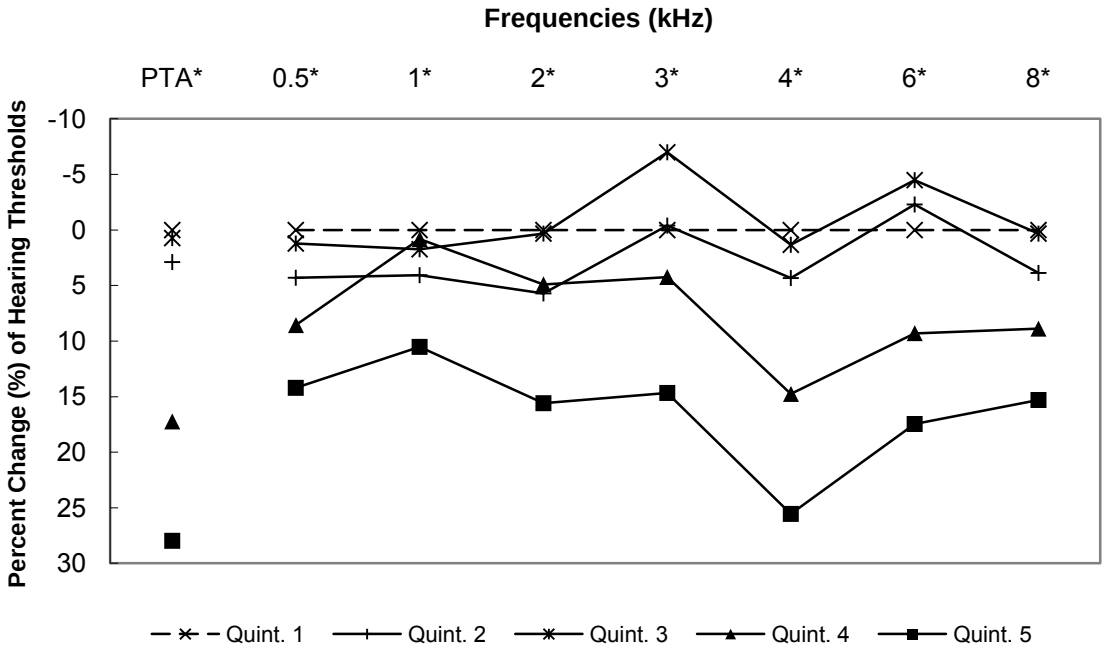


*(a) Distribution of O*NET noise scores in NHANES, considered for sampling weights*



*(b) Distribution of O*NET noise scores in NHANES, not considered for sampling weights*

Figure II-2. Percent change (%) of hearing thresholds (dB) by occupational noise quintile at longest job at each frequency from 0.5 kHz to 8 kHz *(* P-trend<0.05)*



Regression models were adjusted for age, age^2, body mass index, sex, race/ethnicity, ototoxic medication, cumulative cigarette pack-years, hypertension, diabetes, recreation noise and firearm noise

APPENDIX I. O*NET questionnaire.

Instructions for Work Context Questionnaire

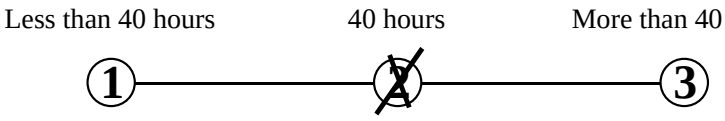
Instructions

In this questionnaire you will be asked about your working conditions. These questions are about your work setting and its possible hazards, the pace of your work, and your dealings with other people.

Read each question carefully and look closely at answer choices after each question. Put an **X** through the number for the answer that best describes *your current job*.

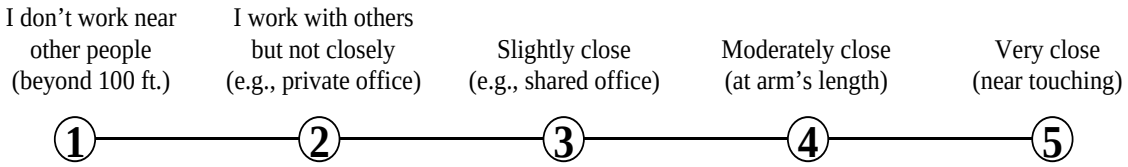
For example:

How many hours do you work in a typical week?

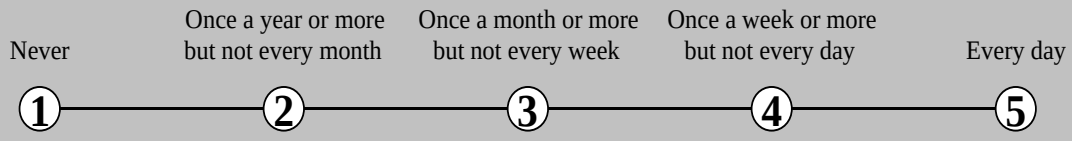


Mark your answer by putting an **X** through the number that represents your answer.
Do not mark on the line between the numbers.

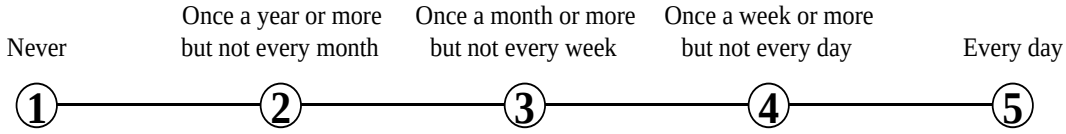
21. How <u>physically close to other people</u> are you when you perform *your current job*?



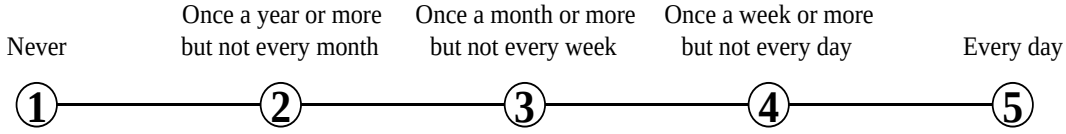
22. In *your current job,* how often are you exposed to <u>sounds and noise levels that are distracting and uncomfortable</u>?



23. In *your current job,* how often are you exposed to <u>very hot</u> (above 90° F) <u>or very cold</u> (under 32° F) temperatures?



24. In *your current job,* how often are you exposed to <u>extremely bright or inadequate lighting conditions</u>?



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CHAPTER III.

Environmental Cadmium and Lead Exposures and Hearing Loss: the National Health and Nutrition Examination Survey, 1999 to 2004

ABSTRACT

Background. Although cadmium and lead are known risk factors for hearing loss in animal models, few epidemiologic studies have been conducted on their associations with hearing ability in the general population.

Objectives. We investigated the associations between blood cadmium and lead exposure and hearing loss in the U.S. general population, while controlling for noise and other major risk factors contributing to hearing loss.

Methods. We examined 3,698 adults aged 20 to 69 years from the National Health and Nutrition Examination Survey (NHANES) 1999-2004. Air conduction hearing thresholds were measured and a pure-tone average (PTA) of frequencies at 0.5, 1, 2 and 4 kHz was computed. Blood cadmium and lead contents were measured by atomic absorption spectrometry or inductively coupled plasma-mass spectrometry. Linear regression models

with either continuous or quintiles both of cadmium and lead were fit on log-transformed PTA, respectively.

Results. The weighted geometric means of blood cadmium and lead were 0.40 (95% confidence interval (CI), 0.39 to 0.42) µg/L and 1.54 (1.49 to 1.60) µg/dL, respectively. After multivariable adjustment for noise exposures and sociodemographic/clinical risk factors, the highest (v. lowest) cadmium quintile had a 13.8% (95% CI, 4.6%, 23.8%) increase in PTA, and the highest lead quintile had a 18.6% (95% CI, 7.4%, 31.1%) increase in PTA. There were linear dose-dependent trends across the quintiles of both cadmium (p-trend=0.0049) and lead (p-trend=0.0001).

Conclusions. These results suggest that low-level exposure to cadmium and lead found in the general population, particularly those less exposed to loud noise, may be important risk factors for hearing loss. Our finding supports the need for efforts to reduce environmental cadmium and lead exposures.

INTRODUCTION

Hearing loss is one of the most common chronic disabling conditions among older adults [1]. More than 35 million people aged 18 years and older suffer from hearing loss in the U.S. in 2008 [2], and the prevalence of hearing loss tends to increase dramatically with advancing age and with growing prevalence of environmental risk factors, including loud noise, and ototoxic industrial chemicals [1-8]. Therefore, identification of risk factors, particularly those that are preventable or may interact with traditional risks, is important.

Experimental studies suggested that lead exposure, even at low levels, induces degeneration in the inner ear receptor cells and latency in auditory nerve conduction velocity [9-12]; cadmium exposure causes apoptosis and destroyed arrangement in inner ear receptor cells leading to an elevation in auditory thresholds [13, 14].

In the general population, the primary sources of cadmium exposure are cigarette smoke, contaminated food intake (shellfish, offal, vegetables), and ambient air particularly in urban, industrial, and contaminated agricultural areas [15]. Primary historical sources of lead exposure (gasoline, solder, paint) were phased out and environmental lead exposure has decreased considerably in the U.S. [16, 17]. However, environmental exposure to low levels of both metals is still widespread [16, 18], and they accumulate in the body that could influence the development of chronic diseases [17, 19, 20].

Nevertheless, no epidemiologic research has been conducted on cadmium, and epidemiologic research on lead has been limited to occupationally high exposed workers

[21-23] and vulnerable children and youth [24, 25]. One recent study has reported an association with lead in elderly men [26]; many studies, however, have been limited, in part by the difficulty in controlling important risk factors in assessing the association between low level exposures and hearing loss.

Our recent study introduced an occupational noise exposure assessment tool using the O*NET noise score, in the absence of personal exposure data, given available job title information [27]. This allowed us to adjust occupational sources noise, an important confounding factor, on hearing loss and to evaluate individual effect of low level cadmium and lead exposures in epidemiologic study. Non occupational noise and other important risk factors on hearing loss were collected through intensive interview and examination in our study population, the National Health and Nutrition Examination Survey (NHANES).

The aim of this study is to investigate the associations of environmental cadmium and lead exposure with hearing loss in representative U.S. adults who participated in the National Health and Nutrition Examination Survey (NHANES) 1999 to 2004**,** while controlling for important potential confounding factors in the associations between blood cadmium and lead and hearing loss, including occupational, firearm and recreational loud noise. We also examined joint effects of cadmium and lead as well as the interaction with occupational noise.

MATERIALS AND METHODS

Study Population. The NHANES 1999-2004, conducted by the National Center for Health Statistics (NCHS; Centers for Disease Control and Prevention (CDC), Atlanta, GA) , is an ongoing series of cross-sectional surveys designed to obtain a representative sample of the civilian non-institutionalized US population. The data were collected through extensive households interviews to obtain information on risk factors, health behaviors, or personal environment. The data were subsequently followed through physical examination and additional interviews at a specially equipped mobile examination center (MEC) [28]. In NHANES 1999 to 2004, half of the subjects aged 20 to 69 years were randomly assigned to participate in the Audiometry Examination Component at MEC. Participants who used hearing aids that were not able to be removed for testing, or who had sufficient ear pain that they could not tolerate test headphones were excluded [29]. The eligible sample size was 5,742 participants; 1,807 in 1999–2000, 2,046 in 2001–2002, and 1,889 in 2003–2004.

Audiometric Measures. Audiometry examination was conducted in a sound-isolated room by health technicians trained by a certified audiologist by the National Institute for Occupational Safety and Health (NIOSH). Instrumentation for the Audiometry Component included an audiometer (Interacoustics Model AD226) with standard headphones (TDH-39) and insert earphones (Etymotic EarTone 3A) [29].

Pure tone air conduction hearing thresholds were obtained for both ears at frequencies of 0.5, 1, 2, 3, 4, 6, and 8 kHz over an intensity range of −10 to 120 decibels (dB). The examinee that did not respond at one or more frequencies was treated as a non-response. As an additional quality measure of the reliability of participant's responses, all audiograms tested the 1 kHz frequency twice in each ear and the audiograms of a 10 dB

or more difference between the 1-kHz test-retest were not accepted [29]. The procedures details of audiometric test procedure have been described elsewhere [29, 30].

We computed the hearing thresholds (dB) at speech frequencies as a pure tone average (PTA) of 0.5, 1, 2 and 4 kHz and at high frequencies as a pure tone average (high-PTA) of 3, 4, and 6 kHz [31]. Hearing loss was defined as a PTA of 25 dB or greater in either ear by the classification of the World Health Organization [32]. Noise notch was defined as the hearing threshold at 3, 4, and/or 6 kHz is at least 10 dB greater than at 1 or 2 kHz and at least 10 dB greater than at 6 or 8 kHz [33, 34].

Of the initial sample of 5,742 participants, eligible for inclusion in the audiometry examination, participants were excluded from analysis because of non-response (N=476) or unreliable response (N=3). Additional 452 participants were excluded with unilateral hearing loss which was defined as more than 10 dB difference between the PTAs of left and right ears. Therefore, 4,811 participants were eligible to the present study.

Blood Cadmium and Lead Measurements. Blood for cadmium and lead was measured at the Environmental Health Sciences Laboratory of the CDC National Center for Environmental Health (NCEH) after confirmation of no background contamination in all collection and storage materials [35, 36]. Cadmium and lead concentrations were measured by a Perkin-Elmer model SIMAA 6000 simultaneous multielement atomic absorption spectrometer with Zeeman background correction in NHANES 1999-2002 [35, 37, 38] and by an inductively coupled plasma-mass spectrometer in NHANES 2003–2004 [39]. Of 4,811 participants with available audiometric measurement, 4,628 had

valid blood cadmium and lead concentrations. The detection limit for cadmium was 0.3 µg/L in NHANES 1999-2002 and 0.2 µg/L in NHANES 2003-2004, and the detection limit for lead was 0.3 µg/dL in all three NHANES cycles. Of study participants, 26% and 17% had cadmium concentrations below the detection limit in NHANES 1999-2002 and NHANES 2003-2004, respectively, and 0.8% of the entire participants had blood lead concentrations below the detection limit [15, 36, 40-42]. For these subjects, we imputed value equal to the detection limit divided by the square root of two [37]. The interassay coefficients of variation ranged from 4.1% to 7.3% in NHANES 1999-2000 and 4.4% to 6.1% in NHANES 2001-2004 for blood cadmium, and from 3.1% to 4.0% in NHANES 1999-2000 and 3.1% to 7.0% in NHANES 2001-2004 for blood lead [35, 38, 39].

Noise Exposure Assessments. Noise exposures (e.g. occupational, firearm, and recreational noise) may be important confounding factors in the associations of blood cadmium and lead with hearing loss. Direct measures of personal noise exposure are not available in the NHANES.

Occupational noise exposures were evaluated by occupational noise estimates through the longest job in participant's entire lives. A recent study conducted by Choi reported a new occupational noise exposure assessment tool using the Occupational Network (O*NET) survey database, applicable if participants' job title information is available in the absence of personal occupational noise exposure data [27]. The occupational noise assessment tool using the O*NET was defined as scale scores (1 to 5) for "Sounds, Noise Levels are Distracting, etc" across the occupation groups of 801 Standardized Occupation Codes (SOC),

In NHANES, participants' longest job titles were obtained by personal interview asking what kind of work the subject was doing the longest [43]. For the questionnaire about longest job, participant answered as text or the same as current job, and the answer was coded to 41 occupation categories in the publicly available NHANES data [44, 45]. To link the O*NET noise estimates to the NHANES longest job categories, we grouped the 801 O*NET SOCs available into the corresponding 41 occupation categories and computed the averages of the O*NET noise scores in each category. For example, "Private household occupations" had the lowest score of 1.80, whereas "Extractive and precision production occupations" had the highest score of 4.37. Because military occupations were not included in the O*NET survey, we finally generated 40 available occupation groups. Of 4,628 participants with available audiometry, blood cadmium and lead components, 4,252 participants had the longest jog information for statistical analyses. We assigned the longest job-related O*NET average score to each participant and used it as a proxy measure of personal occupational noise exposure. Firearm noise exposures and recreation noise exposures were defined by audiometry questionnaires asking if the subject had ever been exposed outside of work to the noise of a firearm a mean of at least once a month for 1 year and if the subject had ever been exposed outside of work to loud noise (e.g., power tools or loud music) for a mean of at least once a month for 1 year. Participants answered either as exposure or non-exposure. Six participants were excluded from analysis as missing data both in firearm noise and recreation noise.

We also created a composite noise exposure variable using three different noise variables (occupational, firearm, and recreational noise), indicating exposure to from none to three noise sources.

Demographic and Hearing-Related Variables. Other demographic and hearing-related variables were obtained during household~~s~~ interview or at MEC. Body mass index (BMI) was calculated as weight in kilograms/height in meters squared (41 missing participants). Use of ototoxic medication was defined as use of any 4 drug class of aminoglycoside, loop diuretics, antineoplastic drugs, or nonsteroidal anti-inflammatory drugs (3 missing participants). Smoking pack-years were computed, and participants were grouped into nonsmokers, smokers less than 20 pack-years, or smokers more than 20 pack-years (368 missing participants). Hypertension was defined as self-reported physician diagnosis, the use of antihypertensive medication, systolic blood pressure ≥ 140mmHg, or diastolic blood pressure ≥ 90 mm Hg at the time of examination (176 missing participants). Diabetes mellitus was defined as self-reported physician diagnosis or the use of antihyperglycemic medication (1 missing participants).

Our study sample was limited to adults who had complete information on these important covariates, and therefore, a total of 3,698 participants were available for data analyses.

Statistical Analysis. All statistical analyses were performed using the SAS survey procedures (SAS 9.2) ~~-~~and the R survey package (R 2.9.1) to account for the complex survey design and sample weights of the NHANES [46, 47]. We computed 6-year sample weights per NCHS recommendations, which were adjusted for oversampling and non-

response of subjects such as ethnic minorities, elderly persons, and low income [28, 48]. The statistical significant level was set as *P* values less than .05.

Differences in demographic and clinical characteristics between subjects with hearing loss and with normal hearing were tested by using survey t-test for continuous variables or Rao-Scott chi-square test for categorical variables.

All regression analyses began with univariate analyses to identify outliers and influential points. Blood lead and cadmium levels appeared to be right skewed and were examined as log-transformed continuous variables and as quintiles. Hearing thresholds in PTA, high-PTA, and individual frequencies were log-transformed to normalize distributions and were handled as linear models. For better interpretation of regression results, we excluded 76 subjects (2.1%) who had zero or negative hearing thresholds (better-than-normal hearing) in our primary linear regression analyses with PTA to avoid adding a constant before log-transformation. Our previous study confirmed that exclusion of those subjects did not impact the overall association between occupational noise exposure and hearing thresholds [27]. Logistic regression was used to estimate odds ratios (ORs) for the dichotomous hearing loss and noise notch outcome. Log-transformed blood lead and cadmium were fit because graphical evaluations using a smoothing method (cubic splines) supported log-linear relationships. We also examined quintiles of blood cadmium and lead, comparing the lowest quintile to the upper four quintiles. To identify the influence of potential confounders, we developed sequential models: model A adjusted for age, age-squared, sex, race/ethnicity education, and either blood lead or blood cadmium for the corresponding cadmium or lead model; model B further adjusted for BMI, ototoxic medication use, pack-years of cigarette smoke, hypertension, and type-

2 diabetes; model C further adjusted for occupational noise exposure; and model D further adjusted for firearm and recreational noise exposures.

RESULTS

Table III-1 shows descriptive characteristics of study participants. The mean of age in the entire population was 42.06 (SE=0.28) years and the means of PTA and high-PTA were 12.78 (SE=0.24) dB and 19.35 (SE=0.37) dB. Overall, 441 subjects (11.9%) had a mild or greater hearing loss. Table III-2 shows age-adjusted geometric means (95% Confidence Interval (CI)) of blood cadmium and blood lead levels by participants characteristics. The geometric means of blood cadmium and lead in the entire population were 0.40 (95% CI, 0.39 to 0.42) µg/L and 1.54 (CI, 1.49 to 1.60) µg/dL, respectively. Subjects with hearing loss (vs. those without hearing loss) had a significantly higher blood cadmium levels (0.46 (CI, 0.42 to 0.50) µg/L vs. 0.40 (CI, 0.38 to 0.42) µg/L) and a significantly higher blood lead levels (1.72 (CI, 1.62 to 1.82) µg/dL vs. 1.52 (CI, 1.47 to 1.58) µg/dL), respectively. Both Blood cadmium and lead levels were different by race/ethnicity and were higher in the subjects who were older aged, less educated, ever smoked exposed to occupation noise and who had less BMI and no diabetes. Blood lead levels, additionally, were higher in the subjects who had noise notch, used ototoxic medication, and exposed to firearm and recreation noise. Blood cadmium and lead levels were correlated with one another.

Table III-3 presents the percent changes in PTA in associations with blood cadmium and lead levels as a log-transformed continuous variable and as quintiles in

various covariate-adjusted models for socio-demographic factors (model A), subsequently chronically clinical risk factors (model B), also occupation noise (model C), and non-occupation noises (Models D). Also, Figure III-1 shows the percent changes in PTA in associations with blood cadmium and lead levels as quintiles in a fully adjusted model (Models D). Increases in blood cadmium and lead levels either as a continuous variable or in quintiles were significantly associated with higher (poorer) hearing thresholds in all models. In the fully adjusted model (Model D). Subjects in the highest quintile of blood cadmium had 13.8% (95% CI, 4.6 to 23.8%) higher hearing thresholds than those in the lowest quintile. An interquartile-range (IQR) increase in the blood cadmium level was associated with a 6.6% (95% CI, 1.9 to 11.6 %) increase in hearing thresholds. Similarly, the subjects in the highest quintile of blood lead had 18.6% (95% CI, 7.4% to 31.1%) higher hearing thresholds than those in the lowest quintile, and an IQR increase of blood cadmium level was associated with a 7.2% (95% CI, 2.8 to 11.8%) increase in hearing thresholds. The similar trend for blood lead was observed in individual frequencies of 0.5, 1, and 4 kHz respectively and in high-PTA; trend for blood cadmium was observed neither in all individual frequencies nor in high-PTA (see Figure III-2).

Table III-4 shows the association of the risk of hearing loss with blood cadmium and blood lead level in different covariate-adjusted models. Also, Figure III-3 shows the percent changes in PTA in associations with blood cadmium and lead levels as quintiles in a fully adjusted model (Models D). There were significant dose–dependent relationships in all models for blood cadmium level. For blood lead level, similarly, there was significant dose–dependent relationship in a model adjusted for socio-demographic and clinical risk factors (Model B), and marginally significant relationship in a model

further adjusted for occupation noise (Models C). The fully adjusted odd ratios (OR) for hearing loss comparing the highest versus the lowest blood cadmium and lead quintiles were 1.7 (95% CI, 1.1 to 2.7) and 1.4 (95% CI, 0.8 to 2.5), respectively.

Table III-5 presents odds ratio of the risk of the noise notch by blood cadmium and blood lead. There were no significant dose–dependent associations of noise notch neither with blood cadmium nor lead level in all different models.

We found an additive joint effect of combined exposures of cadmium and lead on hearing outcomes. Figure III-4 shows the percent changes in PTA in associations with one combined variable consisting of binary blood cadmium and binary blood lead levels in fully adjusted model. Cut-off points for binary groups came from medians of blood cadmium and lead levels respectively. Overall, high-cadmium and high-lead group (v. low and low) had a 19.0% (95% CI, 9.7 to 29.1%) increase in PTA that was even more than sum of that for high-cadmium and low-lead, 7.3% (95% CI, 0.4 to 14.8%), and that for low-cadmium and high-lead, 10.09% (95% CI, 0.4 to 20.8%).

Figure III-5 shows the percent changes in PTA in adjusted associations of blood cadmium and lead levels, modeled as a log-transformed continuous variable, in the subgroups listed in Table III-1. There was significant difference in the association of PTA with blood cadmium IQR increase between non-Hispanic white and non-Hispanic black and between high school educated and more than high school educated subgroups. The association of PTA with blood lead IQR increase was significant different between 40-59 ages and 60 or more ages, between non-Hispanic black and other race ethnicity, and between less than high school educated and high school educated subgroups.

Table III-6 presents the percent changes in PTA in adjusted associations with blood cadmium and lead levels as a log-transformed continuous variable and in quintiles in subgroups at various noise exposures levels; none, a kind, and two or all three kinds of noise exposures; occupation, firearm, and recreation. Also, Figure III-6 shows the percent changes in PTA in associations with blood cadmium and lead levels as a log-transformed continuous variable in subgroups stratified by noise exposures. Among subjects non-exposed to noise, we found significant and high increases of PTA both with blood cadmium and lead levels. Among subjects at single noise exposure, there was significant increase of PTA with blood lead level. There was no association of PTA neither with blood cadmium nor lead levels among subjects at two or three kinds of noise exposures.

DISCUSSION

In a representative sample of US adults who participated in NHANES 1999-2004, environmental cadmium and lead exposures were found to be independent risk factors for hearing loss, while controlling for other important predictors and confounders. We found significant dose-response relationship of blood cadmium and lead levels both with hearing thresholds. On the basis of PTA at speech frequencies, participants in the highest (versus the lowest) blood cadmium and blood lead quintile were likely to have 13.8% (95% CI, 4.6 to 23.8%) and 18.6% (95% CI, 7.4 to 31.1%) higher hearing thresholds in a multivariable-adjusted model, respectively. Significant dose-dependent relationships with blood cadmium and lead levels respectively were retained in all sequential models after adjusting for socioeconomic factors, noise exposures, and other potential risk factors.

This suggests that the associations of cadmium and lead exposure with hearing disability are independent of such risk factors. These increased PTAs by cadmium and lead in the highest (vs. the lowest) quintile were comparable to diabetes (19.9%), 6 years of aging (17.3%, when age is fit linearly), and 2-unit increase of O*NET occupational noise scores (14.8%, corresponding to difference between 'Textile, apparel, and furnishings machine operators' versus 'Executive, administrators, and managers' occupation). The risk was also higher than effect by firearm noise exposure (10.2%) and recreational noise exposure (3.4%).

An association of blood cadmium and lead with PTA was strongly significant among subjects non-exposed to noise, but not significant among subjects highly exposed to noise. Among people less affected from noise, metals emerges markedly as risk factors for hearing disability, whereas people already influenced by high noise may not appear significant hazardous influence of metals.

We also found an additive effect by combined exposure to high cadmium and high lead on increase of hearing thresholds.

In addition, we found that blood cadmium and lead levels were associated with hearing thresholds but never associated with noise notch in NHANES. Association of cadmium and/or lead with hearing disbility, given absence of noise notch, supports that their associations are in actual causal consequences, not by coincidence of high correlation between cadmium and/or lead exposure sources and noise exposure sources.

Few epidemiologic studies have evaluated an association between low-to-high lead exposure and hearing outcome. Our results extend evidence limited in occupational settings on children [21-25] into general population One previous study, over 2,200

elderly men in Eastern Massachusetts, found a significant increased risk of hearing loss with IQR increase of bone lead level at two sites: tibia lead (OR=1.2, 95% CI=0.9, 1.5) and patella lead (OR=1.5, 95% CI=1.1, 1.9) [26]. Our finding (OR of hearing loss with blood lead IQR=1.1, 95% CI=0.9, 1.4) is broadly consistent to that study and confirms the evidence of a dose-response association that was observed among community-dwelling elderly male in the U.S. general population including both male and female.

This is the first epidemiologic study to evaluate an association of hearing loss with cadmium exposure; thus, it is difficult to compare our dose-response association to other studies. Our finding extends biological evidences from previous animal experiments to epidemiologic evidence in human population.

At the low levels of lead and cadmium exposures in NHANES 1999-2004, we observed a significant adverse effect on hearing loss: blood cadmium level $\geq$ 0.8μg/L, and blood lead level $\geq$ 2.8μg/dL, each. The Occupational Safety and Health Administration (OSHA) safety standard, however, is still staying at 44.5 nmol/L (5 μg/L) for cadmium and 1.93 umol/L (38.6 μg/dL) for lead in whole blood [49, 50]. Under the OSHA ‘safe’ standard, people cannot be ‘safe’ from hearing loss. In fact, in a general population of NHANES 1999-2004, geometric means of blood cadmium and lead level were 0.40 μg/L and 1.54 μg/dL far from standard. With growing evidence supporting that chronic cadmium and lead exposure below this standard have various adverse health effects [15, 45, 51, 52], our finding adds the need for changing those standards for public health.

Important strengths of this study include a) the use of a representative sample of the US general population which enables to generalize; b) the adjustment for important

potential confounding in associations of cadmium and lead with hearing loss, particularly noise; c) the use of NHANES data conducted with strict quality control procedures.

Some limitations in this study should be considered. Our study investigated the risk of cadmium and lead exposures on hearing loss, a chronic disease, in NHANES data that is a cross-sectional survey. Cadmium and lead exposures were estimated by blood levels that reflect relatively short-term exposure, but primary sources of environmental lead exposure were banned in U.S.; thus, we cannot rule out a concern that their blood lead levels at current time may not highly correlate with their historical exposures, result in the difficulty to explain a reliable association with hearing loss. Nevertheless, our observation is roughly equivalent to that in a previous study both in cross-sectional and longitudinal design using bone lead, a proxy of cumulative lead exposure [26].

Also, blood cadmium and lead levels were low with some proportion below detection limit. Because subjects below detection limit in cadmium and lead fell in same group as each lowest quintile, this issue did not affect to perform association with hearing loss.

Because we adjusted for a variety of potential risk factors, it is possible to over-control such occupational and environmental factors that may have high correlation with cadmium and lead exposure; therefore, true effects of cadmium and lead exposure on hearing loss may be stronger than observed association.

In summary, the present study supports the hypothesis that environmental cadmium and lead exposures increase the risk of hearing loss among the U.S adults, particularly those less exposed to noise. Our finding adds to the concerns on cadmium

and lead toxicity at low level in public health, and support the need for efforts to reduce environmental cadmium and lead exposure with reducing noise exposure to effectively prevent or delay hearing loss in general population.

Table III-1. Participants characteristics by hearing loss status (N=3698[a])

Characteristic	All participants (N=3698)	Not Hearing Loss (N=3257)	Hearing Loss[b] (N=441)	*P-value*[c]
Occupation noise exposure[d] *(O*NET score)*	3.06 (± 0.02)	3.04 (± 0.02)	3.25 (± 0.04)	*<.0001*
Age *(y)*	42.06 (± 0.28)	40.45 (± 0.29)	54.81 (± 0.66)	*<.0001*
Body mass ndex *(wtkg/htm)*	28.04 (± 0.15)	28.03 (± 0.15)	28.06 (± 0.36)	*0.9414*
Pure tone average hearing thresholds (dB) at speech frequencies[e]	12.78 (± 0.24)	10.98 (± 0.16)	27.03 (± 0.68)	*<.0001*
Pure tone average hearing thresholds (dB) at high frequencies[f]	19.35 (± 0.37)	16.51 (± 0.20)	41.80 (± 0.96)	*<.0001*
Noise notch[g] *(%)*	17.7	16.9	23.6	*0.0128*
Sex *(Male %)*	48.6	46.4	66.3	*<.0001*
Race ethnicity (%)				*<.0001*
Non-Hispanic White	72.5	71.5	80.6	
Non-Hispanic Black	10.5	11.2	4.5	
Mexican American	6.6	7.1	3.4	
Other	10.4	10.2	11.5	
Education (%)				*0.0019*
< High School	16.6	15.1	28.3	
High School	25.1	24.7	28.2	
> High School	58.3	60.2	43.4	
Ototoxic medication *(Current use %)*	15.9	14.8	24.3	*0.0019*
Cumulative cigarette pack-years (%)				*<.0001*
Never	53.7	55.4	40.8	
<20	33.7	34.6	27.3	
≥20	12.5	10.1	31.9	
Hypertension *(%)*	23.2	20.6	43.7	*<.0001*
Diabetes mellitus *(%)*	4.1	3.2	11.4	*<.0001*
Firearm noise exposure *(Exposed %)*	7.5	6.8	13.3	*0.0012*
Reacreation noise exposure *(Exposed %)*	26.0	25.6	29.3	*0.2032*

[a]Participants (N=3698) are the individuals having all interest variables in this study: hearing thresholds, hearing loss, lead, cadmium,age, body mass index, sex, race ethnicity, education, ototoxic medication, cumulative cigarette pack-years, hypertension, diabetes mellitus, occupation noise exposure (O*NET score), firearm noise exposure, and recreation noise exposure.

[b] Hearing loss was defined as pure tone average at speech frequencies > 25 dB.

[c] Survey *t*-test (age-adjusted) for continuous variables and survey (Rao-Scott) Chi-square test for categorical variables were used.

[d] Occupation noise (1 < O*NET noise scale < 5)

[e] Pure tone average at speech frequencies at 0.5, 1, 2, and 4 kHz.

[f] Pure tone average at high frequencies at 3, 4, and 6 kHz.

[g] Noise notch (Hearing threshold at 3,4, and/or 6 kHz is at least 10 dB greater than at 1 or 2 kHz and at least 10 dB greater than at 6 or 8 kHz).

Table III-2. Geometric means and 95% confidence intervals of blood cadmium and lead by participants caracteristics (N=3698[a])

Characteristic	No. (%[b]) of participants	Blood Cadmium (ug/L),[c] (95% C.I.)	*P-value*[d]	Blood Lead (ug/dL),[c] (95% C.I.)	*P-value*[d]
Total	3698	0.40 (0.39 - 0.42)		1.54 (1.49 - 1.60)	
Hearing Loss[e]			*0.0011*		*<.0001*
No	3257 (88.8)	0.40 (0.38 - 0.42)		1.52 (1.47 - 1.58)	
Yes	441 (11.2)	0.46 (0.42 - 0.50)		1.72 (1.62 - 1.82)	
Noise Notch[f]			*0.6182*		*<.0001*
No	3063 (82.3)	0.41 (0.39 - 0.43)		1.50 (1.44 - 1.56)	
Yes	635 (17.7)	0.40 (0.37 - 0.43)		1.78 (1.65 - 1.91)	
Cadmium Quintile *(ug/L)*			.		*<.0001*
≤ 0.2	1047 (29.8)	.		1.28 (1.21 - 1.35)	
0.3	566 (14.9)	.		1.41 (1.30 - 1.52)	
0.4	593 (14.7)	.		1.48 (1.40 - 1.57)	
0.5-0.7	796 (20.6)	.		1.63 (1.52 - 1.74)	
≥ 0.8	696 (20.0)	.		2.14 (2.03 - 2.26)	
Lead Quintile *(ug/dL)*			*<.0001*		.
≤ 0.8	659 (17.8)	0.28 (0.26 - 0.31		.	
0.9-1.3	872 (25.3)	0.37 (0.35 - 0.39		.	
1.4-1.8	689 (19.9)	0.42 (0.39 - 0.45		.	
1.9-2.7	738 (20.2)	0.45 (0.42 - 0.49		.	
≥ 2.8	740 (16.8)	0.56 (0.52 - 0.62		.	
Age *(y)*			*0.0071*		*0.004*
20-39	1650 (44.8)	0.36 (0.34 - 0.38)		1.23 (1.18 - 1.29)	
40-59	1385 (43.8)	0.44 (0.41 - 0.46)		1.75 (1.67 - 1.83)	
60-69	663 (11.3)	0.45 (0.42 - 0.48)		2.09 (1.98 - 2.21)	
Sex			*0.0003*		*<.0001*
Male	1729 (48.6)	0.38 (0.36 - 0.40)		1.94 (1.87 - 2.02)	
Female	1969 (51.4)	0.43 (0.41 - 0.45)		1.24 (1.18 - 1.31)	
Body mass index *(wtkg/htm)*			*0.0033*		*<.0001*
< 30	2484 (69.0)	0.42 (0.39 - 0.44)		1.61 (1.54 - 1.69)	
≥ 30	1214 (31.0)	0.38 (0.36 - 0.40)		1.40 (1.34 - 1.47)	
Race ethnicity			*0.0143*		*<.0001*
Non-Hispanic White	1827 (72.5)	0.40 (0.38 - 0.42)		1.48 (1.42 - 1.55)	
Non-Hispanic Black	750 (10.5)	0.42 (0.39 - 0.45)		1.77 (1.68 - 1.87)	
Mexican American	805 (6.6)	0.39 (0.36 - 0.42)		1.81 (1.69 - 1.95)	
Other	316 (10.4)	0.46 (0.43 - 0.49)		1.60 (1.47 - 1.74)	

Continued in next page

Characteristic	No. (%[b]) of participants	Blood Cadmium (ug/L),[c] (95% C.I.)	*P-value*[d]	Blood Lead (ug/dL),[c] (95% C.I.)	*P-value*[d]
Education			*<.0001*		*<.0001*
< High School	974 (16.6)	0.55 (0.51 - 0.58)		1.99 (1.89 - 2.11)	
High School	849 (25.1)	0.45 (0.42 - 0.48)		1.62 (1.53 - 1.71)	
> High School	1875 (58.3)	0.36 (0.34 - 0.37)		1.41 (1.35 - 1.47)	
Ototoxic medication			*0.9809*		*<.0001*
No	3132 (84.1)	0.40 (0.39 - 0.42)		1.59 (1.53 - 1.66)	
Yes	566 (15.9)	0.41 (0.37 - 0.45)		1.31 (1.23 - 1.39)	
Cumulative cigarette pack-years			*<.0001*		*<.0001*
Never	2105 (53.7)	0.29 (0.27 - 0.30)		1.33 (1.27 - 1.40)	
< 20	1183 (33.7)	0.58 (0.54 - 0.61)		1.81 (1.73 - 1.89)	
≥ 20	410 (12.5)	0.68 (0.61 - 0.76)		1.89 (1.78 - 2.01)	
Current dx of hypertension			*0.0713*		*0.1643*
No	2713 (76.8)	0.41 (0.39 - 0.43)		1.56 (1.50 - 1.62)	
Yes	985 (23.2)	0.38 (0.36 - 0.41)		1.49 (1.40 - 1.59)	
Current dx of diabetes mellitus			*0.0009*		*<.0001*
No	3485 (95.9)	0.41 (0.39 - 0.43)		1.56 (1.51 - 1.62)	
Yes	213 (4.1)	0.32 (0.28 - 0.37)		1.20 (1.07 - 1.35)	
Occupation noise exposure *(O*NET score)*					
Low (< 2.84)	1815 (52.7)	0.37 (0.35 - 0.38)		1.31 (1.25 - 1.38)	
High (> 2.84)	1883 (27.3)	0.45 (0.43 - 0.48)		1.85 (1.77 - 1.92)	
Firearm noise exposure			*0.8723*		*0.0001*
No	3468 (92.5)	0.40 (0.39 - 0.42)		1.52 (1.46 - 1.57)	
Yes	230 (7.5)	0.41 (0.36 - 0.47)		1.94 (1.72 - 2.18)	
Reacreation noise exposure			*0.1842*		*<.0001*
No	2844 (74.0)	0.40 (0.38 - 0.42)		1.47 (1.41 - 1.54)	
Yes	854 (26.0)	0.42 (0.39 0.45)		1.77 (1.67 - 1.88)	

[a]Participants (N=3698) are the individuals having all interest variables in this study: hearing thresholds, hearing loss, lead, cadmium,age, body mass index, sex, race ethnicity, education, ototoxic medication, cumulative cigarette pack-years, hypertension, diabetes mellitus, occupation noise exposure (O*NET score), firearm noise exposure, and recreation noise exposure.

[b] Weighted percentages from survery freq were presented.

[c] Geometric mean blood lead and cadmium levels (Age-adjusted) were presented. For age groups, unadjusted lead and cadmium levels were presented.

[d] Survey *t* -test for binominal groups and Survey *Wald F* -test for categorical groups were used.

[e] Hearing loss was defined as pure tone average at speech frequencies > 25 dB.

[f] Noise notch (Hearing threshold at 3,4, and/or 6 kHz is at least 10 dB greater than at 1 or 2 kHz and at least 10 dB greater than at 6 or 8 kHz).

Table III-3. Percent change (95% CIs) of hearing thresholds (dB) by blood cadmium and lead levels

Variables	No.	Model A[a]	ModelB[b]	ModelC[c]	ModelD[d]
Cadmium					
Log(Cadmium) IQR[e]		6.85 (2.96, 10.90)	7.03 (2.28, 12.00)	6.53 (1.73, 11.56)	6.62 (1.89, 11.56)
Cadmium Quintile *(ug/L)*					
Quintile 1 (0.10-0.20)	1013	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)
Quintile 2 (0.30-0.30)	553	-2.08 (-10.01, 6.56)	-1.02 (-8.75, 7.35)	-1.53 (-9.22, 6.81)	-1.22 (-8.86, 7.07)
Quintile 3 (0.40-0.40)	581	0.98 (-6.11, 8.61)	2.21 (-5.10, 10.08)	1.26 (-5.95, 9.02)	1.68 (-5.60, 9.53)
Quintile 4 (0.50-0.70)	785	5.61 (-2.02, 13.83)	7.07 (-1.07, 15.87)	6.53 (-1.58, 15.32)	6.69 (-1.48, 15.53)
Quintile 5 (0.80-8.50)	690	12.85 (5.83, 20.33)	14.49 (5.17, 24.64)	13.42 (4.18, 23.48)	13.78 (4.55, 23.82)
P -Trend		*0.0006*	*0.0033*	*0.0057*	*0.0049*
Lead					
Log(Lead) IQR[f]		5.95 (1.63, 10.47)	8.33 (3.83, 13.03)	7.58 (3.12, 12.24)	7.21 (2.81, 11.81)
Lead Quintile *(µg/dL)*					
Quintile 1 (0.20-0.80)	629	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)
Quintile 2 (0.90-1.30)	842	-1.39 (-10.86, 9.09)	-0.04 (-9.50, 10.41)	-0.06 (-9.51, 10.38)	-0.50 (-9.94, 9.93)
Quintile 3 (1.40-1.80)	679	4.51 (-5.72, 15.83)	7.30 (-3.05, 18.76)	7.11 (-3.23, 18.54)	6.51 (-3.76, 17.89)
Quintile 4 (1.90-2.70)	734	8.39 (-2.37, 20.33)	11.86 (0.97, 23.92)	11.01 (0.26, 22.91)	10.22 (-0.40, 21.97)
Quintile 5 (2.80-54.00)	738	15.62 (4.49, 27.94)	21.13 (9.43, 34.09)	19.44 (7.96, 32.14)	18.63 (7.35, 31.09)
P -Trend		*0.0007*	*<.0001*	*0.0001*	*0.0001*

[a] Model A was adjusted for age, age^2, sex, race/ethnicity, and education. Cadmium models were further adjusted for lead; lead models were further adjusted for cadmium.

[b] Model B: Metal A + further adjusted for body mass index, ototoxic medication, cumulative cigarette pack-years, current dx of hypertension, and current dx of diabetes.
[c] Model C: Model B + further adjusted for occupation noise.
[d] Model D: Model C + further adjusted for recreation noise, and firearm noise.
[e] Percent change in hearing thresholds for interquartile range (IQR) increase of Log-transformed cadmium: log0.6-log0.2
[f] Percent change in hearing thresholds for interquartile range (IQR) increase of Log-transformed lead: log2.5-log1

TableIII- 4. ORs (95% CIs) of hearing loss by blood cadmium and lead levels

Variables	Hearing loss No./ Participants No.	Model A[a]	ModelB[b]	ModelC[c]	ModelD[d]
Cadmium					
Log(Cadmium) IQR[e]		1.42 (1.18, 1.71)	1.47 (1.14, 1.91)	1.45 (1.11, 1.88)	1.43 (1.12, 1.84)
Cadmium Quintile *(ug/L)*					
Quintile 1 (0.10-0.20)	71/1047	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Quintile 2 (0.30-0.30)	53/566	1.14 (0.67, 1.95)	1.20 (0.71, 2.05)	1.17 (0.69, 1.99)	1.21 (0.71, 2.05)
Quintile 3 (0.40-0.40)	72/593	1.02 (0.69, 1.50)	1.07 (0.72, 1.58)	1.01 (0.68, 1.50)	1.05 (0.71, 1.55)
Quintile 4 (0.50-0.70)	128/796	1.37 (0.93, 2.03)	1.44 (0.96, 2.16)	1.39 (0.92, 2.11)	1.39 (0.91, 2.11)
Quintile 5 (0.80-8.50)	117/696	1.69 (1.19, 2.41)	1.80 (1.14, 2.85)	1.72 (1.08, 2.76)	1.74 (1.12, 2.70)
P -Trend		*0.0014*	*0.0085*	*0.0169*	*0.0129*
Lead					
Log(Lead) IQR[f]		1.11 (0.92, 1.33)	1.17 (0.97, 1.41)	1.15 (0.95, 1.39)	1.13 (0.93, 1.36)
Lead Quintile *(µg/dL)*					
Quintile 1 (0.20-0.80)	21/659	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Quintile 2 (0.90-1.30)	61/872	1.06 (0.56, 2.01)	1.10 (0.57, 2.10)	1.12 (0.58, 2.15)	1.08 (0.55, 2.12)
Quintile 3 (1.40-1.80)	80/689	1.06 (0.59, 1.90)	1.14 (0.62, 2.09)	1.14 (0.61, 2.11)	1.10 (0.58, 2.05)
Quintile 4 (1.90-2.70)	115/738	1.16 (0.66, 2.05)	1.28 (0.72, 2.27)	1.26 (0.70, 2.27)	1.21 (0.67, 2.22)
Quintile 5 (2.80-54.00)	164/740	1.31 (0.75, 2.28)	1.48 (0.84, 2.62)	1.43 (0.80, 2.57)	1.36 (0.75, 2.48)
P -Trend		*0.1349*	*0.0413*	*0.0837*	*0.1204*

[a] Model A was adjusted for age, age^2, sex, race/ethnicity, and education. Cadmium models were further adjusted for lead; lead models were further adjusted for cadmium.

[b] Model B: Metal A + further adjusted for body mass index, ototoxic medication, cumulative cigarette pack-years, current dx of hypertension, and current dx of diabetes.
[c] Model C: Model B + further adjusted for occupation noise.
[d] Model D: Model C + further adjusted for recreation noise, and firearm noise.
[e] Percent change in hearing thresholds for interquartile range (IQR) increase of Log-transformed cadmium: log0.6-log0.2
[f] Percent change in hearing thresholds for interquartile range (IQR) increase of Log-transformed lead: log2.5-log1

Table III-5. ORs (95% CIs) of noise notch by blood cadmium and lead levels.

Variables	Noise notch No./ Participants No.	Model A[a]	ModelB[b]	ModelC[c]	ModelD[d]
Cadmium					
Log(Cadmium) IQR[e]		0.91 (0.79, 1.06)	0.88 (0.74, 1.03)	0.86 (0.73, 1.01)	0.86 (0.73, 1.01)
Cadmium Quintile *(ug/L)*					
Quintile 1 (0.10-0.20)	187/1047	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Quintile 2 (0.30-0.30)	83/566	0.69 (0.48, 0.98)	0.69 (0.48, 0.99)	0.67 (0.47, 0.96)	0.68 (0.48, 0.97)
Quintile 3 (0.40-0.40)	123/593	1.29 (0.89, 1.88)	1.29 (0.88, 1.88)	1.23 (0.85, 1.79)	1.26 (0.87, 1.81)
Quintile 4 (0.50-0.70)	109/796	0.73 (0.53, 1.02)	0.70 (0.49, 1.00)	0.68 (0.48, 0.97)	0.68 (0.48, 0.98)
Quintile 5 (0.80-8.50)	133/696	0.94 (0.68, 1.29)	0.87 (0.60, 1.26)	0.84 (0.58, 1.22)	0.84 (0.58, 1.23)
P -Trend		*0.5974*	*0.4320*	*0.3140*	*0.3224*
Lead					
Log(Lead) IQR[f]		1.19 (0.97, 1.47)	1.20 (0.99, 1.47)	1.17 (0.95, 1.43)	1.15 (0.94, 1.42)
Lead Quintile *(µg/dL)*					
Quintile 1 (0.20-0.80)	94/659	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Quintile 2 (0.90-1.30)	126/872	0.92 (0.65, 1.32)	0.93 (0.65, 1.33)	0.92 (0.64, 1.33)	0.90 (0.63, 1.29)
Quintile 3 (1.40-1.80)	107/689	0.76 (0.51, 1.13)	0.77 (0.52, 1.15)	0.76 (0.51, 1.13)	0.74 (0.49, 1.11)
Quintile 4 (1.90-2.70)	133/738	0.92 (0.58, 1.45)	0.93 (0.59, 1.45)	0.90 (0.57, 1.41)	0.87 (0.56, 1.37)
Quintile 5 (2.80-54.00)	175/740	1.32 (0.83, 2.10)	1.34 (0.84, 2.13)	1.26 (0.78, 2.03)	1.23 (0.76, 1.97)
P -Trend		*0.2198*	*0.1863*	*0.3182*	*0.3506*

[a] Model A was adjusted for age, age^2, sex, race/ethnicity, and education. Cadmium models were further adjusted for lead; lead models were further adjusted for cadmium.

[b] Model B: Metal A + further adjusted for body mass index, ototoxic medication, cumulative cigarette pack-years, current dx of hypertension, and current dx of diabetes.
[c] Model C: Model B + further adjusted for occupation noise.
[d] Model D: Model C + further adjusted for recreation noise, and firearm noise.
[e] Percent change in hearing thresholds for interquartile range (IQR) increase of Log-transformed cadmium: log0.6-log0.2
[f] Percent change in hearing thresholds for interquartile range (IQR) increase of Log-transformed lead: log2.5-log1

Table III-6. Multivariate-adjusted[a] percent change (95% CIs) of hearing thresholds (dB) by blood cadmium and lead levels at various noise exposures.

Variables	None noise exposure[a]	Noise exposure 1[b]	Noise exposure 2[c]
Cadmium			
Subjects No.	1385	1673	564
Log(Cadmium) IQR[e]	10.73 (3.23, 18.79)	2.43 (-4.21, 9.53)	9.70 (-2.35, 23.23)
Cadmium Quintile *(ug/L)*			
Quintile 1 (0.10-0.20)	0 (Reference)	0 (Reference)	0 (Reference)
Quintile 2 (0.30-0.30)	-7.02 (-10.38, 5.93)	-2.06 (15.36, 13.32)	22.32 (-4.65, 56.92)
Quintile 3 (0.40-0.40)	-0.81 (-10.96, 10.51)	0.45 (-11.35, 13.83)	10.81 (-10.44, 37.09)
Quintile 4 (0.50-0.70)	5.09 (-7.87, 19.88)	4.12 (-6.72, 16.23)	16.09 (-5.26, 42.25)
Quintile 5 (0.80-8.50)	22.38 (8.16, 38.47)	4.14 (-8.86, 18.99)	23.78 (-1.93, 56.23)
P -Trend	*0.0151*	*0.5240*	*0.0756*
Lead			
Subjects No.	1385	1673	564
Log(Lead) IQR[f]	7.47 (0.20, 15.26)	8.67 (1.91, 15.88)	3.87 (-4.39, 12.84)
Lead Quintile *(μg/dL)*			
Quintile 1 (0.20-0.80)	0 (Reference)	0 (Reference)	0 (Reference)
Quintile 2 (0.90-1.30)	6.22 (-7.05, 21.37)	-10.53 (-21.89, 2.48)	12.11 (-16.58 50.66)
Quintile 3 (1.40-1.80)	9.98 (-3.08, 24.80)	5.35 (-11.40, 25.26)	5.11 (-16.89, 32.92)
Quintile 4 (1.90-2.70)	15.60 (1.91, 31.12)	11.99 (-4.04, 30.69)	2.21 (-20.71, 31.74)
Quintile 5 (2.80-54.00)	21.17 (3.06, 42.46)	18.66 (2.33, 37.59)	13.98 (-13.16, 49.60)
P -Trend	*0.0060*	*0.0008*	*0.7288*

[a] Models were adjusted for cadmium, age, age2, sex, race/ethnicity, education, body mass index, ototoxic medication, cumulative cigarette pack-years, current dx of hypertension, and current dx of diabetes.

[a] Subjects un-exposed at occupation, firearm and recreation noises.

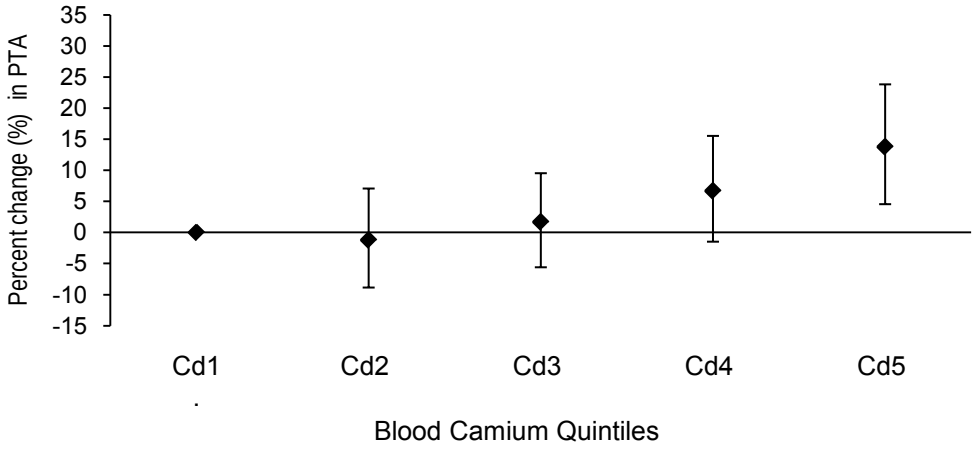
[b] Subjects exposed at one kind of occupation, firearm and recreation noises.

[c] Subjects exposed at two or three kinds of occupation, firearm and recreation noises.

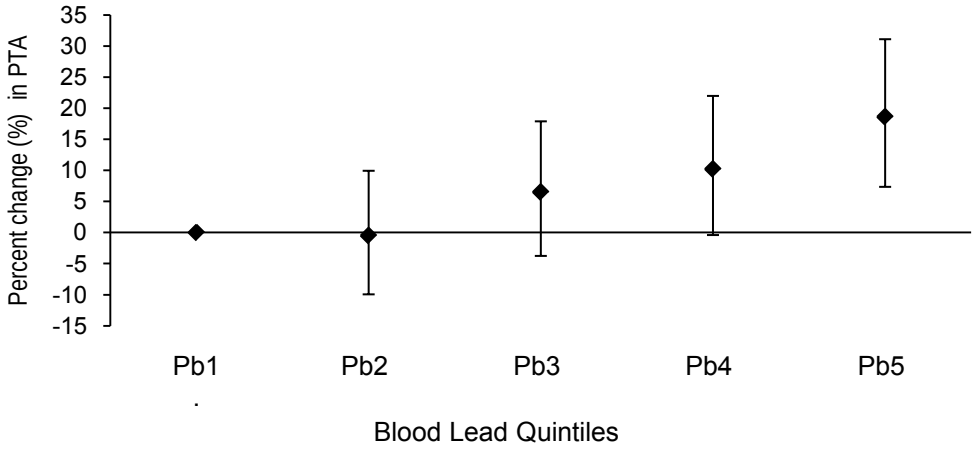
[e] Percent change in hearing thresholds for interquartile range (IQR) increase of Log-transformed cadmium: log0.6-log0.2

[f] Percent change in hearing thresholds for interquartile range (IQR) increase of Log-transformed lead: log2.5-log1

Figure III-1. Percent change (95% CIs) of hearing thresholds (dB) by blood cadmium and lead levels



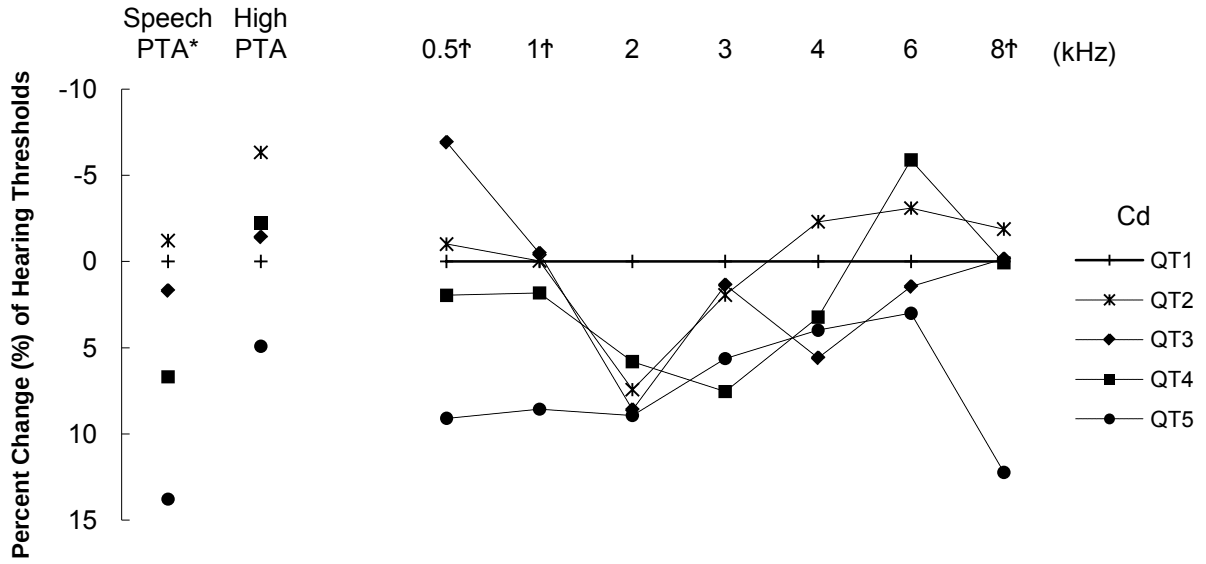
(a) by Cadmium levels



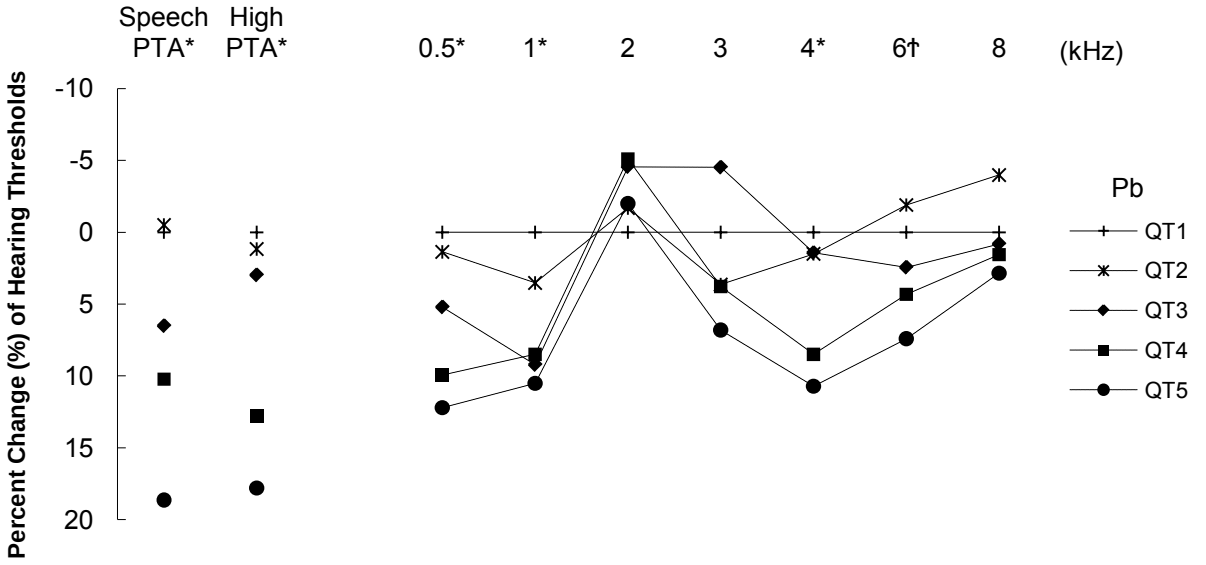
(b) by Lead levels

Models were adjusted for age, age^2, sex, race/ethnicity, education, body mass index, ototoxic medication, cumulative cigarette pack-years, current dx of hypertension, current dx of diabetes, occupation noise, recreation noise, and firearm noise. Cadmium models were further adjusted for lead; lead models were further adjusted for cadmium.

Figure III-2. Percent change (%) of hearing thresholds (dB) by blood cadmium and lead levels at each frequency from 0.5 kHz to 8 kHz.



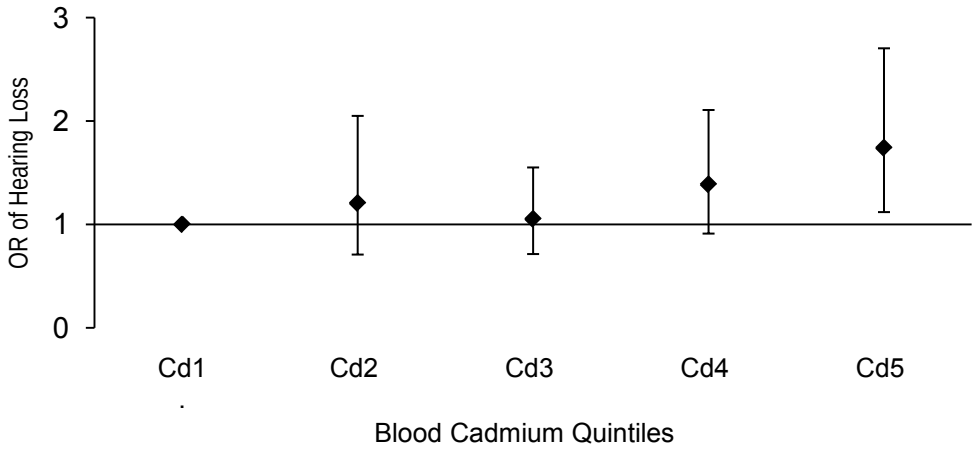
(a) by Cadmium levels



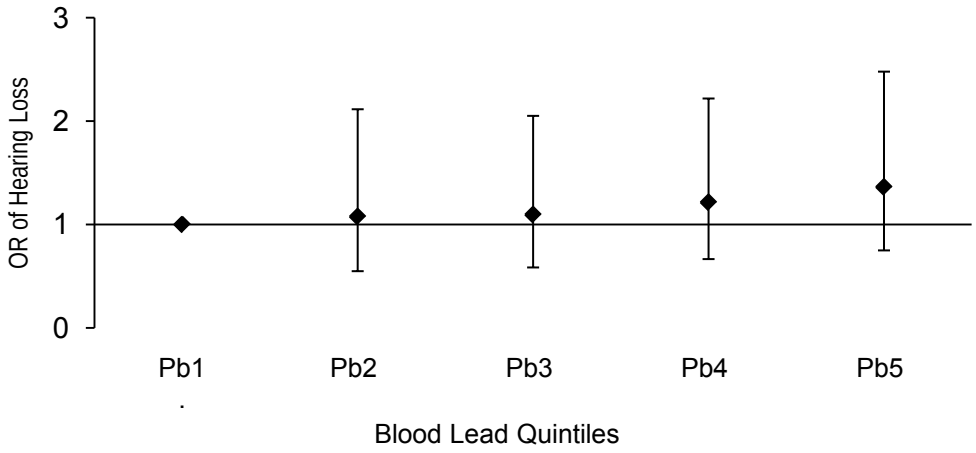
(b) by Lead levels

Models were adjusted for age, age^2, sex, race/ethnicity, education, body mass index, ototoxic medication, cumulative cigarette pack-years, current dx of hypertension, current dx of diabetes, occupation noise, recreation noise, and firearm noise. Cadmium models were further adjusted for lead; lead models were further adjusted for cadmium.
*Significant trend across quintiles *($p<0.05$)*

Figure III-3. ORs (95% CIs) of hearing loss by blood cadmium and lead levels.



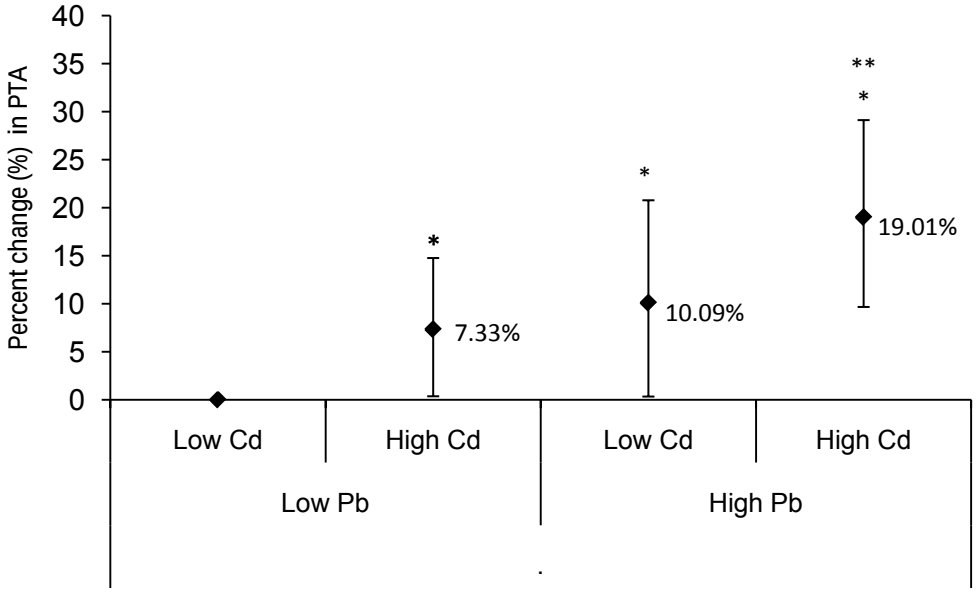
(a) by Cadmium levels



(b) by Lead levels

Models were adjusted for age, age^2, sex, race/ethnicity, education, body mass index, ototoxic medication, cumulative cigarette pack-years, current dx of hypertension, current dx of diabetes, occupation noise, recreation noise, and firearm noise. Cadmium models were further adjusted for lead; lead models were further adjusted for cadmium.

Figure III-4. Multivariate-adjusted[a] percent change (95% CIs) of hearing thresholds (dB) by combined exposures of lead and cadmium.



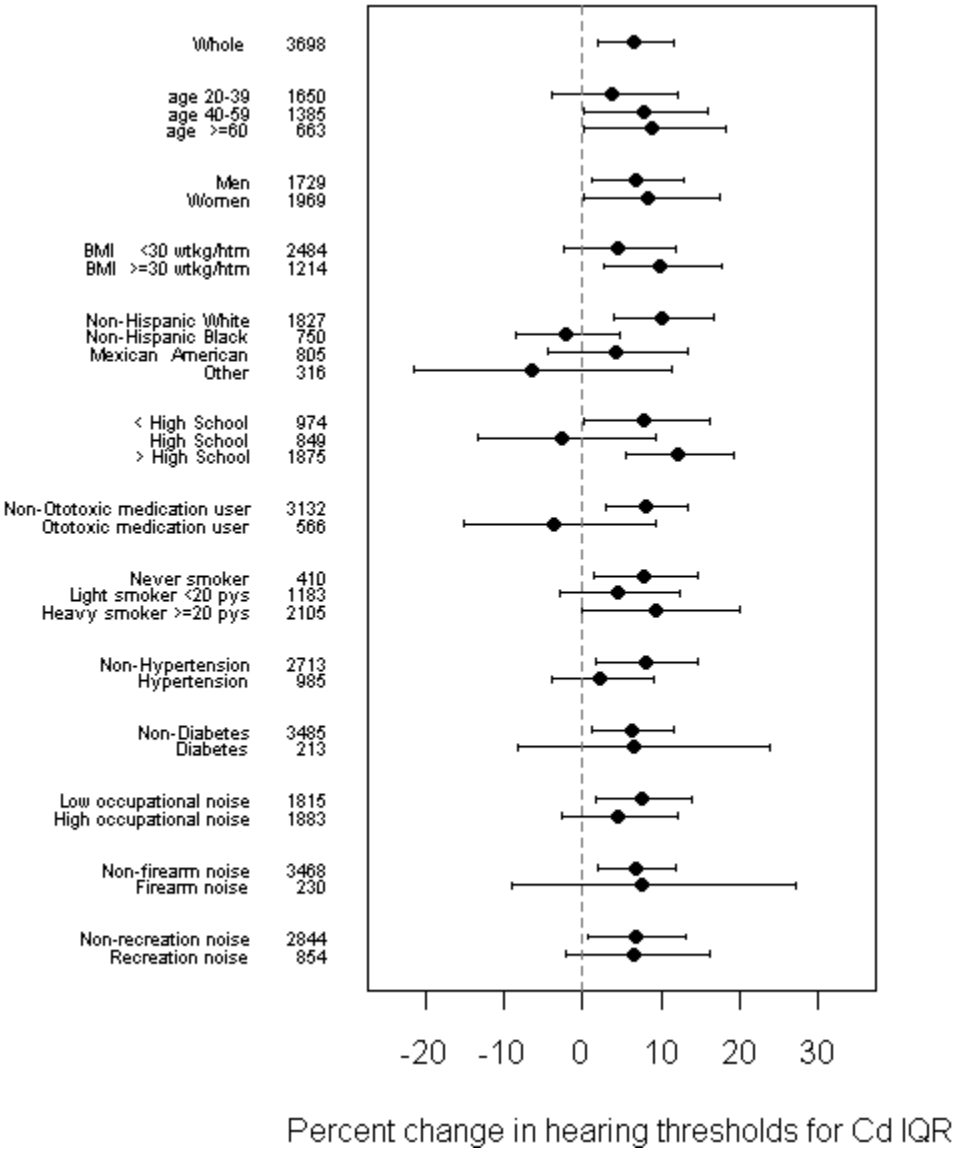
[a] Regression model was adjusted for age, age^2, bmi, sex, race/ethnicity, education, ototoxic medication, cumulative cigarette packyears, current dx of hypertension, current dx of diabetes, occupation noise, recreation noise and firarm noise.

[*] Comparison with [low Cd/low Pb] group.

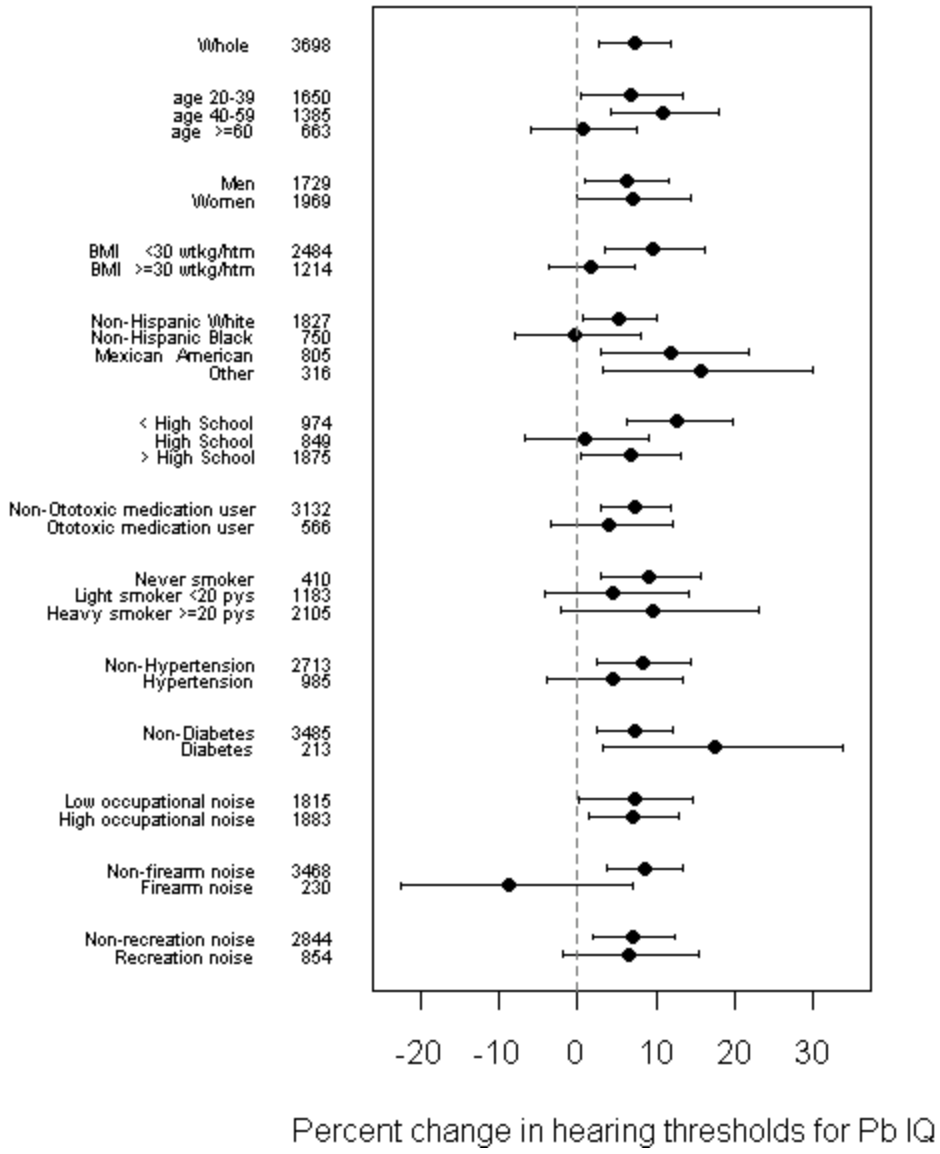
[**] Comparison with [low Cd/high Pb] group.

[***] Comparison with [high Cd/high Pb] group.

Figure III-5. Multivariate-adjusted[a] Percent change (95% CIs) of hearing thresholds (dB) for cadmium IQR[b] and lead IQR[c] increase by participants characteristics



(a) For cadmium



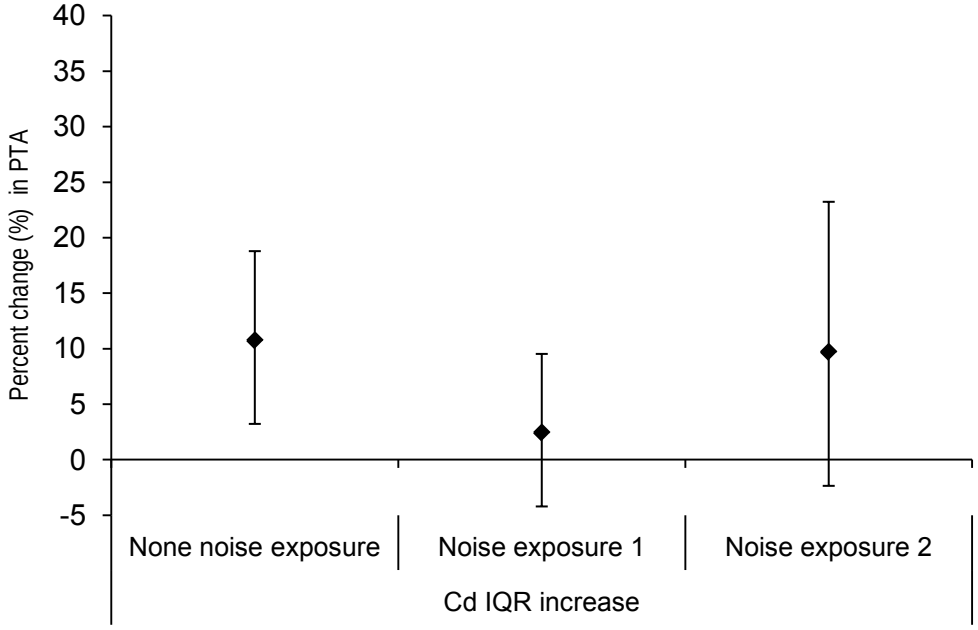
(b) For lead

[a]Regression model was adjusted for age, age^2, bmi, sex, race/ethnicity, education, ototoxic medication, cumulative cigarette packyears, current dx of hypertension, current dx of diabetes, occupation noise, recreation noise and firarm noise.

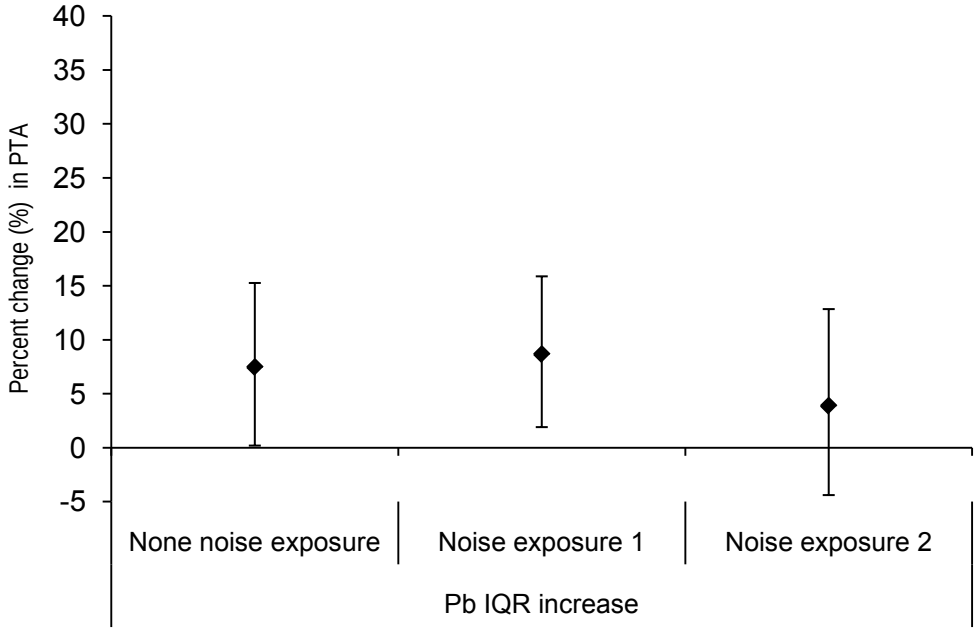
[b]Percent change in hearing thresholds for interquartile range (IQR) increase of Log (cadmium): log0.6-log0.2

[c]Percent change in hearing thresholds for interquartile range (IQR) increase of Log (lead): log2.5-log1

Figure III-6. Multivariate-adjusted[a] Percent change (95% CIs) of hearing thresholds(dB) for cadmium IQR[b] and lead IQR[c] increase at various noise exposures.



(a) For cadmium



(a) For lead

[a] Regression model was adjusted for age, age^2, bmi, sex, race/ethnicity, education, ototoxic medication, cumulative cigarette packyears, current dx of hypertension, current dx of diabetes, occupation noise, recreation noise and firarm noise. Cadmium models were further adjusted for lead; lead models were further adjusted for cadmium.

[b] Percent change in hearing thresholds for interquartile range (IQR) increase of Log (cadmium): log0.6-log0.2

[c] Percent change in hearing thresholds for interquartile range (IQR) increase of Log (lead): log2.5-log1

None noise exposure: subjects un-exposed at occupation, firearm and recreation noises.

Noise exposure 1: subjects exposed at one kind of occupation, firearm and recreation noises.

Noise exposure 2: subjects exposed at two or three kinds of occupation, firearmand recreation noises.

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CHAPTER IV

Dietary Intakes of antioxidants, Calcium, and Magnesium and Hearing Disability: the National Health and Nutrition Examination Survey 2001-2004

ABSTRACT

Background: Hearing loss is one of the common chronic health disabilities experienced by older adults, and the number of people with hearing loss tends to increase dramatically with advancing age. Dietary β-carotene, vitamin C, and vitamin E intake act as free radical scavengers and have been proposed to reduce the risk of hearing loss. Those antioxidant agents have also been reported to reduce noise–induced vasoconstriction and act in synergy with dietary magnesium intake in animal experiments. Calcium plays an important role in the pathogenesis of hearing loss, and thus, the impact of dietary antioxidants on hearing loss may depend on dietary calcium intake.

Objective: This study investigated whether higher intakes of dietary antioxidants (β-carotene, vitamins C and E), calcium and magnesium, and their combinations are beneficially associated with attenuation in hearing disability among adults.

Methods: We examined 2,607 adults from the National Health and Nutrition Examination Survey (NHANES) 2001-2004, a representative sample of the U.S. general population. Air-conduction hearing threshold was computed as a pure-tone average (PTA) of frequencies at 0.5, 1, 2 and 4 kHz. Quantitative dietary intake data were obtained by means of a 24-hour dietary recall interview. Antioxidant composite intakes were computed by summing the percentile rank scores of each antioxidant (either β-carotene and vitamin C or all three). Each dietary variable was first adjusted for total energy intake and then categorized into quartile.

Results: After controlling for potential confounders including occupational and non-occupational noise exposures and sociodemographic/clinical risk factors, the highest quartiles of β-carotene, calcium, and a composite of β-carotene plus vitamin C had 14.7% (95% confidence interval (CI), 7.4%, 21.4%), 8.9% (95% CI, 1.29%, 15.9%), and 13.0% (95% CI, 5.9%, 19.6%) reductions in PTA, respectively, and significant linear dose-dependent trends across the quartiles were seen. No significant association was found with intakes of vitamin C, vitamin E, magnesium, and the composite intake of all three antioxidants. There were significant synergistic interactions between the composite of β-carotene and vitamin C and both calcium and magnesium.

Conclusion: We found that higher intakes of β-carotene, calcium, and β-carotene plus vitamin C may reduce the risk of hearing loss. Antioxidant intakes combined with high calcium and/or magnesium intakes may be highly effective to reduce the risk of hearing loss. Our finding provides preliminary results for public health strategies to prevent or delay the hearing disability.

INTRODUCTION

Hearing loss is a major public health concern affecting more than 35 million people, reported by more than 17% of the adult population, in the U.S [1]. The prevalence of hearing loss rises significantly because of an aging population, growing use of listening devices, and ambient industrial chemicals [2]; the Alameda study reported the prevalence of age-adjusted hearing impairment in persons aged 50 years and older at four times intervals from 1965 to 1994 (n = 5108) [3].

Hearing loss affects communication, thereby it is associated with social isolation, educational opportunities, and job productivity, as well as economic success [4, 5]; in addition to cost of medical treatment or hearing aids, the hearing impaired persons are likely to be low income or unemployed (Average loss of income from underemployment per hearing impaired person was $9,741 in 1999 in US economy [6].) Therefore, identification of protective factors on hearing loss, with avoidance from known risk factors, is important.

The major clinical issue of whether diet could affect hearing loss came with the knowledge that noise-stress-induced metabolic activity, which in turn induces free radicals formation in inner ear, is a key mechanism in hearing loss [7-11]. This new understanding indicates antioxidants may be effective to prevent noise-induced hearing loss. In fact, animal experiments observed that antioxidants of β-carotene (metabolized to vitamin A in vivo), vitamin C and E respectively reduce free radicals formation and have therapeutic effect on hearing loss [7, 10, 12-18].

However, human-based epidemiologic studies of the associations of dietary β-carotene, vitamin C and E with hearing loss were inconsistent, despite the theoretical and

biological evidences [19-23]. A recent animal study indicates that although neither those antioxidants nor magnesium agent individually may have reliable reduction on hearing loss, together these antioxidants the mineral magnesium may act in synergistically to effectively prevent hearing loss [24]. One effect of magnesium is to reduce noise–induced vasoconstriction that occurs with free radical formation [9, 25-27]. Interestingly, calcium intake may act similarly to prevent hearing loss, with combined intakes of antioxidants, because excess calcium on the inner ear hair cells surface also is known to protect hearing loss by antibiotics [28-31]. A human case study, however, did not observe that, calcium supplementation protects against hearing loss [32].

The primary purpose of this study is to identify whether higher intakes of dietary antioxidants (β-carotene, vitamins C and E), calcium and magnesium are beneficially associated with attenuation in hearing disability in a well-defined general US population, and furthermore, to investigate the synergistic effect in their combined dietary intakes to effectively prevent hearing disability.

MATERIALS AND METHODS

Study Population.The NHANES is an ongoing series of cross-sectional surveys that collected health and nutritional information from a representative sample of the US civilian, non-institutionalized US population by using a complex, multistage, probability-sampling design. The survey, conducted by the National Center for Health Statistics (NCHS; Centers for Disease Control and Prevention (CDC)), includes an initial extensive households interview, followed by a standardized physical examination and an additional

questionnaire in specially equipped mobile examination centers (MECs), among the participants selected at random based on demographic distributions [33, 34]. Further details of the NHANES sampling process are available [34].

Data for this study included NHANES 2001-2002 and 2003-2004. NHANES 1999-2000 was excluded in this study because NHANES 1999-2000 does not provide a subclassified dietary intake data ; for example, NHANES 1999-2000 included only total carotenoid data but NHANES 2001-2004 had discrete carotenoid family data including β-carotene . [35-37]. In each survey cycle, half of the subjects aged 20 to 69 years were randomly assigned to participate in the Audiometry Examination Component. Subjects were excluded if they wore hearing aids and could not remove them for testing or if they had sufficient ear pain and could not tolerate headphones at the time of the exam [38]. The eligible sample size was 3,935 participants; 2,046 in 2001–2002, and 1,889 in 2003–2004, and we combined 2-year cycles of data to analyze 4 years of data per NCHS recommendations [33].

Audiometric Measurement. Audiometry examination was performed in a mobile examination center sound-isolated room by health technicians trained by a NIOSH (National Institute for Occupational Safety and Health) certified audiologist. Instrumentation for the Audiometry Component included an audiometer (Interacoustics Model AD226) with standard headphones (TDH-39) and insert earphones (Etymotic EarTone 3A) [39].

Pure tone air conduction hearing thresholds were obtained for each ear at frequencies from 0.5 to 8 kHz. We computed as a pure tone average (PTA) hearing

thresholds (dB) at speech frequencies (0.5, 1, 2 and 4 kHz), and as a pure tone average (high-PTA) hearing thresholds at high frequencies (3, 4, and 6 kHz) [1, 4].

To measure of the reliability of the participant's responses, the 1 kHz frequency was tested twice in each ear, and the pure tone audiograms that had a 10 dB or more difference between two tests were not accepted [39]. The participant who did not respond at one or more frequencies was coded as a non-response and treated as missing. Further details of audiometric test procedure have been described elsewhere [39, 40].

Of the initial sample of 3,935 participants eligible for inclusion in the audiometry examination, 324 (8.2%) participants were excluded from analysis because a test was not performed at all or at any frequency, and 3 participants were excluded by a 10 dB or more difference between the 1-kHz test-retest thresholds. Additional 297 (7.5%) participants were excluded as unilateral hearing loss which was defined as more than 10 dB difference between the PTAs of left and right ears. Therefore, audiometric results for 3311 participants were eligible in the present study.

Dietary Intake Assessment. β-carotene, vitamin C, vitamin E, calcium, and magnesium Intakes were assessed by a 24-hour dietary recall (24-h DR) interview of NHANES 2001 to 2004. The DR interview contains a list of all the foods and beverages consumed except plain drinking water and their detailed descriptions and amounts during the 24-hour period prior to the interview (midnight to midnight) [36, 37, 41].

In NHANES 2001, dietary intake data were collected using the NHANES computer-assisted dietary interview system (CADI), a multiple-pass recall method that provides instructions to interviewers for recording information about foods [36]. From

NHANES 2002 to 2004, data were collected using the US Department of Agriculture's dietary data collection instrument, the Automated Multiple Pass method (AMPM), a fully computerized recall method that includes an extensive compilation of standardized food-specific questions and possible response options [36, 37, 42]. To avoid errors from misreporting, individuals with unreliable or incomplete DR records were excluded as noted by the National Center for Health Statistics [43].

These data were then coded and linked to a database of foods and their nutrient composition. Calculations of total daily nutrient intakes were derived from these data. The University of Texas Food Intake Analysis System (FIAS, version 3.99) with the USDA 1994-98 Survey Nutrient Database was used for coding intakes for processing the 2001 intakes [36], and USDA's Food and Nutrient Database for Dietary Studies, 2.0 (FNDDS 2.0) was used for processing the 2002-2004 intakes [36, 37].

Of 3,311 participants with available audiometric measurements, 3,220 participants were eligible for dietary β-carotene, vitamin C, vitamin E, calcium, and magnesium intakes to the present study. Each dietary variable was adjusted for energy, using the residual method, in analysis [44].

Noise Exposure Assessment. Occupational noise exposures were evaluated by occupational noise estimates through a participant’s longest job tiles obtained by personal interview asking what kind of work the subject was doing the longest [45]. A recent study conducted by Choi reported a new occupational noise exposure assessment tool using the Occupational Network (O*NET) survey database, and validated its applicability in epidemiologic study of noise-induced hearing loss in a well-defined general population, NHANES [46]. This study introduced a useful tool to estimate the occupational noise as

scale scores (1 to 5) for "Sounds, Noise Levels are Distracting, etc." across the occupation groups of 801 Standardized Occupation Codes (SOC), if job title information is available in the absence of personal occupational noise exposure data. In the NHANES occupation questionnaire for the longest job, the participant answered as text or the same as current job, and the answer was coded to the 3-digit NCHS (National Center for Health Statistics) Occupational Classification Source Codes, which were collapsed into 41 occupation categories in the publicly available NHANES data [47, 48]. To link the O*NET noise estimates to 41 NHANES occupation categories, we grouped the 801 SOCs available in the O*NET into the corresponding 41 occupation categories and computed the averages of the O*NET noise scores in each category. For example, “Private household occupations” had the lowest score of 2.34, whereas “Textile, apparel, and furnishings machine operations” had the highest score of 4.59. Because military occupations were not included in the O*NET survey, we finally generated 40 available occupation groups. Finally, we assigned the longest job-related O*NET noise score to each participant as an occupation noise exposure.

Firearm noise exposures were defined by audiometry questionnaire asking if the subject had ever been exposed outside of work to the noise of a firearm a mean of at least once a month for 1 year. Recreation noise exposures were determined by audiometry questionnaire asking if the subject had ever been exposed outside of work to loud noise (e.g., power tools or loud music) for a mean of at least once a month for 1 year. Of 3,220 participants with available dietary data, 3,019 participants had available occupation, recreation, and firearm noise exposure.

Sociodemographic/Clinical Risk Factors. Other demographic and other hearing-related variables were obtained during a household's interview or at MEC.

Body mass index (BMI) was calculated as weight in kilograms/height in meters squared. Use of ototoxic medication was defined as use of any 4 drug class of aminoglycoside, loop diuretics, antineoplastic drugs, or nonsteroidal anti-inflammatory drugs. Smoking pack-years were computed, and participants were grouped into nonsmokers, smokers less than 20 pack-years, or smokers more than 20 pack-years. Hypertension was defined as self-reported physician diagnosis, the use of antihypertensive medication, systolic blood pressure ≥ 140mmHg, or diastolic blood pressure ≥ 90 mm Hg at the time of examination. Diabetes mellitus was defined as self-reported physician diagnosis or the use of antihyperglycemic medication.

Our study sample was limited to adults who had complete information on these important covariates, and therefore, a total of 2,607 participants were available for data analyses.

Antioxidant Composite Intake. The antioxidants composite score was computed by using the dietary composite scoring system based on percentile ranks of dietary intakes, to evaluate the effect of overall antioxidant intake [49]. We calculated 2 composite scores: (a) β-carotene plus vitamin C; (b) β-carotene plus vitamin C plus vitamin E. We first ranked and clustered the 2,607 subjects into 100 percentiles, by the order of energy-adjusted dietary intake [44] of each β-carotene, vitamin C, and vitamin E from the lowest into the highest one. If the subject had the highest intake of vitamin C, we assigned 100 for his/her dietary vitamin C score. Then, we defined the antioxidant

composite score of (a) β-carotene plus vitamin C (0≤scale≤200) by summing the 2 rank scores of β-carotene and vitamin C intakes. Similarly, the antioxidant composite score of (b) β-carotene plus vitamin C plus vitamin E (0≤scale≤300) was calculated by summing the 3 rank scores of β-carotene, vitamin C and vitamin E intakes.

Statistical analysis. All statistical analyses were performed using the SAS survey procedures (SAS 9.2) and the R survey package (R 2.9.1) to account for the complex survey design and sample weights of the NHANES 2001-2004 [50, 51]. We computed 4-year sample weights per NCHS recommendations and the sample weights were incorporated into all analyses, which were adjusted for oversampling and non-response of subjects such as ethnic minorities, elderly persons, and low income [52]. The statistical significant level was set as *P* values less than .05.

All regression analyses began with univariate analyses to identify outliers and influential points. Dietary variables of β-carotene, vitamin C, vitamin E, calcium, and magnesium and antioxidant composite variables were categorized into quartiles, respectively. To evaluate the combined effect of antioxidant composites intakes with calcium and magnesium intakes, we made 4 intake classes as low/low, low/high, high/low, high/high of the antioxidant composite score of (a) [β-carotene plus vitamin C] or (b) [β-carotene plus vitamin C plus vitamin E] by calcium or magnesium.

Hearing thresholds at PTA appeared to be right skewed and log-transformed to normalize distributions. For better interpretation of the regression results, we excluded 49 subjects who had zero or negative hearing thresholds (better-than-normal hearing) in our primary linear regression analyses with PTA at speech frequencies; 57 subjects with PTA

at high frequencies. Previous research confirmed that linear regressions in subjects with only positive hearing thresholds showed consistent patterns to those of linear regression in all available subjects in the NHANES population [46].

Models were adjusted for age, age-squared to capture nonlinear effects, sex, race/ethnicity, bmi, ototoxic medication, cumulative cigarette packyears, current diagnosis of hypertension, and current diagnosis of diabetes, occupational noise exposures, recreational noise exposures, and firearm noise exposures.

RESULTS

General Characteristics. Table IV-1 shows the characteristics of the study population. The study subjects included 2,607 adults aged 20 to 69 years (mean 42.06 (SE=0.33)). After accounting for four-year sampling weights, cluster and strata of the NHANES complex design, the mean of the PTA at speech frequencies and high frequencies was 12.68 (SE=0.35) dB and 18.78 (SE=0.59) dB. Overall, subjects had occupation noise exposure of O*NET noise score 3.06 (SE=0.02), which means that participants were averagely exposed almost "Once a month or more but not every week (score 3)" to “distracting and uncomfortable noise levels” at their occupations. 7.9% of subjects were exposed to firearm noise, and 27.3% were exposed to recreation noise.

Dietary Intakes and Hearing Thresholds. Table IV- 2 shows the percent changes in PTA in associations with intakes of β-carotene, vitamin C, vitamin E, calcium, magnesium, a composite of β-carotene plus vitamin C, and a composite of β-carotene plus vitamin C plus vitamin E as quartiles. From here, a composite of β-carotene plus

vitamin C is referred to as AC1 (antioxidant compound 1), and a composite of β-carotene plus vitamin C plus vitamin E is referred to as AC2 (antioxidant compound 2). After adjustment for potential confounders including sociodemographic factors, clinical risk factors, occupational and non-occupational noise exposures; β-carotene, AC1, and calcium intakes across quartiles had dose-dependent trends with reductions in PTA (better hearing ability), respectively. Compared with subjects in the lowest quartile of β-carotene, there was a significantly different reduction in PTA even in the second quartile of β-carotene (Q2: -8.76% (95% confidence interval (CI), -16.58 to -0.20), and consistently increasing reduction into the highest quartile (Q3: -12.98% (95% CI, -19.73 to -5.66), and Q4: -14.69% (95% CI, -21.38 to -7.42)). AC1 also showed significantly different reduction in PTA from the second quartiles (Q2: -12.89% (95% CI, -19.71 to -5.49)) and more difference in the third and highest quartile (Q3: -15.12% (95% CI, -22.08 to -7.53), and Q4: -13.01% (95% CI, -19.58 to -5.90)) with the lowest reduction. Calcium intake began to present statistically significant and increasing reduction in PTA from the third quartile (Q3: -8.43% (95% CI, -15.38 to -0.92), and Q4: -8.87% (95% CI, -15.87 to -1.29)).

No dose-dependent trends were found between percent change of PTA and intakes of vitamin C, vitamin E, magnesium, and AC2 across quartiles. Compared with subjects in the lowest quartiles, however, vitamin C, AC2, and magnesium showed reduction in PTA at their second, third, and highest quartiles, respectively, but most are not statistically significant differences and are not increasing in a reduction trend (vitamin C Q2: -6.52% (95% CI, -13.51 to 1.04), Q3: -7.41% (95% CI, -15.98 to 2.04), and Q4: -6.49% (95% CI, -13.75 to 1.38); AC2Q2: -7.93% (95% CI, -17.48 to 2.74), Q3:

-7.07% (95% CI, -14.07 to 0.50), and Q4: -7.55% (95% CI, -16.49 to 2.33); .and magnesium Q2: -8.66% (95% CI, -16.14 to -0.51), Q3: -9.25% (95% CI, -18.44 to 0.97), and Q4: -7.93% (95% CI, -18.16 to 3.59)). Vitamin E showed a positive difference in PTA (poorer hearing ability) at their second, third, and highest quartiles, respectively, compared to the lowest quartile of vitamin E.

The same trends were also observed in PTA at high frequencies (see Table IV-3). Dose-dependent reduction trends were statistically significant across intake quartiles for β -carotene, AC1, and calcium, and even for vitamin E, magnesium, AC2, and marginally, vitamin C in PTA at high frequencies.

Dietary Combined Effect. We evaluated whether combined intakes of dietary antioxidants (β-carotene, vitamins C and E, and their composites) and calcium and magnesium are beneficially associated with reduction in PTA. Table IV-4 shows the percent changes in PTA in associations with a combined variable of binary antioxidants and binary calcium or of binary antioxidants and magnesium in fully covariates-adjusted models. Cut-off points for binary dietary groups were defined on the basis of the first points that had significant difference with the lowest quartiles for β-carotene, vitamins C and E, calcium, and magnesium, AC1, and AC2 respectively, in associations with PTA; for calcium intake, Q1, 2 vs. Q3, 4; for the others, Q1 vs. Q2, 3, 4.

There are statistically significant reductions of PTA in [high-β-carotene/low-calcium], [high-β-carotene/high-calcium], [high-β-carotene/high-magnesium] groups among combination with β-carotene, in [high-vitamin C/high-calcium], [high-vitamin C/high-magnesium]; in [high-AC1/low-calcium], [high-AC1/ high-calcium], [high-AC1/

high-magnesium] among combination with AC1; and in [high-AC2/high-calcium], [high-AC2/high-magnesium] among combination with AC2. A synergistic effect was observed between β-carotene and both calcium and magnesium, between AC1 and both calcium and magnesium, and between AC2 and calcium (see Table IV-4). Among them, a combination with AC1 was the most effective to reduce PTA. Figure IV-1 presented percent changes of PTA at different levels of AC1 and calcium and magnesium intakes.

The magnitude of PTA reduction in the [high-AC1/high-calcium] group (vs. [low-AC1/low-calcium]) was greater than the sum of those in [low-β-AC1/high-calcium] and those in [high-AC1/low-calcium]; -18.77% (95% CI,-25.78, -11.09%) > -4.60% (95% CI, -14.87, 6.92%) plus -6.68% (95% CI, -18.02, 6.22%); and the reductions were significantly different from both of those groups, respectively. The magnitude of PTA reduction in the [high-AC1/high-magnesium] group (vs. [low-AC1/low-magnesium]) was greater than the sum of those in [low-AC1/high-magnesium] and those in [high-AC1//low-magnesium]; -15.41% (95% CI,-22.61, -7.54%) > -0.22% (95% CI, -10.54, 11.29%) plus -6.68% (95% CI, -18.02, 6.22%); and the reductions were significantly different from those in the [low-AC1/high-magnesium] group. The similar synergetic trends were also observed in β-carotene both with calcium and magnesium and in AC2 with calcium.

In higher intakes of vitamin C combined with both calcium and magnesium and higher intake of AC2 combined with magnesium, there were significant reductions in PTA but no synergetic effects by dietary combined intakes.

DISCUSSION

In a representative sample of the US population, the NHANES 2001-2004 evidenced that high intakes of dietary antioxidants (β-carotene, and a composite of β-carotene plus vitamin C) and calcium were independent protective factors on hearing loss among adults, and the antioxidants intakes played beneficial in synergy with high calcium and/or magnesium intakes to effectively prevent hearing loss.

At even low levels, people who intake dietary β-carotene, vitamin C, calcium, magnesium, and antioxidant composites (β-carotene plus vitamin C, β-carotene plus vitamin C plus vitamin E) had a protected effect against increase in pure tone average (PTA) hearing thresholds at speech frequencies versus those who did not intake nearly as much. Also, we found significant dose-dependent trends that increased intakes of dietary β-carotene, calcium, and a composite of β-carotene plus vitamin C accelerated the reduction in PTA.

At high frequencies, enhanced reduction in PTA was observed for each dietary factor. Even magnesium and a composite of β-carotene plus vitamin C plus vitamin E had significant dose-dependent reduction trends in PTA, which they did not have at speech frequencies. Our finding about the enhanced effect at high frequencies suggests that the protective effect by dietary intake may be associated with hearing loss particularly related to noise exposure.

Between antioxidants intakes and calcium/magnesium intakes, there were significant synergistic interactions on reduction in PTA. Combined intake of an antioxidant composite of β-carotene plus vitamin C with calcium/magnesium was the

most effective in reduction of PTA. Subjects both in high antioxidant (β-carotene plus vitamin C) intake and high calcium/magnesium intake groups had -18.77% (95% CI,-25.78, -11.09%)/ -15.41% (95% CI,-22.61, -7.54%) reductions in PTA (vs. both low intakes), and those reductions were also even greater than the sum of reductions by either high antioxidant intake or high calcium/magnesium intake. This suggests that combined dietary intakes of antioxidant with calcium/magnesium acts in synergy to prevent hearing loss.

The protective effect size by combined dietary intakes may roughly compensate the risk by the diabetes condition (15.40%), male vs. female (15.94%), and 6 years of aging (18.98%, when age is fit linearly), and one-unit increase of O*NET occupation noise scores (17.39%, corresponding to risk difference by noise between 'Fabricators, assemblers, inspectors, and samplers' occupations and 'Executive, administrators, and managers' occupations) on increase of hearing thresholds.

Numerous animal studies have suggested associations of hearing disability with antioxidants, calcium, and magnesium. However, few epidemiologic studies have investigated this; previous studies observed that association with β-carotene (vitamin A) and vitamin C and E were inconsistent [19-23], no association with calcium [32], and an association with magnesium [20].

This is the first epidemiologic study to observe an association of hearing disability with dietary calcium. Also, this study confirmed a protective effect of β-carotene (vitamin A) and vitamin C on hearing loss that was biologically enabled but has been controversial in human data. Moreover, this study extends the evidence of a synergistic protective

effect of antioxidants with magnesium intake on hearing loss, which has been suggested in animal experiments [24], into human data, and additionally found a synergistic protective effect with calcium intake on hearing loss.

An association with vitamin E was not observed. A possible explanation is by a difference in antioxidant free radical scavenging ability (results in prevention on hearing loss) because of differences in mechanism and action sites between vitamin E and other antioxidant vitamins [16, 53]. The scavenging of free radicals by β-carotene or vitamin C occurs in the aqueous phase, while vitamin E usually comes from lipophilic sources such as fish oil and scavenges free radical in the cell membrane [17, 18, 54]. Another possible explanation is that dietary vitamin E intake may be too low to show an association in NHANES. Although the association was not observed in NHANES, we cannot exclude the possibility that hearing loss may be associated with vitamin E in higher dietary levels or in both diet and supplements.

Given inevitable risk factors, our finding suggests, eating foods that contain β-carotene, vitamin C, calcium, and magnesium contributes to effectively reduce the risk of hearing loss. β-carotene is found in many yellow and orange vegetables, eggs, butter, and liver; vitamin C is plentiful in citrus fruit; calcium and magnesium are commonly found in milk (particularly for calcium) and other dairy, green leafy vegetables, nuts and whole grain, and fish.

The main strengths of this study include a) the use of a representative sample of the US general population, including oversampled minority populations with sampling weights, which overcomes selection bias and enables the observed results to be

generalized; b) the adjustment for important potential confounding in associations of dietary intake with hearing loss, including risk factors; c) the use of NHANES data conducted with strict quality control procedures.

This study has several limitations to be considered. Although NHANES data is a well-defined representative sample of the U.S., a causal-effect relationship cannot be referred to between food consumption and hearing loss, because the data are a cross-sectional observation. Furthermore, this study includes only dietary nutrition but excludes one through the supplements; we may not observe an association between overall nutrition and hearing loss. We also cannot rule out bias from dietary assessment using a 24-hour dietary recall. 24-hour dietary recall may induce recall bias in an interview, and may be restricted to explain representative and usual diet patterns of participants, however, such bias is likely to be non-differential for participants and lead to a true association towards the null.

In summary, after controlling confounders, dietary antioxidants, calcium, magnesium, and their combined intakes have a protective effect going beyond adverse effects by traditional risk factors on hearing loss. This study provides dietary strategies of prevention and therapeutic treatment of hearing loss.

Table IV-1. Participants characteristics, NHANES 2001-2004[a]

Characteristic	Participants (N=2607)[b]
Pure Tone Average Hearing Thresholds *(dB)* at speech frequencies[c]	12.68 (± 0.35)[e]
Pure Tone Average Hearing Thresholds *(dB)* at high frequencies[d]	18.78 (± 0.59)
Netrient	
β-carotene *(mg)*	1945.37 (± 100.21)
Vitamin C *(mg)*	90.62 (± 3.44)
Vitamin E *(mg)*	3.68 (± 0.17)
β-carotene + Vitamin C *(Dietary score)*[f]	96.43 (± 1.61)
β-carotene + Vitamin C + Vitamin E *(Dietary score)*[g]	145.21 (± 2.28)
Calcium *(mg)*	879.71 (± 16.27)
Magnesium *(mg)*	286.01 (± 3.88)
Age *(y)*	42.06 (± 0.33)
Body mass ndex *(wtkg/htm)*	27.98 (± 0.14)
Noise exposures	
Occupation noise exposure[h] *(O*NET score)*	3.06 (± 0.02)
Firearm noise exposure *(Exposed %)*	7.9[i]
Reacreation noise exposure *(Exposed %)*	27.3
Sex *(Male %)*	47.8
Race ethnicity (%)	
Non-Hispanic White	73.1
Non-Hispanic Black	11.2
Mexican American	6.7
Other	9.0
Education (%)	
< High School	14.9
High School	25.1
> High School	60.0
Ototoxic medication *(Current use %)*	14.4
Cumulative cigarette packyears (%)	
Never	54.5
<20	33.2
≥20	12.3
Hypertension *(%)*	23.6
Diabetes mellitus *(%)*	4.5

[a] Four-year sample weights applied.

[b] Participants (N=2607) are the individuals having all interest variables in this study: hearing thresholds, hearing loss, age, body mass index, sex, race ethnicity, ototoxic medication, cumulative cigratte pack-years, hypertension, diabetes mellitus, occupaiton noise exposure, firearm noise exposure, and recreation noise exposure.

[c] Pure tone average at speech frequencies at 0.5, 1, 2, and 4 kHz.

[d] Pure tone average at high frequencies at 3, 4, and 6 kHz.

[e] Weighted mean (± SE) (all such values).

[f] Dietary compund score is sum of ranked percentages of β-carotene and Vitamin C intakes (0<dietary score<200).

[g] Dietary compund score is sum of ranked percentages of β-carotene, Vitamin C, and Vitamin E intakes (0<dietary score<300).

[h] O*NET noise score (1 < Noise scale < 5).

[i] Weighted percentages (all such values).

Table IV-2. Multivariate-adjusted[a] percent change (95% CIs) of hearing thresholds (dB) by dietary intakes quartiles (Q)[b] .

	Q 1	Q 2	Q 3	Q 4	*p-Trend*
β -Carotene	0 (Ref)	-8.76 (-16.58 , -0.20)	-12.98 (-19.73 , -5.66)	-14.69 (-21.38 , -7.42)	*0.0002*
Vitamin C	0 (Ref)	-6.52 (-13.51 , 1.04)	-7.41 (-15.98 , 2.04)	-6.49 (-13.75 , 1.38)	*0.1445*
Vitamin E	0 (Ref)	5.59 (-3.17 , 15.15)	9.51 (-2.12 , 22.52)	3.39 (-5.31 , 12.90)	*0.4012*
β- Carotene + Vitamin C[c] (AC1)	0 (Ref)	-12.89 (-19.71 , -5.49)	-15.12 (-22.08 , -7.53)	-13.01 (-19.58 , -5.90)	*0.0012*
β- Carotene + Vitamin C +Vitamin E[c] (AC2)	0 (Ref)	-7.93 (-17.48 , 2.74)	-7.07 (-14.07 , 0.50)	-7.55 (-16.49 , 2.33)	*0.1409*
Calcium	0 (Ref)	-0.79 (-9.95 , 9.29)	-8.43 (-15.38 , -0.92)	-8.87 (-15.87 , -1.29)	*0.0110*
Magnesium	0 (Ref)	-8.66 (-16.14 , -0.51)	-9.25 (-18.44 , 0.97)	-7.93 (-18.16 , 3.59)	*0.2108*

[a] Adjusted for age, age2, sex, race/ethnicity, ototoxic medication, cumulative cigarette pack-years, current dx of hypertension, current dx of diabetes, occupation noise, recreation noise and firearm noise.

[b] Each dietary intake or dietary compound intake was categorized into quartiels.

[c] Antioxidant composit (AC) score is sum of ranked percentages of each β-carotene and Vitamin C (and Vitamin E) intake.

Table IV-3. Multivariate-adjusted[a] percent change (95% CIs) of hearing thresholds (dB) at high frequencies by dietary intakes quartiles (Q)[b].

	Q 1	Q 2	Q 3	Q 4	*p-Trend*
β-Carotene	0 (Ref)	-2.88 (-11.43 , 6.49)	-9.88 (-16.34 , -2.92)	-14.94 (-21.40 , -7.95)	*<.0001*
Vitamin C	0 (Ref)	-4.15 (-12.37 , 4.84)	-3.60 (-12.69 , 6.43)	-7.63 (-14.73 , 0.06)	*0.0895*
Vitamin E	0 (Ref)	6.30 (-2.44 , 15.82)	8.30 (-3.87 , 22.00)	2.85 (-6.27 , 12.86)	*0.5215*
β- Carotene + Vitamin C[c] (AC1)	0 (Ref)	-6.13 (-13.67 , 2.08)	-11.52 (-19.75 , -2.44)	-14.08 (-19.79 , -7.96)	*<.0001*
β- Carotene + Vitamin C +Vitamin E[c] (AC2)	0 (Ref)	-9.31 (-17.03 , -0.88)	-4.19 (-12.10 , 4.43)	-11.10 (-18.74 , -2.74)	*0.0359*
Calcium	0 (Ref)	0.56 (-7.17 , 8.93)	-8.01 (-16.03 , 0.78)	-7.06 (-14.62 , 1.16)	*0.050*
Magnesium	0 (Ref)	-7.17 (-15.86 , 2.42)	-11.09 (-20.20 , -0.94)	-10.07 (-18.14 , -1.21)	*0.0324*

[a] Adjusted for age, age2, sex, race/ethnicity, ototoxic medication, cumulative cigarette pack-years, current dx of hypertension, current dx of diabetes occupation noise, recreation noise and firearm noise

[b] Each dietary intake or dietary compound intake was categorized into quartiels.

[c] Antioxidant composit (AC) score is sum of ranked percentages of each β-carotene and Vitamin C (and Vitamin E) intake.

Table IV-4. Multivariate-adjusted[a] Percent change (95% CIs) of hearing thresholds(dB) by a combination of dietary intakes

	Calcium[d]				Magnesium[d]			
	Low[c] /Low[d]	Low /High	High/Low	High/High	Low[c] /Low[d]	Low/High	High/Low	High/High
ß-carotene[c]	0 (Ref)[b]	-3.1 (-15.3 , 10.7)	-8.8 (-16.0 , -1.0)	-17.1 (-24.8 , -8.6)[1 2]	0 (Ref)	-2.7 (-14.3 , 10.3)	-7.1 (-15.8 , 2.5)	-15.0 (-22.9 , -6.4)[1]
Vitamin C	0 (Ref)	-9.0 (-17.6 , 0.6)	-6.6 (-14.7 , 2.3)	-13.4 (-21.0 , -5.1)	0 (Ref)	-8.3 (-19.8 , 4.9)	-6.0 (-15.4 , 4.4)	-12.6 (-21.2 , -3.0)
Vitamin E	0 (Ref)	-4.1 (-11.7 , 4.2)	9.7 (0.7 , 19.6)[1]	-1.3 (-9.3 , 7.5)[2]	0 (Ref)	-12.3 (-25.6 , 3.5)	3.1 (-11.6 , 20.3)[1]	-4.8 (-15.9 , 7.9)
β-carotene + Vitamin C (AC1)	0 (Ref)	-4.6 (-14.9 , 6.9)	-11.4 (-19.0 , -3.0)	-18.8 (-25.8 , -11.1)[1 2]	0 (Ref)	-0.2 (-10.5 , 11.3)	-6.7 (-18.0 , 6.2)	-15.4 (-22.6 , -7.5)[1]
β-carotene + Vitamin C + Vitamin E (AC2)	0 (Ref)	-5.7 (-15.3 , 5.0)	-5.5 (-13.8 , 3.5)	-13.7 (-21.2 , -5.6)[2]	0 (Ref)	-10.5 (-19.6 , -0.3)	-9.6 (-19.7 , 1.6)	-14.1 (-21.5 , -6.0)

[a] Regression model was adjusted for age, age[2], bmi, sex, race/ethnicity, ototoxic medication, cumulative cigarette packyears, current dx of hypertension, current dx of diabetes, occupation noise, recreation noise and firearm noise

[b] *Ref,* reference

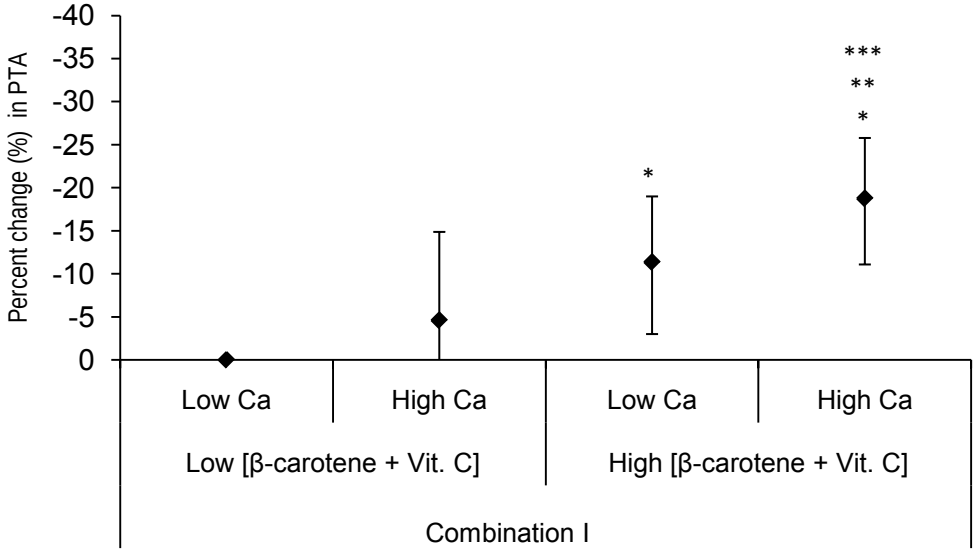
[c] Intake in a antioxidant (row) agent

[d] Intake in a calcium or magnesium (column) agent

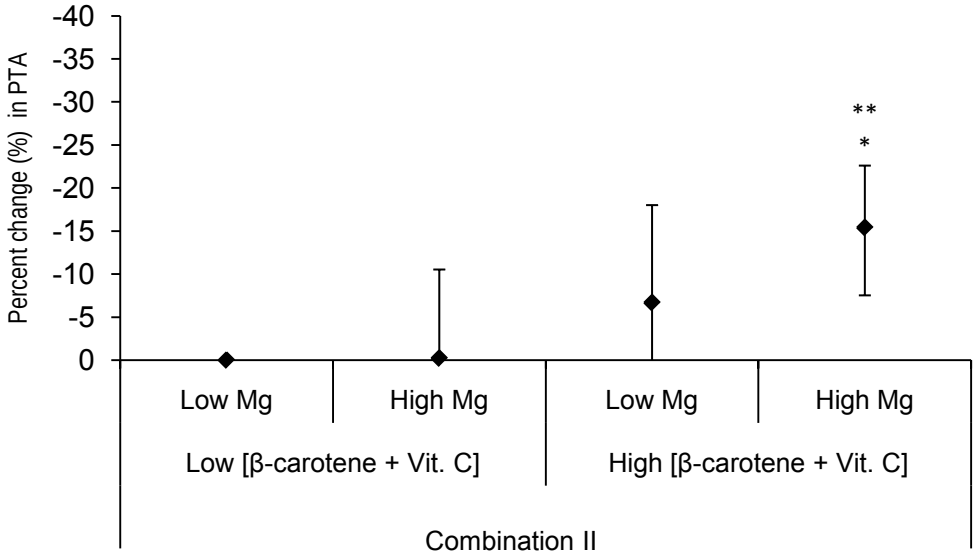
[1] Comparison with the group of low antioxidant and high calcium or magnesium *($p<0.05$)*.

[2] Comparison with the group of high antioxidant and low calcium or magnesium *($p<0.05$).*

Figure IV-1. Multivariate-adjusted[a] Percent change (95% CIs) of hearing thresholds(dB) by a combined intake of AC1(β-carotene + Vitamin C) with calcium.



(a) AC1 (β-carotene + vitamin C) / calcium



(b) AC1 (β-carotene + vitamin C) / magnesium

[a] Regression model was adjusted for age, age^2, bmi, sex, race/ethnicity, ototoxic medication, cumulative cigarette packyears, current dx of hypertension, current dx of diabetes, occupation noise, recreation noise and firarm noise.

[*] Comparison with [low AC1] / [low calcium or magnesium] intake group *(p<0.05).*

[**] Comparison with [low AC1] / [high calciumor magnesium] intake group *(p<0.05).*

[***] Comparison with [high AC1] / [low calcium or magnesium] intake group *(p<0.05)* .

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CHAPTER V

Therapeutic Effect of Dietary intake on Noise-Induced Hearing Loss and Metals- Induced Hearing Loss: the National Health and Nutrition Examination Survey 2001-2004

ABSTRACT

Background. The prevalence of hearing loss increases significantly with an aging population as well as growing risk factors of noise exposures, such as occupation and recreation noise (Chapter II), and industrial ototoxic chemicals exposures, such as lead, cadmium (Chapter III) [1]. Our recent epidemiologic study in U.S. population observed that dietary antioxidants intake (β-carotene, vitamins C and E) combined with calcium and magnesium is beneficially associated with attenuation in hearing disability (Chapter IV). With avoiding known risk factors (Chapter II and III) and taking known protective factors (Chapter IV), in order to effectively prevent hearing loss, it is important to identify how protective factors beneficially interact with risk factors on hearing loss.

Objective. This study investigated whether higher intakes of dietary antioxidants, calcium and magnesium are beneficially associated with attenuation in noise-induced hearing loss and metals-induced hearing loss among adults.

Methods. This is a cross-sectional study comprising 2,607 adults for dietary interaction with noise and 2,517 adults for dietary interaction with metals on hearing loss from the National Health and Nutrition Examination Survey (NHANES) 2001-2004. Air-conduction hearing threshold was computed as a pure-tone average (PTA) of frequencies at 0.5, 1, 2 and 4 kHz. Quantitative dietary intake data were obtained by means of a 24-hour dietary recall interview. Occupation noise and non-occupation noise exposures were estimated through participant's longest job using an occupation noise exposure assessment tool using the O*NET noise score (Chapter II) [2] and through intensive questionnaires, respectively. Blood cadmium and lead contents were measured by atomic absorption spectrometry in NHANES 2001-2002 and by inductively coupled plasma-mass spectrometry in NHANES 2003-2004. Linear regression models for either noise or metals were fit on log-transformed PTA as stratified models by various dietary intakes classes.

Results. By dietary intakes level, there was attenuated association of PTA with occupation noise. Among overall subjects, a unit increase in the O*NET occupation noise score was associated with a 19.16% (95% confidence interval (CI)=12.00 to 26.77%) multivariate adjusted increase in PTA. Among low intake subjects of antioxidants (β-carotene plus vitamin C) combined with calcium, there was high increase (poorer) in PTA with unit occupation noise (34.87% (95% CI=20.21 to 51.32%)), whereas high intake subjects of antioxidants combined with calcium showed attenuation in PTA

increase (10.59% (95% CI=3.28 to 18.42%)). The similar trend was also observed between high vs. low intake groups of antioxidants combined with magnesium. For the association of blood cadmium and lead with PTA, there was attenuation trend by dietary intakes level for antioxidants combined with neither calcium nor magnesium.

Conclusion. We found that higher intakes of dietary antioxidants, calcium and magnesium may reduce hazardous effect of chronic noise exposure on hearing loss among adults. The effect of cadmium and lead exposures on hearing loss was not likely to be attenuated in dietary intakes among adults. Our finding provides preliminary results for dietary strategies to effectively prevent hearing loss.

INTRODUCTION

Hearing loss is a major public health concern that increases dramatically with an aging population and with growing environmental factors of noise exposures and other ototoxic chemicals [1, 3-9]. Hearing impairment affects communication ability and emotional status, and results in economic loss such as medical expense and unemployment [10-12].

The most direct way to prevent hearing loss is to identify potential risk factors and to avoid identified factors. However, if risk factors were unavoidable at all or to some extent, it is important to explore ways to reduce susceptibility for those factors on hearing loss.

This thesis identified risk factors of occupation noise exposure in Chapter II, cadmium and lead exposures in Chapter III, and protective factors through dietary intake in Chapter IV. Given inevitable noise and metals sources, Chapter V investigated how and how much dietary intake is able to reduce susceptibility for those exposures on hearing loss in a human population.

An advance of knowledge in the hearing loss mechanism has provided a clinical issue to effectively attenuate hearing loss. Noise exposure was reported to be associated with reactive oxygen species (ROS) formation and reduced blood flow [13, 14], and cadmium and lead exposures also are associated with ROS generation [15-20], which result in cell death in the inner ear and hearing loss. Higher intake of dietary antioxidants (β-carotene, vitamin C and E) is beneficially associated with reduction in ROS generation; animal experiments observed that antioxidants intake reduced the ROS and

hearing loss that were generated particularly by noise, cadmium, and lead exposures [19, 21-31] .

Also, those antioxidants intakes were observed to act in synergy with magnesium and calcium intake to effectively attenuate hearing loss in animal study by Le Prell and in a human study shown in Chapter IV [32].

The aims of this study are to investigate the effect modification by dietary antioxidants (β-carotene, vitamin C and E), calcium and magnesium intakes have in the association of noise, cadmium, and lead exposure with hearing loss, and furthermore, given inevitable exposures of noise and metal in a general human population, to effectively reduce individual susceptibility for noise-induced hearing loss and/or metals-induced hearing loss.

MATERIALS AND METHODS

Study Population. The NHANES is an ongoing series of cross-sectional surveys that collected health and nutritional information from a representative sample of the US civilian, non-institutionalized US population by using a complex, multistage, probability-sampling design. The survey, conducted by the National Center for Health Statistics (NCHS; Centers for Disease Control and Prevention (CDC)), includes an initial extensive households interview, followed by a standardized physical examination and an additional questionnaire in specially equipped mobile examination centers (MECs), among the

participants selected at random based on demographic distributions [33, 34]. Further details of the NHANES sampling process are available [34].

Data for this study included NHANES 2001-2002 and 2003-2004. NHANES 1999-2000 was excluded in this study because NHANES 1999-2000does not provide a subclassified dietary intake data ; for example, NHANES 1999-2000 included only total carotenoid data but NHANES 2001-2004 had discrete carotenoid family data including β-carotene . [35-37]. A continuous survey, NHANES, had changed focus on a variety of health and nutrition measurements to meet emerging needs [33]. In each survey cycle, half of the subjects aged 20 to 69 years were randomly assigned to participate in the Audiometry Examination Component. Subjects were excluded if they wore hearing aids and could not remove them for testing or if they had sufficient ear pain and could not tolerate headphones at the time of the exam [38]. The eligible sample size was 3,935 participants; 2,046 in 2001–2002, and 1,889 in 2003–2004, and we combined 2-year cycles of data to analyze 4 years of data per NCHS recommendations [33].

Audiometric Measures. Audiometry examination was performed in a mobile examination center sound-isolated room by health technicians trained by a NIOSH (National Institute for Occupational Safety and Health) certified audiologist. Instrumentation for the Audiometry Component included an audiometer (Interacoustics Model AD226) with standard headphones (TDH-39) and insert earphones (Etymotic EarTone 3A) [39].

Pure tone air conduction hearing thresholds were obtained for each ear at frequencies from 0.5 to 8 kHz, and we computed as a pure tone average (PTA) hearing thresholds (dB) at speech frequencies (0.5, 1, 2 and 4 kHz) [8, 10].

To measure of the reliability of the participant's responses, the 1 kHz frequency was tested twice in each ear, and the pure tone audiograms that had a 10 dB or more difference between two tests were not accepted [39]. The participant who did not respond at one or more frequencies was coded as a non-response and treated as missing. Further details of audiometric test procedure have been described elsewhere [39, 40].

Of the initial sample of 3,935 participants eligible for inclusion in the audiometry examination, 324 (8.2%) participants were excluded from analysis because a test was not performed at all or at any frequency, and 3 participants were excluded by a 10 dB or more difference between the 1-kHz test-retest thresholds. Additional 297 (7.5%) participants were excluded as unilateral hearing loss which was defined as more than 10 dB difference between the PTAs of left and right ears. Therefore, audiometric results for 3311 participants were eligible in the present study.

Dietary Intake Assessment. β-carotene, vitamin C, vitamin E, calcium, and magnesium Intakes were assessed by a 24-hour dietary recall (24-h DR) interview of NHANES 2001 to 2004. The DR interview contains a list of all the foods and beverages consumed except plain drinking water and their detailed descriptions and amounts during the 24-hour period prior to the interview (midnight to midnight) [36, 37, 41].

In NHANES 2001, dietary intake data were collected using the NHANES computer-assisted dietary interview system (CADI), a multiple-pass recall method that

provides instructions to interviewers for recording information about foods [36]. From NHANES 2002 to 2004, data were collected using the US Department of Agriculture's dietary data collection instrument, the Automated Multiple Pass method (AMPM), a fully computerized recall method that includes an extensive compilation of standardized food-specific questions and possible response options [36, 37, 42]. To avoid errors from misreporting, individuals with unreliable or incomplete DR records were excluded as noted by the National Center for Health Statistics [43].

These data were then coded and linked to a database of foods and their nutrient composition. Calculations of total daily nutrient intakes were derived from these data. The University of Texas Food Intake Analysis System (FIAS, version 3.99) with the USDA 1994-98 Survey Nutrient Database was used for coding intakes for processing the 2001 intakes [36], and USDA's Food and Nutrient Database for Dietary Studies, 2.0 (FNDDS 2.0) was used for processing the 2002-2004 intakes [36, 37].

Of 3,311 participants with available audiometric measurements, 3,220 participants were eligible for dietary β-carotene, vitamin C, vitamin E, calcium, and magnesium intakes to the present study. Each dietary variable was adjusted for energy, using the residual method, in analysis [44].

Noise Exposure Assessment. Occupational noise exposures were evaluated by occupational noise estimates through a participant’s longest job tiles obtained by personal interview asking what kind of work the subject was doing the longest [45]. A recent study conducted by Choi reported a new occupational noise exposure assessment tool using the Occupational Network (O*NET) survey database, and validated its applicability in epidemiologic study of noise-induced hearing loss in a well-defined general population,

NHANES [2]. This study introduced a useful tool to estimate the occupational noise as scale scores (1 to 5) for "Sounds, Noise Levels are Distracting, etc." across the occupation groups of 801 Standardized Occupation Codes (SOC), if job title information is available in the absence of personal occupational noise exposure data. In the NHANES occupation questionnaire for the longest job, the participant answered as text or the same as current job, and the answer was coded to the 3-digit NCHS (National Center for Health Statistics) Occupational Classification Source Codes, which were collapsed into 41 occupation categories in the publicly available NHANES data [46, 47]. To link the O*NET noise estimates to 41 NHANES occupation categories, we grouped the 801 SOCs available in the O*NET into the corresponding 41 occupation categories and computed the averages of the O*NET noise scores in each category. For example, “Private household occupations” had the lowest score of 2.34, whereas “Textile, apparel, and furnishings machine operations” had the highest score of 4.59. Because military occupations were not included in the O*NET survey, we finally generated 40 available occupation groups. Finally, we assigned the longest job-related O*NET noise score to each participant as an occupation noise exposure.

Firearm noise exposures were defined by audiometry questionnaire asking if the subject had ever been exposed outside of work to the noise of a firearm a mean of at least once a month for 1 year. Recreation noise exposures were determined by audiometry questionnaire asking if the subject had ever been exposed outside of work to loud noise (e.g., power tools or loud music) for a mean of at least once a month for 1 year. Of 3,220 participants with available dietary data, 3,019 participants had available occupation, recreation, and firearm noise exposure.

We also created a composite noise exposure variable using three different noise variables (occupational, firearm, and recreational noise), indicating exposure to from none to three noise sources. Noise composite exposure was defined to 4 classes; none, a kind, two kinds, and all three kinds of noise exposures at occupation, firearm, and recreation. Occupation noise exposures were defined as high half O*NET scored subjects (vs. low half scored subjects), and firearm and recreation noise exposures were determined by questionnaires.

Blood lead & cadmium. Blood for cadmium and lead was measured at the Environmental Health Sciences Laboratory of the CDC National Center for Environmental Health (NCEH) after confirmation of no background contamination in all collection and storage materials [48, 49]. Cadmium and lead concentrations were measured by a Perkin-Elmer model SIMAA 6000 simultaneous multielement atomic absorption spectrometer with Zeeman background correction in NHANES 1999-2002 [48, 50, 51] and by an inductively coupled plasma-mass spectrometer in NHANES 2003–2004 [52]. Of 4,811 participants with available audiometric measurement, 4,628 had valid blood cadmium and lead concentrations. The detection limit for cadmium was 0.3 μg/L in NHANES 1999-2002 and 0.2 μg/L in NHANES 2003-2004, and the detection limit for lead was 0.3 μg/dL in all three NHANES cycles. Of study participants, 26% and 17% had cadmium concentrations below the detection limit in NHANES 1999-2002 and NHANES 2003-2004, respectively, and 0.8% of the entire participants had blood lead concentrations below the detection limit [49, 53-56]. For these subjects, we imputed value equal to the detection limit divided by the square root of two [50]. The interassay coefficients of variation ranged from 4.1% to 7.3% in NHANES 1999-2000 and 4.4% to

6.1% in NHANES 2001-2004 for blood cadmium, and from 3.1% to 4.0% in NHANES 1999-2000 and 3.1% to 7.0% in NHANES 2001-2004 for blood lead [48, 51, 52].

Sociodemographic/Clinical Risk Factors. Other demographic and hearing-related variables were obtained during households interview or at MEC.

Body mass index (BMI) was calculated as weight in kilograms/height in meters squared. Use of ototoxic medication was defined as use of any 4 drug class of aminoglycoside, loop diuretics, antineoplastic drugs, or nonsteroidal anti-inflammatory drugs. Smoking pack-years were computed, and participants were grouped into nonsmokers, smokers less than 20 pack-years, or smokers more than 20 pack-years. Hypertension was defined as self-reported physician diagnosis, the use of antihypertensive medication, systolic blood pressure ≥ 140mmHg, or diastolic blood pressure ≥ 90 mm Hg at the time of examination. Diabetes mellitus was defined as self-reported physician diagnosis or the use of antihyperglycemic medication.

Our study sample was limited to adults who had complete information on these important covariates; therefore, a total of 2,607 participants were finally eligible for data analyses between dietary intakes and noise exposure, and 2,517 participants were finally eligible for analyses between dietary intakes and metals exposures.

Antioxidant Composite Intake. The antioxidants composite score was computed by using the dietary composite scoring system based on percentile ranks of dietary intakes, to evaluate the effect of overall antioxidant intake [57]. We calculated 2 composite scores: (a) β-carotene plus vitamin C; (b) β-carotene plus vitamin C plus vitamin E.

In population for interaction study between dietary intakes and noise exposures, we first ranked and clustered the 2,607 subjects into 100 percentiles, by the order of energy-adjusted dietary intake [44] of each β-carotene, vitamin C, and vitamin E from the lowest into the highest one. If the subject had the highest intake of vitamin C, we assigned 100 for his/her dietary vitamin C score. Then, we defined the antioxidant composite score of (a) β-carotene plus vitamin C ($0 \leq scale \leq 200$) by summing the 2 rank scores of β-carotene and vitamin C intakes. Similarly, the antioxidant composite score of (b) β-carotene plus vitamin C plus vitamin E ($0 \leq scale \leq 300$) was calculated by summing the 3 rank scores of β-carotene, vitamin C and vitamin E intakes.

In population for interaction study between dietary intakes and metals exposures, we first ranked and clustered the 2,517 subjects into 100 percentiles, by the order of energy-adjusted dietary intake of each β-carotene, vitamin C, and vitamin E from the lowest into the highest one. Then, we defined the antioxidant composite scores of (a) β-carotene plus vitamin C ($0 \leq scale \leq 200$) and (b) β-carotene plus vitamin C plus vitamin E ($0 \leq scale \leq 300$) with same procedures.

Statistical analysis. All statistical analyses were performed using the SAS survey procedures (SAS 9.2) and the R survey package (R 2.9.1) to account for the complex survey design and sample weights of the NHANES 2001-2004 [58, 59]. We computed 4-year sample weights per NCHS recommendations and the sample weights were incorporated into all analyses, which were adjusted for oversampling and non-response of subjects such as ethnic minorities, elderly persons, and low income [60]. The statistical significant level was set as *P* values less than .05.

All regression analyses began with univariate analyses to identify outliers and influential points. Dietary variables of β-carotene, vitamin C, vitamin E, calcium, and magnesium and antioxidant composite variables were categorized into quartiles, respectively. To evaluate the combined effect of antioxidant composites intakes with calcium and magnesium intakes, we made 4 intake classes as low/low, low/high, high/low, high/high of the antioxidant composite score of (a) [β-carotene plus vitamin C] or (b) [β-carotene plus vitamin C plus vitamin E] by calcium or magnesium

Hearing thresholds at PTA appeared to be right skewed and log-transformed to normalize distributions. For better interpretation of the regression results, we excluded subjects who had zero or negative hearing thresholds (better-than-normal hearing) in our primary linear regression analyses; 49 subjects and 47 subjects were excluded in population for interaction study with noise exposure and in subpopulation for interaction study with metals exposures, respectively. Previous research confirmed that linear regressions in subjects with only positive hearing thresholds showed consistent patterns to those of linear regression in all available subjects in the NHANES population [2].

To evaluate the interaction between dietary intakes and noise exposures, occupation noise exposure was examined as a continuous variable, and overall noise was examined as a 4 classed categorical variable in dietary stratified models. Models were adjusted for potential confounders of age, age-squared to capture nonlinear effects, sex, race/ethnicity, bmi, ototoxic medication, cumulative cigarette packyears, current diagnosis of hypertension, and current diagnosis of diabetes. Refer to Chapter II (Table II-6 , model C).

To identify the interaction between dietary intakes and metals, blood cadmium and lead levels were examined as log-transformed continuous variables and as quintiles in dietary stratified models. Models were adjusted for potential confounders of age, age-squared to capture nonlinear effects, sex, race/ethnicity, education, bmi, ototoxic medication, cumulative cigarette packyears, current diagnosis of hypertension, current diagnosis of diabetes, occupational noise, firearm noise, and recreation noise. Refer to Chapter III (Table III-3, model D).

RESULTS

General Characteristics. Table V-1 shows the characteristics of the study population. The study subjects included 2,607 adults aged 20 to 69 years (mean 42.06 (SE=0.33)) who participated in the interaction study between dietary exposures and noise exposures on PTA. After accounting for four-year sampling weights, cluster and strata of the NHANES complex design, the mean of PTA at speech frequencies and high frequencies was 12.68 (SE=0.35) dB and 18.78 (SE=0.59) dB. Overall, subjects had occupation noise exposure of O*NET noise score 3.06 (SE=0.02), which means that participants were averagely exposed almost "Once a month or more but not every week (score 3)" to “distracting and uncomfortable noise levels” at their occupations. 7.9% of subjects were exposed to firearm noise, and 27.3% were exposed to recreation noise.

A study population for interaction analysis between dietary exposures and metals exposures on PTA was a subpopulation of Table V-1 where 90 subjects were excluded because their blood cadmium and lead contents were not available.

Noise Exposures and Dietary Intakes. We evaluated whether the association between noise exposures and hearing ability was modified by subjects' characteristics in dietary intakes. Table V-2 presents percent changes in PTA in associations with occupation noise (O*NET noise score) as a continuous variable in various dietary intakes groups stratified by AC1 and calcium (panel A) and in various dietary intakes groups stratified by AC1 and magnesium (panel B). AC1 refers to an antioxidant composite of β-carotene and vitamin C. Dietary intake groups were defined on the basis of effective dietary intakes levels in reduction of PTA (better hearing ability). See Chapter IV for details.

After adjustment for all potential confounders, in overall subjects, a unit increase in the O*NET occupation noise score was associated with a 19.16% (95% confidence interval (CI)=12.00 to 26.77%) increase in PTA. Subjects had different levels of change in PTA with occupation noise at different dietary intakes classes. Subjects in the [low-AC1 / low-calcium] group had 34.87% (95% CI=20.21 to 51.32%) increase in PTA with a unit occupation score. The magnitude of increase in PTA with occupation noise was attenuated in subjects in dietary groups of [low-AC1 / high-calcium], [high-AC1 / low-calcium], and [high-AC1 / high-calcium] (6.69% (95% CI=-8.78 to 24.78%), 18.30% (95% CI=5.64 to 32.48%), and 10.59% (95% CI=3.28 to 18.42%) see panel A). Subjects in the [low-AC1 / low-magnesium] group had a 27.93% (95% CI=12.30 to 45.73%) increase in PTA with a unit occupation score; the increase in PTA was reduced in

subjects in dietary groups of [low-AC1 / high-magnesium], [high-AC1 / low-magnesium], and [high-AC1 / high-magnesium] (13.24% (95% CI=0.32 to 27.82%), 13.52% (95% CI=-0.02 to 28.90%), and 16.19% (95% CI=8.02 to 24.98%) see panel B).

In NHANES, because subjects who were exposed to firearm and recreation noise were small in number, observing the different changes in PTA with individual firearm noise and recreation noise exposures in dietary stratified models was restricted. This study used an overall noise variable that combined three kinds of noise exposures as occupation, firearm, and recreation, in order to observe the effect with noise including firearm and recreation. Percent changes in PTA in associations with overall noise exposure in the various dietary intakes groups were available in Table V-3 (a stratified model by AC1 and calcium (panel A) and by AC1 and magnesium (panel B). When we considered overall noise exposure including occupation, firearm, and recreation, we observed well-defined attenuation in increase in PTA with noise exposure depending on dietary antioxidants, calcium, and magnesium intakes.

Metal Exposures and Dietary Intakes. We evaluated whether the association of hearing ability with cadmium and lead exposures was modified by dietary intakes characteristics.

Table V-4 shows percent changes in PTA in associations with blood lead or blood cadmium levels as a log-transformed continuous variable and as quintiles in a fully adjusted model in various dietary intakes groups stratified by AC1 and calcium (panel A) and stratified by AC1 and magnesium (panel B). No interactive attenuation trends by dietary antioxidants, calcium, and magnesium intakes were shown in associations with

blood lead or cadmium levels in PTA changes. In association with blood cadmium, PTA changes for the highest cadmium quintile is even higher in the dietary group of [high-AC1 / high-calcium] than in the other dietary groups.

DISCUSSION

In a representative sample of US adults who participated in NHANES 1999-2004, we found that dietary intakes of antioxidants, calcium, and magnesium beneficially reduced susceptibility to noise exposure risk on hearing loss, but was not likely to affect susceptibility to cadmium and lead exposure risk on hearing loss among adults.

We ran regression analyses dealing with association of noise, cadmium, and lead exposures with pure tone average hearing thresholds (PTA) in stratified models by dietary intake class. PTA was highly significantly increased with increased noise exposure among poor dietary intake people; however, increased PTA size with noise exposure was attenuated among high rich intake people of dietary antioxidants, calcium, and magnesium. Our finding adds the epidemiologic evidence that dietary antioxidants, and magnesium intake attenuates the noise effect on hearing loss [61].

The risk effect of cadmium, and lead exposure on PTA increase was not modified by different dietary intake. Although previous animal experiments suggested that antioxidants intake reduced the risk on hearing loss caused by cadmium and lead exposures [27, 31, 57], this study did not observe protective evidence in a human

population. PTA changes with cadmium exposure were even inverse increase trends by dietary intakes. A possible explanation is by /evidenced through the high correlation between metals exposure (particularly cadmium) sources and dietary intakes sources: vegetables and fish consumption in a/the general population. Another possible explanation is that dietary intake may be too low to show a protective effect on metals-induced hearing loss in NHANES. Although the association was not observed in NHANES, we cannot exclude the possibility that impact of cadmium and lead on hearing loss may be attenuated by dietary intakes, and thus, this area needs more epidemiologic studies.

The main strengths of this study include a) the use of a representative sample of the US general population, including oversampled minority populations with sampling weights, which overcomes selection bias and enables the observed results to be generalized; b) the adjustment for important potential confounding factors; c) the use of NHANES data conducted with strict quality control procedures.

This study has several limitations to be considered. Although NHANES data is a well-defined representative sample of the U.S., a causal-effect relationship cannot be referred to between food consumption and hearing loss, or between noise and metal exposures and hearing loss, because the data are a cross-sectional observation.

In addition, our interest risk factors, cadmium and lead exposures of participants, were estimated by blood cadmium and lead levels, and may reflect relatively short-term exposure. Because most of the primary sources of lead exposure were banned in the US, lead toxicity may be of particular concern among older adults that were already exposed

to high levels of lead, which accumulates in body. Thus, we cannot rule out a concern that their blood lead levels at the current time may not highly correlate with their historical exposures in a general population, which results in the difficulty to explain a reliable association with hearing loss. Nevertheless, the risk of lead-induced hearing loss in our cross-sectional study using blood lead was observed to be roughly equivalent to those in a previous study both in cross-sectional and longitudinal design using bone lead, a proxy of cumulative lead exposure [11].

Furthermore, this study includes only dietary nutrition but excludes one through the supplements; we may not observe an association between overall nutrition and hearing loss. We also cannot rule out bias from dietary assessment using a 24-hour dietary recall. 24-hour dietary recall may induce recall bias in an interview, and may be restricted to explain the representative and usual diet patterns of participants; however, such bias is likely to be non-differential for participants and lead to a true association towards the null.

In summary, this study suggests that dietary antioxidants, calcium, magnesium, and their combined intakes may have a therapeutic effect on noise-induced hearing loss in a/the general population. Metals-induced hearing loss was not likely to be attenuated by dietary intake in the general population, even in evidences in previous animal studies. Our finding provides preliminary results for dietary strategies to effectively prevent hearing loss.

Table V-1. Participants characteristics, NHANES 2001-2004[a]

Characteristic	Participants (N=2607)[b]
Pure Tone Average Hearing Thresholds *(dB)* at speech frequencies[c]	12.68 (± 0.35)[e]
Pure Tone Average Hearing Thresholds *(dB)* at high frequencies[d]	18.78 (± 0.59)
Netrient	
β-carotene *(mg)*	1945.37 (± 100.21)
Vitamin C *(mg)*	90.62 (± 3.44)
Vitamin E *(mg)*	3.68 (± 0.17)
β-carotene + Vitamin C *(Dietary score)*[f]	96.43 (± 1.61)
β-carotene + Vitamin C + Vitamin E *(Dietary score)*[g]	145.21 (± 2.28)
Calcium *(mg)*	879.71 (± 16.27)
Magnesium *(mg)*	286.01 (± 3.88)
Age *(y)*	42.06 (± 0.33)
Body mass ndex *(wtkg/htm)*	27.98 (± 0.14)
Noise exposures	
Occupation noise exposure[h] *(O*NET score)*	3.06 (± 0.02)
Firearm noise exposure *(Exposed %)*	7.9[i]
Reacreation noise exposure *(Exposed %)*	27.3
Sex *(Male %)*	47.8
Race ethnicity (%)	
Non-Hispanic White	73.1
Non-Hispanic Black	11.2
Mexican American	6.7
Other	9.0
Education (%)	
< High School	14.9
High School	25.1
> High School	60.0
Ototoxic medication *(Current use %)*	14.4
Cumulative cigarette packyears (%)	
Never	54.5
<20	33.2
≥20	12.3
Hypertension *(%)*	23.6
Diabetes mellitus *(%)*	4.5

[a] Four-year sample weights applied.

[b] Participants (N=2607) are the individuals having all interest variables in this study: hearing thresholds, hearing loss, age, body mass index, sex, race ethnicity, ototoxic medication, cumulative cigratte pack-years, hypertension, diabetes mellitus, occupaiton noise exposure, firearm noise exposure, and recreation noise exposure.

[c] Pure tone average at speech frequencies at 0.5, 1, 2, and 4 kHz.

[d] Pure tone average at high frequencies at 3, 4, and 6 kHz.

[e] Weighted mean (± SE) (all such values).

[f] Dietary compund score is sum of ranked percentages of β-carotene and Vitamin C intakes (0<dietary score<200).

[g] Dietary compund score is sum of ranked percentages of β-carotene, Vitamin C, and Vitamin E intakes (0<dietary score<300).

[h] O*NET noise score (1 < Noise scale < 5).

[i] Weighted percentages (all such values).

Table V-2. Multivariate-adjusted[a] percent change (95% CIs) of hearing thresholds (dB) by occupation noise at various dietary intakes status.

Variables	Overall	Dietary intakes status			
A. AC1 (β-carotene plus Vitamin C) * Calcium					
		Low AC1		High AC1	
		/ Low Ca	/ High Ca	/ Low Ca	/ High Ca
Subjects No.	2558	372	266	912	1008
Occupation Noise *(O*NET unit score)* [b]	19.2 (12.0 , 26.8)	34.9 (20.2 , 51.3)	6.7 (-8.8 , 24.8) [1]	18.3 (5.6 , 32.5)	10.6 (3.3 , 18.4) [1]
B. AC1 (β-carotene plus Vitamin C) * Magnesium					
		Low AC1		High AC1	
		/ Low Mg	/ High Mg	/ Low Mg	/ High Mg
Subjects No.	2558	266	372	367	1553
Occupation Noise *(O*NET unit score)* [b]	19.2 (12.0 , 26.8)	27.9 (12.3 , 45.7)	13.2 (0.3 , 27.8)	13.5 (0.0 , 28.9)	16.2 (8.0 , 25.0)

[a] Regression models were adjusted for age, age[2], bmi, sex, race/ethnicity, ototoxic medication, cumulative cigarette packyears, current dx of hypertension, current dx of diabetes, occupation noise, recreation noise and firearm noise.

[b] Percent change of hearing thresholds for one unit score increase of occupation noise.

[1] Comparison with low AC1 (β-carotene plus Vitamin C) and low (calcium or magnesium) intake group *($p<0.05$).*

[2] Comparison with low AC1 (β-carotene plus Vitamin C) and high (calcium or magnesium) intake group *($p<0.05$).*

[3] Comparison with high AC1 (β-carotene plus Vitamin C) and low (calcium or magnesium) intake group *($p<0.05$).*

Table V-3. Multivariate-adjusted[a] percent change (95% CIs) of hearing thresholds (dB) by overall noise exposure at various dietary intakes status.

Variables	Overall	Dietary intakes status			
A. AC1 (β-carotene plus Vitamin C) * Calcium					
		Low AC1		High AC1	
		/ Low Ca	/ High Ca	/ Low Ca	/ High Ca
Subjects No.	2558	372	266	912	1008
Noise exposure level[b]					
None noise exposure	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)
Noise exposure 1	15.3 (6.5 , 24.8)	20.6 (-5.1 , 53.4)	30.9 (2.9 , 66.5)	16.7 (2.9 , 32.4)	4.3 (-4.9 , 14.5)
Noise exposure 2	25.2 (12.8 , 39.0)	29.2 (0.6 , 66.0)	43.4 (7.1 , 92.1)	19.0 (0.8 , 40.6)	17.6 (-0.7 , 39.3)
Noise exposure 3	41.9 (19.2 , 68.9)	69.7 (27.0 , 126.7)	34.6 (-10.8 , 103.1)	49.5 (20.0 , 86.2)	-4.6 (-30.7 , 31.5)
P -Trend	*<.0001*	*0.0025*	*0.0530*	*0.0031*	*0.1937*
B. AC1 (β-carotene plus Vitamin C) * Magnesium					
		Low AC1		High AC1	
		/ Low Mg	/ High Mg	/ Low Mg	/ High Mg
Subjects No.	2558	266	372	367	1553
Noise exposure level[b]					
None noise exposure	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)
Noise exposure 1	15.3 (6.5 , 24.8)	39.3 (13.7 , 70.7)	13.4 (-8.2 , 40.1)	24.1 (2.3 , 50.5)	8.2 (-1.0 , 18.2)
Noise exposure 2	25.2 (12.8 , 39.0)	61.6 (23.6 , 111.1)	14.9 (-12.2 , 50.4)	40.3 (13.6 , 73.3)	14.9 (-2.1 , 34.9)
Noise exposure 3	41.9 (19.2 , 68.9)	62.7 (9.9 , 140.9)	56.1 (13.2 , 115.4)	32.1 (-8.0 , 89.6)	19.2 (-3.2 , 46.7)
P -Trend	*<.0001*	*0.006*	*0.0387*	*0.0036*	*0.0301*

[a] Regression models were adjusted for age, age^2, bmi, sex, race/ethnicity, ototoxic medication, cumulative cigarette packyears, current dx of hypertension, current dx of diabetes, occupation noise, recreation noise and firearm noise.

[b] Subjects exposed at non, one, two, and all kinds of occupation, firearm or recreation noises.

Table V-4. Multivariate-adjusted[a] percent change (95% CIs) of hearing thresholds (dB) by blood admium and lead levels at various dietary intaks status

Variables	Overall	Dietary intakes status			
A. AC1 (β-carotene plus Vitamin C) * Calcium					
		Low AC1		High AC1	
		/ Low Ca	/ High Ca	/ Low Ca	/ High Ca
Subjects No.	2470	359	258	880	973
Cadmium					
Log(Cadmium) IQR[b]	8.5 (3.3 , 14.0)	4.2 (-4.8 , 14.1)	5.1 (-10.7 , 23.5)	14.3 (5.0 , 24.4)	5.4 (-3.1 , 14.7)
Cadmium Quintile *(ug/L)*					
Quintile 1 (0.10-0.10)	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)
Quintile 2 (0.20-0.30)	5.8 (-6.7 , 19.8)	2.5 (-16.7 , 26.1)	8.5 (-29.2 , 66.2)	0.2 (-22.9 , 30.1)	13.1 (-6.3 , 36.4)
Quintile 3 (0.40-0.40)	9.4 (-3.2 , 23.7)	0.2 (-21.6 , 28.2)	17.0 (-29.9 , 95.4)	19.7 (-5.5 , 51.5)	14.1 (-8.5 , 42.2)
Quintile 4 (0.50-0.70)	10.7 (-2.7 , 26.0)	5.8 (-17.1 , 35.2)	30.2 (-17.4 , 105.2)	10.6 (-15.4 , 44.6)	11.6 (-10.4 , 39.0)
Quintile 5 (0.80-7.00)	23.0 (8.6 , 39.3)	5.0 (-17.6 , 33.7)	19.1 (-21.9 , 81.5)	28.4 (-1.9 , 68.1)	29.9 (7.2 , 57.3)
P -Trend	*0.0022*	*0.7922*	*0.2862*	*0.0061*	*0.0912*
Lead					
Log(Lead) IQR[c]	5.5 (1.7 , 9.5)	4.0 (-5.0 , 13.9)	4.2 (-8.4 , 18.4)	3.7 (-3.5 , 11.5)	5.9 (-2.1 , 14.5)
Lead Quintile *(µg/dL)*					
Quintile 1 (0.20-0.80)	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)
Quintile 2 (0.90-1.20)	2.4 (-10.3 , 16.9)	-5.95 (-29.1 , 24.8)	32.6 (3.2 , 70.5)	4.2 (-13.1 , 24.9)	-6.1 (-22.8 , 14.2)
Quintile 3 (1.30-1.70)	7.3 (-4.9 , 21.2)	-1.71 (-22.1 , 24.0)	19.9 (-12.8 , 64.7)	-1.4 (-19.9 , 21.3)	10.5 (-6.1 , 30.1)
Quintile 4 (1.80-2.60)	15.5 (3.6 , 28.9)	6.69 (-15.6 , 34.9)	25.1 (-6.2 , 66.7)	16.2 (-3.5 , 39.9)	16.0 (-5.1 , 41.9)
Quintile 5 (2.70-41.50)	18.6 (6.0 , 32.7)	7.55 (-13.2 , 33.3)	38.1 (-2.7 , 96.1)	11.9 (-8.5 , 36.9)	20.0 (1.0 , 42.5)
P -Trend	*0.0005*	*0.2946*	*0.1822*	*0.1341*	*0.0179*

Continued in next page

Variables	Overall	Dietary intakes status			
B. AC1 (β-carotene plus Vitamin C) * Magnesium					
		Low AC1		High AC1	
		/ Low Mg	/ High Mg	/ Low Mg	/ High Mg
Cadmium					
Subjects No.	2470	260	357	352	1501
Log(Cadmium) IQR[b]	8.5 (3.3 , 14.0)	5.7 (-8.3 , 21.7)	2.9 (-8.4 , 15.5)	14.3 (2.7 , 27.3)	7.5 (0.4 , 15.1)
Cadmium Quintile *(ug/L)*					
Quintile 1 (0.10-0.10)	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)
Quintile 2 (0.20-0.30)	5.8 (-6.7 , 19.8)	4.7 (-18.2 , 34.0)	3.4 (-30.4 , 53.5)	0.0 (-35.2 , 54.4)	8.7 (-7.5 , 27.7)
Quintile 3 (0.40-0.40)	9.4 (-3.2 , 23.7)	-7.5 (-38.1 , 38.2)	1.5 (-31.0 , 49.3)	10.2 (-32.0 , 78.6)	13.2 (-4.8 , 34.6)
Quintile 4 (0.50-0.70)	10.7 (-2.7 , 26.0)	-0.7 (-26.7 , 34.4)	21.6 (-19.8 , 84.5)	15.9 (-19.9 , 67.6)	7.3 (-11.8 , 30.6)
Quintile 5 (0.80-7.00)	23.0 (8.6 , 39.3)	1.0 (-30.6 , 46.9)	9.6 (-25.2 , 60.5)	23.5 (-13.2 , 75.8)	26.2 (5.2 , 51.5)
P -Trend	*0.0022*	*0.8822*	*0.4378*	*0.0234*	*0.0442*
Lead					
Log(Lead) IQR[c]					
Lead Quintile *(µg/dL)*	5.5 (1.7 , 9.5)	7.7 (-5.4 , 22.5)	2.9 (-5.8 , 12.4)	2.9 (-10.8 , 18.6)	6.6 (0.1 , 13.6)
Quintile 1 (0.20-0.80)	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)
Quintile 2 (0.90-1.20)	2.4 (-10.3 , 16.9)	10.9 (-17.1 , 48.2)	19.5 (-5.9 , 51.8)	26.6 (-1.8 , 63.2)	-7.0 (-21.6 , 10.3)
Quintile 3 (1.30-1.70)	7.3 (-4.9 , 21.2)	6.9 (-24.9 , 52.1)	17.1 (-5.0 , 44.2)	9.5 (-16.1 , 43.1)	7.0 (-6.3 , 22.2)
Quintile 4 (1.80-2.60)	15.5 (3.6 , 28.9)	30.2 (-9.1 , 86.6)	11.6 (-7.8 , 35.0)	25.9 (-12.8 , 81.7)	14.3 (-0.5 , 31.3)
Quintile 5 (2.70-41.50)	18.6 (6.0 , 32.7)	17.5 (-16.6 , 65.7)	25.4 (1.2 , 55.4)	17.1 (-12.7 , 57.2)	18.2 (2.7 , 36.1)
P -Trend	*0.0005*	*0.2237*	*0.1956*	*0.5176*	*0.0033*

[a] Regression models were adjusted for age, age^2, bmi, sex, race/ethnicity, education, ototoxic medication, cumulative cigarette packyears, current dx of hypertension, current dx of diabetes, occupation noise, recreation noise and firearm noise.

[b] Percent change in hearing thresholds for interquartile range (IQR) increase of Log-transformed cadmium: log0.6-log0.2

[c] Percent change in hearing thresholds for interquartile range (IQR) increase of Log-transformed lead: log2.5-log1

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CHAPTER VI

Conclusion

The first study of this thesis supports the hypothesis that occupational noise exposure increases the risk of hearing loss across various occupations in the general population, after controlling for potential confounding factors on hearing loss. Utilization of the O*NET noise exposure data would allow us to perform epidemiologic studies of occupational noise exposure in the general population and to better understand the health effects of occupational noise exposure.

The second study of this thesis supports the hypothesis that environmental cadmium and lead exposures increase the risk of hearing loss among adults, particularly those less exposed to loud noise, while controlling for noise exposure and other major factors contributing to hearing loss. Our finding suggests the need for reducing environmental cadmium and lead exposure to effectively prevent hearing loss in the general population, with reducing noise exposure.

The third study of this thesis found that higher intakes of β-carotene, calcium, and β-carotene plus vitamin C independently reduces the risk of hearing loss, and that higher antioxidants intake acts in synergy in combination with higher calcium and/or

magnesium intake to reduce the risk of hearing loss, in the general population. This study provides dietary strategies to effectively prevent or delay hearing loss.

The fourth study of this thesis found that higher intakes of dietary antioxidants, calcium and magnesium, reduce individual susceptibility to noise risk on hearing loss in the general population. This study observed that those dietary intakes were not likely to reduce susceptibility to heavy metals risk on hearing loss in a human population, although there were evidences in animal experiments.

Overall, this thesis provides evidence that noise and heavy metals are important risk factors on hearing loss, and that dietary intake plays a protective role on hearing loss, in the general population. This thesis provides preliminary results for public health strategies in prevention and therapeutic treatment of hearing loss.