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Sex-Based Differences in Hearing Loss: Perspectives from Non-Clinical Research to Clinical Outcomes

Dillan F. Villavisanis, B.A.[1,2], **Elisa R. Berson**[3], **Amanda M. Lauer, Ph.D.**[1], **Maura K. Cosetti, M.D.**[4], **Katrina M. Schrode, Ph.D.**[1]

[1]Department of Otolaryngology – Head & Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[2]Department of Otolaryngology – Head & Neck Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[3]Division of Otolaryngology, Department of Surgery, Yale University School of Medicine, New Haven, CT, USA

[4]Department of Otolaryngology – Head & Neck Surgery, New York Eye and Ear infirmary of Mount Sinai, New York, NY, USA

Abstract

Introduction—It is estimated over 466 million people worldwide have disabling hearing loss, and untreated hearing loss is associated with poorer health outcomes. The influence of sex as a biological variable on hearing loss is not well understood, especially for differences in underlying mechanisms which are typically elucidated through non-clinical research. Although the inclusion of sex as a biological variable in clinical studies has been required since 1993, sex reporting has only been recently mandated in NIH funded non-clinical studies.

Objective—This article reviews the literature on recent non-clinical and clinical research concerning sex-based differences in hearing loss primarily since 1993, and discusses implications for knowledge gaps in the translation from non-clinical to clinical realms.

Conclusions—The disparity between sex-based requirements for non-clinical versus clinical research may inhibit a comprehensive understanding of sex-based mechanistic differences. Such disparities may play a role in understanding and explaining clinically significant sex differences and are likely necessary for developing robust clinical treatment options.

Introduction

The World Health Organization estimates that about 466 million people worldwide have disabling hearing loss, and that by 2050 this number will rise to 900 million.(1) In addition to its pervasiveness, the effects of untreated hearing loss can be both diverse in breadth and profound in effect. In children, these effects include impaired or delayed language and speech development(2,3), poorer educational performance(4,5), and impaired cognitive

Corresponding author: Katrina M. Schrode, kschrod1@jhmi.edu, Johns Hopkins University School of Medicine, Department of Otolaryngology – Head & Neck Surgery, 720 Rutland Ave., Baltimore, MD, 21205.

development(6). In older adults, hearing loss has been independently associated with dementia(7–9), cognitive impairment(8,10,11), major depressive disorder(12) social isolation(13) and increased risk of hospitalizations(14), falls(15), and mortality(16). In this article, we present the current state of non-clinical and clinical research regarding sex-differences in hearing loss, emphasize recent studies that build on earlier research, and discuss how non-clinical sex-bias and sex-omission may hinder our ability to understand and interpret clinically significant sex differences.

Among clinical studies (in humans) where sex has been a variable of interest, research has demonstrated differences in the trajectory of hearing loss between aging men and women. In the Baltimore Longitudinal Study on Aging, hearing ability at most ages and frequencies tested was found to decline more than twice as fast for men compared to women(17), particularly at higher frequency regions(18,19). The reasons for these sex differences is unclear. It has long been assumed that men are exposed to more damaging noise over a lifetime, which may exacerbate age-related hearing loss (ARHL). In some studies, sex differences are closely associated with higher occupational noise exposure in men e.g.,(20). However, other studies have found that sex differences in hearing persist even when accounting for noise exposure history(21). One factor that may explain variability in study results is that self-reporting of human noise exposure histories may differ from actual exposure(22,23). Despite robust evidence that aging males are at greater risk of hearing loss than their female counterparts, the clinical and underlying mechanistic etiologies for these sex-based differences remain poorly understood. In addition, few, if any, sex-specific initiatives, guidelines or treatments for hearing loss exist.

Mechanistic pathways are typically discovered through animal-based non-clinical research, because variables influencing hearing outcome, such as genetics, acoustic experience, and exposure to ototoxic drugs, can be precisely controlled. However, only a small number of non-clinical studies [for example: (Guimaraes, Zhu, Cannon, Kim, & Frisina, 2004; Henry, 2002; Milon et al., 2018)] directly address sex differences in hearing loss (Table 1). Although the passage of the Revitalization Act in 1993 required the inclusion of men and women in NIH funded clinical research(28), the NIH did not require the inclusion of male and female animals in non-clinical research until January of 2016(29). In non-clinical studies, male animals have been used proportionally more than female animals in studies on age-related(30) and noise-induced(31) hearing loss (NIHL), a trend known as sex bias. Another common trend is sex-omission, wherein investigators do not report the sex of their subjects or do not test for statistical differences between the sexes.

The prevalence of these two issues has inhibited investigators from discovering and understanding sex-based differences in hearing loss. We present research here as an update on sex differences following the Revitalization Act in 1993, while providing reference to earlier literature which contains the basis for this recent work. We believe addressing and improving sex-bias and omission will help facilitate development of more effective clinical treatment and prevention options.

Non-Clinical Research

Non-clinical research, or research based in animal models, demonstrate certain advantages over human participants because the environmental conditions, auditory input/stimuli, and other possibly confounding factors that may occur in humans can be minimized or controlled. Additionally, studies in animals allow for detailed analysis of anatomical and physiological aspects of the central and peripheral auditory system.

The ultimate goal is to understand sex differences in the mechanisms of hearing loss in humans, but much of the existing literature consists of studies conducted on non-human mammals. Hearing loss research takes two basic forms – physiological/anatomical and behavioral – and this review focuses on the former, as recent animal studies rarely measure behavior. The hope is that the essence of those findings ultimately will prove to be relevant to humans because of the similarities in physiology and anatomical organization among mammals. Studies of auditory sex differences have been performed in a wide variety of nonmammalian species, including praying mantises,(32) frogs,(33) and birds(34). However, because the vast majority of non-clinical research uses mammals due to the similarities in physiology and anatomical organization with humans (Beery & Zucker 2011), we will limit our discussion to mammalian studies.

Sex Bias in Non-Clinical Research

Non-clinical research across many disciplines has typically neglected sex as a biological variable(36). Sex bias has been identified in cardiovascular(37), surgical(38), dermatology(39), otolaryngology(40), rhinology(41), and neuroscience(35,42) research. A systematic review of sex bias in neuroscience research evaluated over 6,000 manuscripts for the period 2010–2014 and found that while sex omission decreased from 47% to 19%, sex-bias persisted, as the proportion of investigations using only male animals increased from 31% to 40%(42). It is worth noting that this bias typically arises as a result of practical issues - having fertile females in an animal colony with individual cages may be disruptive, produce stress, and produce injuries. Moreover, samples sizes in studies of non-human primates tend to be too small to identify statistically significant sex differences.

Two studies analyzed sex bias in non-clinical auditory neuroscience research on age-related hearing loss (ARHL)(30) and noise-induced hearing loss (NIHL)(31). Both studies found that sex-bias was present at rates consistent with the results of other large-scale analyses of sex bias in neuroscience(42) and cardiovascular(37) research. However, studies on ARHL more often reported sex and showed less sex bias compared to those on NIHL(30,31). Only a small proportion (15%) of ARHL studies that used both sexes discussed or analyzed sex-based results(30), a rate comparable to studies analyzing sex-based results in general neuroscience (~20%)(35).

Noise Induced Hearing Loss

One of the main advantages of studying NIHL in animal models is that the acoustic experience can be precisely controlled throughout the study period and/or the animal's

lifetime. The most common metric for assessing the effects of a controlled sound exposure on auditory sensitivity in animals is the auditory brainstem response (ABR).

Some animal studies have demonstrated frequency-dependent sex differences following noise exposure, but results differ by species and by strain within species. In studies of CBA/CaJ and C57Bl/6 mice, exposure to ~100 dB SPL noise for two hours resulted in males generally having higher ABR thresholds than females at frequencies above 12 or 16 kHz(27,43). In the ventral cochlear nucleus, there were statistically significant effects of sex on excitatory and inhibitory synapse immunolabeling.[46]

In chinchillas, following exposure to 150 dB pSPL impulse noise, males demonstrated less high-frequency hearing loss and more low-frequency hearing loss than females as measured by distortion-product otoacoustic emissions (DPOAE) (McFadden, Henselman, & Zheng, 1999). Males also showed increased inner hair cell loss compared to females(44); however, it is worth mentioning that DPOAEs are rather insensitive to sex differences. In contrast, male and female Mongolian gerbils exposed to a loud tone for 1 hour showed no significant differences in ABR thresholds shifts(45).

The results of these studies provide evidence for sex-based differences in response to noise. Further studies may be particularly useful in understanding if sex-based differences in NIHL derive from exposure or susceptibility to occupational noise as discussed in “Sex Based Differences in Humans” below.

Age-Related Hearing-Loss

Within non-clinical hearing loss research, CBA/CaJ and CBA/J mice serve as a representative model for human ARHL due to their progressive hearing loss beginning late in life(46). C57Bl/6 mice have also been used in aging research, because they demonstrate rapidly deteriorating auditory ability as a function of age(46) due to a mutation in an age-related hearing loss (*Ahl*) locus on chromosome 10(47). These sex-differences in these well-characterized animal populations have provided insight into the genetic mechanisms underlying sex differences in ARHL.

Without noise exposure, male CBA/CaJ mice show earlier and larger increases in behavioral detection thresholds than females(48). Studies have also shown that old CBA males have higher ABR and cochlear nerve envelope response (CNER) thresholds than females of the same age (Guimaraes et al., 2004; Henry, 2004) and that DPOAE levels decrease on average at earlier ages in males than females(25). Compound action potential thresholds, however, were shown to be higher in female CBA/CaJ and CBA/J mice than males beginning at about 24 months of age(49). In contrast, aged C57 female mice had higher ABR and CNER thresholds than males of the same age (Henry 2002; Henry 2004).

Findings of sex-based differences in aging non-human primates is mixed. In one study aging females had shorter latencies and larger ABR peak 1 amplitudes compared to aging males(50); however, in a follow up with the same cohort, the only sex-based difference was in thresholds at 32 kHz(51). Another study on aging female rhesus monkeys indicated a significant interaction between age and sex for ABR latencies(52).

Because ARHL is associated with poorer health outcomes, non-clinical research in this area has particular implications for care for our aging population. Mechanistic sex-based differences that can only be revealed through non-clinical research may yield new insights in effectively treating men and women as they age.

Sound Therapy/Augmented Acoustic Environments (AAEs)

Contrary to intuition, an augmented acoustic experience/environment (AAE), specifically a chronic or nightly exposure to moderate intensity sound, has been proposed as a potential therapy to increase protection of the inner ear–an effect called “toughening.” Previous research has indicated that exposure to AAEs may be beneficial in mitigating the effects of early-onset hearing loss(53,54) and slowing the effects of ARHL(55); however, in some cases, male and female mice have differing outcomes following exposure to an AAE. It is important for future investigations to include sex as a variable of interest and explore the possibility of sex differences in AAE exposure.

A series of studies tested the effects of AAE in strains of mice that exhibit early-onset progressive hearing loss, DBA/2J (DBA) and C57BL/6 (C57). Mice variously demonstrated an increase or decrease in ABR thresholds, loss of neurons in VCN, or loss of outer hair cells, in different studies. Some of these effects were sex-specific, but the effects also depended on frequency content of the AAE and strain of the mouse(56,57). Sex-specific effects were eliminated in ovariectomized or orchidotomized mice, suggesting a potential role for sex hormones in modulating the effects of AAEs(58–60).

There is also evidence that sex interacts with the effects of AAEs in older mice. In CBA/CaJ mice aged 22–23 months, males demonstrated lower ABR thresholds and higher hair cell counts while females demonstrated opposite effects(61). Males also had decreased levels of a marker for the inhibitory neurotransmitter GABA in the primary auditory cortex, while females had increased levels(61). However, there were no such sex difference in the inferior colliculus(61). Importantly, female animals were post-menopausal prior to the commencement of the study, which the authors suggest resulted in estrogen levels that were lower than those of age-matched males used in the same study(61); studies on estrogen and hormonal effects on hearing loss are discussed below.

Ototoxicity & Pharmaceutical Therapies

Because hearing ability and sensitivity may vary between males and females, ototoxic agents and otoprotective therapies could demonstrate sex-specific damage or efficacy, respectively. Review of published literature suggests that a clear understanding of this relationship remains elusive.

In guinea pigs treated with gentamicin, females had significantly larger ABR threshold shifts compared to males, even when treated with lower doses than males(62). However, male Long-Evans rats demonstrated significant shifts in DPOAE thresholds and amplitudes after fewer days of exposure to kanamycin than females(63). Another study found that JP-8 jet fuel (a petroleum derived fuel similar to that used by commercial aircrafts) exacerbated DPOAE threshold shifts and outer hair cell loss induced by noise exposure in male Fischer 344 rats, but not females(64).

Sex differences in response to otoprotective agents have also been identified. Suberoylanilide hydroxamic acid (SAHA), a histone deacetylase inhibitor(65), has demonstrated otoprotective capabilities against hearing loss caused by exposure to ototoxic chemicals and medications in mice(66). In a recent study, SAHA protected hearing in mice exposed to octave-band noise, but the frequency at which hearing was best protected differed between the sexes(27). Treatment with a combination of antioxidant vitamins and magnesium resulted in smaller permanent ABR threshold shifts and reduced outer hair cell loss(67). However, the study was only conducted in male mice, because previous work had identified sex differences in the effects of antioxidants.

Experiments by Shen et al. (2007) demonstrated sex differences in the efficacy of T-type calcium channel blockers trimethadione and ethosuximide.(68) Treatment of male C57BL/6J mice with trimethadione following noise exposure yielded significantly smaller ABR temporary threshold shifts (TTS) after 24 hours of noise exposure compared to controls, and this protection was not observed in female mice. The authors postulated that this difference could be attributed to either small sample size or differences inexpression of α1I subunit of T-type calcium channel in SGNs.

Such sex-based differences in ototoxicity and otoprotective therapies have clear implications for translational and clinical research. A more robust understanding of the sex-specific detrimental effects of ototoxic agents and impact of otoprotective agents will allow health practitioners to identify if sex portends a higher risk for ototoxic effects or greater efficacy of otoprotective agents.

Hormones & Menopause

Some investigators have suggested that sex differences in hearing may result from hormonal differences between males and females. In particular, estrogen plays a significant role in both the development of the inner ear and the hearing process(69). Mice lacking estrogen receptor (ER) β were deaf at one year of age and were missing the entire organ of Corti(70).

Megalin, which functions as an endolytic receptor for estrogen, is highly expressed in the cochlea within the marginal cells of the stria vascularis(71). Megalin knockout mice exhibit significant hearing loss at three months of age, along with common anatomical markers of presbycusis(72). Genes including WBP2 which act as a transcriptional coactivator for receptors including ER α, and the estrogen-related receptor gamma (ESRRG) gene, are also implicated in hearing(73,74). In particular, male ESRRG knock-out mice demonstrated thresholds of 15 dB better than female mice at 12 weeks(74). Prolactin, on the other hand, is expressed in the cochleas only of older animals(75) and has been implicated in threshold shifts in female BALB/c mice 6–12 months of age (76).

The role of hormone replacement therapy (HRT) has also been explored at the non-clinical level to understand potential impacts on the progression of hearing-loss. The combination of progestin and estrogen hormone replacement therapy decreased auditory sensitivity and outer hair cell function in mice, potentially accelerating age-related hearing-loss(77). These studies demonstrate that understanding of sex-specific hormones may have implications for

understanding the mechanisms, progression, and severity of hearing-loss between males and females.

Clinical Research

Non-clinical research in animal models provides an understanding of the effects of noise exposure, aging, drugs, and hormones on functional, behavioral, and anatomical outcomes in animal models, which establishes a framework for translational and clinical research in humans. Despite broader inclusion of women over the last 25 years, investigation of treatment effects between men and women remains complex(78). Investigation of these differences in treatment is necessary to elucidate potential avenues of hearing-loss prevention and to personalize hearing-loss care to achieve the best clinical outcomes in humans. Below, we summarize sex-based differences in clinical research on hearing-loss in humans.

Sex Bias in Clinical Research

Because NIH funded clinical trials have mandated the inclusion of men and women since 1993, sex bias is essentially absent from current clinical research. A search for ‘hearing-loss’ on ClinicalTrials.gov produced 564 trials; of these, 562 included females in the eligibility criteria and 560 included males. Many of these studies elevated the association of hearing-loss and other disease states and health and well-being. For instance, ACHIEVE study is an ongoing study that investigates the presence of hearing-loss with the goal of following cognition, social abilities, and quality of life for three years.(79)

Sex Based Differences in Humans

As previously discussed, hearing-loss has associations with poorer health outcomes, including associations with dementia(7–9), increased risk of falls(15), and mortality(16). ARHL is of significant clinical importance due to its high prevalence in the growing aging population. It has been demonstrated that in men, ARHL occurs earlier(80), more often(19,20), and more intensely(17). These observations have historically been attributed to differential noise exposure, but some studies have shown sex differences even when taking noise exposure history into account(17,81).

Sex differences are particularly strong in NIHL. Occupation accounts for 2–3% of hearing-loss in men older than 45, although it accounts for less than 1 percent of hearing-loss in young men and all women(82). A study of over 95,000 industrial noise-exposed workers demonstrated lateral differences in hearing, the “ear effect,” are greater among men compared to women, with the right ear being more sensitive. The maximum ear effects differed between males and females at 4 kHz (2.5 dB) and 0.5 kHz (1.5 dB), respectively(83). A Norwegian study also demonstrated that men without occupational noise exposure experienced improved hearing, a finding that was not significant for women(84,85). Because the effects of occupational noise exposure tend to be stronger in men than women, studies of NIHL sometimes focus primarily on men(86). This sex-omission present in many NIHL studies could result in a limited overall understanding of NIHL.

The loss of auditory nerve fibers in absence of threshold shifts, known as “hidden hearing-loss” as termed by Charles Liberman, has been hypothesized to cause difficulties in speech discrimination and temporal processing.(87) This quickly expanding domain of hearing-loss research has implications for uncovering deficits and mechanisms that underlie the process of hearing decline. Although studies on this topic sometimes include both males and females, group sizes tend to be small and not matched for sex; thus, sex differences have not yet been revealed.(88,89)

While sex-based differences in ARLH and NIHL humans are generally consistent, their mechanistic roots and etiologies are more ambiguous. Continued study and acknowledgment of these differences is essential to developing targeted preventions and treatments for ARHL and NIHL in both sexes.

Hormones

Hormones and hormonal changes have demonstrated varying effects in influencing audition(90). Clinical research is consistent with non-clinical research suggesting that estrogen may protect against hearing-loss. Menopause, which is associated with a decline in the production of hormones such as estrogen and progesterone, has been shown to significantly escalate the process of hearing-loss.(91) In a study involving postmenopausal women, those using estrogen therapy experienced protective effects against hearing-loss in comparison to both a group receiving estrogen in combination with progesterone and a control group(92), a finding which has been confirmed by subsequent studies(93). Moreover, auditory brainstem response differences between post-menopausal women and controls substantiate the role of estrogen receptors(94). Decreased ovarian function is associated with hearing-loss, with one study suggesting it may be related to high-frequency air conduction, hearing that occurs through air near the ear (as opposed to bone conduction), in the right ear(95). This finding may be contextualized by a previous finding that treatment of menopausal women with Tibolone resulted in greater improvements in the right ear compared to the left, possibly attributable to higher density of ER-α and ER-β in the right ear.(96) Menopausal women also demonstrated a rapid decline in hearing at 3 kHz(97). Further evidence for the role of estrogen in protecting hearing comes from studies of Turner’s syndrome(98). Women with Turner’s syndrome do not produce estrogen and young patients often exhibit otitis media and progressive sensorineural hearing-loss(99), potentially due to cochlear dysfunction(100).

Genetic & Hereditary Basis of Hearing-Loss

There has been extensive research on the genetic basis of hearing-loss, especially the nonsyndromic *GJB2* mutation encoding the gap junction beta 2 protein Connexin 26. The mutation is found in about half of patients with nonsyndromic autosomal recessive hearing-loss(101). Studies on *GJB2* mutation and hearing-loss tend to involve few subjects. Also, larger studies often did not report results based on sex(102). Other studies that did evaluate interactions with sex did not find these interactions significant(103).

Disease Associations

Studies have examined the associations between a variety of diseases and risk factors and the development of hearing-loss. One investigation demonstrated that poorer hearing sensitivity was associated with increased resting heart rate in both men and women(104). However, in men worse hearing sensitivity was also associated with high triglycerides and a smoking history, while in women poorer hearing sensitivity was associated with increased BMI (body mass index), increased pulse-wave velocity, and low ankle-arm index. In a separate study, risk factors associated with hearing-loss included hypertension and occupational noise exposure for white men, low total hip bone mineral density for black men, and poor cognitive status and smoking for black women(20).

Other investigators found associations between diabetes and hearing-loss(105). In the Reykjavik study, diabetes, decreased BMI, and osteoarthritis were associated with hearing-aid utilization in men(106). Meanwhile the absence of history of angina, normal cognitive status, and increased physical activity were associated with hearing-aid use in women. Factors relevant to abdominal fat, including weight, BMI, total adipose tissue, and waist circumference were associated with high-frequency hearing in men and low-frequency hearing in women(107).

In addition to demonstrated associations with disease, hearing-loss has sex-specific associations with mental health. A study using National Health and Nutrition Examination Survey (NHANES) data determined that an association existed between moderate to worse speech and high-frequency hearing-loss and depression in women ages 52–69, but not men of any age(108). These findings reveal the necessity of screening for depression and, given the differences in sex, the potential need to target interventions accordingly.

Clinical Treatments

Treatment responses and outcomes can vary between sexes, so understanding these effects is necessary to avoid patient harm. There have been several studies that have looked at hearing-aid use and disuse, where women are more likely to seek hearing-aids, use hearing-aids, and have greater expectation of improved hearing(109),(110). Of note, men who had a steeper audiogram slope reported greater nonregular use. Nevertheless, a review that evaluated the why people opt against wearing a hearing-aid reported that less than half of studies surveyed in their review specifically looked at the effect of sex(111).

Similar studies have also investigated cochlear implant use and issues; however, studies have shown that outcomes following CIs do not appear to be sex specific(112). While women employ more cognitive strategies for speech comprehension, differences in the performance ability of men versus women for cochlear implants show that men performed better with complex listening situations(113).

Women are more likely than men to experience ototoxic effects of drugs(114). Calcium channel blockers had a positive effect on women’s hearing while B-adrenergic medication and antihistamine cold preparations had a negative impact on women’s hearing(115). In contrast men did not experience any notable change in hearing following usage of the drugs. On the other hand, salicylate use was found to be protective against hearing-loss in men, but

not women(20). This difference may related to sex differences in the elimination rate of salicylates, although a considerable body of literature indicated that salicylates are detrimental to hearing(116).

Future studies to understand differences in drug effects may mitigate adverse reactions and enhance future therapeutic treatment. Sex differences need to be accounted for to improve drug safety, and in the case of hearing-loss, to better understand the drug's profile to mediate potential ototoxic affects.

Conclusions

Sex differences in ARHL and NIHL have long been recognized but remain poorly understood, likely in part due to sex-bias and omission in non-clinical research. Additional sex-specific auditory non-clinical research is necessary to better bridge the gap between non-clinical work on hearing-loss and sex-specific clinical findings. Accounting for sex differences will yield more effective hearing-loss prevention techniques and more personalized treatment of hearing disorders. It is critical that the sex of the subjects be clearly identified in papers, as the omission of subject sex may affect interpretation and reproducibility.

As hearing-loss presents differently in men and women and has many disease associations, an awareness of sex-specific differences can help tailor treatment. For example, men exposed to occupational noise and menopausal women both face a risk of hearing-loss, but for different reasons that require different preventative measures. Moreover, preliminary studies investigating the adverse effects of some drugs on hearing show that there may be differences in the frequency of adverse events between men and women. Therefore, it is important to know the risks that individuals of each sex face when considering drug treatments.

Ultimately, research efforts within non-clinical and clinical research need to account for sex as a biological variable. These differences are critical to yield robust non-clinical and clinical research that can facilitate translation to viable screening, prevention, and treatment strategies.

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Table 1:

Summary of selected recent non-clinical studies primarily investigating sex differences in hearing loss.

Study	Focus	Species	Ages (days)	Methods	Difference Found	Differences
Guimaraes et al. 2004	ARHL	CBA	63–87, 420–492, 729–870	ABR (3 – 48 kHz); DPOAE (L1=65 L2=50 dB SPL, f1/f2=1.25; 5.6 to 44.8 kHz)	Yes	Male DPOAE levels decreased with age while female DPOAE levels did not decrease after menopause; young and middle-aged male and female ABR thresholds were the same, while female ABR thresholds were lower than males
Henry 2002	ARHL	C57BL/6	50, 100, 200, 300, 400	ABR (8 – 56 kHz); CNER (8 – 56 kHz; two tone burst difference 900 Hz – 1.2 kHz)	Yes	Male CNER and ABR threshold levels demonstrated less severe threshold elevations at high frequencies after 100 days of age
Milon et al. 2018	NIHL, otoprotectivity	B6CBAF1/J	70	Noise exposure (2hr octave band noise 101 dB SPL centered at 11.3 kHz); SAHA treatment (3 days before exposure and 2 hr after noise exposure); ABR (8 – 32 kHz, at 24hr, 8 days, and 15 – 21 days after SAHA treatment)	Yes	Females demonstrated smaller baseline compound threshold shifts at 16 and 24 kHz and permeant threshold shifts at 16, 24, and 32 kHz; frequency of protective effect for females was at 16 kHz and males at 24 kHz for permeant threshold shifts
Willott & Bross 2004	AAE	C57BL/6	31, 345, 160–420	AAE (mean SPL 70 dB, 12 hours nightly); ABR (4 – 24 kHz); histology (HCs, SGCs, AVCN)	Yes	Females demonstrated higher ABR threshold shifts than males beginning at 6 months of age; males demonstrated more severe loss of AVCN neurons than females

Abbreviations: AAE – augmented acoustic environment; ABR – auditory brainstem response; ARHL – age-related hearing loss; AVCN – cochlear nucleus; CNER – cochlear nerve envelope response; DPOAE – distortion product otoacoustic emissions; HCs – hair cells; NIHL – noise induced hearing loss; SAHA – Suberoylanilide hydroxamic acid; SGNs – spiral ganglion cells