Sex-Linked Biology and Gender-Related Research Is Essential to Advancing Hearing Health

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Abstract: There is robust evidence that sex (biological) and gender (behavioral/social) differences influence hearing loss risk and outcomes. These differences are noted for animals and humans—in the occurrence of hearing loss, hearing loss progression, and response to interventions. Nevertheless, many studies have not reported or disaggregated data by sex or gender. This article describes the influence of sex-linked biology (specifically sex-linked hormones) and gender on hearing and hearing interventions, including the role of sex-linked biology and gender in modifying the association between risk factors and hearing loss, and the effects of hearing loss on quality of life and functioning. Most prevalence studies indicate that hearing loss begins earlier and is more common and severe among men than women. Intrinsic sex-linked biological differences in the auditory system may account, in part, for the predominance of hearing loss in males. Sex- and gender-related differences in the effects of noise exposure or cardiovascular disease on the auditory system may help explain some of these differences in the prevalence of hearing loss. Further still, differences in hearing aid use and uptake, and the effects of hearing loss on health may also vary by sex and gender. Recognizing that sex-linked biology and gender are key determinants of hearing health, the present review concludes by emphasizing the importance of a well-developed research platform that proactively measures and assesses sex- and gender-related differences in hearing, including in understudied populations. Such research focus is necessary to advance the field of hearing science and benefit all members of society.

Key words: Audiology, Auditory Rehabilitation, Gender, Hearing, Hearing loss, Hormones, Research, Sex.

(Ear & Hearing 2023;44;10–27)

IDEA

Inclusion, Diversity, Equity, Accessibility Article.

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INTRODUCTION

Sex and gender influence and intersect with each other to shape patterns of behavior, health, disease, and injury (Krieger 2003; Day et al. 2016), necessitating sex and gender considerations in the design, analysis, and reporting of hearing health research. However, the effects of sex and gender on hearing often are overlooked. This oversight in hearing research can lead to bias and limit the generalizability of research findings and their applicability to clinical practice (Sims et al. 2010). In addition, consistent with the concept of intersectionality introduced over three decades ago in the context of law (Crenshaw 1989), it is now widely accepted that sex and gender can intersect with factors such as race, ethnicity, age, education, and socioeconomic position in the context of health. Excellence in hearing research cannot be achieved without the full inclusion and participation of all members of society. Understanding how sex and gender affect hearing and hearing health will contribute to the goal of enhancing the quality of science, practice, and public health.

Although they are different constructs, confusion can result because the terms *sex* and *gender* are often used interchangeably by researchers (King 2010; Day et al. 2016; Heidari et al. 2016). While distinct definitions of *sex* and *gender* are provided in Table 1, it is important to note that these concepts are interrelated and entangled (Einstein 2012; Clayton & Tannenbaum 2016; Heidari et al. 2016; Tannenbaum et al. 2019; Flatt et al. 2022). *Sex* refers to biological differences between males and females. The labels male/female originate from reproductive structure, functions, phenotype, and genotype relating to sex-linked biology. In general, the sex-linked biology of most individuals aligns with a male/female categorization; however, some individuals do not fit this categorization such as those with intersex traits or variations in sex-specific chromosomes and hormones (Day et al. 2016; Cameron & Stinson 2019). Language such as *sex-linked biology* should be used when referring to physiologic differences associated with male and female bodies (Short et al. 2013). In humans, measures of sex are often not independent from the effects of gender (Springer et al. 2012; Short et al. 2013; Clayton & Tannenbaum 2016).

Gender is a social construct shaped by the environment, experience, and socio-cultural factors that influences and emphasizes differences between men and women and contributes to masculinity and femininity (Short et al. 2013). Gender identity is how an individual sees themselves and experiences one's own gender (Fleming & Agnew-Brune 2015) and is not limited to the binary man/woman designation. We do not know about gender unless individuals are asked about their gender identity, in which case, we could preference gender by cis- or trans-. Cisgender men and women have an identity that is

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<zdoi; 10.1097/AUD.0000000000001291>

TABLE 1. Sex and gender definitions

Term	Definition
Sex	• Characteristics of reproductive structure, functions, phenotype, and genotype, differentiating the male from the female organism. • Complicated term with many different meanings, both historical and contemporarily, as well as colloquially and therefore more precise terms should be used in its place.
Sex-linked biology	• Includes chromosomal sex (XX, XY, and more), gonadal hormones, menstruation, genital secretions, secondary sex characteristics, sex-steroid-sensitive physiology of nonreproductive tissues, pregnancy, and menopause • Terms male, female, and intersex (or their chormosomoal complements) should be used when referring to sex-linked biology
Gender	• Identification as masculine, feminine or something else, and association with a social role or set of behavioral and cultural traits; a category to which a person belongs on this basis. • Gender is the result of a complex combination of gender role, gender expression, gender identity, and gender modality. • Understood to exist on a continuum and is not binary (gender diverse person); although terms man and woman are commonly used when referring to one's gender
Gender-identity	• A person's concept of self as being masculine, feminine, or ambivalent, based in part on physical characteristics, parental responses, and psychological and social pressures. It is the internal experience of gender role. • A person's sense of self as a member of a particular gender. • Cisgender is someone whose gender identity aligns with their sex assigned at birth. • Transgender is someone who identifies differently from their sex assigned at birth.

Clayton and Tannenbaum (2016); Kronk & Dexheimer (2020); Krieger (2003); Short et al. (2013); Tannenbaum et al. (2019).

congruent with their sex (male/female) assigned at birth, while transgender men and women have an identity that is incongruent with their sex assigned at birth. Gender-related differences in health are understood to reflect both social and biological factors (Short et al. 2013). The labels man/woman hold broader meaning (Tseng 2008; Nielsen et al. 2021) and should be used along with other gender identities instead of male/female when referring to psychosocial factors under study.

The term *sexual and gender minority* (SGM) includes but is not limited to individuals who identify as lesbian, gay, bisexual, transgender, queer or questioning, intersex, nonbinary (LGBTQ+) or those who exhibit attractions and behaviors which do not align with heterosexual or traditional gender norms (National Academies of Sciences, Engineering, and Medicine [NASEM] 2020). Terms continue to evolve for how SGM individuals describe their gender identity, sexual orientation, and expression (Flatt et al. 2022). Adults identifying as SGM account for about 7% of adults in the United States and 4% in Canada, with representation in every generation (Statistics Canada 2021; Jones 2022). Overall, the proportion of the population identifying as SGM is greater for younger than older adults. The number of adults 50 years of age and older who identify as SGM is expected to double by 2060 (Fredriksen-Goldsen & Kim 2017).

Generalizability of research requires consideration of sex-linked biology and gender. In many hearing studies, sex or gender have not been disaggregated in analyses and many studies have been conducted mainly in men or male animals (Lauer & Schrode 2017; Beery 2018; Pittman et al. 2021). Recognizing the need for the inclusion of women in research, the National Institutes of Health (NIH) Revitalization Act of 1993 was passed in the United States and reaffirmed by the passing of the 21st Century Cures Act of 2016, which required the participation of women and minorities in clinical research and the reporting of outcomes by sex, race, and ethnicity. Despite mandates by major funding agencies, the integration of sex and gender into the design of hearing research has been slow and there has been no standard practice for reporting sex and gender in research outcomes (Heidari et al. 2016; NASEM 2020). Moreover, few studies have investigated disparities in hearing health outcomes based on sexual orientation (Kelly-Campbell & Atcherson 2012) and no studies have been published investigating hearing health outcomes in gender diverse people. Thus, it is unclear if research results can be applied equally across all sexes and genders. Inclusion of all sexes and genders in hearing research, including stratified analyses by sex or gender, is needed to inform hearing health promotion, public policies and programs to prevent or treat hearing loss, and reduce health disparities. Integrating sex-linked biology and gender into research on hearing and hearing healthcare can advance both theory and practice by improving study reproducibility and social equality in scientific outcomes (Tannenbaum et al. 2019).

The purpose of this article is to reflect on our current understanding of the role of sex-linked biology and gender in hearing health, provide examples of sex-linked biology and gender analyses and reporting in hearing health research, identify key gaps in the literature, and make proposals for advancing theory and practice. As a starting point, we note the current epidemiologic trends in hearing loss by sex-linked biology and gender. Next, we review the observed associations between sex hormones and hearing, including observed sex-related differences in noise-induced hearing loss (NIHL). We also describe how varying noise exposure patterns between men and women may be a driver of sex-related differences in hearing loss observed across the lifespan. (Usually if persons identify as men or women, their traits are considered sex-related differences unless those traits are thought to depend solely on social phenomena determined by one's phenotypic expression. Here, hearing loss differences between men and women arising from varying noise exposure patterns are considered sex-related differences even though gendered experiences might have contributed to those differences). Then research is reviewed to examine how sex-linked biology and gender could modify the observed associations between cardiovascular disease and hearing loss and between hearing loss and cognitive decline. Connections between sex and gender and self-reported hearing loss (SRHL) and their implications for hearing aid use and family-centered rehabilitation are considered. Finally, key considerations for advancing hearing research are discussed, recognizing that sex-linked biology and gender are key determinants of health that are critical to scientific discovery and achieving health equity.

We offer a caveat to this review. Sex and gender are reported as simple binary classifications (male/female, man/woman, boy/girl) despite recognizing that binary classifications are antiquated. However, most human research reviewed was limited to two choices and did not capture both sex and gender, making it impossible to assess if intersex, transgender or nonbinary individuals participated in the research. It is important to acknowledge that considering sex or gender as only two categories may be too imprecise to be useful in health research (Nielsen et al. 2021), resulting in misclassification and threatening the validity of research (Bauer et al. 2017; Cameron & Stinson 2019). We use the terms sex-linked biology and sex-related differences when discussing physiologic hearing differences between sexes but recognize that in most research reports involving humans, sex was not clearly measured and likely includes effects of gender. We limit our use of the terms male/female to animal research and when measures of sex were clearly delineated (as reflected by sex hormones, external genitalia, internal reproductive organs, etc.). Otherwise, we use the terms the boy/girl or man/woman when discussing the literature. We use the terms gender and gender-related differences when discussing psychosocial factors (e.g., behavioral, social, psychological, and other factors) but similarly recognize these areas of research are not free from the influence of sex-linked biology.

Differences in Measured Hearing Loss

Sex-related differences in hearing begin prenatally and continue throughout the life course. The prevalence of congenital hearing loss among full-term infants varies by sex assigned at birth with more male (1.8 per 1000 live births) than female (1.2 per 1000 live births) infants being born with hearing loss (Van Kerschaver et al. 2013). Prevalence of congenital hearing loss also varies by geographic location (Centers for Disease Control and Prevention 2018), suggesting that sex-linked biology, environmental factors, and social factors may all contribute to congenital hearing loss. Prenatal environmental and social factors may interact with sex-linked biological differences to further the hearing loss disparity between sexes at birth. Observed differences in hearing loss between adolescents identified as boys and adolescents identified as girls are similarly evident in the literature. Research suggests that adolescent boys have twice the odds of having hearing loss compared with adolescent girls, even after controlling for age, race, income, noise exposure, and health factors (Hoffman et al. 2019). While sex-related biological factors may make males more vulnerable to hearing loss than females, gender-related behaviors and experiences may drive an accumulation of risk throughout the life course that may result in differing patterns of hearing loss between sexes.

Differences between men and women when hearing was measured using pure-tone thresholds have been observed in cross-sectional and longitudinal studies of adults examining age-related changes in hearing. Results from population-based studies reporting sex-related differences in the incidence and prevalence of hearing loss are displayed in Tables 2 and 3, respectively. Although there were slight variations in the definitions of incident and prevalent hearing loss across studies, most found that men, compared with women, were at increased risk for incident pure-tone hearing loss in the speech frequency range over a 5- and 15-year period (Table 2), and that more men than women had prevalent hearing loss (Table 3). When stratified by age group, the prevalence ratio (men:women) for adults varied between 1.1:1 and 3.3:1, with highest ratios observed during the mid-life years (Lin et al. 2011b; Mick et al. 2021a). In addition to age, the prevalence of hearing loss differs by generation and geography. Specifically, the prevalence of hearing loss among adults 25 to 64 years old examined between 1999 and 2004 was significantly lower at 500, 2000, and 4000 Hz for men and women when compared with their counterparts tested between 1959 and 1962 (Hoffman et al. 2010). Around the world, the hearing loss (better ear PTA 0.5, 1, 2, 4 kHz > 40 dB HL) prevalence ratio (men:women) for adults age 15 years and older varied between 1.0:1 for studies based in China and parts of India, to 2.4:1 in Australia (Mathers et al. 2003). These differences over age, time, and across populations further implicate social and environmental determinants of hearing health and suggest that further generational changes may emerge with social changes related to economic stability, working conditions, access to education, and better, more accessible, health care.

It is important to balance the representation of women and men (including SGM when possible) in research to increase the generalizability of study findings, to ensure that all persons benefit fully from research findings, and to minimize the potential to create and exacerbate health care inequities and hearing health disparities between sexes. The percentage of women participants in the epidemiologic studies reviewed in Tables 2 and 3 ranged from 59.2% in the Framingham Heart Study (Mościcki et al. 1985; Gates et al. 1990) to 32.0% in the Baltimore Longitudinal Study of Aging (BLSA), with BLSA being one of the few studies in which men substantially outnumbered women (Brant et al. 1996). Furthermore, in many studies, the percentages of men and women varied with age, with higher percentages of women in older age decades, partly because women live longer than men. Notably, in contrast with the sex distributions in samples mentioned earlier, other studies of adults may be less balanced and have a greater proportion of men than women, especially for studies investigating military (Henry et al. 2020) or occupational noise exposure (Masterson et al. 2013, 2016a).

Sex-Linked Biology and Hearing

Understanding the role of hormones in maintaining auditory function will help advance therapies for protecting people against hearing loss. The main sex hormones, including the androgens, estrogens, and progesterone, have a wide range of effects on bodily functions, including hearing. Evidence suggests that estrogens play an important role in differences between males and females in auditory function (Tables 2 and 3). Testosterone, a type of androgen, may also affect auditory sensitivity (McFadden et al. 2006). While sex hormone exposures begin in-utero and progress throughout life, the focus here is on estrogens in adulthood—specifically in females/women. Note, however, that estrogens are present in males but at significantly lower levels than in females.

There are three major endogenous estrogens: estrone, estradiol, and estriol, with levels determined by the reproductive

TABLE 2. Distribution of incident hearing loss (5-year and 15-year follow-up) by sex from population-based studies in adults

Author	Study—location	Year	Hearing loss definition	Age range	Women % (95% CI)	Men % (95% CI)	OR (95% CI), HR (95%, CI), or *P* value
5-year incidence							
Cruickshanks et al. (2003)	EHLS—USA	1998–2000	PTA 0.5, 1, 2, 4 kHz >25 dB HL (either ear)	48–92	18.5 (16.1–20.8)	27.4 (23.5–31.2)	0.001
				48–59	7.0 (4.8–9.2)	19.1 (14.8–23.4)	–
				60–69	18.1 (14.0–22.2)	35.0 (27.2–42.8)	–
				70–79	45.2 (37.9–52.5)	59.1 (44.6–73.6)	–
				80–92	94.7 (87.3–100.0)	100.0 (…)	–
Mitchell et al. (2011)	BMHS—Australia	1997–2004	PTA 0.5, 1, 2, 4 kHz >25 dB HL (better ear)	55–99	18.0 (14.7–21.3)	17.9 (13.8–21.9)	OR = 1.0 (0.7–1.5)
				55–59	5.5 (0.7–1.0)	4.8 (0.1–9.4)	–
				60–69	13.9 (9.8–18.1)	18.4 (12.3–24.5)	–
				70–79	28.7 (21.2–36.2)	28.4 (19.2–37.7)	–
				80–99	62.5 (35.9–89.1)	20.0 (0–50.2)	–
Fischer et al. (2015)	BOSS—USA	2005–2008	PTA 0.5, 1, 2, 4 kHz >25 dB HL (either ear)	21–79	5.8 (4.4–7.2)	11.6 (9.4–13.8)	OR = 2.3 (1.6–3.2)
				21–34	0.0 (0.0–4.7)	3.9 (0.5–13.2)	–
				35–44	3.2 (1.3–5.1)	7.1 (4.1–10.2)	–
				45–54	5.3 (3.2–7.4)	11.4 (8.0–14.8)	–
				55–64	7.4 (4.0–10.8)	21.4 (15.0–27.9)	–
				65–79	27.3 (15.5–39.0)	16.1 (5.5–33.7)	–
15 year incidence							
Cruickshanks et al., 2015	EHLS—USA	2009–2010		48–59	29.5 (25.4–33.6)	54.3 (48.6–59.9)	HR = 2.2 (1.9–2.7)
				60–69	71.1 (65.6–76.6)	83.5 (76.4–90.6)	
				70–79	93.0 (87.9–98.2)	95.3* (69.8–100.0)	
				80–92	100.0 (–)		

**Combined 70–92.*

BMHS indicates Blue Mountains Hearing Study; BOSS, Beaver Dam Offspring Study; CI, confidence interval; EHLS, Epidemiology of Hearing Loss Study; HR, hazards ratio; PTA, pure tone average; OR, odds ratio.

cycle, pregnancy, and age. Once estrogens are secreted into the blood, some become bound to a hormone-binding globulin, while others diffuse across the cell membrane and bind to the estrogen receptors (ER), alpha (ERα), and beta (ERβ). The two ERs are products of discrete genes found on separate chromosomes and are thought to have opposing biological actions. Activation of the ERs results in the modulation of expression of many genes important for key cell functions. Receptor-independent effects of estrogen may also be mechanistically involved in hearing.

Estrogen Receptors in the Auditory System • The expression of ERα and ERβ has been observed in the cochlea of the mouse and rat, specifically in the nuclei of inner and outer hair cells as well as in spiral ganglion neurons (Stenberg et al. 1999; Meltser et al. 2008). Beyond the cochlea, ERα and ERβ have been localized in the mouse central auditory pathway and found predominantly in the ventral cochlear nucleus, nucleus of the trapezoid body, the lateral- and medio-ventral periolivary nuclei, the dorsal lateral lemniscus, and the inferior colliculus (Charitidi & Canlon 2010). The medial geniculate nucleus was negative for both ERα and ERβ, whereas the auditory cortex was positive for ERα. The lateral superior olive, the ventral lateral lemniscus, and the central nucleus of the inferior colliculus expressed only ERβ. The differential localization of ERα and ERβ may indicate distinct roles for these two receptors in modulating auditory processing (Charitidi & Canlon 2010). To date, no sex-related differences have been noted in patterns of ER expression either in the peripheral or central auditory systems (Meltser et al. 2008; Charitidi & Canlon 2010). However, this does not negate the possibility of sex-hormones interacting with other factors or their expression being shaped by the environment or exposures to affect hearing.

Estrogens have been shown to modulate the physiological and behavioral output of the central auditory system, improving sound detection and localization abilities, which are important for mating and communication in songbirds and fish (Sisneros et al. 2004; Remage-Healey et al. 2008; Tremere et al. 2009; Maney & Pinaud 2011). In the gerbil, estrogens also affect cochlear ionic homeostasis through direct nongenomic actions (Lee & Marcus 2001), potentially altering the mechano-electrical transduction and sensitivity of hair cells. These fast nongenomic actions of estrogens likely modulate auditory processing via transcription factors for ERα and ERβ. As such, deviations in estrogen levels or perturbations of estrogen-related auditory neural activity can affect hearing (Frisina et al. 2021).

Studies in mice have demonstrated that, in the absence of any external exposures, high-frequency hearing sensitivity declines with age, more so in males than females (Henry 2004). It is important to note that the sex-related difference in hearing thresholds decreases with increasing age (Guimaraes et al. 2004). A strong argument for this pattern of observed sex-related differences is the change in estrogen levels with age (Frisina et al. 2021). ER expression in the cochleae of fish and mammals is affected by age (Maruska & Fernald 2010; Motohashi et al. 2010). When the levels of estrogens are high, the ER become downregulated, as has been demonstrated in the rat cochlea during different stages of development and pregnancy (Simonoska et al. 2009a). Moreover, greater loss of hair cells and spiral ganglion neurons in the basal part of the cochlea, accompanied by hearing loss, was found in aged ERβ-deficient mice

TABLE 3. Distribution of prevalent hearing loss by sex from population-based studies in adults

Author	Study—location	Year	Hearing loss definition	Age range	Women % (95% CI)	Men % (95% CI)	OR (95% CI) or *P* value
Cruickshanks et al. (1998)	EHLS—USA	1993–1995	PTA 0.5, 1, 2, 4 kHz >25 dB HL (worse ear)	48–92	36.2	58.6	OR = 4.4 (3.7–5.2)
				48–59	10.2	32.7	–
				60–69	28.1	61.8	–
				70–79	54.6	83.0	–
				80–92	86.1	96.6	–
Wilson et al. (1999)	South Australia	1996–?	PTA 0.5, 1, 2, 4 kHz ≥25 dB HL (worse ear)	≥15	18.4 (12.5–24.3)	26.0 (17.0–34.9)	OR = 1.7 *<0.05*
Helzner et al. (2005)	Health ABC—USA	2001–2002	PTA 0.5, 1, 2 kHz >25 dB HL (worse ear)	73–84	57.5	62.7	OR = 1.2 (1.0–1.4)
Mitchell et al., 2011	BMHS—Australia	1997–2004	PTA 05, 1, 2, 4 kHz >25 dB HL (better ear)	55–99	29.2	38.0	OR = 1.7 (1.4–2.0)*
				55–59	5.4	11.9	–
				60–69	17.0	28.7	–
				70–79	45.2	55.0	–
				80–99	77.7	79.0	–
Lin et al. (2011)	NHANES—USA	2001–2008	PTA 0.5, 1, 2, 4 kHz >25 dB HL (both ears)	20–29	0.35 (0–0.79)	0.48 (0–1.4)	–
				30–39	0.79 (0–1.8)	2.5 (0.14–4.9)	–
				40–49	4.5 (0.94–8.1)	8.7 (5.0–12.4)	–
				50–59	6.1 (3.6–8.6)	20.3 (14.5–26.2)	–
				60–69	16.8 (12.1–21.5)	39.2 (31.7–46.8)	–
				70–79	48.5 (38.5–58.5)	63.4 (56.2–70.5)	–
				≥80	75.6 (69.7–81.5)	84.6 (79.0–90.3)	–
Lin et al. (2011)	NHANES—USA	2005–2006	PTA 0.5, 1, 2, 4 kHz >25 dB HL (better ear)	≥70	58.2 (50.7–65.6)	69.8 (63.6–75.9)	OR = 1.7 (1.1–2.6)
Mick et al. (2021)	CLSA—Canada	2012–2015	PTA 0.5, 1, 2, 4 kHz >25 dB HL (better ear)	45–85	15.3 (14.7–15.9)	20.7 (20.1–21.4)	<0.05
				45–49	2.2 (1.4–3.0)	2.8 (1.8–3.8)	
				50–54	3.0 (2.2–3.7)	5.6 (4.5–6.8)	
				55–59	6.3 (5.1–7.5)	8.8 (7.4–10.1)	
				60–64	10.2 (8.8–11.7)	16.2 (14.5–17.8)	
				65–69	16.7 (14.9–18.5)	27.8 (25.5–30.1)	
				70–74	29.2 (26.4–31.9)	38.3 (35.4–41.2)	
				75–79	46.4 (43.3–49.5)	57.1 (54.0–60.1)	
				80–85	64.8 (61.2–68.4)	75.9 (72.6–79.1)	

**Only for ages <80.*

BLSA, Baltimore Longitudinal Study of Aging; BMHS, Blue Mountains Hearing Study; BOSS, Beaver Dam Offspring Study; CI, confidence interval; CLSA, Canadian Longitudinal Study of Aging; EHLS, Epidemiology of Hearing Loss Study; FHS, Framingham Heart Study; Health ABC, Health Aging and Body Composition; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

compared with controls (Simonoska et al. 2009b). In rats, 17β-estradiol protected hair cells against gentamycin in vitro, and this protection was mediated by ERs (Nakamagoe et al. 2011). Complementary to the cellular and molecular effects, physiological evidence of estrogenic effects on the auditory system exists. Treatment with tamoxifen (5 mg total dose/60 day time release subcutaneous pellet, Innovative Res. Am., Sarasota, FL), an estrogen antagonist, results in decreases in contralateral suppression of distortion-product (DP) otoacoustic emissions (OAEs) in aging female mice (Thompson et al. 2006). Longer latencies in auditory brainstem responses (ABR) in ovariectomized rats compared with intact rats were reversed by estrogen treatment, and subtle interpeak latency differences suggest hormonal involvement at central as well as peripheral levels (Coleman et al. 1994).

Sex Hormones and the Menstrual Cycle • Changes in hearing sensitivity occur during the menstrual cycle for mammals, including humans. In a small study of women with normal hearing, OAE amplitudes and frequencies, OAE contralateral suppression, and ABR latencies fluctuated with estradiol levels of the menstrual cycle and were indicative of increased hearing sensitivity around the time of ovulation (Al-Mana et al. 2010). Consistent with this, Souza et al. (2017) noted that the best hearing thresholds were found when estradiol was at its maximum peak in the menstrual cycle and postulated an estrogen oto-protective effect. However, during pregnancy, when progesterone and estradiol levels are exceptionally high, pregnant people usually experience increases in pure-tone thresholds (Goh & Hussain 2012), as well as other negative effects, such as prolonged latencies of ABR waveforms, including decreased temporal synchrony (Tandon et al. 1990). Finally, among women ages 45 to 55, those identified as being premenopausal had significantly better extended-high-frequency (8 to 16 kHz) hearing than those that identified as postmenopausal (Zhang et al. 2018).

Association Between Sex Hormones and Hearing Dysfunction • Animal model studies show that the most used form of hormone replacement therapy (HRT), composed of an estrogen and a progesterone, can hurt hearing, whereas an estrogen alone can be helpful (Coleman et al. 1994; Price et al. 2009). For example, Williamson et al. (2019) gave long-term HRT to aging female mice with bilateral ovariectomies and measured ABRs along with serum hormone levels, during and after the HRT treatments. The estrogen-monotherapy animals had lower thresholds and higher amplitudes compared with combination HRT and progesterone-alone groups and the observed effects appeared permanent. These results were consistent with experiments that displayed higher levels of type 1 insulin-like growth factor receptor (IGF-1R) in the cochlear stria vascularis of both estrogen and progesterone monotherapy animal groups compared with combination treatment animals. Notably, IGF-1R plays a vital role in mediating antiapoptotic cell death responses.

These findings in animals are consistent with hearing loss measured in older women who have taken combination HRT. Guimaraes et al. (2006) found that older women who had taken combination HRT had worse hearing (elevated audiometric thresholds, reduced DPOAE amplitudes, worse speech-in-noise perception) than women of the same age and health histories who never took HRT, or relative to women who took an estrogen alone. Consistent with this, Dubno et al. (2008) found that women (about half of whom reported a history of HRT) with higher serum progesterone levels in their blood had faster age-related declines in word recognition than women with lower levels. Examining observational study data from the Nurses' Health Study II, women who used HRT had worse hearing than those who never used HRT, with longer duration use associated with higher risk for hearing impairment (Curhan et al. 2017). Generally, an estrogen-alone medication delivered in reasonable doses is good for hearing (Singer et al. 1996; Garcia-Segura et al. 2001; Rudziński & Krejza 2002); unfortunately, estrogen can increase risk for cancer or stroke, limiting its utility as an oto-protectant.

Sex-Linked Biology in the Study of Noise-Induced Hearing Loss (NIHL) and Drug Discovery

Historically, female animals have been understudied or excluded in many areas of scientific research with the exception of reproductive research (Lauer & Schrode 2017). One common rationale is that including female animals adds variance, a conclusion that has been called into question (Beery 2018). This pervasive practice enshrouds consequential sex-linked biological differences in physiology, injury response, and the efficacy of therapeutics that may affect the prevention, treatment, and management of disease. The recent increased focus on sex as a biological variable has uncovered numerous examples of differences in the response to injury, including injuries and pathologies of a neural etiology (Tierney et al. 2017; Roy-O'Reilly & McCullough 2018; Yue et al. 2019). Equally as important, abundant evidence demonstrates that sex-linked biology influences the efficacy of current therapeutics for injuries and pathologies of a neural etiology (Sramek et al. 2016; Canevelli et al. 2017; Nasser & Afify 2019).

The increased focus on sex-linked biology extends to the study of NIHL, a condition with neuropathological components. Animal studies demonstrate that sex-linked biology influences susceptibility to NIHL, and that females are relatively protected in comparison to males (McFadden et al. 1999; McFadden et al. 2000; Milon et al. 2018; Fernandez et al. 2020). Similar patterns in the susceptibility to NIHL have also been demonstrated in prospective and retrospective studies in humans (Gallo & Glorig 1964; Berger et al. 1978; Axelsson & Lindgren 1981).

In addition to NIHL, sex-related differences in age-related hearing loss (ARHL) have been documented (see Tables 2 and 3). As in NIHL, sensory cell loss is a pathophysiological component of ARHL, a form of acquired hearing loss that may be, at least partially, related to noise exposure (Wu et al. 2020). Studies in male mice demonstrate that noise exposures that produce only transient elevations in auditory thresholds accelerate cochlear aging and degeneration of the spiral ganglia as a long-term effect (Fernandez et al. 2015). Due to the interconnectedness of NIHL and ARHL with respect to sensory cell loss, it is conceivable that therapeutics developed for NIHL may prove effective against some ARHL. Moreover, studies designed to exploit the sex-linked biology and gender differences in noise exposure histories may help disambiguate the inter-connected mechanisms of NIHL and ARHL.

Evidence also suggests that sex-linked biology may influence the efficacy of potential hearing loss therapeutics (Milon et al. 2018; Rouse et al. 2020). The observed sex-linked differences in susceptibility to NIHL and the efficacy of therapeutics may be activational and organizational [for an introduction to activational and organizational effects of hormones see McCarthy and Arnold (2011)]. These sex-linked biological differences underscore the critical need to acquire a deeper mechanistic understanding, without which it is reasonable to foresee obstacles in the development of efficacious therapeutics for men and women.

The study of NIHL is already inherently challenging because small changes to the intensity, duration, or frequency composition of the noise exposure can dramatically alter the severity of NIHL. Furthermore, a variety of factors aside from sex-linked biological differences (e.g., age, prior hearing loss, cortisol levels, circadian changes in gene expression, and genetic mutations) can influence injury severity following noise exposure (Cederroth et al. 2019; Shuster et al. 2019). That is, similar noise exposures may cause a temporary threshold shift (with or without cochlear synaptopathy) or a permanent threshold shift in animals with different biological profiles. It is therefore critical to appropriately power and design NIHL experiments to detect changes in outcomes when the data are disaggregated by sex. Additional consideration should be given when designing and calibrating a noise exposure paradigm to produce a desired severity of NIHL. A noise exposure paradigm that produces a moderate permanent threshold shift in male animals may produce a smaller permanent threshold or even a temporary threshold shift in female animals such that the effects of the intervention being investigated may be masked. From a mechanistic standpoint, studying the role of sex hormones in NIHL and their potential as therapeutics also requires thoughtful experimental design. Strategies for controlling levels of sex steroids in animals include surgical and pharmacological gonadectomy with and without hormone replacement therapies, using serial injections, osmotic pumps, or slow-release pellets, each of which presents experimental challenges and considerations (McCarthy et al. 2012).

Targeted approaches for investigating the role of sex-linked biology and sex hormones in NIHL include the use of estrogen receptor or aromatase conditional knockout animals. Other approaches include the administration of compounds that selectively bind to specific receptors. There are a variety of estrogen receptor-selective compounds that target the two classical ER introduced earlier (ERα and ERβ) as well as a category of FDA-approved selective estrogen receptor modulators that display tissue-specific and receptor specific actions (Paterni et al. 2014; Pinkerton & Thomas 2014). Indeed, the utilization of knockout animals for the two classical ER and estrogen receptor-selective compounds has already advanced our understanding of the role of sex-linked biology and sex hormones in NIHL (Meltser et al. 2008; Charitidi et al. 2009).

Despite the widespread prevalence of NIHL (Nelson et al. 2005; Carroll et al. 2017), no FDA-approved therapies exist for the treatment of NIHL. It is important to note that, careful and deliberate study of sex-linked differences in NIHL may prove critical in the development of novel therapeutics. The refinement of experimental techniques and models to study sex-linked differences will aid in the advancement of our understanding of the molecular underpinnings. There is an armamentarium of genetic and pharmacologic approaches for the study of sex-linked differences and the actions of sex hormones. However, given the relative nascency of our understanding of sex-linked biological differences in hearing, even simple considerations such as appropriately powering a study to analyze data separately by sex, can be important.

Adverse drug effects on hearing may also vary by sex. For example, women taking beta-adrenergic medication and antihistamine cold preparations had poorer hearing than women not taking these medications (Lee et al. 1998; Mills et al. 1999). Similar differences were not observed in men; however, the results in women may be confounded by the indication for the prescription medication. Furthermore, the sample size was insufficient to evaluate an interaction between the medications and hormone supplements. Women have previously been shown to be at increased risk for adverse drug reactions compared with men, possibly due to the fact that women are treated with doses used in clinical trials carried out in men (Franconi et al. 2007). Thus, evidence suggests that differences in oto-protective and oto-therapeutic medications and adverse reactions to certain medications may be sex-dependent. It is crucial to investigate the complexity of the effects of sex-linked biology differences on drug responses to improve drug development, efficacy, and safety.

Gendered Experiences With Noise Exposures

Apart from the sex-linked biological differences between sexes described earlier, which may result in differential vulnerability in the hearing ability of men and women, there are also differential noise exposures resulting from gendered experiences and social patterning that may lead to differential hearing consequences among men, women, and SGM. Because occupational and recreational noise exposure is differentially distributed across populations, it likely contributes to differing rates of NIHL between groups. In essence, gendered experiences (culture and lived experience) can contribute to biological expression of hearing ability.

In a nationwide survey (NHIS), approximately 23.2% of boys and 13.5% of girls (<18 years of age) in the United States reported firearm noise exposure. Boys exposed to firearm noise reported wearing hearing protection more consistently than girls, possibly because girls were unintentionally, rather than intentionally, exposed (Bhatt et al. 2020). In a sample of 96 adolescents (10 to 19 years old), boys reported about twice as many high-risk noise activities compared with girls (Warner-Czyz & Cain 2016). Early life noise exposures may explain, at least partially, why adolescent boys have a higher prevalence of hearing loss compared with girls. Importantly, animal models suggest that early noise exposures may accelerate ARHL (Kujawa & Liberman 2006); therefore, early life noise exposures not only contribute to early differences in hearing between boys and girls but may manifest later in longitudinal trajectories. Still, a longitudinal analysis of pure-tone thresholds from older men and women (mean age 68 years old) with mild-sloping to moderately severe hearing loss at baseline, found that rates of threshold change over time did not differ between groups with positive and negative noise exposure histories (Lee et al. 2005). Additional longitudinal analysis from various life stages, especially pre- and postmenopause in women, could help determine how sex-linked biological factors and gender-related factors combine to affect the hearing health of people over the life course.

High levels of occupational noise remain a problem in all regions of the world (Concha-Barrientos et al. 2005; Nelson et al. 2005; World Health Organization 2021). Based on a population survey in the United States (NHANES 1999 to 2004), approximately 26.3% of working-age men (18.5 million) and 6.7% of working-age women (3.9 million) reported being exposed to hazardous noise on the job (Tak et al. 2009). Of those exposed to hazardous levels of noise, 31.1% of men (5,737,000 men) and 49.3% of women (1,937,000 women) reported not using hearing protection (Tak et al. 2009). Nevertheless, when required to use hearing protection at work, it appears that more women than men are compliant. A Canadian study found that when required to use hearing protection based on occupation, 90.1% of women and 77.0% of men reported that they always or often used hearing protection (Feder et al. 2017). In this same study, among those formerly or currently working in an occupation with hazardous noise, 52.6% of men and 33.8% of women reported working in noise for more than 5 years (Feder et al. 2017). In the United States, the prevalence of NIHL is greatest in mining, construction, and manufacturing occupations that are predominantly filled by men (Masterson et al. 2016a). Given these gendered experiences of occupational noise exposure and use of hearing protection, it is understandable that NIHL is more prevalent among men compared with women. In both the United States and Canada, men had twice the odds of NIHL compared with women (Nelson et al. 2005; Masterson et al. 2013, 2016a, 2016b).

In a study comparing men and women who had comparable noise exposure levels and duration of occupational exposure, men had a much higher prevalence of NIHL compared with women (OR = 4.2; 95% CI: 3.2–5.5), suggesting that the differences may be related to sex-linked biology and susceptibility rather than only gendered experiences or behavioral habits (Wang et al. 2021). However, despite attempting to balance occupational noise exposure and other covariates between men and women, observed differences at the time of study may be reflecting differences in hearing that were present before employment (potentially from hormones and gendered experiences).

Another consideration regarding gender representation in research on NIHL is that, while it appears that most exposed workers are men, it could be argued that past research has been biased toward industry sectors where dosimetry measurements are available, thereby leading to an under-representation of women and SGM whose occupations and work environments have been understudied. Sex-linked biology and gender representation in research on NIHL has implications for hearing health policy and health promotion and raises interesting questions as to what determines people's options and capabilities to protect their hearing and maintain communication function at work.

Human Audiometric Phenotypes

Pure-tone hearing thresholds are consistently poorer for men than women (Table 3). Sex-linked biology and gendered experiences may underlie the differences in audiogram configurations observed in older adults. One approach to distinguish between the effects of sex-linked biology or gendered experiences (e.g., occupational noise exposure) on the audiogram is to assess how certain cochlear pathologies affect audiometric patterns. Studies of laboratory animals raised in carefully controlled environmental conditions identified a metabolic component of ARHL associated with a decline in the endocochlear potential (EP) (Schmiedt et al. 2002; Schmiedt 2010). This "metabolic presbyacusis," or age-related degeneration of the cochlear lateral wall and decline of the EP, largely accounts for threshold elevations observed in laboratory animals raised in quiet and may underlie the characteristic gradually sloping audiogram observed in some older humans. In contrast, "sensory presbyacusis" more likely relates to sensory cell losses resulting from the accumulated effects of a lifetime of environmental exposures (e.g., exposure to noise and ototoxic drugs) that result in more precipitously sloping audiograms. In humans, audiograms from 865 adults ≥50 years of age from a 30+-year longitudinal study of ARHL at the Medical University of South Carolina (MUSC) were classified using machine-learning techniques into distinct patterns associated with metabolic and sensory presbyacusis (Dubno et al. 2013). Evidence supporting metabolic and sensory phenotypes in audiograms from older adults was derived from demographic information (age, sex), environmental exposures (noise exposure histories), and stability or changes in audiometric phenotypes as individuals aged. Results showed that individuals with audiogram configurations classified as metabolic phenotypes were significantly older, more frequently women than men, and less likely to report positive noise histories compared with individuals with audiogram configurations classified as sensory phenotypes. Finally, audiometric threshold configurations were more likely to resemble that of metabolic than sensory phenotypes with increasing age (Vaden et al. 2017). In future studies, it will be of interest to assess generational changes in audiometric phenotypes of ARHL that may reflect changes in gender-related differences in the social determinants of hearing loss.

Cardiovascular Risk Factors and Hearing Loss

Another risk factor for ARHL may be vascular disease (Schuknecht & Gacek 1993; Kurata et al. 2016). Epidemiology studies have documented generally small but statistically significant associations between well-known cardiovascular disease (CVD) risk factors (e.g., hypertension, smoking, diabetes, dyslipidemia, and obesity) and hearing loss, after adjusting for sex and other potential confounding factors (Curhan et al. 2013; Cruickshanks et al. 2015; Lin et al. 2016; Rigters et al. 2016). However, averaging data across sex can obscure important differences. Generally, sex-linked biology is considered an important modifier of many exposure-outcome associations. For example, there is strong evidence that associations between CVD risk factors and ischemic heart disease and stroke are stronger for women than men (Wilson et al. 2002; Yusuf et al. 2004; Huxley & Woodward 2011; Peters et al. 2013, 2014; Peters & Woodward 2018; de Ritter et al. 2020). However, few studies have analyzed sex-linked biology as an effect-modifying factor of the association between CVD risk factors and hearing loss. Furthermore, there is very little in the hearing health literature examining associations between female-specific risk factors for CVD (e.g., premature menopause, early menarche, complications of pregnancy, and polycystic ovarian disease) and hearing loss, with some exceptions (Hederstierna et al. 2010; Svedbrant et al. 2015; Curhan et al. 2017).

It is not clear if or to what degree sex-linked biology influences associations between certain CVD risk factors and hearing loss, as the literature is sparse and results inconsistent. Rigters et al. (2016) and Nagahama et al. (2018) demonstrated that diabetes and elevated body mass index (BMI) are more likely to affect hearing in women than men; however, no sex-related differences in the association between diabetes and hearing loss emerged in the Health ABC study (Helzner et al. 2005). Conversely, higher blood pressure, smoking, and obesity were associated with higher hearing thresholds among men but not women (Helzner et al. 2005; Rigters et al. 2016). In the longitudinal Epidemiology of Hearing Loss Study (EHLS), women with high cardiovascular risk factor profiles were 2.7 times more likely to have incident hearing loss during 15 years of follow-up compared with women with low risk factor profiles (73% compared with 27%, respectively) whereas men with a high-risk factor profile had twice the risk compared to men with a low risk factor profile (93% compared with 47.3%, respectively) (Cruickshanks et al. 2015). In a longitudinal study conducted in Japan, hemoglobin A1c levels >8% (indicative of diabetes) was associated with incident hearing loss among nonsmoking women and men, but the association was stronger for women (OR = 2.4) versus men (OR = 1.5) (Nagahama et al. 2018).

Notably, sex-related associations between certain CVD risk factors and hearing loss may interact with other factors. In an analysis of data from the Canadian Longitudinal Study on Aging (CLSA), an interaction between age and obesity among women was noted, whereby the association was present among women aged 55 to 64 years, but not in other age groups. In this same study, cross-sectional associations between composite measures of cardiovascular risk and hearing loss were also strongest among 55 to 64 year old women (Mick et al. 2021b). Using data from the Health ABC study, Helzner et al. (2005) reported that the risk of hearing loss associated with smoking was stronger in Black women (OR = 2.9) versus other sex/race groups, and that the risk associated with hypertension was stronger in White men (OR = 1.3) versus other sex/race groups.

There also appears to be a trend toward stronger associations between CVD itself (distinct from CVD risk factors) and hearing loss in women. Gates et al. (1993) analyzed data from the Framingham study and found that women with hearing loss had about twice the odds of a history of a CVD event (coronary heart disease, heart attack, stroke, or intermittent claudication) compared with women without hearing loss, but a similar association was not observed in men. Moreover, effect sizes did not change after adjusting for CVD risk factors, suggesting that the effect of risk factors (e.g., smoking, hypertension, obesity) on hearing is operating through the onset of CVD rather than CVD risk factors acting directly on hearing. Torre et al. (2005) reported that women with a history of myocardial infarction were twice as likely to have cochlear impairment measured using DPOAEs than women without a history of myocardial infarction, whereas the association was not significant for men.

Women experience worsening cardiovascular risk factor profiles during and after menopause (Peters et al. 1999; Auro et al. 2014), but the extent to which these changes are a result of the biological effects of menopause versus chronological aging is debated (Atsma et al. 2006; Matthews et al. 2009). Moreover, women may be diagnosed with cardiovascular risk factors later in life and at a more advanced stage of disease than men, owing to gender-related rather than sex-related differences (Appelman et al. 2015). Known treatment disparities in managing cardiovascular risk factors, especially among young women, may lead to worse health outcomes (Udell et al. 2018). An alternative explanation for stronger associations between cardiovascular risk factors and hearing loss in women may be the presence, in men, of important but unmeasured risk factors masking the (presumably smaller) associations with cardiovascular risk factors. For example, as discussed earlier, lifetime noise exposure, which is difficult to quantify, is generally greater for men than women.

Taken together, these studies suggest that sex modifies the relation between CVD, its risk factors, and hearing, with women potentially at increased risk compared with men. Furthermore, the results from the Health ABC study and CLSA suggest that other factors such as race and age may also be interacting with sex and need to be considered carefully in study designs and analyses. Differences in CVD risk factors and hearing loss by sex and race can induce complexity in hearing research. Adjusting rather than disaggregating data for factors such as sex, race, and age can obscure differences that are important to advance our understanding of cardiovascular disease and its risk factors for hearing loss.

Hearing Loss, Cognition, and Dementia

Health conditions such as CVD risk factors and CVD itself may increase risk of hearing loss. However, hearing loss may be a risk factor for other health conditions such as cognitive decline. In models that statistically adjust for sex, hearing loss in cognitively normal persons at baseline is prospectively associated with cognitive decline and with the development of dementia (Lin et al. 2011a; Deal et al. 2017; Loughrey et al. 2018). The association between hearing and cognition is also found in individuals with mild cognitive impairment (MCI) who are at high risk of developing dementia, after adjusting for sex (Quaranta et al. 2014). Hearing loss, whether measured by self-report, pure-tone audiometry or supra-threshold tests of auditory processing, is associated with lower scores on cognitive tests (Amieva et al. 2015; Dupuis et al. 2015; Loughrey et al. 2018; Armstrong et al. 2020). However, similar to the discussion earlier, adjusting for sex may be obscuring important differences.

Given the prevalence of hearing loss and the degree of association between hearing loss and incident dementia (an approximate 2-fold risk), hearing loss is a large, potentially modifiable, risk factor at the population level (Livingston et al. 2017, 2020), possibly due to direct causal relationships with cognitive decline or to associations with poorer physical, psychological or social health outcomes, including hypertension and diabetes (Helzner et al. 2005), depression (Acar et al. 2011), social isolation (Mick et al. 2014), and decline in functional activities of daily living (Dalton et al. 2003). There are several hypothesized mechanisms that may account for auditory-cognitive associations (Lindenberger & Baltes 1994; Baltes & Lindenberger 1997; Wingfield et al. 2005; Whitson et al. 2018; Uchida et al. 2019; Griffiths et al. 2020). It is possible that (a) additional cognitive resources are required to process poor quality sensory input, (b) hearing loss causes enduring negative consequences to cognitive reserve and overall brain function, (c) hearing loss results in social isolation, which negatively affects cognition, and (d) there are common causes underpinning auditory and cognitive declines. These hypotheses are not necessarily mutually exclusive and may differ according to sex and gender.

Notably, cognitive decline differs between men and women. Although cognitively normal men tend to show steeper change in cognitive performance than women (McCarrey et al. 2016), Alzheimer's disease (AD) is more prevalent in women (Snyder et al. 2016; Ferretti et al. 2018; Alzheimer's Association 2019), even after accounting for their longer lifespan (Einstein 1999; Podcasy & Epperson 2016; Pike 2017). Despite the noted sex-linked differences in hearing described earlier, very few studies have examined auditory-cognitive associations stratified by sex. In the Health ABC study, lower scores on a simple cognitive screening measure (a modified version of the Mini-Mental State Examination) were associated with pure-tone hearing loss (PTA of 0.5, 1, 2 kHz > 25 dB HL) in Black women (OR = 1.45; 95% CI: 1.14–1.84) but not in Black men, White men, or White women (Helzner et al. 2005). In another study (Al-Yawer et al. 2022), the hearing thresholds of healthy older women, but not men, were negatively correlated with scores on the Montreal Cognitive Assessment (MoCA) (Nasreddine et al. 2005), an indication of cognitive impairment, even when hearing-dependent items were excluded. Similarly, results from the Korean Longitudinal Study of Ageing have shown that self-reported hearing loss was associated with cognitive impairment measured using the Mini-Metal State Examination in women but not men (Lyu & Kim 2018). Moreover, among women enrolled in the Nurses' Health Study, those with self-reported hearing loss at baseline had a higher risk of incident subjective cognitive function decline at follow-up compared with women without hearing loss (Curhan et al. 2020). However, opposite patterns have also been observed. In a study in the United States (NHANES 2010–2011), Huang et al. (2020) observed that moderate/severe hearing loss (PTA of thresholds at 0.5, 1, 2, and 4 kHz in the better hearing ear > 40 dB HL) was associated with global cognitive function only in men. Still, other studies of aging have not found evidence of differences in auditory-cognitive associations between men and women (Lindenberger & Baltes 1994; Phillips et al. n.d.).

In general, women tend to outperform men on tests of verbal memory and men tend to outperform women on tests of visual memory (Vogel et al. 2003; Hirnstein et al. 2019). Decades of research have also confirmed a small but robust finding that men have more asymmetric brain organization than women (Hirnstein et al. 2019). Interestingly, hearing loss has been associated with smaller volumes in the right hippocampal and medial temporal lobe regions, structures that are intimately involved in memory processing (Lin et al. 2014; Rudner et al. 2019; Giroud et al. 2021), but these studies did not disaggregate the data by sex. It is possible that sex-linked biological differences in auditory-cognitive associations become evident as cognitive performance declines due to neurological disease. Recent evidence suggests sex-related differences in sensory-cognitive relationships in participants with MCI (Al-Yawer et al., n.d.); women with hearing loss were more likely to fail the MoCA and an auditory verbal memory test than women with normal hearing, whereas men only showed an effect of hearing loss on a visual memory test. These findings raise the intriguing possibility which hearing loss has different implications for the cognitive performance of men and women. There are several reasons why sex may influence auditory-cognitive associations, and this open question deserves research attention.

Perceived Hearing Difficulty, Self-Reported Hearing Loss, and Hearing Aid Use

In addition to studies in which hearing is measured audiometrically, some studies provide data on differences between men and women in *perceived* hearing difficulty, typically measured with self-report tools. Recent work by (Humes 2021) found sex-related differences in scores on the Hearing Handicap Inventory for the Elderly-Screening Version (HHIE-S) (Ventry & Weinstein 1982, 1983) for clinical (n = 6850) and population (n = 4003) samples. The significant effect of sex on HHIE-S scores was observed in each sample after controlling for age and hearing loss. Men reported greater perceived hearing difficulties than women. Similar findings were noted in the CLSA with men having 1.37 higher odds of self-reported hearing difficulty based on a single question compared with women, after adjusting for important confounders including age and hearing thresholds (Hämäläinen et al. 2021).

SRHL and perceived hearing difficulty can be inferred from the time delay between the first suspicion of hearing problems and when a person seeks help at a clinic. It is assumed that adults will seek help when their perceived difficulties reach a critical point at which they are ready to take action to address their hearing difficulties. Acting on perceived difficulties may be more related to gender than sex-linked biology. A robust literature highlighting the unwillingness of many men to seek help for their problems has implications for overall health (Galdas et al. 2005), and there are likely similar implications for hearing health. In two separate studies of hearing aid outcomes conducted at Indiana University (IU), older adults were asked about the time delay (in years) between first noticing hearing problems and seeking help (Humes et al. 2009, 2010). In each study, men reported delays roughly twice the length of delays reported by women, even after adjusting for age and hearing loss. Similarly, in a longitudinal study investigating hearing aid adoption, women were more likely than men to adopt hearing aids at any given time point during follow-up, although there were no gender differences between adopters and non-adopters overall (Simpson et al. 2019). These results suggest that, compared with men, women present earlier to seek help at a clinic when perceived hearing difficulties arise and that they adopt hearing aids sooner after becoming candidates for hearing aids. Interestingly, factors that predict delays in hearing aid uptake among first-time users vary between men and women as well. Men with perceived problems in communication interactions with others tend to wait longer to seek help; whereas women with a negative affect and low feeling/thinking personality scores on the Myers-Briggs Type Inventory tend to delay seeking help (Humes et al. 2009, 2010). This pattern of findings suggests that there may be gender-related differences in help-seeking attitudes warranting more nuanced approaches toward hearing health care promotion and practice.

Differences in Hearing Aid Use by Men and Women: EuroTrak • Conducted online for The European Hearing Instrument Manufacturers Association (EHIMA) since 2009, the EuroTrak survey includes information on SRHL, hearing aid use, hearing aid satisfaction, daily use time, and benefits of hearing aid use, as well as reasons for nonuse [for more details see Bisgaard and Ruf (2017)]. EuroTrak data have not previously been stratified according to sex. Here, we present EuroTrak data on the prevalence of SRHL and hearing aid use from the 2009, 2012, 2015, and 2018 surveys for Germany, France and the UK pooled (n = 175,629) and stratified by sex (men:women = 1.04:1). Any notable sex-related variations in hearing and hearing aid use described below also likely reflect social factors. Of these 18,496 respondents, (10.5%) reported a hearing problem. Consistent with findings discussed earlier, the prevalence of SRHL was significantly higher in men (11.4%) than women (9.7%) ($p < 0.05$). For all age groups ≤74 years of age, men had a higher prevalence of SRHL compared with women. However, prevalence was higher for respondents ≥75 years of age, with women reporting a 48% prevalence of SRHL compared with 35% for men. Of those with SRHL, about one-third reported using hearing aids. More women with SRHL (39.1%) than men (34.4%) reported using a hearing aid ($p < 0.05$); however, on average, hearing aid daily use time was roughly equivalent between women (8.3 hours) and men (8.1 hours).

The EuroTrak survey measures hearing aid satisfaction with 24 questions related to the fitting process, sound quality, product features, and benefit in various listening situations. Each of the questions uses a seven-point Likert scale, which ranges from "very dissatisfied" to "very satisfied", including a neutral midpoint. When pooling across questions, 77% of hearing aid users reported being "somewhat satisfied," "satisfied," or "very satisfied" with their device and this did not vary between men and women. However, responses to 4 of the 24 questions did reveal small but significant ($p < 0.05$) differences whereby more women than men were satisfied with the visibility of hearing aids to others (77.5% versus 73.7%, respectively) and the quality of service during hearing aid fitting (84.8% versus 82.5%, respectively). More women than men were dissatisfied with changing batteries (9.0% versus 6.5%, respectively) and the ability to manage acoustic feedback (18.5% versus 15.6%, respectively). These differences seem likely to be explained more by physical or practical aspects of wearing or handling hearing aids than by benefit from amplification.

Respondents rated their hearing loss as mild, moderate, severe, or profound and the reasons for nonuse of hearing aids were analyzed for the 50% of nonusers with the most severe SRHL. A total of 27 reasons for hearing aid nonuse were presented and the respondents rated the degree to which each reason applied to them on a five-point scale ranging from "Definitely not a reason" to "Definitely a reason." The results are dichotomized as a "Reason" (the two highest ratings or the midpoint "Somewhat a reason") or "Not a reason" (the two lowest ratings). Depending on the question, the sample size varied between 2147 and 2908. Significant differences between men and women ($p < 0.05$) were seen for 4 of the 27 reasons. More women than men stated that hearing aid discomfort (42% versus 38%); vision or dexterity problems (36% versus 27%); and the opinion of other users (24% versus 18%) were reasons for nonuse. However, more men (28%) than women (20%) reported hearing loss for only high-pitched sounds was a reason for nonuse. It is not uncommon for women to be older than men with the same degree of hearing loss and to be physically smaller than men, which might explain differences related to comfort, vision, and dexterity. As discussed earlier, men are more likely to have a hearing loss categorized as a sensory phenotype, which may explain why more men than women are disinclined to use a hearing aid due to a loss mainly in the higher frequencies. Finally, the finding that the influence of the opinions of other hearing aid users was higher for women than men seems to be the only difference not likely explained by age or anatomy and it may reflect gender- rather than sex-related differences.

Gender and the Social Context for Hearing Rehabilitation

In addition to effects of sex on the biological underpinnings of hearing loss and associated risk factors and comorbidities, gender norms and expectations are likely to influence the lived experience of people who have hearing loss. Clearly, findings of differences between men and women in measures of audiometric thresholds, self-reported perceptions of hearing difficulties, delays in help-seeking, and reasons for nonuse of hearing aids have implications for rehabilitation involving the use of hearing technologies. In addition, a better understanding of the gender-specific factors that may influence functioning and social participation by older adults living with hearing loss could be key to advancing nontechnological aspects of person- and family-centered audiologic rehabilitation.

There has been a shift from the biophysical medical approach to a social model of hearing healthcare that is family-centered (Singh & Launer 2021). Hearing loss may disrupt social relationships; conversely, social relationships may support help-seeking for and coping with hearing loss. Gender plays an important role in defining individuals' personal and social identities and in influencing how people interact in their social relationships. A better understanding is needed regarding how gender might affect the important connections between hearing and social relationships, including relationships with significant others and even with health professionals.

Gender, Social Support, and Hearing Health • Social support refers to the quality of relationships with others who provide emotional, instrumental, and informational support (Broadhead et al. 1988; Cohen 2004). Decades of research suggest that social support has a significant positive influence on physical and mental health outcomes (Holt-Lunstad & Uchino 2015). Social support can vary by gender; for example, it has been reported that men are likely to receive support from their romantic partners while women are likely to receive support from those in other relationships such as friends, relatives, and peers (Kaplan & Hartwell 1987; Tang et al. 2008). Little research has investigated associations between social support and hearing health outcomes, but in general, the pattern that emerges is that better outcomes are observed for individuals who report having more social support (Hickson et al. 2014; Singh et al. 2015; Moser et al. 2017) or who attend audiology appointments with a significant other (Singh & Launer 2016). Social support is a pillar of family-centered care (FCC) and the broad consensus is that superior health outcomes along dimensions such as patient well-being, treatment adherence, and patient satisfaction are observed when care is provided following principles consistent with FCC [for a review see Rathert et al. (2013); Singh and Launer (2016)]. However, many questions remain regarding how gender may influence varying types of social support that could promote more positive hearing health outcomes.

Early qualitative research on adjustment to hearing loss reported gender-related differences, with greater social support for men with hearing loss compared with women with hearing loss (Hétu et al. 1993; Hallberg 1999). Insofar as social support is more often a role assumed by women than by men, conforming to such gender norms can have implications for women such as increasing levels of stress and anxiety. Recently, SRHL was found to be associated with both loneliness and lower levels of social support among older adults in the CLSA (Mick et al. 2018). Social support was measured using the Medical Outcomes Survey-Social Support Scale, which measures overall-, affectionate-, emotional-informational-, tangible-, and positive interactional-social support (Sherbourne & Stewart 1991). Effect measure modification by gender was not seen for any of the associations except between tangible social support (e.g., financial assistance) and SRHL, which was significantly stronger for women (odds ratio 1.47, 95% CI: 1.24–1.73) than for men (odds ratio: 1.17, 95% CI: 1.03–1.33) (Mick et al. 2018). The stronger association between SRHL and tangible social support for women than for men may interact with other gender-related social determinants (e.g., income, education) when cost is a barrier to seeking hearing health care and adhering to recommended treatments. Sorely lacking is large-sample quantitative research to investigate the role of social support in rehabilitation for different subgroups of people with hearing loss, including those of different ages, racial/ethnic backgrounds, and gender identities.

Gender in Patient-Clinician Relationships • Being perceived as a man or a woman may elicit different responses from one's hearing care professional (HCP) (Clark et al. 2021). Consequently, the diagnosis and treatment of hearing loss may vary according to gender (Mauvais-Jarvis et al. 2020), although this topic remains to be investigated specifically in hearing health care. Interestingly, there is also evidence to suggest that health outcomes may be influenced by the gender of one's HCP. Here, we present new data that explores the extent to which attitudes toward FCC held by an HCP are associated with hearing aid adoption in persons living with hearing loss. Hearing aid adoption rates were calculated over a span of five months of patient visits for 83 HCPs (66 women, 15 men, 2 who did not disclose their gender). To measure attitudes toward FCC, the HCPs completed a modified version of the 18-item Patient-Practitioner Orientation Scale (Krupat et al. 2000) adapted for use in hearing health care (Ali et al., 2019). A sample item is the following: "The hearing care practitioner is the one who should decide what gets talked about during an appointment?" Responses were made on a 6-point Likert scale ranging from 1 "strongly agree" to 6 "strongly disagree," with higher values interpreted to be more consistent with positive attitudes toward FCC. Overall, greater hearing aid adoption was observed for clinicians who had more positive attitudes toward FCC (Figure 1). Notably, the magnitude of the relationship between hearing aid adoption and attitudes toward FCC was stronger for men than women HCPs. In particular, less hearing aid adoption was observed for men who reported less positive attitudes toward providing care from a patient-centered perspective. This correlation raises the possibility that sociodemographic variables such as gender may influence patient outcomes through indirect effects such as the HCP's endorsement of FCC.

In summary, there is evidence to suggest that there is a differential effect of hearing loss on one's social relationships and the availability of various types of social support such that the pursuit of rehabilitation and the effect of rehabilitation on patient outcomes may depend on the gender of a person living with hearing loss, the gender of those in a person's social network, and even the gender of a person's HCP. There has been a lack of focus on the influence of sex-linked biology and gender on the lived experience of hearing loss and outcomes of audiologic rehabilitation, although there are some notable exceptions of prescient work observing gender-related differences in how individuals experience and cope with hearing loss (Garstecki & Erler 1999; Hallberg 1999; Wallhagen et al. 2004). Moving forward, a sex- and gender-based analysis (Canadian Institutes of Health Reserach [CIHR] 2019) can potentially clarify how subgroups experience hearing loss and rehabilitation to inform the development of relevant and tailored services for individuals in the context of FCC.

DISCUSSION

In this article, we have highlighted how hearing is likely influenced in multifactorial ways, involving both sex-linked biological factors and gendered environmental and societal factors. However, serious gaps remain in our understanding of how biological factors such as hormones, the social environment in which we work, live, and play, or interactions between these factors affect hearing health, rehabilitation, and functional outcomes. Better evidence is also needed to guide policies concerning hearing health care and the delivery of person-centered and family-centered hearing health care. Investigating how sex-linked biology and gender influence protective factors (e.g., estrogen) and risk factors (e.g., CVD) for hearing loss will help to establish evidence-based recommendations for prevention and treatment and spur future research. Hence, it is important to develop a research platform that proactively measures and assesses differences in hearing health and care, as it relates to sex and gender.

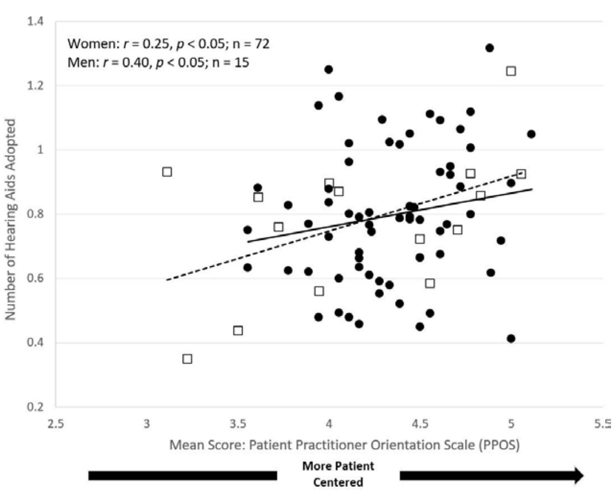

Fig. 1. Hearing aid adoption rates in patients depicted as a function of mean scores on the PPOS for hearing care professionals who are men (open squares; dashed line) and women (filled circles; solid line). PPOS, Patient-Practitioner Orientation Scale.

Documented differences in the hearing abilities of male and female animals and men and women are abundant. It appears that the characteristics that underlie sex- and gender-related differences in hearing are both endogenous and exogenous and change throughout the life course. To explain vulnerabilities and highlight potential interventions, a conceptual framework that centers sex and gender in hearing health is needed. Figure 2 introduces a conceptual model of the role of sex-linked biology and gender in the prevention, causes, treatment, and rehabilitation of hearing loss across the life course. Our goal in presenting this model is to provide a starting point for research and clinical conversations, not to include all interconnected pathways and hearing health outcomes. As denoted by black solid arrows, both social determinants of health and more proximal risk factors can contribute to hearing loss and resultant hearing capacity. Hearing capacity can affect other capacities such as cognition; multiple capacities, separately and together, can affect earlier- and later-life functioning. Furthermore, sex-linked biology and gender are shown as antecedents of most nodes in Figure 2 (purple dashed arrows). Finally, interventions to disrupt the causal chain (blue dot arrows), such as health promotion activities or person-centered integrated care, are likely to be modified by sex-linked biology and gender. Although gender is elevated toward the top of conceptual framework (in purple) to highlight its importance, it should be noted that gender *is* a social determinant of health. Taken together, this model is a heuristic framework and can suggest a research agenda leading to important insights into the dynamics of sex and gender on hearing health. Crucial opportunities to enhance treatment may arise from future research on the sex-linked and gender-based disparities in audiometric and self-reported measures of hearing and in aspects of audiologic rehabilitation including help-seeking, adoption, and use of hearing aids, and FCC.

Although not depicted in Figure 2, factors such as race, ethnicity, and disability are also determinants of hearing health. Intersections of sex and gender with society's other social categorizations (e.g., class, race, and disability) may shape one's lived experiences and health (Crenshaw 1989). These experiences are important to consider, especially when they contribute to worsening discrimination and exclusion. Termed intersectionality, this framework highlights that when multiple minority statuses overlap, each associated with disadvantages, the combined result is an independent system of disadvantage greater than what would be expected given each minority status alone (Alvidrez et al. 2021). Intersectionality also helps us understand privilege and access to health care. One example is that women with hearing loss or people of color with hearing loss, when

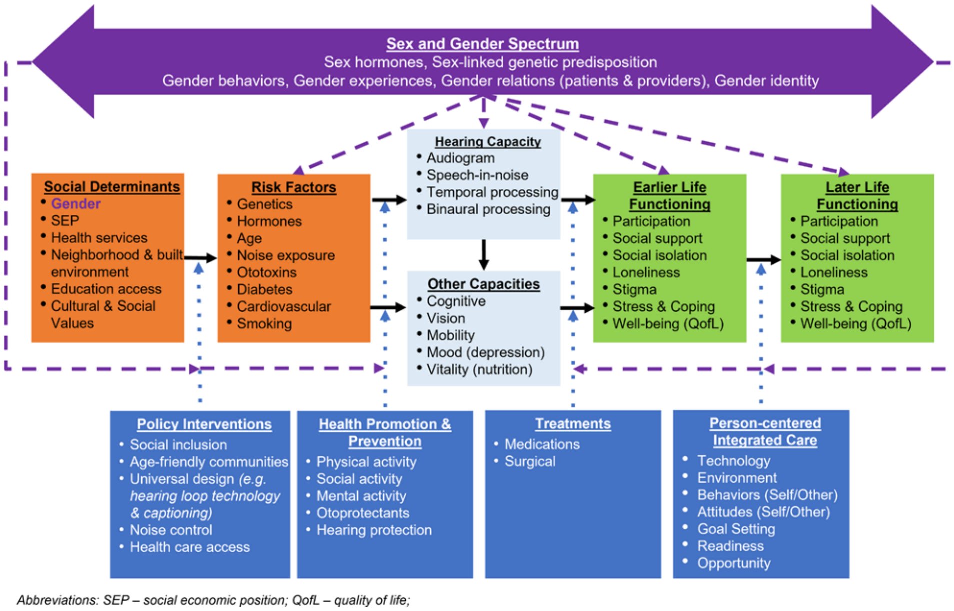

Fig. 2. A life course framework for sex, gender, and hearing health. In this framework, sex-linked biology and gender (purple arrows) alone and through proximal risk factors (orange box) influences hearing capacity and response to interventions (blue boxes and arrows). One's hearing capacity affects other physical capacities and earlier and later life functioning. Gender, also a social determinant of health (orange box), and gender-related experiences and behaviors determine an individual's perception of hearing impairment, help-seeking behavior, and use of hearing health services (green boxes). Social determinants of health working alone and together also contribute to the prevalence of risk factors, subsequent hearing loss, access to care and successful rehabilitation. Gender also influences help-seeking behaviors and relations with health care providers which may alter therapeutic outcomes among those with hearing loss.

compared with their counterparts, are less likely to use a hearing aid (Bainbridge & Ramachandran 2014; McKee et al. 2019). Additionally, there is a monotonic decrease in hearing aid use with decreasing income (Bainbridge & Ramachandran 2014). This suggests that Black and Brown women, especially those of lower socioeconomic position, may be especially disadvantaged in regard to receiving hearing health care. To our knowledge, an intersectional framework has yet to be applied to hearing science or audiologic rehabilitation research. Consideration of intersectionality will be important to advance inclusion, diversity, equity and accessibility so that we may better understand the barriers to healthy hearing and construct policies, programs, and rehabilitation approaches that work for everyone, including those with overlapping layers of disadvantage (Nieman et al. 2022; Schuh & Bush 2022).

As has been recommended for research in other domains (Heidari et al. 2016), sex and gender equity should also guide hearing research. We suggest integrating a sex-linked biological variable into research when appropriate. Including both males and females is important for conducting rigorous, ethical, and reproducible science that could result in the discovery of sex-linked differences in hearing and their underlying mechanisms (Clayton & Collins 2014; Tannenbaum et al. 2019). For example, the influence of sex-linked biology on the effects of a hearing loss intervention may be relevant for drug tolerability, efficacy, and toxicity (adverse effects) and subsequent treatment. Studies interested in understanding sex-linked biological differences in hearing health should consider physiological measurements like sex hormones or asking study participants about their sex assigned at birth. Research is particularly needed to understand the effects of long-term hormone use and gender affirmation surgeries on hearing in transgender and intersex individuals.

Likewise, researchers should integrate gender as a social determinant of health into research using qualitative, quantitative, or mixed methods (Einstein 2012). Our article focused on males/females and men/women, but there are deep health inequities and a lack of inclusion in research that continues to be experienced by SGMs. An inclusive research structure for SGM populations is warranted, ideally with a research agenda constructed in collaboration with SGM individuals (NASEM 2020; Marrone et al. 2022). Steps should also be taken to create a more sex- and gender-inclusive science by constructing research questions that extend beyond binary choices of man/woman (Cameron & Stinson 2019). Studying both sex-linked biology and gender may not be possible in all studies, but when warranted by the underlying research question, hearing research should include, collect, and report data separately by sex-linked biology and gender (NASEM 2020).

Researchers should describe how sex-linked biology and gender was measured, report the prevalence of sex and gender diversity in research samples, and be alert to the possibility that aggregated data runs the risk of masking important differences between and within groups (NASEM 2020). Following this logic, studies should be designed with enough participants to power analyses that could detect differences due to sex-linked biology and gender (Tannenbaum et al. 2019), and ideally, to explore these differences over a range of ages, races, ethnicities, socioeconomic position, disability, or comorbid conditions. Results, including tables and figures, should then be disaggregated by sex or gender (and any measured intersectional factor), depicting effect size by strata. Lastly, data summarized in this article were derived from high-income countries and results may differ for low- and middle-income countries (LMIC) and in some regions of high-income countries. Considering that 80% of the world's population live in LMIC (World Health Organization 2021), there is a need to carry out this work in other countries, especially where the power and dynamic roles of women vary by culture.

We are at a precipice in our research and clinical practice that demands the incorporation sex-linked biology and gender-based approaches. The field of hearing science, our research agendas, and the communities we serve are broad and diverse. Thus, it is imperative that our research include those diverse members of society in all areas of hearing science research. Failure to do so limits the generalizability of our study findings, preventing some populations from benefiting from research and scientific advancements.

ACKNOWLEDGMENTS

Portions of this work were supported: (a) with resources and the use of facilities at the VA Rehabilitation Research and Development (RR&D) National Center for Rehabilitative Auditory Research (NCRAR) [Center Award #C2361C/I50 RX002361] at the VA Portland Health Care System in Portland, Oregon (K.M.R.); (b) by the National Institutes of Health, National Institute on Deafness and Other Communication Disorders (P50 DC000422), the National Center for Advancing Translational Sciences of the National Institutes of Health (UL1 TR001450) in a facility constructed with support from Research Facilities Improvement Program (C06 RR 014516) from the National Institutes of Health/National Center for Research Resources at the Medical University of South Carolina (J.R.D.); (c) by the National Institutes of Health, National Inst. on Aging (P01 AG009524) (R.D.F.); (d) by the National Institutes of Health (R01DC013817), the Department of Defense (MR130240), and the Carolyn Frenkil Foundation (R.H.); (e) an infrastructure and operating grant to the Canadian Consortium on Neurodegeneration in Aging (CCNA) from the Canadian Institutes of Health Research (CNA-137794) for CCNA Team 17 principal investigators (P.M., N.A.P., M.K.P.-F.). Anovum, the agency holding the core dataset and responsible for the EuroTrak surveys of The European Hearing Instrument Manufacturers Association (EHIMA), provided the data presented in the present paper by N.B. (aggregate data for all EuroTrak survey results are published at www.ehima.com).

All authors contributed equally to the original and revised work. J.R.D. wrote the section on differences in measured hearing loss and if those differences reflect sex-linked biological or gendered-related determinants. B.C. and R.D.F. wrote the section on sex-linked biology and hearing. R.H. and B.S. wrote the section on sex-linked biology in the study of noise-induced hearing loss. P.M. wrote the section on associations between cardiovascular disease and hearing. N.A.P. wrote about the association between hearing loss and cognition. L.E.H. contributed the section on sex-related differences in perceived hearing difficulties while NB wrote the section on sex-related differences in hearing aid use. Authors K.P.F. and G.S. wrote the section on gender and the social context for hearing rehabilitation. K.M.R. wrote the introduction, discussion, and section on hearing loss and gendered exposures to noise from a public health perspective. K.P.F. and J.R.D. were also involved in editing the paper. All authors discussed the implications of the article and commented on the manuscript at all stages.

The authors have no conflicts of interest to disclose.

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Received August 29, 2021; accepted August 29, 2022; published online ahead of print November 17, 2022.

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