Title

The Interrelationship of Tinnitus and Hearing Loss Secondary to Age, Noise Exposure, and Traumatic Brain Injury

Permalink

https://escholarship.org/uc/item/79z650zb

Journal

Ear & Hearing, 43(4)

ISSN

0196-0202

Authors

Clifford, Royce Ellen
Ryan, Allen F

Publication Date

2022-07-01

DOI

10.1097/aud.0000000000001222

# AUTHOR QUERIES

## AUTHOR PLEASE ANSWER ALL QUERIES

As stated in the “Information for Authors” section on the website, if your paper’s published length exceeds 12 pages, there is a charge of $125 per page (for example, for a 13 printed page article, the charge is $125; for 14 printed pages the charge is $250). No changes in overall content to reduce page number will be allowed after the manuscript is accepted for publication. Page charges will be billed after print publication.

AQ1—For indexing purposes, please confirm that author names have been correctly identified as given names (blue) and surnames (red). Color in the byline will not appear on the final published version.

AQ2—For indexing purposes, please confirm that author names have been correctly identified as given names (blue), surnames (red), and suffixes (black). Color in the byline will not appear on the final published version.

AQ3—Per style, numerals should not be used in the beginning of the sentence. Hence, please rephrase the sentence “37.5% (95% CI 37.4, 37.6) gave evidence for tinnitus, mean” accordingly.

AQ4—Please cite "‡" in Table 1.

AQ5—Per style, numerals should not be used in the beginning of the sentence. Hence, please rephrase the sentence “55,254 (26.1%) sustained tinnitus...” accordingly.

AQ6—Please provide publisher name for reference Standardization, I. S. for. (2017).

AQ1: Names are correct.
AQ2: Names are correct.
AQ3: "Tinnitus was either self-reported, diagnosed, or both in 37.5% (95% CI, 37.4 to 37.6)."
AQ4: This statement is a second sentence to the previous statement and should follow " ... Digital Content 1). It is not a separate paragraph and should not require a separate mark.
AQ5: Tinnitus preceded hearing difficulties in 55,254 (26.1%) and 54,822 (25%) had hearing difficulties prior to tinnitus.
AQ6: Reference should be as follows:
Acoustics Committee for ISO/TC 43 (2017). Acoustics - Statistical distribution of hearing thresholds related to age and gender. Third edition. ISO 7029:2017 (E).

# The Interrelationship of Tinnitus and Hearing Loss Secondary to Age, Noise Exposure, and Traumatic Brain Injury

AQ2

Royce Ellen Clifford,[1,2,3] VA Million Veteran Program, and Allen F. Ryan[1,2]

AQ1

**Objective:** Tinnitus has been the No. 1 disability at the Veteran Administration for the last 15 years, yet its interaction with hearing loss secondary to etiologies such as age, noise trauma, and traumatic brain injuries remains poorly characterized. Our objective was to analyze hearing loss and tinnitus, including audiogram data, of the Million Veteran Program within the context of military exposures in an aging population.

**Design:** Health records, questionnaires, audiograms, and military data were aggregated for 758,005 Veteran participants in the Million Veteran Program 2011 to 2020, with relative risks (RR) calculated for ancestries, sex, hearing loss and military exposures such as combat, blast, and military era served. A multivariate model with significant demographic measures and exposures was then analyzed. Next, audiogram data stratified by sex were compared for those with and without tinnitus by two methods: first, mean thresholds at standard frequencies were compared to thresholds adjusted per ISO 7029:2000E age and sex formulae. Second, levels for those ≤40 years of age were compared with those 41 and older. Finally, a proportional hazards model was examined to ascertain the timing between the onset of tinnitus and hearing loss, calculated separately for electronic health record diagnoses (ICD) and self-report.

AQ3 **Results:** ~~37.5% (95% CI, 37.4 to 37.6) gave evidence for tinnitus~~, mean age 61.5 (95% CI, 61.4 to 61.5), range 18 to 112 years. Those with hearing loss were 4.15 times (95% CI, 4.12 to 4.15) as likely to have tinnitus. Americans of African descent were less likely to manifest tinnitus (RR 0.61, 95% CI, 0.60 to 0.61), as were women (RR 0.65, 95% CI, 0.64 to 0.65). A multivariate model indicated a higher RR of 1.73 for traumatic brain injury (95% CI ,1.71 to 1.73) and daily combat noise exposure (1.17, 95% CI, 1.14 to 1.17) than age (0.998, 95% CI, 0.997 to 0.998). Subjects ≤40 years of age had small but significantly elevated hearing thresholds through all standard frequencies compared to Veterans without tinnitus, and the effect of tinnitus on hearing thresholds diminished with age. In the hazard model, those >40 with new onset of tinnitus were at risk for hearing loss sooner and with greater incidence than those who were younger. The rate of hearing loss following tinnitus approached 100%. In contrast, only approximately 50% of those who self-reported hearing loss initially were at risk for later hearing loss, in contrast to ICD comparison, where those with ICD of hearing loss were more likely to sustain an ICD of tinnitus subsequently.

**Conclusions:** Evidence suggests that the occurrence of tinnitus in the military is more closely related to environmental exposures than to aging. The finding that tinnitus affects hearing frequencies across the audiogram spectrum suggests an acoustic injury independent of tonotopicity. Particularly for males >40, tinnitus may be a harbinger of audiologic damage predictive of later hearing loss.

**Key Words** Age-related hearing loss, Hearing loss, Military, Noise-induced hearing loss, Tinnitus, Traumatic brain injury

**Abbreviations:** EHR = electronic health record; ICD = International Classification of Diseases; ISO = International Standards Organization; MVP = Million Veteran Program; R = a statistical program; RR = relative risk; TBI = traumatic brain injury; VA = Veterans Administration; VINCI = VA Informatics and Computing Infrastructure.

(Ear & Hearing 2022;00;00–00)

Tinnitus, defined as noise perceived in the absence of external sound, has been the number one disability at the US Veteran Administration for over the last 15 years (Veterans Benefits Administration 2020). Even when it is not bothersome, tinnitus is comorbid with hearing loss, cognitive dysfunction, depression including risk of suicide, neuroticism, sleep disorders, and/or anxiety, in at least half of tinnitus patients (Crönlein et al. 2016; Hébert et al. 2011; Maes et al. 2013; McCormack et al. 2014; Shargorodsky et al. 2010; Stockdale et al. 2017). Societal costs include loss of productivity, missed days of work, time lost because of health care visits, expense of palliative treatments such as cognitive behavioral therapy, and equipment for relief from the persistent phantom sound (Maes et al. 2013; Stockdale et al. 2017). However, despite its prevalence in an estimated 50 million US adults who complain of ringing in their ears, with 16 million describing a daily occurrence, its intimate relationship with hearing difficulties remains poorly characterized (Shargorodsky et al. 2010).

In addition to extricating tinnitus from hearing loss, finding a definitive treatment requires mechanistic distinction between the etiologies of tinnitus, that is, age, chronic acoustic exposure, traumatic brain injury (TBI), and exposure to blast, since there is evidence of different patterns of damage (Hoffer et al. 2009). Age-related and acoustic trauma exhibit different audiogram signatures, that is, an aging “slope” versus a noise “notch” (Gates et al. 2000; Rabinowitz et al. 2006). Sorting out disparate causes has been difficult because of the low numbers of participants in most studies.

Not a small part of the difficulty in finding a definitive treatment resides in separating the pathophysiologic site of tinnitus from other auditory impairments. Tinnitus is highly correlated with hearing loss, both epidemiologically and genetically (Cederroth et al. 2019; Clifford et al. 2020; Nondahl et al. 2011; Shargorodsky et al. 2010; Shore et al. 2016). Studies show that up to 37.3% of those with hearing loss manifest tinnitus, and, conversely, the majority of those with tinnitus have measurable hearing loss (Henry et al. 2014; Shargorodsky et al. 2010). Recent Mendelian Randomization studies have indicated that the inference of causality may be bidirectional (Clifford et al. 2020). However, these two auditory impairments appear to have separate anatomic pathways: tinnitus is generally thought to be associated with central neural changes in response to peripheral neural deafferentation (Eggermont 2015; Elgoyhen et al. 2015), while hearing loss is more directly related to cochlear sensory damage (Kujawa & Liberman 2015). The genetic/molecular/anatomic location where the two may diverge is unknown, and this distinction is critical for the development of curative treatments.

---

[1] Research Department, VA Healthcare San Diego, La Jolla, CA; [2] Division of Otolaryngology-Head and Neck Surgery, Department of Surgery, University of California San Diego School of Medicine, La Jolla, CA; and [3] Visiting Scientist, Harvard University School of Public Health, Boston, MA.

Data access: Individual de-identified data accessible through grant approval at the Veterans Administration and on VA servers; R Code upon request

0196/0202/XXX/00XX-00/0 • Ear & Hearing • Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved • Printed in the U.S.A.

<zdoi; 10.1097/AUD.0000000000001222>

Currently, several large-scale research studies are characterizing and analyzing auditory consequences of military exposures. The Noise Outcomes in Servicemembers Epidemiology Study (NOISE) is an ongoing, prospective, longitudinal study collecting comprehensive detailed exposure and audiologic information on active Servicemembers and recently separated Veterans. Subjects are enrolled at two sites: Portland, OR and San Antonio, TX. It employs on-site collection of audiometric data, historical data, and comprehensive questionnaires on service and noise histories. In its first 690 participants, the study notes a 45% prevalence of tinnitus and at least 22% hearing loss in a relatively young population (average age 34, range 19 to 61) (Henry et al. 2021).

The Million Veteran Program (MVP), in contrast, is a retrospective mega-study on aging with over 800,000 participants. It consists of a population with prior exposure to artillery, noise from ships, guns, TBI, and blast identical to the NOISE study. MVP contains questionnaires, genomics, and links to electronic health records (EHR), and is proving particularly beneficial for the study of complex polygenic traits associated with environmental exposure (Clifford et al. 2019; Khera et al. 2018; Reisberg et al. 2017; Vona et al. 2017). By mining this database, our objective is to analyze tinnitus within the context of different military exposures in an aging population, and to explore tinnitus’ relationship with hearing loss both within the standard audiogram and over time.

## MATERIALS AND METHODS

### Study Population and Tinnitus Assessment

MVP is a retrospective, cohort study with ongoing enrollment since 2011, and its design has been previously described (Gaziano et al. 2016). Briefly, Veterans have been enrolled at more than 50 Veteran Administration Medical Centers nationwide through 2021. At the time of this study, 819,307 participants had filled out surveys, answering questions regarding tinnitus, hearing, military experience, and injuries related to combat, and/or had EHR information, including clinical diagnoses, audiograms, and Active-Duty military history information. Age and sex were verified in the Defense Enrollment Eligibility Reporting System. Ancestry was determined genomically based on the most commonly-represented groups at the VA, that is, European, African, Asian, and Hispanic and those of overlapping genetic ancestry were eliminated from this category (Fang et al. 2019).

Tinnitus was ascertained by either self-report or an ICD-9/ICD-10 diagnosis of tinnitus in the EHR (*n* = 284,073; Flowchart, Fig. 1). Subjects with diagnosis codes of “pulsatile” F1
or “objective” tinnitus were excluded (n = 2,497).

### Hearing Assessment

~~Certified~~ audiologists at the VA conduct all audiological examinations in a certified sound-treated booth using a Grason-Stadler clinical audiometer (Eden Prairie, MN). The QUASAR Audiogram Module (© Grason-Stadler) software program automatically enters and transmits all data to the VA Central Data Warehouse. Hearing loss was determined from audiologic evidence of any threshold >25 dB in either ear at any standard frequency (0.5, 1, 2, 3, 4, 6, or 8 kHz), self-report of hearing difficulty, hearing aid use, or diagnosis of sensorineural hearing loss in the EHR (Flowchart, Fig. 2; Dawes et al. 2014; Henry F2
et al. 2021; Joseph et al. 2018). Participants with diagnoses of “conductive hearing loss”, “mixed hearing loss”, “unilateral hearing loss”, “sudden hearing loss”, “ototoxic”, “acoustic neuroma”, or air-bone gap >10 dB at any frequency were excluded from analyses (n = 60,991).

“Best Hearing Ear ” and “Worst Hearing Ear” were determined by comparing pure-tone thresholds averages at 0.5, 1, 2,

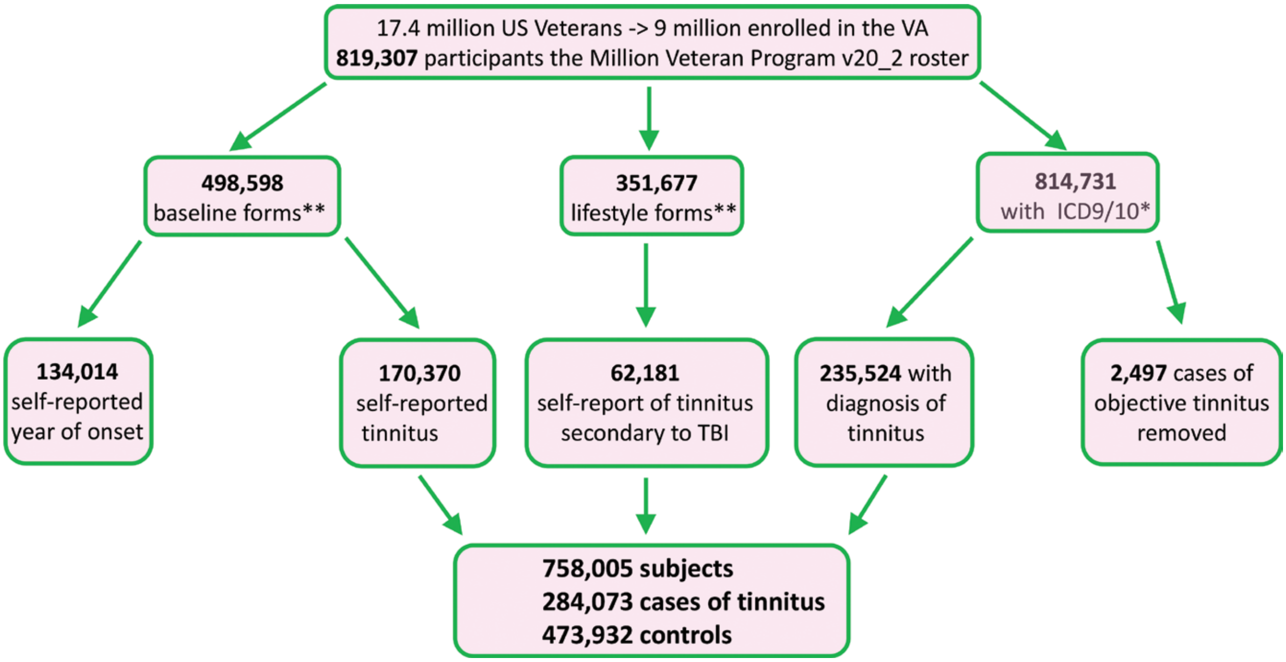

Fig. 1. Flowchart for cases of tinnitus. *Total MVP participants with any in-patient or outpatient diagnoses, available 1991 to 2020. **Excludes participants who did not answer questions before and after tinnitus questions and had no ICD diagnosis. ICD indicates International Classification of Diseases; and MVP, Million Veteran Program.

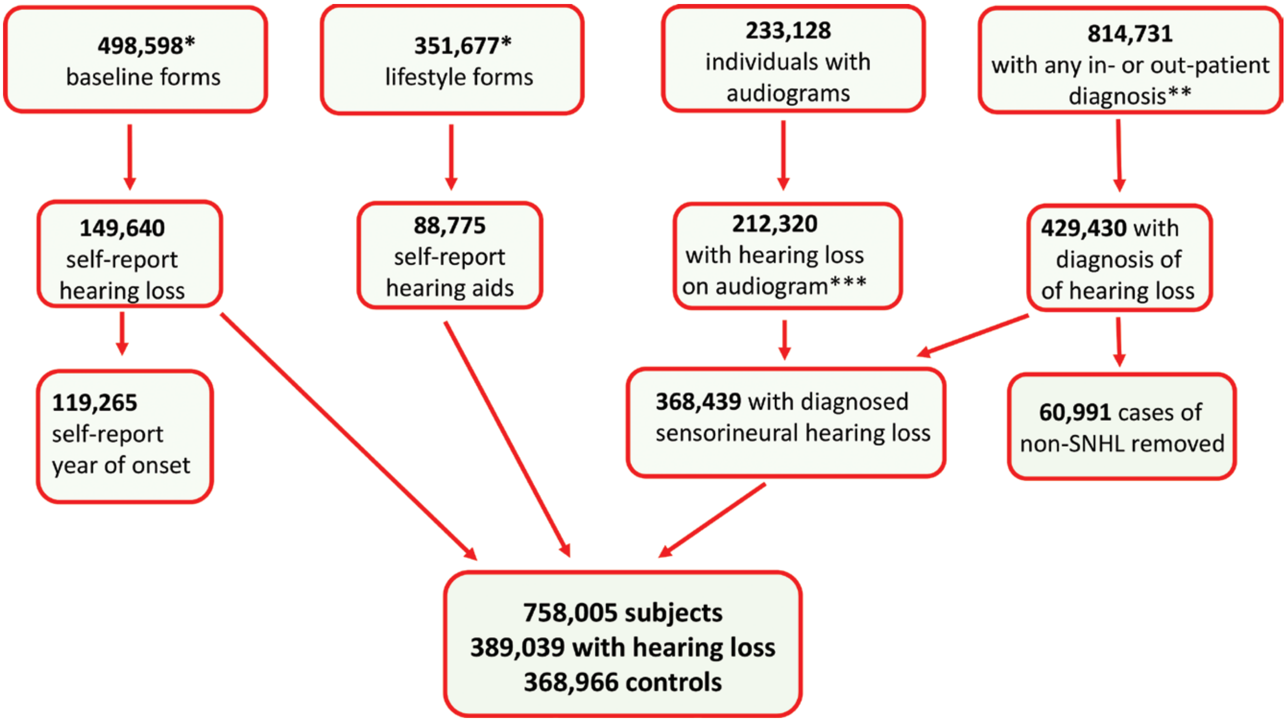

Fig. 2. Flowchart for cases of hearing difficulties. *Veterans who did not answer questions before or after tinnitus questions and had no ICD diagnosis were removed. **Total MVP participants with diagnoses available 1991 to 2020. ***Defined as any frequency threshold (0.5, 1, 2, 3, 4, 6, or 8 kHz) > 25 dB. ICD indicates International Classification of Diseases; and MVP, Million Veteran Program.

and 4 kHz (Cruickshanks et al. 1998). If the average was equal in both ears, right ear thresholds were used. Hearing levels were adjusted for age and sex to obtain “Best Ear – adjusted values” and “Worst Ear – adjusted values” via International Standards Organization 7029:2017(E) computations, which corrects to the median normal hearing for age and sex (see Supplemental Digital Content 1 http://links.lww.com/EANDH/B11, which describes details of methods) (ISO 2017)

## Exposure Assessment

Veterans were queried regarding their era of service, ranging from World War I through post 9/11, and whether they were deployed to a combat zone during that time (yes or no). If deployed, they were asked whether they encountered unanticipated detonations, blasts, received incoming fire, were under fire in a vehicle, or engaged in combat, utilizing answers as a surrogate for acoustic exposure. Answers from 1 to 5 were scored on a Likert Scale, from 1 = “never” to 5 = “daily or almost daily”.

Traumatic brain injury (TBI) prevalence was established from either ICD diagnosis of head injury or any self-reported symptom following head trauma (*n* = 150,011). Symptoms included being dazed, confused, or seeing stars, loss of consciousness from less than a minute through longer than 20 minutes, or self-report of symptoms following TBI, that is, ringing in the ears, imbalance, headache, or memory problems. Blast exposure was ascertained from self-report of proximity to detonated mines or improvised explosive devices with or without TBI.

## Statistical Analysis

Data was extracted from the MVP data bank within the Structured Query Language Server Management Studio 18 in VA Informatics and Computing Infrastructure (VINCI) and analyzed in R version 4.0.2 (©R Foundation for Statistical Computing). A Poisson model was created with tinnitus as the outcome and risk ratio as measurement, since for a large dataset, a Poisson model on a binary variable with robust standard errors is less biased and error prone than a binomial model (Chen et al. 2018). Variables were chosen based on their known clinical association with tinnitus as well as inclusion in the MVP surveys and ICD’s (Tables 1A and 1B in Supplemental Digital Content, http://links.lww.com/EANDH/B11—Correlations of Variables, ρ-values for Correlations).

Unadjusted regression was performed to ascertain significance of individual variables with tinnitus as a binary outcome. Relative risk (RR) for tinnitus was calculated for individual variables consisting of sex, ancestry, age at enrollment in MVP, era during which the Veteran served, frequency of combat acoustic exposure, TBI, exposure to blast, and/or comorbidity with hearing loss.

A multivariable model was then calculated as an adjusted model, including only complete cases (N = 142,078). The best-fitting multivariable logistic model included sex, ancestry, age at baseline enrollment, era served, a categorical measure of noise exposure in combat, TBI, blast exposure, and association with hearing loss, including age’s interaction with military service and TBI’s interaction with blast. Age was used as a continuous variable because when used as a categorical variable, the model failed to converge. Results were tested for multicollinearity via a generalized variance inflation factor, McFadden’s Pseudo-$R^2$ for goodness-of-fit, and Wald tests for significance of explanatory variables (Table 2 in Supplemental Digital Content, http://links.lww.com/EANDH/B11—Hypothesis Testing). Anova between models and AIC reduction was used to arrive at the final model.

Females have served in combat since 2015. To assess whether the lower percentage of tinnitus identified in females was related to combat exposure, interactive terms of sex with combat exposure was tested in the model and found to be not significant (Table 3 in Supplemental Digital Content, Interaction of Gender and Combat Exposure http://links.lww.com/EANDH/B11). Since $r^2$ for military service to age ranged from −0.25 to 0.36 (ρ-values < 0.0001, Tables 1 and 2 in Supplemental Digital Content, the interaction of military era served with age was tested. Correlation of TBI and blast was 0.24 (ρ-value < 0.0001) and this interaction was tested as well and used in the model.

We used two methods to ascertain the effect of tinnitus on the audiogram. First, means of each audiogram frequency were adjusted for sex and age via International Standard Organization ISO 7029:2017(E) formulae, then compared for those with and without tinnitus (ISO 2017). Next, unadjusted comparisons were made between those ≤40 years of age and those above, separated by sex.

For incidence, calculations of tinnitus versus onset of hearing loss was fashioned in a Cox cumulative proportional hazard model, examining those who had a reported year of onset of tinnitus and hearing loss either by self-report or ICD diagnosis date (N = 255,409). Left censoring consisting of removal of those who either had both events during the same year, or removal of those with the event occurring prior to the predictor. Because clinical diagnoses are available only from 1981, we analyzed self-reports and ICD/audiogram data separately. Interval measured was years between the two events or years between the initial event and enrollment in MVP, if no final event had been reported.

All de-identified information, including demographics, surveys, diagnoses, and audiogram data is located in VINCI within a protected workspace on VA computers. This study was approved by the Veterans Affairs Central institutional review board.

## RESULTS

### Demographics

The cohort consists of 758,005 Veterans with EHR diagnoses, surveys, audiograms, and/or demographics (Table 1). T1 Prevalence of tinnitus overall was 37.5% (95% CI, 37.3 to 37.6). and overall mean age at time of MVP enrollment was 61.46

**TABLE 1. Demographics of tinnitus in MVP with 95% Cis**

| | N* | % of cohort | Tinnitus | % with tinnitus | Relative risk (95% CI) |
|---|---|---|---|---|---|
| Totals | 758,005 | 100% | 284,073 | 37.5% | |
| Hearing loss | 389,039 | 51.3% | 231,260 | 59.4% | 4.15 (4.12–4.15) |
| Sex | | | | | |
| Male | 686,677 | 90.6% | 266,107 | 38.8% | 1.00 |
| Female | 71,209 | 9.4% | 17,960 | 25.2% | 0.65 (0.64–0.65) |
| Ancestry | 599,051 | 79.0% | 227,380 | 38.0% | |
| European | 428,002 | 56.5% | 176,999 | 41.4% | 1.00 |
| Black | 115,757 | 15.3% | 28,969 | 25.0% | 0.61 (0.60–0.61) |
| Hispanic | 47,788 | 6.3% | 18,408 | 38.5% | 0.93 (0.92–0.93) |
| Asian | 7,504 | 1.0% | 3,004 | 40.0% | 0.97 (0.94–0.97) |
| Age at time of enrollment | 758,005 | 100.00% | 284,073 | 37.5% | |
| 18–29 | 22,723 | 3.0% | 6,420 | 28.2% | 1.00 |
| 30–39 | 51,799 | 6.8% | 15,426 | 29.8% | 1.05 (1.03–1.05) |
| 40–49 | 69,124 | 9.1% | 21,617 | 31.3% | 1.11 (1.08–1.11) |
| 50–59 | 137,894 | 18.2% | 45,044 | 32.7% | 1.16 (1.13–1.16) |
| 60–69 | 260,783 | 34.4% | 107,985 | 41.4% | 1.47 (1.43–1.47) |
| 70–79 | 150,779 | 19.9% | 64,486 | 42.8% | 1.51 (1.48–1.51) |
| 80–89 | 57,178 | 7.5% | 20,712 | 36.2% | 1.28 (1.25–1.28) |
| 90–100 | 7,692 | 1.0% | 2,378 | 30.9% | 1.09 (1.05–1.09) |
| 100–110 | 33 | 0.0% | 5 | 15.2% | 0.54 (0.24–0.54) |
| Era of military service | 730,666 | 96.4% | 278,411 | 38.1% | |
| Post 9/11 | 92,840 | 12.2% | 39,763 | 42.8% | 1.00 |
| Gulf War | 111,721 | 14.7% | 36,582 | 32.7% | 0.76 (0.76–0.76) |
| 1975–1990 | 120,534 | 15.9% | 39,546 | 32.8% | 0.77 (0.76–0.77) |
| Vietnam | 305,397 | 40.3% | 126,208 | 41.3% | 0.96 (0.96–0.96) |
| 1955–1964 | 46,399 | 6.1% | 17,880 | 38.5% | 0.90 (0.89–0.90) |
| Korea | 36,096 | 4.8% | 12,810 | 35.5% | 0.83 (0.82–0.83) |
| Post-WWII | 2,041 | 0.3% | 640 | 31.4% | 0.73 (0.69–0.73) |
| WWII | 15,313 | 2.0% | 4,860 | 31.7% | 0.74 (0.72–0.74) |
| Pre-WWII | 325 | 0.04% | 122 | 37.5% | 0.88 (0.76–0.88) |
| Combat exposure | 264,678 | 34.9% | 123,955 | | |
| Never deployed | 105,599 | 39.9% | 37,299 | 35.3% | 1.00 |
| Not exposed | 27,643 | 10.4% | 12,020 | 43.5% | 1.23 (1.21–1.23) |
| Few times/deployment | 39,235 | 14.8% | 19,831 | 50.5% | 1.43 (1.41–1.43) |
| Few times/mo | 19,366 | 7.3% | 10,606 | 54.8% | 1.55 (1.53–1.55) |
| Few times/wk | 23,700 | 9.0% | 13,555 | 57.2% | 1.62 (1.60–1.62) |
| Daily/almost daily | 49,135 | 18.6% | 30,644 | 62.4% | 1.77 (1.75–1.77) |
| TBI† | 150,011 | 19.8% | 93,500 | 62.3% | 1.81 (1.79–1.81) |
| Blast exposure | 67,615 | 8.9% | 41,850 | 61.9% | 1.29 (1.28–1.29) |

*Number of those who answered positively to a particular category. Does not include those who did not answer that category or for which information was not available.

†TBI defined by ICD diagnosis or self-report of symptoms after head injury (list of diagnoses in Supplemental ~~Digital~~ Content 1). Includes 22,431 who stated they sustained a TBI secondary to blast.

AQ4 ‡Includes 22,431 who stated they sustained a TBI from blast.

CI, confidence interval; ICD, International Classification of Diagnosis; RR, relative risk; TBI, traumatic brain injury.

(95% CI, 61.42 to 61.49, range 18 to 112). Of these, 7.0% either self-reported or carried a diagnosis of tinnitus only, 30.5% had evidence of both tinnitus and hearing loss, and 20.8% hearing difficulties only (Table 4 in Supplemental Digital Content, http://links.lww.com/EANDH/B11—comparison of frequencies of tinnitus and hearing loss).

Females in this cohort were 0.65 times less at risk to sustain tinnitus than males (95% CI, 0.642 to 0.659). Those of African ancestry carried a 0.61 relative risk (RR) compared to Europeans (95% CI, 0.60 to 0.61), and those of Hispanic ancestry were 0.93 times less likely than Europeans to sustain tinnitus (95% CI, 0.92 to 0.93). The highest prevalence of tinnitus per age bracket occurred at 70-79 (RR 1.51, 95% CI, 1.48 to 1.55), and there was a sequential rise, then a drop in the oldest brackets, as seen in other studies (Shargorodsky et al. 2010). In contrast, although the "era of military service" correlation varied with age from −0.25 to 0.36 (Table 1A in Supplemental Digital Content, http://links.lww.com/EANDH/B11), change in RR over different military eras showed no consistent pattern overall. Post-9/11 Veterans were more likely to report tinnitus than in any other era.

Exposures addressed in this study included extent of noise exposure in a combat zone, traumatic brain injury (TBI) and blast. Military exposure based on amount of time in combat revealed an increase in relative risk from 1.23 (95% CI, 1.21 to 1.23) for "a few" exposures during an entire deployment, compared to 1.77 (95% CI, 1.75 to 1.77) for those exposed "daily or almost daily". TBI was almost twice as likely to be associated with tinnitus (RR 1.81, 95% CI, 1.79 to 1.81). Blast exposure with or without injury incurred a 1.29 times risk of tinnitus (95% CI, 1.28 to 1.29). By far the biggest risk of tinnitus was associated with hearing loss, as those with hearing loss were 4.15 times as likely to have tinnitus (95% CI, 4.12 to 4.19).

In the multivariable model, females once again appeared to be less at risk for tinnitus, with a RR of 0.90 (95% CI, 0.87 to 0.90) compared with males (Table 2). Using genetic T2

**TABLE 2. Multivariable model of tinnitus (N = 142,078 complete cases)**

| | N | N With Tinnitus | % Tinnitus | Risk Ratio (95% CI) |
|---|---|---|---|---|
| Hearing loss* | 76,261 | 62,781 | 82.3% | 2.48 (2.44–2.48)† |
| Sex | | | | |
| Male | 136,082 | 73,972 | 54.4% | 1.00 |
| Female | 5,996 | 2,289 | 38.2% | 0.90 (0.87–0.90)† |
| Ancestry | | | | |
| European | 115,513 | 63,457 | 54.9% | 1.00 |
| African American | 16,689 | 7,044 | 42.2% | 0.89 (0.87–0.89)† |
| Asian | 1,381 | 760 | 55.0% | 1.03 (0.99–1.03) |
| Hispanic | 8,495 | 5,000 | 58.9% | 1.01 (0.99–1.01) |
| Age‡ | 142,078 | 76,261 | 53.7% | 1.00 (1.00–1.00) |
| Military era served | | | | |
| Post-9/11 | 18,619 | 10,477 | 56.3% | 1.00 |
| Gulf War | 15,035 | 7,983 | 53.1% | 0.73 (0.67–0.73)† |
| 1975–1990 | 14,183 | 7,738 | 54.6% | 0.77 (0.69–0.77)† |
| Vietnam | 76,208 | 42,208 | 55.4% | 0.97 (0.88–0.97) |
| 1955–1964 | 5,031 | 2,352 | 46.8% | 1.55 (1.04–1.55) |
| Korea | 7,714 | 3,443 | 44.6% | 2.09 (1.26–2.09) |
| Post-WWII | 391 | 169 | 43.2% | 0.64 (0.08–0.64) |
| WWII | 4,786 | 1,841 | 38.5% | 2.19 (0.83–2.19) |
| Pre-WWII | 111 | 50 | 45.0% | 4.35 (1.68–4.4) |
| Age × military era served | | | | |
| Post-9/11 | 18,619 | 10,477 | 56.3% | |
| Gulf War | 15,035 | 7,983 | 53.1% | 1.00 (1.00–1.00) |
| 1975–1990 | 14,183 | 7,738 | 54.6% | 1.00 (1.00–1.00) |
| Vietnam | 76,208 | 42,208 | 55.4% | 1.00 (1.00–1.00) |
| 1955–1964 | 5,031 | 2,352 | 46.8% | 0.99 (0.99–0.99)† |
| Korea | 7,714 | 3,443 | 44.6% | 0.99 (0.98–0.99)† |
| Post-WWII | 391 | 169 | 43.2% | 1.00 (0.98–1.00) |
| WWII | 4,786 | 1,841 | 38.5% | 0.98 (0.97–0.98) |
| Pre-WII | 111 | 50 | 45.0% | 0.98 (0.97–0.98)† |
| Military exposure in combat | | | | |
| Never exposed | 2,283 | 10,016 | 438.7% | 1.10 (1.07–1.10)† |
| Few times total | 32,841 | 16,624 | 50.6% | 1.13 (1.10–1.13)† |
| Few time/mo | 16,341 | 8,984 | 55.0% | 1.15 (1.12–1.15)† |
| Few times/wk | 19,891 | 11,380 | 57.2% | 1.14 (1.11–1.14)† |
| Daily/almost daily | 41,512 | 25,895 | 62.4% | 1.17 (1.14–1.17)† |
| TBI§ | 78,101 | 54,133 | 69.3% | 1.73 (1.71–1.73)† |
| Blast | 57,776 | 35,644 | 61.7% | 0.98 (0.96–0.99) |
| TBI × blast | | | | 1.03 (1.01–1.03) |

*Definition of hearing loss—self-report of hearing difficulties, ICD diagnosis of hearing loss, or any standard pure tone frequency in either ear 25 dB.*

*†p < Bonferroni correction = 0.05/35 = $1.43 \times 10^{-3}$.*

*‡Age was used here as a discrete variable. Binning was removed from this model because it failed to converge.*

*§TBI either by self-report in combat or ICD.*

*ICD, International Classification of Diseases; RR, risk ratio; TBI, traumatic brain injury.*

ancestry identification (Fang et al. 2019), those of African ancestries also appeared to be slightly less likely to sustain tinnitus (RR 0.89, 95% CI, 0.87 to 0.89) than those of European descent. Hispanics and Asians had non-significant differences from Europeans in their susceptibility to tinnitus. While age interacted with military era significantly for some eras, the RR was close to 1.0 for all categories. In the multivariable model, age overall was not a risk, in contrast to civilian studies (Nondahl et al. 2011; Shargorodsky et al. 2010).

Participants who sustained a TBI had a 1.73 times risk of sustaining tinnitus (95% CI, 1.71 to 1.73), and blast per se did not appreciably increase the risk of tinnitus (RR 1.03, 95% CI, 1.01 to 1.03). In addition, TBI interaction with blast did not reach significance (*p* value $4.89 \times 10^{-3}$). Increasing exposure to combat showed a minimal increase from a few times during deployment to almost daily. Once again, the highest risk was for those with hearing loss, whether by audiogram, diagnosis, or self-report, with 2.48 times risk of tinnitus (95% CI, 2.44 to 2.48).

## Audiograms

We compared audiograms for those with and without tinnitus by adjusting for age in two ways. First, we compared average hearing thresholds of those with and without tinnitus ($n = 233{,}128$ individuals with audiograms) adjusted for age and sex via ISO 7029:2000E standards (Fig. 3 and Tables 5 and 6 in Supplemental Digital Content, http://links.lww.com/EANDH/B11, showing individual mean frequencies). Mean age for women at time of audiogram was 51.4 (SD 14.8); mean age for men 64.2 (SD 13.9), thus the unadjusted audios may not be comparable between sexes. Second, we compared average hearing threshold for those ≤40 with those >40 (n = 18,322 and 214,806, respectively) (Fig. 4). At each standard audiogram frequency, younger and age-adjusted data points demonstrated small but discernably elevated thresholds for those with tinnitus (Tables 7 and 8 in Supplemental Digital Content, http://links.lww.com/EANDH/B11, mean frequencies for younger and older Veterans). Women >40 had better hearing than men > 40, particularly at higher frequencies. Overall, audiograms for those with and without tinnitus manifest parallel "shapes".

F3
F4

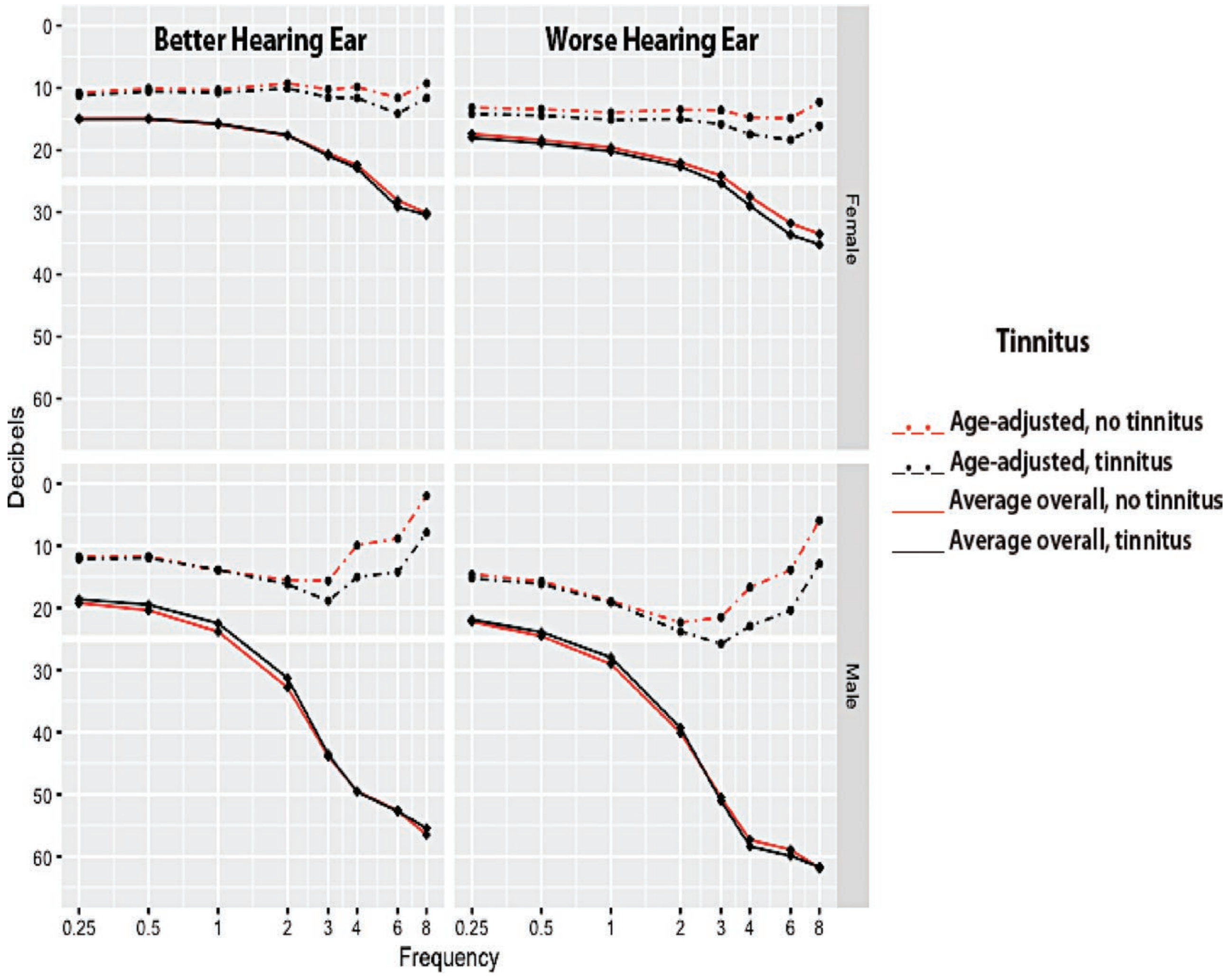

Fig. 3. Audiograms with and without tinnitus. When adjusted for sex and age according to International Standard Organization (ISO 7029:2000E) formulae (ISO, 2000) participants' hearing show elevated thresholds compared to non-tinnitus ears. Top audiograms are females, mean age 51.4 (SD 14.8), bottom audiograms are males, mean age 64.1 (SD 13.9)."Noise notch" is defined by a higher threshold at mid-frequencies (i.e., 3 to 6 kHz). than at 8 kHz (Rabinowitz et al. 2006). Error bars are too small to visualize. See Table 5 in Supplemental Digital Content, http://links.lww.com/EANDH/B11 for ρ-values per frequency.

When corrected for age, a “noise-notch” or increase in threshold at 3 to 6 kHz was evident in both sexes.

### Incidence of Tinnitus Versus Incidence of Hearing Loss

We were interested in the sequence of events from tinnitus to hearing loss and vice versa. Of 211,798 who had data for both hearing loss and tinnitus, either self-reported or in the EHR, 101,722 or 48.0% sustained hearing loss and tinnitus within the same year, and were not considered in this analysis. ~~55,254 (26.1%) sustained tinnitus initially and 54,822 (25.9%) had hearing difficulties preceding tinnitus (data not shown).~~ Since
AQ5 ICD’s in the medical record have only been available since 1991, health record diagnoses and self-report were analyzed separately. Comparing timing of tinnitus to the onset of hearing deficits, males >40 years of age were at higher risk than other
F5 groups measured by either self-report or ICD (Fig. 5 and Tables 8A to 8D in Supplemental Digital Content, http://links.lww.com/EANDH/B11, which have individual hazard analyses by time interval). At 10 years post-onset of tinnitus, males >40 had a 68.9% (95% CI, 68.6 to 69.6) incidence of hearing loss ICD, compared with females >40 with 48.4% (95% CI, 45.8 to 50.8) incidence. Similarly, self-report indicated that males >40 had an incidence of 14.7% (95% CI, 14.5 to 15.0), compared with females of the same age who manifested an 8.3% (95% CI, 7.3 to 9.2) incidence (Figs. 5A, C). At the end of reporting periods older females had “caught up” with males.

In contrast, younger males with hearing loss were at higher risk for tinnitus than older males, measured either by ICD or self-report (ρ-value < 0.0001) (Figs. 5B, D). At the 10-year mark, 52.1% of males ≤40 (95% CI, 50.1 to 54.1) carried a diagnosis of tinnitus, compared with 38.2% (95% CI, 37.9 to 38.5) of older males. Finally, while well over 80% of all those diagnosed ~~initially~~ with tinnitus went on to sustain hearing loss by any measure, self-report revealed that those who reported hearing loss did not of necessity go on to report tinnitus—only 45.0% of older males (95% CI, 33.7 to 54.3) and 37.7% (95% CI, 23.8 to 49.1) of older females reported tinnitus at the end of the period.

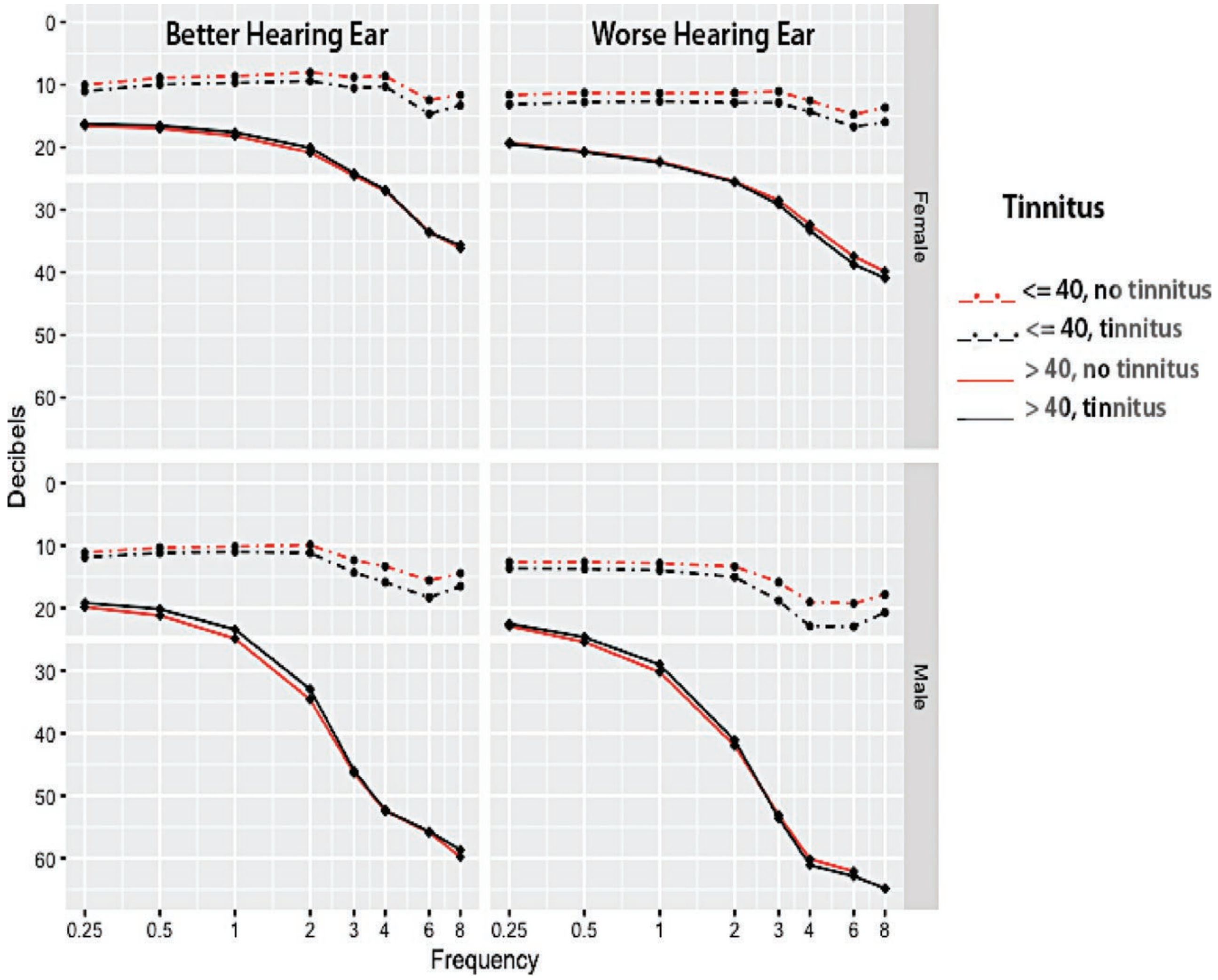

Fig. 4. Audiograms for participants less than or equal to 40 yrs of age compared with those over 40 yrs old. In younger tinnitus ears, thresholds are significantly and consistently elevated (ρ values < 0.001). Audiogram thresholds parallel each other, describing the same “shape”. For older Veterans, thresholds for those with and without tinnitus are identical. Males have consistently higher thresholds than females. Error bars are too small to visualize. See Table in Supplemental Digital Content, http://links.lww.com/EANDH/B11 for t-scores and ρ-values.

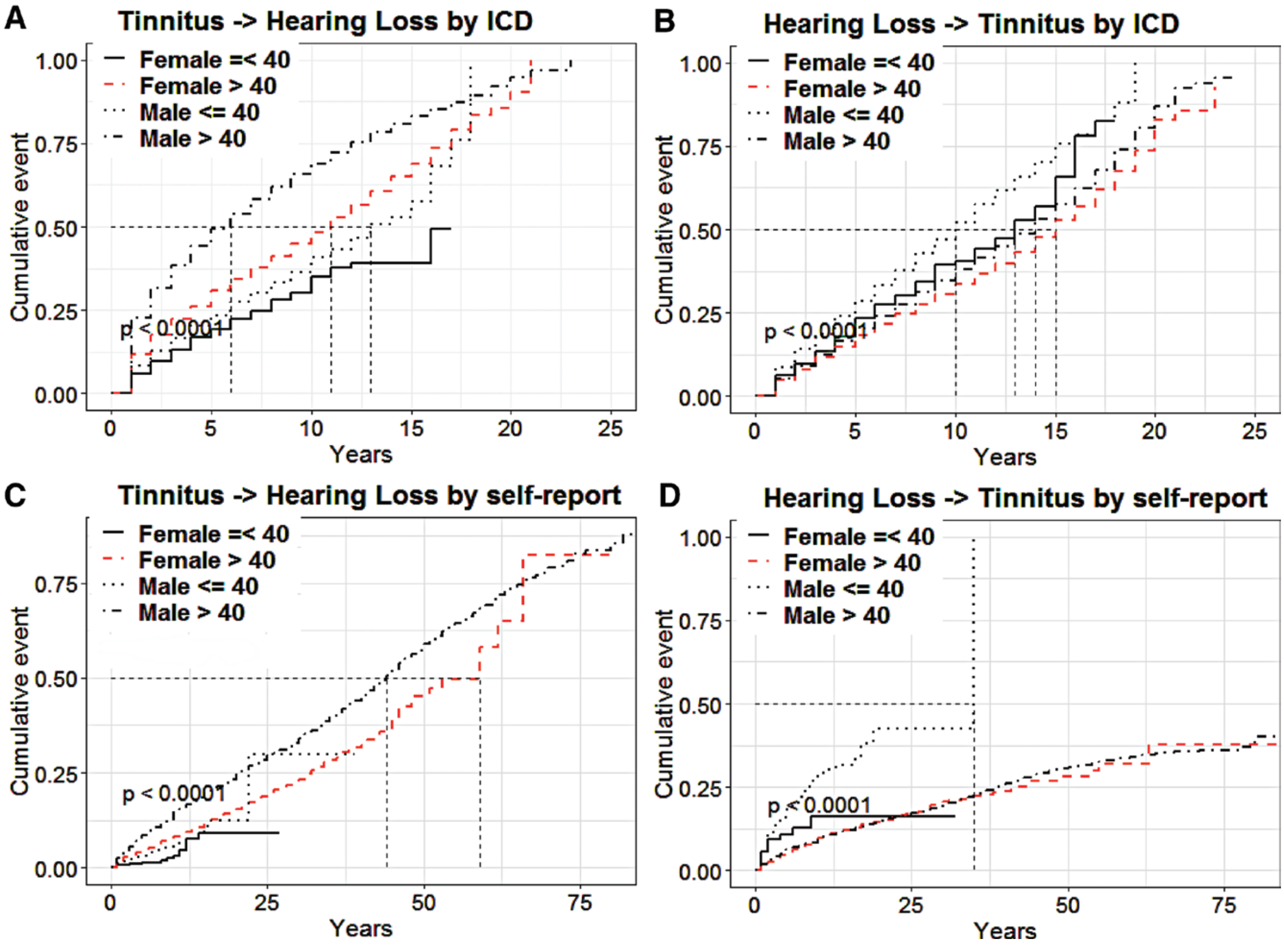

Fig. 5. Hazard models for interval between tinnitus and hearing loss. A, ICD. interval from tinnitus to hearing loss. B, ICD interval hearing loss to tinnitus. C, Self-reported interval tinnitus to hearing loss. D, Self-reported interval hearing loss to tinnitus. ICD's only available since 1991. ICD indicates International Classification of Diagnosis.

## DISCUSSION

It is imperative to separate the diverse etiologies of tinnitus ~~and~~ differentiate its pathology from ~~those of~~ hearing loss ~~in order to~~ develop a focused approach to treatment. Because age-related hearing loss, noise-induced tinnitus, TBI, and blast exposure appear to have singular mechanisms of injury, approaches to treatment and ultimate cure may of necessity be targeted to specific etiologies. Age-related tinnitus in the absence of measurable hearing loss is associated with a decrease in gray matter volume within the auditory cortex, subcortical auditory nuclei, and brainstem, including the inferior colliculus (Galazyuk et al. 2012; Landgrebe et al. 2009) with no loss of peripheral sensory cells or cochlear neurons (Longenecker et al. 2014) while chronic noise leads to more peripheral sensory damage, with glutamate toxicity leading to loss of cochlear inner hair cell synapses initially, followed by cochlear sensory cell and peripheral spiral ganglion nerve cell deficits (Kujawa & Liberman 2015). TBI may be more focused intracranially and associated with more wide-spread glutamate toxicity and neuroinflammation of variable areas of the brain and brainstem, with onset of microglial activation, peripheral neutrophil recruitment, and infiltration of lymphocytes and monocyte-derived macrophages, a potentially massive initial inflammatory response that may become chronic over time (Simon et al. 2017). Blast with or without TBI, on the other hand, is a diffuse intracranial event, with axonal and small vessel injury in the brain and brainstem, as well as damage at the interface of areas of different densities, such as the fluid-filled inner ear adjacent to air-filled middle ear (Simon et al. 2017; Yamamoto et al. 2018). Thus, with blast injury, there may be both central and peripheral mechanisms. These areas of injuries, secondary to different etiologies, can all lead to tinnitus. Occam's razor might dictate a consistent anatomic and pathophysiologic pathway of tinnitus generation through disparate etiologies; however, a tinnitus mechanism of onset remains to be discovered.

Prevalence of tinnitus in this MVP cohort is 37.5% compared with 9.6% to 25.3% in US populations with similar ages (Bhatt et al. 2016; Nondahl et al. 2011; Shargorodsky et al. 2010). This is lower than the 53% reported in the NOISE study (Henry et al. 2021). Tinnitus prevalence with hearing loss, as seen in 51.3% of our cohort, compares to 30.2% in the US population (Shargorodsky et al. 2010) and tinnitus increases the risk of hearing loss prevalence by over a factor of 4, as seen in other studies (Clifford et al. 2019). Comparisons of sex and ethnicities in civilian versus military populations show similar protection from acoustic injury in females and African Americans (Lin et al. 2011).

When examined alone, relative risk for tinnitus increases with age, from 1.05 for ages 18-29, to 1.51 at ages 70 to 79, then drops off sequentially after age 79, similar to civilian reports (Gopinath et al. 2010; Shargorodsky et al. 2010). However when age is examined in the multivariable model, RR = 1.00 (95% CI, 1.00 to 1.00). Similarly, while amount of time in combat shows a sequential increase related to time of exposure to gunfire, artillery, mortars, and aircraft noise, among other sources, its interaction with age is non-significant at any level of exposure (data not shown).

Another interaction of age with noise trauma may be seen in the military era served. Those in previous wars are now older and would be presumed to have increased effects of age; nevertheless, in this study, there is a disruption of this trend, and, in fact, the most recent eras with the youngest Veterans have the highest risk. This finding suggests a number of possibilities. On the one hand, military personnel may be more attuned to reporting hearing loss and tinnitus than in previous wars. Consistent with this, the NOISE cohort, which reported a 53% incidence of tinnitus consists of Active-Duty service members and only recently separated Veterans, with a lower average age of 34. Another possibility is that the lower 9.4% case fatality rate in recent wars compared with 13.3% during the Vietnam conflict has led to higher percentages of morbidities (Nessen et al. 2018). A third possibility is that acoustic trauma in the military evinces tinnitus in those genetically susceptible, and that genetic differences across combat eras overshadow the age-related influence.

The largest RR for military exposures occurs with TBI (RR 1.733, 95% CI, 1.71 to 1.73), higher than recurrent noise exposure in combat, consistent with NOISE results (Henry et al. 2021). In MVP, exposure to noise in combat and risks of TBI appear to interfere with the progression of age-related tinnitus. Surprisingly, the effects of blast alone, with or without TBI is statistically non-significant, as is the interaction of TBI and blast. Thus, it appears to be the effects of blast, rather than exposure itself, which can lead to tinnitus. The effects may be secondary to proximity and strength of blast, which was not measured in this study (Remenschneider et al. 2014).

The correlation of hearing difficulties to tinnitus in this study is 0.41 (ρ-value < 0.0001). and the RR of sustaining tinnitus given hearing loss is 4.15 (95% CI, 4.12 to 4.15). Like tinnitus, hearing loss is a consequence of acoustic trauma in combat, TBI, and aging. We approached this relationship in two ways – by looking at audiograms of those with and without tinnitus and by examining the temporal pattern of the onset of tinnitus versus the onset of hearing loss.

By looking at age-adjusted audiograms as well as hearing for those under 40 years of age, we attempted to diminish the effects of age. The finding of parallel audiogram patterns in younger Veterans may indicate an initial tinnitus injury independent of the anatomic/neurologic division of hearing into its range of frequencies, denoted “tonotopicity”. A tonotopic arrangement of nerve fibers occurs throughout the cochlea and auditory pathway, from spiral ganglion nerve fibers through all cochlear-related nuclei included in the brainstem, intracranial areas, and up through the primary auditory cortex. If tinnitus were related to a specific frequency or range of frequencies, it might reveal itself through the audiogram. While the standard audiogram does not reflect the entire range of human hearing; nevertheless, although the differences were not clinically significant (≤5 dB at all frequencies), the pattern was consistent across frequencies studied (Shim et al. 2009; Wiley et al. 1998).

In addition, the cumulative hazard model shows that tinnitus can be a harbinger of hearing loss, and this is influenced by age: those over 40 years of age were at more risk for tinnitus progressing to hearing loss than younger participants, who were somewhat more vulnerable to tinnitus after manifesting hearing loss (ρ-value < 0.0001). It is well known that hearing loss can occur prior to tinnitus; however, our finding of the onset of tinnitus prior to measurable auditory injury may dictate a closer look at changes in audiograms that are considered “within normal limits” and lead to earlier protection of vulnerable individuals from further auditory trauma. Other studies have also proposed tinnitus as a harbinger of future hearing loss (Griest & Bishop 1998). Cochlear synaptopathy, or permanent loss of synapses from the inner hair cell to the cochlear neuron has been shown in both aged and noise-exposed animals to occur prior to any detectable hearing loss on audiogram and could play a role in the initial auditory injury, leading to self-reported hearing loss, tinnitus, or both, depending on the integral genomic vulnerabilities of an individual (Kujawa & Liberman 2015). The fact that either by self-report or ICD diagnosis, all males and females over 40 with tinnitus are >80% likely to sustain hearing difficulties indicates that tinnitus may predict hearing loss, and warrants increased caution for self-protection of susceptible individuals from further environmental noise damage.

Limitations to this investigation include variations in the definition of hearing loss, ranging from self-report of hearing difficulties to pure-tone averages, to overall audiogram levels within standard audiogram frequencies. These variations in phenotype definition have led to disparities in the comparison of different studies of tinnitus and hearing (Guest et al. 2016; Spankovich et al. 2017; Wells et al. 2019). The study of tinnitus is also hampered by its subjective nature. Changes in reporting requirements for disability occurred in the VA system in 2006, after which it was incumbent upon the VA to award disability based on subjective findings, a fact which may have increased reporting of tinnitus. In addition, this study currently has no access to records outside the military nor are any VA diagnoses available for the period prior to 1992, thus limiting further diagnostic verification. Nevertheless, it should be noted that the self-report questionnaire specifically asked about the diagnosis and 66.4% of those reporting tinnitus carried ~~a~~ VA diagnosis, indicating a reasonable verification of findings.

Another consideration is the fact that self-reported hearing difficulty followed over time led to tinnitus less than 50% of the ~~time~~, while ~~the ICD~~ had an inexorable course to 100%. One possibility is reporting bias. Since this lack of tinnitus reporting involves fairly elderly Veterans, this may be an artifact of generational stoicism. On the other hand, it may be that those who carried an ICD of hearing loss had more severe hearing loss than those who self-reported and those with self-reported hearing loss never reached some threshold of injury necessary for tinnitus to manifest itself.

Here, we take note of three findings. First, the interaction of etiologies, that is, chronic noise and TBI, appears to interrupt the civilian age-related progression of tinnitus in the military population. Second, this hearing loss associated with tinnitus affects all standard frequencies of the audiogram. This suggests that the physiologic injury and repair pathway for acoustic injury may branch off to tinnitus and hearing loss outside of the tonotopic separation of the hearing pathway. Further studies of high-frequency audiometry will be required for verification.

Third, individuals with tinnitus, particularly those over 40, are at high risk for subsequent hearing loss.

This study is unique in that it affords researchers a first look at the rich acoustic data in the Million Veteran Program, including tinnitus and hearing loss, associated with audiograms and VA health records of over three-quarters of a million Veterans. Future studies will include closer examination of effects of TBI and blast injury and identifying the genomic underpinnings of these separate etiologies. The enormous amount of data within the MVP will allow researchers to study these concepts in greater detail than ever before possible.

---

## ACKNOWLEDGMENTS

This study was funded by VA RR&D MVP_010. A. F. R. is a co-founder of Otonomy, Inc, which develops slow-release therapies for the ear. He serves on its Scientific Advisory Board in an unpaid capacity and holds a small equity position. This relationship has been approved by the Conflict-of-Interest Committee of the VA San Diego Healthcare System. The company played no role in the work presented here.

The authors have no conflicts of interest relevant to this article to disclose.

Address for correspondence: Royce Ellen Clifford, Building 13, 117A, Veteran Administration Medical Research Foundation, 3350 La Jolla Village Drive, San Diego, CA 92161. E-mail: r2clifford@health.ucsd.edu

Received September 9, 2021; accepted February 5, 2022

## REFERENCES

Bhatt, J. M., Lin, H. W., Bhattacharyya, N. (2016). Prevalence, severity, exposures, and treatment patterns of tinnitus in the United States. JAMA Otolaryngol Head Neck Surg, *92697*, 1–7.

Cederroth, C. R., PirouziFard, M., Trpchevska, N., Idrizbegovic, E., Canlon, B., Sundquist, J., Sundquist, K., Zöller, B. (2019). Association of genetic vs environmental factors in Swedish adoptees with clinically significant tinnitus. *JAMA Otolaryngol Head Neck Surg, 145*, 222–229.

Chen, W., Qian, L., Shi, J., Franklin, M. (2018). Comparing performance between log-binomial and robust Poisson regression models for estimating risk ratios under model misspecification. *BMC Med Res Methodol, 18*, 63.

Clifford, R. E., Baker, D., Risbrough, V. B., Huang, M., Yurgil, K. A. (2019). Impact of TBI, PTSD, and hearing loss on tinnitus progression in a US Marine cohort. *Mil Med, 184*, 839–846.

Clifford, R. E., Hertzano, R., Ohlemiller, K. K. (2019). Untangling the genomics of noise-induced hearing loss and tinnitus: Contributions of Mus musculus and Homo sapiens. *J Acoust Soc Am, 146*, 4007.

Clifford, R. E., Maihofer, A. X., Stein, M. B., Ryan, A. F., Nievergelt, C. M. (2020). Novel risk loci in tinnitus and causal inference with neuropsychiatric disorders among adults of European ancestry. *JAMA Otolaryngol Head Neck Surg, 146*, 1015–1025.

Crönlein, T., Langguth, B., Pregler, M., Kreuzer, P. M., Wetter, T. C., Schecklmann, M. (2016). Insomnia in patients with chronic tinnitus: Cognitive and emotional distress as moderator variables. *J Psychosom Res, 83*, 65–68.

Cruickshanks, K. J., Wiley, T. L., Tweed, T. S., Klein, B. E., Klein, R., Mares-Perlman, J. A., Nondahl, D. M. (1998). Prevalence of hearing loss in older adults in Beaver Dam, Wisconsin. The Epidemiology of Hearing Loss Study. *Am J Epidemiol, 148*, 879–886.

Dawes, P., Fortnum, H., Moore, D. R., Emsley, R., Norman, P., Cruickshanks, K., Davis, A., Edmondson-Jones, M., McCormack, A., Lutman, M., Munro, K. (2014). Hearing in middle age: A population snapshot of 40- to 69-year olds in the United Kingdom. *Ear Hear, 35*, e44–e51.

Department of Veterans Affairs, U., & Benefits Administration, V. (2020). Annual Benefits Report (ABR) - Fiscal Year 2020.

Eggermont, J. J. (2015). The auditory cortex and tinnitus - a review of animal and human studies. Eur J Neurosci, 41, 665–676.

Elgoyhen, A. B., Langguth, B., De Ridder, D., Vanneste, S. (2015). Tinnitus: Perspectives from human neuroimaging. *Nat Rev Neurosci, 16*, 632–642.

Fang, H., Hui, Q., Lynch, J., Honerlaw, J., Assimes, T. L., Huang, J., Vujkovic, M., Damrauer, S. M., Pyarajan, S., Gaziano, J. M., DuVall, S. L., O'Donnell, C. J., Cho, K., Chang, K. M., Wilson, P. W. F., Tsao, P. S., Sun, Y. V., Tang, H.; VA Million Veteran Program. (2019). Harmonizing genetic ancestry and self-identified race/ethnicity in genome-wide association studies. *Am J Hum Genet, 105*, 763–772.

Galazyuk, A. V., Wenstrup, J. J., Hamid, M. A. (2012). Tinnitus and underlying brain mechanisms. *Curr Opin Otolaryngol Head Neck Surg, 20*, 409–415.

Gates, G. A., Schmid, P., Kujawa, S. G., Nam, B., D'Agostino, R. (2000). Longitudinal threshold changes in older men with audiometric notches. *Hear Res, 141*, 220–228.

Gaziano, J. M., Concato, J., Brophy, M., Fiore, L., Pyarajan, S., Breeling, J., Whitbourne, S., Deen, J., Shannon, C., Humphries, D., Guarino, P., Aslan, M., Anderson, D., LaFleur, R., Hammond, T., Schaa, K., Moser, J., Huang, G., Muralidhar, S., Przygodzki, R., et al. (2016). Million Veteran Program: A mega-biobank to study genetic influences on health and disease. *J Clin Epidemiol, 70*, 214–223.

Gopinath, B., McMahon, C. M., Rochtchina, E., Karpa, M. J., Mitchell, P. (2010). Incidence, persistence, and progression of tinnitus symptoms in older adults: The Blue Mountains Hearing Study. *Ear Hear, 31*, 407–412.

Griest, S. E., & Bishop, P. M. (1998). Tinnitus as an early indicator of permanent hearing loss. A 15 year longitudinal study of noise exposed workers. *AAOHN J, 46*, 325–329.

Guest, H., Munro, K. J., Prendergast, G., Howe, S., Plack, C. J. (2017). Tinnitus with a normal audiogram: Relation to noise exposure but no evidence for cochlear synaptopathy. *Hear Res, 344*, 265–274.

Hébert, S., Fullum, S., Carrier, J. (2011). Polysomnographic and quantitative electroencephalographic correlates of subjective sleep complaints in chronic tinnitus. *J Sleep Res, 20*(1 Pt 1), 38–44.

Henry, J. A., Griest, S., Reavis, K. M., Grush, L., Theodoroff, S. M., Young, S., Thielman, E. J., Carlson, K. F. (2021). Noise outcomes in servicemembers Epidemiology (NOISE) study: Design, methods, and Baseline results. *Ear Hear, 42*, 870–885.

Henry, J. A., Roberts, L. E., Caspary, D. M., Theodoroff, S. M., Salvi, R. J. (2014). Underlying mechanisms of tinnitus: Review and clinical implications. *J Am Acad Audiol, 25*, 5–22; quiz 126.

Hoffer, M. E., Donaldson, C., Gottshall, K. R., Balaban, C., Balough, B. J. (2009). Blunt and blast head trauma: Different entities. *Int Tinnitus J, 15*, 115–118.

ISO. (2000). Acoustics - Statistical distribution of hearing thresholds as a function of age, (A. International Standards Organization Technical Committee 43, Ed.; Vol. 2000). ISO.

Joseph, A. R., Shaw, J. L., Clouser, M. C., MacGregor, A. J., Galarneau, M. R. (2018). Impact of blast injury on hearing in a screened male military population. *Am J Epidemiol, 187*, 7–15.

Khera, A. V., Chaffin, M., Aragam, K. G., Haas, M. E., Roselli, C., Choi, S. H., Natarajan, P., Lander, E. S., Lubitz, S. A., Ellinor, P. T., Kathiresan, S. (2018). Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet, 50*, 1219–1224.

Kujawa, S. G., & Liberman, M. C. (2015). Synaptopathy in the noise-exposed and aging cochlea: Primary neural degeneration in acquired sensorineural hearing loss. *Hear Res, 330*(Pt B), 191–199.

Landgrebe, M., Langguth, B., Rosengarth, K., Braun, S., Koch, A., Kleinjung, T., May, A., de Ridder, D., Hajak, G. (2009). Structural brain changes in tinnitus: Grey matter decrease in auditory and non-auditory brain areas. *Neuroimage, 46*, 213–218.

Lin, F. R., Niparko, J. K., Ferrucci, L. (2011). Hearing loss prevalence in the United States. *Arch Intern Med, 171*, 1851–1852.

Longenecker, R. J., Chonko, K. T., Maricich, S. M., Galazyuk, A. V. (2014). Age effects on tinnitus and hearing loss in CBA/CaJ mice following sound exposure. *Springerplus, 3*, 542.

Maes, I. H., Cima, R. F., Vlaeyen, J. W., Anteunis, L. J., Joore, M. A. (2013). Tinnitus: A cost study. *Ear Hear, 34*, 508–514.

McCormack, A., Edmondson-Jones, M., Fortnum, H., Dawes, P., Middleton, H., Munro, K. J., Moore, D. R. (2014). The prevalence of tinnitus and the relationship with neuroticism in a middle-aged UK population. *J Psychosom Res, 76*, 56–60.

Nessen, S. C., Gurney, J., Rasmussen, T. E., Cap, A. P., Mann-Salinas, E., Le, T. D., Shackelford, S., Remick, K. N., Akers, K. S., Eastridge, B. J., Jenkins, D., Stockinger, Z. T., Murray, C. K., Gross, K. R., Seery, J., Mabry, R., Holcomb, J. B. (2018). Unrealized potential of the US military battlefield trauma system: DOW rate is higher in Iraq and Afghanistan than in Vietnam, but CFR and KIA rate are lower. *J Trauma Acute Care Surg, 85*(1S suppl 2), S4–S12.

Nondahl, D. M., Cruickshanks, K. J., Huang, G. H., Klein, B. E., Klein, R., Nieto, F. J., Tweed, T. S. (2011). Tinnitus and its risk factors in the Beaver Dam offspring study. *Int J Audiol, 50*, 313–320.

Rabinowitz, P. M., Galusha, D., Slade, M. D., Dixon-Ernst, C., Sircar, K. D., Dobie, R. A. (2006). Audiogram notches in noise-exposed workers. *Ear Hear, 27*, 742–750.

Reisberg, S., Iljasenko, T., Läll, K., Fischer, K., Vilo, J. (2017). Comparing distributions of polygenic risk scores of type 2 diabetes and coronary heart disease within different populations. *PLoS One, 12*, e0179238.

Remenschneider, A. K., Lookabaugh, S., Aliphas, A., Brodsky, J. R., Devaiah, A. K., Dagher, W., Grundfast, K. M., Heman-Ackah, S. E., Rubin, S., Sillman, J., Tsai, A. C., Vecchiotti, M., Kujawa, S. G., Lee, D. J., Quesnel, A. M. (2014). Otologic outcomes after blast injury: The Boston Marathon experience. *Otol Neurotol, 35*, 1825–1834.

Shargorodsky, J., Curhan, G. C., Farwell, W. R. (2010). Prevalence and characteristics of tinnitus among US adults. *Am J Med, 123*, 711–718.

Shim, H. J., Kim, S. K., Park, C. H., Lee, S. H., Yoon, S. W., Ki, A. R., Chung, D. H., Yeo, S. G. (2009). Hearing abilities at ultra-high frequency in patients with tinnitus. *Clin Exp Otorhinolaryngol, 2*, 169–174.

Shore, S. E., Roberts, L. E., Langguth, B. (2016). Maladaptive plasticity in tinnitus — triggers, mechanisms and treatment. Nat Rev Neurol, 12, 150–160.

Simon, D. W., McGeachy, M. J., Bayır, H., Clark, R. S., Loane, D. J., Kochanek, P. M. (2017). The far-reaching scope of neuroinflammation after traumatic brain injury. *Nat Rev Neurol, 13*, 171–191.

Spankovich, C., Gonzalez, V. B., Su, D., Bishop, C. E. (2018). Self reported hearing difficulty, tinnitus, and normal audiometric thresholds, the National Health and Nutrition Examination Survey 1999-2002. *Hear Res, 358*, 30–36.

~~Standardization, I. S. for. (2017). INTERNATIONAL STANDARD ISO Acoustics — Statistical distribution of hearing thresholds related to age (Vol. 2017).~~ **AQ6**

Stockdale, D., McFerran, D., Brazier, P., Pritchard, C., Kay, T., Dowrick, C., Hoare, D. J. (2017). An economic evaluation of the healthcare cost of tinnitus management in the UK. *BMC Health Serv Res, 17*, 577.

Vona, B., Nanda, I., Shehata-Dieler, W., Haaf, T. (2017). Genetics of tinnitus: Still in its infancy. *Front Neurosci, 11*, 236.

Wells, H. R. R., Freidin, M. B., Zainul Abidin, F. N., Payton, A., Dawes, P., Munro, K. J., Morton, C. C., Moore, D. R., Dawson, S. J., Williams, F. M. K. (2019). GWAS identifies 44 independent associated genomic loci for self-reported adult hearing difficulty in UK biobank. *Am J Hum Genet, 105*, 788–802.

Wiley, T. L., Cruickshanks, K. J., Nondahl, D. M., Tweed, T. S., Klein, R., Klein, R., Klein, B. E. (1998). Aging and high-frequency hearing sensitivity. *J Speech Lang Hear Res, 41*, 1061–1072.

Yamamoto, S., DeWitt, D. S., Prough, D. S. (2018). Impact & Blast traumatic brain injury: Implications for therapy. *Molecules, 23*, E245.